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Abstracts

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CHRONIC COLD STRESS ENHANCES HIPPOCAMPAL NOREPINEPHRINE RELEASE IN RESPONSE TO A NOVEL STRESSOR. E.D. Abercrombie and L.K. Nisenbaum

We previously have observed that both the basal and stress-induced level of extracellular norepinephrine (NE) in hippocampus of rat is maintained at a normal level despite the loss of up to 60% of the tissue content of NE in that structure (Abercrombie et al., 1989, J. Neurosci., 9:4062). This is an example of the remarkable capacity for adaptation to conditions of increased demand generally characteristic of catecholamine systems. In the present experiments, we have studied hippocampal NE release in another case where the system is thought to be operating under conditions of increased demand, i.e., chronic stress. In vivo microdialysis was used to examine the release of hippocampal NE in control rats and in animals previously exposed to cold stress for 20 days. Resting NE level as well as NE release evoked by a novel stressor (intermittent tail shock) were investigated. The extracellular level of 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of the NE precursor dopamine, also was measured. In control animals the resting level of NE obtained in dialysates was 13.5 pg/sample (corrected for probe recovery) and in chronically cold-stressed animals this value was 16.5 pg/sample ($p>.05$, n.s.). The peak increase in extracellular NE resulting from exposure to 30 min intermittent tail shock was 21 pg/sample in control animals (54%) and 31 pg/sample in chronically cold-stressed animals (82%). The stress-induced increase in NE efflux in the chronically cold-stressed animals was significantly greater than that observed in controls. In addition, the resting level of DOPAC in dialysates did not differ between the two groups. A stress-induced increase in hippocampal DOPAC was observed, however, which was significantly greater in the chronically cold-stressed group. These data demonstrate directly that exposure to prior chronic stress results in enhanced hippocampal release of NE in response to a subsequent novel stressor. The observed changes in DOPAC level suggest that this enhanced response may be due, in part, to increased activation of tyrosine hydroxylase by the tail shock in chronically cold-stressed animals.

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EFFECTS OF DOPAMINERGIC NEURONES IMPLANTED IN NEONATES ON OPIOID MODIFICATIONS INDUCED BY NEONATAL DOPAMINERGIC LESION. D.N. Abrous[1], M. Manier[2], L. Stinus[1], C. Feuerstein[2], F. Mennicken[2], M. Le Moal[1], J.P. Herman[1]

The functional effects of dopaminergic (DA) neurones implanted in newborn hosts on post-lesion modifications of opioid systems-related parameters have been investigated. The mesotelencephalic DA system of 3 days old rats was destroyed by the injection of 6-hydroxydopamine into the forebrain bundle. A suspension obtained from embryonic mesencephali and containing dopaminergic neurones was injected in the striatal complex 5 days after the lesion. The lesion led to the disappearance of DA innervation of the striatum and the nucleus accumbens. Implanted DA neurones survived and reinnervated the host tissues. Unilateral lesion and graft were used to study the effects of the transplants on the activity level of intra-striatal methionin-enkephalinergic (Met-Enk) neurones. Intra-striatal Met-Enk content was quantified by an image analyser 8 months after grafting. The lesion induced a lasting increase of Met-Enk immunohistochemistry staining in the ipsilateral striatum. The implantation of DA neurones led to the reversal of this lesion-induced increase. Bilateral lesions and grafts were used to investigate the effects of implanted neurones on alteration of locomotor activity induced by the intra-accumbens injection of DALA[2]-Met[5]-Enkephalinamide (DALA). The lesion induced a marked increase of the locomotor response activation evoked by the injection of DALA in comparison to that observed in non-lesioned control rats. This effect was reversed by the grafts. The lesion induced also a behavioural hypersensitivity as revealed by a direct DA agonist (apomorphine) and a loss of the amphetamine induced-locomotor activation. These modifications were also reversed by the grafted neurones. In conclusion DA neurones transplanted in neonatal host survive, reinnervate the host tissue and are able to normalize the functioning of host structures.

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FUNCTIONAL DIFFERENCES BETWEEN D1 AND D2 DOPAMINERGIC RECEPTORS IN A CONDITIONED MOTOR TASK. M. Amalric*, M. Berhow, I. Polis and G.F. Koob.

The striatum as well as the limbic structures receive afferents from the two main dopaminergic systems of the CNS (the nigrostriatal and the mesolimbic pathways respectively) and form an interface between cortical inputs and thalamic, limbic and hypothalamic outputs. These structures may be the locus of activities integrating sensory informations in order to perform conditioned acts.

To further investigate dopamine functions in the execution of a conditioned motor task, we have modified dopamine activity (either by making lesions of dopaminergic neurons or by blocking dopamine receptors) in rats trained to release a lever after a presentation of a visual cue in a reaction time task (RT). The destruction of the mesolimbic dopaminergic neurons produced by 6-OHDA injection into the nucleus accumbens did not affect the performance of the subjects. In contrast, 6-OHDA lesion of the dopaminergic nigrostriatal neurons impaired the motor performance by increasing the RT needed to release the lever after the stimulus. Intrastriatal microinjections of a dopamine receptor antagonist (haloperidol) induced a similar effect on RTs. The specific role of the D1 and D2 dopamine receptors in the execution of the task was then investigated. The systemic injection of a mixed D1/D2 receptor antagonist (alpha-flupenthixol) induced a dose-dependent increase in RTs, followed by an arrest of the performance for the highest dose. The D1 receptor antagonist, SCH 23390, did not impair performances, at any dose injected sub-cutaneously (5, 10 and 20 µg/kg). In contrast, a specific D2 receptor antagonist (raclopride, 50, 100 and 200 µg/kg) increased dose-dependently the number of long trials as well as RTs.

Thus, the nigrostriatal dopaminergic system appears to be a sensitive site for sensorimotor integration, necessary to perform a RT motor task after a cue stimulus and D2 dopaminergic receptors appear to be more specifically involved than the D1 receptors in the execution of this conditioned motor task.

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LOCOMOTOR ACTIVITY FOLLOWING MICROINJECTIONS OF MORPHINE INTO DIFFERENT PARTS OF THE PALLIDUM. Y.E. Anagnostakis, V.P. Zis and C. Spyraki

Enkephalin injected into the pallidum elicits activity reminiscent of that induced by systemic amphetamine. Behavioral studies indicate a differential role of the various types of pallidal opiate receptors in the mediation of locomotor activity. However, it is still an open question as to whether the opiate systems of the different pallidal regions influence distinctively locomotion. We approached the question with the following experiments. Male Sprague-Dawley rats were allocated in three groups (N=8-9/group) according to the pallidal region (dorsal, medial, ventral) that was implanted with cannulae (24 G). Coordinates, taken from bregma, were as follows: dorsal (A:-0.8, L:±2.8, V:-5.7 mm), medial (A:-0.8, L:±2.8, V:-6.7 mm) and ventral (A:-0.3, L:±2.5, V:-7.7 mm). Three days after the implantation, for each animal, locomotion was measured for 45 min before and for 90 min after the injection of saline (0.5μl) or morphine HCl (5.0, 7.5, 10.0 μg/0.5μl). Injections were performed bilaterally via a 28 G needle, inserted 0.5 mm below the guide cannula. The results showed 1. No statistically significant differences in terms of baseline locomotion between the three pallidal areas. 2. At all doses tested, morphine induced locomotion following injection in the dorsal or the ventral pallidum. 3. The highest locomotion was manifested after injection of morphine into the medial pallidum. This effect was seen only at the 7.5 μg dose, the other two being ineffective in this pallidal compartment. The data failed to give evidence for a differential role of dorsal and ventral pallidum in morphine induced locomotion. Further studies are necessary in order to elucidate the dose-response effect of morphine injected into the medial part.

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STRAIN-DEPENDENT INTERACTION BETWEEN STRESS AND OXOTREMORINE ON MOUSE LOCOMOTOR ACTIVITY

A. Badiani, C Castellano and A. Oliverio

A growing body of data shows that various kinds of both acute and chronic stress activate the cholinergic system and that this activation may play a pivotal role in a number of behavioral correlates of stress.

In the present study the locomotor behavior of unstressed and stressed mice of two inbred strains, DBA/2 and C57 BL/6, was investigated. Animals were tested, in a toggle-floor boxes apparatus, 30' after saline or oxotremorine treatment (i.p.). A dose of oxotremorine that did not depress the activity of naive mice (0.01 mg/kg), was chosen. Stressed mice were injected 24 h after either a single two hours-session of tube restraining (acute stress) or the last of fourteen daily stress sessions.

Acute stress did not modify the depressant effect of oxotremorine upon locomotor behavior of both strains.

On the contrary, chronic stress induced a clear sensitization of DBA but not C57 mice to the depressant effect of oxotremorine.

These findings show that chronic stress may result in modifications of the cholinergic function and of its behavioral correlates, and that these changes are modulated by the genetic make-up.

Moreover the present results are consistent with previously reported neuroanatomical and neurochemical differences between the cholinergic systems of these two strains.

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CHRONIC STRESS INDUCES A STRAIN-DEPENDENT SENSITIZATION TO AMPHETAMINE EFFECT ON LOCOMOTION. A. Badiani, S. Cabib and S. Puglisi-Allegra.

The present study investigates the effects of chronic restraint stress on amphetamine-induced locomotor hyperactivity in two inbred mouse strains, DBA/2 (DBA) and C57BL/6 (C57).

Stressed mice of both strains underwent ten daily stress sessions, each consisting of two hours of tube restraining. Unstressed and stressed mice were treated (i.p.) with d-amphetamine 0.5 mg/kg (Amph) or saline solution (Sa) and, immediately after injections, tested for locomotor activity in toggle-floor boxes.

In unstressed DBA mice, Amph did not increase locomotor activity, in comparison with Sal-injected group. On the contrary, 24 h after the last stress session, an increase of locomotor activity was observed in Amph-injected mice in comparison with Sal-injected group. These results indicate that chronic stress induces a sensitization to the effect of Amph on locomotor behavior of DBA mice.

By contrast, in unstressed C57 mice, Amph induced an increase of locomotion in comparison with Sal-injected group while, 24 h after the last stress session, no difference was evident between Amph- and Sal-injected groups.

These findings suggest that genotype and stress can interact in modulating the effects of amphetamine on mouse locomotor behavior.

Moreover the different responses to chronic stress of DBA and C57 strains are discussed in terms of the different alterations of DA presynaptic receptors observed in the mesolimbic systems of these strains following chronic stress.

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DISCRIMINATION OF PHENCYCLIDINE-LIKE DRUGS AND SIGMA-AGONISTS AS ANIMAL MODELS OF SCHIZOPHRENIA

Robert L. Balster

There is a reasonable rationale for the use of acute and/or chronic effects of phencyclidine (PCP) as an animal model of schizophrenic disease, and some basis for presuming that an alteration in PCP receptor function may underlie some aspects of this condition. In this regard, drug discrimination studies of PCP-like drugs in animals can provide a means of studying the perceptual experience of PCP intoxication. Although the search for PCP antagonists as possible antipsychotic drugs has been unsuccessful, continued basic research on the neurobehavioral pharmacology of PCP-receptor acting drugs may provide important insights into psychiatric conditions. The assignment of a role for the "sigma receptor" in schizophrenia is less clear, and depends upon which sigma binding site is being discussed. The historic sigma receptor defined by WR Martin and his colleagues is probably isomorphic with the PCP receptor, and there is considerable evidence from drug discrimination studies that the acute effects of many so-called sigma agonists are PCP-receptor mediated. Another, high-affinity site has been discovered which has been referred to by many as the sigma receptor. This site has not been clearly associated with behavioral effects of drugs. Although some drugs with indications of antipsychotic activity displace ligands for this site, it is not proven that selective agonists at this site are psychotomimetic. Thus, the involvement of this high-affinity sigma site in psychiatric disease awaits further clarification.

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EFFECT OF MUSCARINIC AGONISTS ON THE FREQUENCY OF TYPE II HIPPOCAMPAL THETA RHYTHM: POSSIBLE INVOLVEMENT OF M_1 MUSCARINIC RECEPTORS. J.C. Barnes and F.F. Roberts .

It is believed that hippocampal theta rhythm may be important for the normal processing of memory and in view of the interest in the cholinergic system in cognitive function, we have investigated the effects of a range of muscarinic agonists and antagonists on type II (atropine-sensitive) theta rhythm.

In the isoflurane anaesthetised rat, the EEG recorded from the CA1 region of the hippocampus consisted of theta rhythm with frequencies varying from 2 to 5Hz. Intravenous administration of arecoline (0.1-1.0mg/kg), oxotremorine (0.1-1.0mg/kg), arecaidine propargyl ester (0.1-0.3mg/kg) and aceclidine (1.0-10.0mg/kg) produced a dose-dependent increase in the frequency of theta rhythm, the highest frequencies produced ranging from 6.1±0.2Hz (arecoline) to 8.0±0.3Hz (oxotremorine). Higher doses could not be used because of the toxicity of these drugs. In contrast, pilocarpine and AF102B, up to doses of 10mg/kg, produced little or no increase in the frequency of theta rhythm above 5Hz. In fact, pilocarpine (10mg/kg) antagonised the response to 0.3mg/kg arecoline, indicating that pilocarpine was acting as a partial agonist.

In an attempt to identify the possible muscarinic receptor subtype mediating the agonist effects, we compared the ability of scopolamine (40-80µg icv) and the M_1 selective antagonist, pirenzepine (160-240µg icv) to antagonise the response to arecoline. Both antagonists produced a dose-related attenuation of the enhanced frequency produced by arecoline, showing a potency difference of less than 5 fold. Compared with the relative affinities of these two antagonists obtained from radioligand binding studies, this result indicates that the increase in the frequency of theta rhythm produced by muscarinic agonists may be mediated through central M_1 receptors.

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ANALYSIS OF ANXIOLYTIC AND ANTIDEPRESSANT DRUG EFFECTS IN THE PIGEON. J.E. Barrett

The discovery of novel clinically-effective anxiolytic drugs that appear to act through specific serotonin (5-HT) receptor subtypes has generated considerable interest. One focus has been that of attempting to develop new, reliable preclinical models for detecting potential anxiolytic activity of these compounds because they do not produce consistent effects in most mammalian models. However, using punished responding of pigeons, it has been shown that compounds such as buspirone and ipsapirone, as well as 8-OH-DPAT, which interact with the 5-HT1A receptor subtype, produce consistent and reliable increases in responding that are similar in magnitude to those found with the benzodiazepines. This model appears to be sensitive and selective for other compounds that act at this site (e.g., flesinoxan, gepirone, SM 3997 and spiroxatrine), as well as at other sites where there is some indication of clinical effectiveness such as the 5-HT2 antagonists. Studies using receptor binding, drug discrimination and central drug administration will be summarized in an effort to clarify the possible bases of these effects and suggest some reasons why the pigeon may be a good system for the evaluation of these novel anxiolytic compounds. Studies using drug discrimination procedures in which antidepressants are established as discriminative stimuli in the pigeon will also be discussed to provide further information on the potential utility of this species in evaluating the behavioral and neurochemical bases of antidepressant drug action.

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A COMPARISON OF THE EFFECTS OF GEPIRONE ON SPATIAL MEMORY. R.P. Barrett, M.J. Rowan.

Previous research has shown that interference with serotonergic transmission can produce deficits in spatial memory when combined with a partial reduction of the cholinergic system (Richter-Levin G. & Segal M. Brain Research, 477, 404-7, 1989). The aim of this study was to investigate whether the 5-HT_{1A} receptor ligand gepirone alone could affect spatial memory acquisition and recall in a manner similar to that produced by atropine. A modified Morris water maze was used. A four arm radial maze was placed into the water bath (1m diameter). The task set for the animals was to find a hidden submerged platform at the end of one of the arms. Male Wistar rats (250g-300g) were used. After every two trials the platform was moved in a clockwise direction from the northern arm to the eastern arm etc. There were 4 pairs of trials per day. Two experiments were carried out. In the first the effect of gepirone (7 mg/kg ip, n = 9) was compared to that of water (n = 9). The animals were dosed 30 minutes before the first trial on each day. The second experiment was to compare the effect of atropine (50 mg/kg ip, n = 6) over two days. The animals were dosed 20 minutes before the first trial on each day.

Both the gepirone group and the atropine group were slower to learn platform position and adjust to position changes than the control group. The control groups significantly improved their performance on the second of each pair of trials to each arm on all days ($P < 0.05$). There was no significant difference between the first and second trial of each pair in the gepirone or atropine treated animals, except day 3 for the gepirone group ($P < .01$).

The present study indicates that gepirone alone can produce a similar deficit to atropine in the spatial learning test.

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DENERVATION SUPERSENSITIVITY OF 5HTIC - BUT NOT OF 5HTIA - and 5HT$_2$ - RECEPTORS H.H.G. Berendsen, C.L.E. Broekkamp and A.M.L. van Delft.

Recently we found that selective activation of 5HT1A receptors results in lower lip retraction (LLR) and that direct or indirect activation of 5HTIC receptors induces penile erections (PE) in rats (Berendsen et al. Pharmacol Biochem Behav 33: 821, 1989; Berendsen et al. Psychopharmacol, 1990 in press). Activation of $5HT_2$ receptors results in head shakes (Yap and Taylor Neuropharmacol 22: 801, 1983). In this study the effects of 5,7 dihydroxytryptamine (5,7 DHT) and p-chlorophenylalanine (PCPA) treatment on drug induced LLR, PE and head shakes were evaluated.

Rats were lesioned by unilateral i.c.v. injection of 5,7-DHT (100 µg/rat) or depleted by i.p. injection of PCPA (150 mg/kg 72, 48 and 24 hours before the test). LLR induced by (±)-8-hydoxy-dipropylamino tetralin HBr (8-OH-DPAT) was not affected by 5,7 DHT or PCPA lesions. Neither the number of head shakes induced by the $5HT_2$ agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCL (DOI) was changed after 5,7 DHT and PCPA pretreatment. The PE response after injection of the 5HTIC agonist 1-(meta-chlorephenyl)-piperazine HCl (mCPP) was strongly enhanced in both 5,7 DHT and PCPA pretreated rats. The dose response curve was shifted to the left: the optimal dose of mCPP to induce the maximal response was about 20% of the optimal dose in the controls (1 mg/kg). The effect of the 5HT reuptake inhibitor paroxetine on the other hand was strongly reduced after 5,7 DHT pretreatment, and the PE response to the 5HT reuptake inhibitor citalopram in PCPA pretreatment was also reduced. The results suggest that 5HT1C receptors are more subject to denervation supersensitivity than 5HT1A and $5HT_2$ receptors.

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OPIOID ANTAGONIST EFFECTS OF BUPRENORPHINE ON SCHEDULE-CONTROLLED RESPONDING OF RHESUS MONKEYS.

Jack Bergman and Sara E. Johnson

The opioid buprenorphine has mu-agonist and antagonist actions and recently has been shown also to have kappa-antagonist actions in rodents, pigeons, and squirrel monkeys. In the present experiments, mu- and kappa-antagonist effects of buprenorphine on schedule-controlled behavior were compared with those of Mr2266, which also has both mu- and kappa-antagonist actions. Initially, cumulative doses of levorphanol (0.1-3.0 mg/kg), U50,488 (0.03-0.3 mg/kg), buprenorphine (0.01-3.0 mg/kg) and Mr2266 (0.03-3.0 mg/kg) were studied in rhesus monkeys responding under a 30-response fixed-ratio (FR30) schedule of food presentation. Next, the effects of levorphanol and U50,488 were redetermined in the presence of doses of buprenorphine and Mr2266 that did not alter rates of responding.

Levorphanol, U50,488, and Mr2266 produced dose-related decreases in rates of FR30 responding whereas buprenorphine did not appreciably affect responding at doses studied. However, buprenorphine produced dose-related rightward shifts in the dose-effect functions for both levorphanol and U50,488. Doses as low as 0.01 mg/kg produced an approximately 3 fold shift; higher doses (0.1-0.3 mg/kg) produced as much as a 30-100 fold rightward shift in the effects of both agonists. The effects of levorphanol and U50,488 also were antagonized by Mr2266: lower doses (0.03-0.1 mg/kg) produced an approximately 3-6 fold rightward shift whereas the highest dose (1.0 mg/kg) produced an approximately 10-30 fold shift in the behavioral effects of the agonists. These results are consistent with previous findings that Mr2266 is a nonselective mu/kappa antagonist and indicate that similar doses of buprenorphine comparably antagonize the effects of mu and kappa agonists in rhesus monkeys. Supported by USPHS grants RR00168, MH07658, DA03774.

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FACILITATION OF 8-OH-DPAT-INDUCED SPONTANEOUS TAIL-FLICKS BY PUTATIVE 5-HT_{1C} AGONISTS IN THE RAT.

K. Bervoets, M.J. Millan and F.C. Colpaert.

Binding studies suggest the following classification of CNS serotonin (5-HT) receptors: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_2 and 5-HT_3. It is possible that various 5-HT receptor subtypes do not only act independently but also *interact* in the mediation of their functional effects. Recently, we characterized spontaneous tail-flicks (STFs) induced by 8-OH-DPAT as a novel model of 5-HT_{1A} receptor activation[1]. In this study, putative agonists at 5-HT_{1C}/5-HT_2 receptors were evaluated for their influence upon this behaviour. Male Wistar rats (200-220g) were gently restrained in horizontal plastic cylinders such that the tail hung freely. After 5 min adaptation, STFs were counted over 5 min. An STF was defined as an elevation of the tail to a level higher than the body axis. All drugs were injected s.c. 30 min prior to the test except 8-OH-DPAT (10 min). The standard dose of 8-OH-DPAT was 0.63 mg/kg. 8-OH-DPAT induced a mean of 54.0 ± 6.9 STFs. The 5-HT_{1B}/5-HT_{1C} agonists, TFMPP and mCPP, and the 5-HT_{1C}/5-HT_2 agonists, DOI and quipazine, were inactive alone but enhanced the action of 8-OH-DPAT at lowest effective doses of 0.63, 2.5, 0.04 and 0.63 mg/kg, respectively. In their presence, the dose-response curve for 8-OH-DPAT was shifted to the left. The putative, selective 5-HT_{1B} agonist, CGS 12066B (0.16-10.0 mg/kg) was inactive. The 5-HT_{1C}/5-HT_2 antagonist, ritanserin (0.63 mg/kg), did not affect the action of 8-OH-DPAT but blocked the potentiation induced by TFMPP and DOI. The 5-HT_{1A} partial agonists, flesinoxan and buspirone, did not induce STFs when given alone but did so in the presence of TFMPP or DOI. We conclude that an agonist action at 5-HT_{1C} and/or 5-HT_2 receptors potentiates the efficacy of agonists acting at 5-HT_{1A} receptors. These data suggest that there is a functional interaction between 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors in the expression of their functional effects.

[1] Millan, M.J. et al: Neurosci. Lett. 107 (1989) 227-232.

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MODULATION OF IN VIVO 5-HT_{1A} RECEPTOR-MEDIATED RESPONSES BY DOI AND RITANSERIN

D.J. Bill, M. Knight, E.A. Forster and A. Fletcher

Recent reports have indicated a functional interaction between central 5-HT_2 and 5-HT_{1A} receptors.(eg: Arnt and Hyttel, European J. Pharmacol 161:45,1989). We have examined the effects of selective 5-HT_2 ligands on two in vivo responses to 5-HT_{1A} receptor activation: the behavioural syndrome in rats (flat posture and forepaw treading), and hypothermia in both rats and mice.

The potencies of 5-HT_{1A} agonists to induce a syndrome were measured by a quantal up/down method (Fletcher and Forster, Br. J. Pharmac 96:304P,1989) using probit analysis. Rectal (mice) or oesophageal (rats) body temperatures were measured 15 and 30 min. following the administration of submaximal hypothermic doses of 8-OHDPAT (0.8 or 0.3 mg/kg sc for mice or rats respectively). The 5-HT_2 agonist DOI (Glennon et al., J. Med. Chem 29:194,1986) or the 5-HT_2 antagonist ritanserin were administered 30 min. before the 5-HT_{1A} agonists.

DOI (0.1-2.5 mg/kg sc) markedly increased the potency of 8-OH-DPAT, buspirone or gepirone to induce the syndrome. DOI attenuated 8-OHDPAT-induced hypothermia in mice (by 79% maximally at 1 mg/kg sc) and rats (by 81% maximally at 1 mg/kg ip). Ritanserin (0.1-3.0 mg/kg sc) had no effect on 8-OHDPAT-induced syndrome but significantly enhanced 8-OHDPAT-induced hypothermia in mice (by 61% at 0.3 mg/kg ip; $p<0.01$) and rats (by 35% at 0.3 mg/kg ip; $p<0.05$). At these doses neither DOI or ritanserin alone modified body temperature significantly.

These data indicate that the 5-HT_{1A} receptors mediating hypothermia or syndrome may differ in terms of their functional association with 5-HT_2 receptors. 5-HT_2 receptors may directly facilitate the activation of 5-HT_{1A} receptors mediating the syndrome, whereas 5-HT_2 receptors involved in thermoregulation may exert an action physiologically opposed to that of 5-HT_{1A} receptor stimulation.

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CONTRIBUTION OF α_1-ADRENERGIC RECEPTORS TO THE BEHAVIOURAL EXPRESSION OF THE "VTA SYNDROM".

G. Blanc, F. Trovero, P. Vezina, D. Hervé, J. Glowinski and J.P Tassin.

The ventral tegmental area (VTA) contains the A 10 group of dopaminergic (DA) cell bodies which innervate the frontal and cingular cerebral cortices as well as several subcortical structures. In addition, the cerebral cortex is innervated by the ascending noradrenergic (NA) pathway which passes through or projects to the VTA. Bilateral high frequency lesions of the VTA induce a behavioural syndrom characterized by a permanent locomotor hyperactivity. We have shown that an intact NA innervation was necessary to obtain this locomotor hyperactivity. Therefore, we have investigated what type of NA receptors was involved in this regulation. Among different NA antagonists, only prazosin (0.5mg /kg i.p), an α_1-adrenergic receptor blocker, was able to antagonize the locomotor hyperactivity induced by electrolytic lesions of the VTA. Indeed, neither propranolol nor yohimbine (β and α_2-adrenergic receptor antagonists, respectively) were able to reproduce the effect of prazosin. The results demonstrate that the stimulation by NA of α_1-adrenergic receptors plays an important physiological role in the expression of rat locomotor hyperactivity obtained by electrolytic lesions of the VTA. Since the development of the amplitude of the locomotor hyperactivity observed with the lesioned animals was proportional to the development of denervation supersensitivity of cortical D1 receptors, our results suggest that α_1-adrenergic receptors modulate the sensitivity of cortical D1 receptors.

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BEHAVIOURAL EFFECTS OF INTERLEUKIN-1 ARE DEPENDENT ON VASOPRESSINERGIC NEUROTRANSMISSION

R.M. Bluthé, R. Dantzer, R. Franklin and K.W. Kelley

Fever is part of an adaptive response to infection which is refered to as "behavioural sickness" and which involves non specific behavioural changes. This response can be induced by peripheral or central injections of endogenous pyrogens such as interleukin-1 (Il-1) and its extent is limited by endogenous antipyretic signals such as vasopressin (AVP).

Since part of the extra-hypothalamic innervation of the brain is androgen-dependent, we investigated whether castration enhances sensitivity to Il-1. This was the case as demonstrated by the lowering of the dose of Il-1 necessary to decrease social investigation of a juvenile conspecific by male rats when injected peripherally (from 5 to 1 ug/rat) or centrally (from 2 to 1 ng/rat) after castration.

A more direct demonstration of the role of AVP in the behavioural effects of Il-1 was provided by the observation that icv injected dPTyr(Me)AVP (15 ng/rat), an antagonist of AVP V1 receptors, enhanced the behavioural effects of Il-1 (1 ng/rat, icv) in intact but not in castrated male rats. The effects of AVP are under investigation.

These results support the concept of a functional antagonism between brain vasopressin and Il-1, the mechanisms of which are currently under study.

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ANXIOLYTIC EFFECTS OF A NEW STRUCTURAL CLASS OF 5-HT-3 ANTAGONISTS. F. Borsini, D. Templeton*, M. Turconi, M. Nicola, P. Schiantarelli and A. Donetti

Recently, a novel class of 5-HT-3 antagonists (esters and amides of 2,3-dihydro-2-oxo-lH-benzimidazole-l-carboxylic acid) was found on the basis of activity on Bezold-Jarisch reflex and affinity for 3H-ICS 205-930 binding sites. Now, we report that amido derivatives bearing a hydrogen or an alkyl substituent in position 3 of the benzimidazolone nucleus may be active in the light/dark exploratory test, an animal model of anxiety, in mice. In particular compounds labeled DAU 6215, BIMU 0001 and BIMU 0011, bearing hydrogen, ethyl and n-hexyl substituents, respectively, increase the percent of time spent in the light compartment at doses ranging from 1 to 10 μg/kg via intraperitoneal route given 45 min before the 3-min period of testing. DAU 6215 at a dose of 10 μg/kg via oral route reduced the aggressiveness of cynomolgus monkeys when faced with an operator at the same extent as did GR38032F at 100 μg/kg. These data provide additional evidence that 5-HT-3 receptor antagonists might represent new potential drugs for the treatment of anxiety.

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DIFFERENTIAL EFFECTS OF D-1 AND D-2 DOPAMINE AGONISTS IN MPTP-TREATED SQUIRREL MONKEYS.

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Dyskinesias represent a major complication of L-DOPA therapy in Parkinson's disease. The time-course for L-DOPA-induced dyskinesias does not always coincide with the antiparkinsonian effects of the drug. This suggests that different neural mechanisms may underlie the antiparkinsonian and dyskinetic effects of L-DOPA. We have used a range of dopamine agonists with differing selectivity and efficacy for D-1 and D-2 receptors, to examine whether different subclasses of dopamine receptors are involved in mediating different motor responses in MPTP-treated squirrel monkeys.

Administration of the indirect non-selective agonist L-DOPA (5-40 mg/kg p.o. plus carbidopa, fixed dose ratio 2:1), the non-selective agonist apomophine (0.025-0.2 mg/kg i.m.) or the selective D-2 agonist (+)-PHNO (0.625-5.0 ug/kg s.c.) induced a dose-dependent increase in locomotor activity. In contrast, treatment with the selective partial D-1 agonist SKF38393 (5-30 mg/kg s.c.) caused a reduction in locomotor activity. Chorea was observed only following treatment with L-DOPA. In contrast, dystonia was induced by either administration of L-DOPA or (+)-PHNO. Treatment with apomorphine in doses up to 0.2 mg/kg failed to induce significant dystonia, although a small increase was observed at the highest dose. Administration of SKF38393 did not induced dystonia; a small reduction in spontaneous dystonia was observed.

These data indicate that D-2 receptor stimulation appears essential for antiparkinsonian activity, and also implicate D-2 receptors in the genesis of dystonia, but not chorea. In contrast, D-1 receptor stimulation appeared responsible for the induction of chorea and possibly dystonia.

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SEXUAL ORIENTATION OF ADULT MALE RATS AFFECTED BY PERINATAL ATD-TREATMENT.

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Testosterone (T), through its estradiol (E_2) metabolite, seems essential for sexual differentiation of male rats. ATD (1,4,6-androstatriene-3,17-dion) blocks aromatization of T to E_2. Pregnant rats were treated with ATD or oil. Some male pups were neonatally treated with a silastic implant containing ATD. Three groups of males were formed: (1) controls (n=14); (2) prenatal ATD (n=12); (3) pre- plus neonatal ATD (n=18). As adults these males were regularly tested for partner preference behavior, i.e. sexual orientation, in a 3-compartment-box[1] with tethered stimulus animals: a sexually active ♂ and an estrous ♀. Time spent in the compartment with the male subtracted from time spent in the compartment with the female was used as a measure of sexual orientation. Effects of 8OH-DPAT (a $5HT_{1\alpha}$ agonist) were studied in 2 tests (0.2 mg, 0.4 mg/kg resp, 30 min before testing). It was found that males perinatally treated with ATD had lower preference scores for the estrous ♀ than other males. All males showed normal sexual behavior except the perinatally ATD treated males, which did not ejaculate. 8OH-DPAT restored ejaculations in this group and resulted in higher preference scores of all males for estrous female partners.

Conclusion: sex behavior and sexual orientation of adult males seems to be organized perinatally by the E_2 metabolite of testosterone.

[1] A.K. Slob et al. Physiol Behav **41:** 571-576, 1987

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ALPHA ADRENERGIC RECEPTORS ARE INVOLVED IN THE COGNITIVE ENHANCEMENT CAUSED BY INTRACEREBROVENTRICULAR ANGIOTENSIN II. J.J. Braszko and K. Wisniewski

Pretreatment of rats with prazosin (PRA), an alpha 1 adrenergic receptors blocker, abolished the increase of the rate of learning of conditioned avoidance responses, caused by intra-cerebroventricular angiotensin II. Yohimbine (YOH), an alpha 2 receptors blocker, reversed the effect of AII. PRA did not affect and YOH abolished the improvement of recall of a passive avoidance behaviour caused by AII. The stereotypies produced by apomorphone (APO) or amphetamine (AMP) were enhanced by AII. PRA changed neither stereotypy but it abolished the AII effect in both cases. Also YOH did not alter the APO stereotypy and, roughly, the effect of the combined, with AII, treatment was additive. No significant changes of the exploratory motor activity were caused by PRA, YOH and their combinations with AII.
These findings indicate that the functioning alpha 1 and alpha 2 adrenergic receptors are necessary for the facilitation of learning by AII while only alpha 2 receptors appear to be involved in the AII improvement of recall. The central dopaminergic system may in part be responsible for the modulation by PRA and YOH of effects of AII on learning and recall.
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FAMILIARISATION WITH DRUGS BEFORE CONDITIONING A TASTE AVERSION, AS A METHOD FOR DRUG DISCRIMINATION.
C.L.E. Broekkamp

Drugs are usually classified as anxiolytics, antidepressants, antipsychotics or other therapeutic agents. This classification becomes less useful in the light of information that antidepressants are effective in anxiety disorders and that compounds like buspirone, ipsapirone and gepirone, which were developed as anxiolytics, behave as antidepressants in medical practice and animal models for depression. An alternative method for drug classification is to group compounds on the basis of similarities in behavioural effects. Examples of such methods are drug discrimination and cross-tolerance methods. We use familiarisation to drugs followed by a conditioned taste aversion with a reference compound as a method to compare drugs. The procedure starts with four days on which mice are injected with a compound under investigation. On day five of the experiment the water deprived mice are offered drinking water sweetened with sucrose. Shortly after drinking, a known reference compound is injected. Two days later the animals are tested for a conditioned taste aversion. There is no conditioned taste aversion when the unknown compound has effects similar to the reference compound (cross-familiarisation). We identified thusfar separate aversions for 5-HT_{1A} agonists, 5-HT_2 antagonists, dopamine uptake inhibitors, noradrenaline uptake inhibitors and serotonin uptake inhibitors. An example of a surprising result is that the conditioned taste aversion induced by amphetamine is not due to the release of dopamine but to the release of serotonin and noradrenaline. Familiarisation with amphetamine prevents the conditioned taste aversion with fenfluramine and maprotiline but not with nomifensine or buproprion. This procedure has the potential to be used in many instances were the more time consuming drug-discrimination procedure has proved to be useful.

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6-HYDROXYDOPAMINE LESIONS OF THE MEDIAL PREFRONTAL CORTEX AND ACQUISITION OF MAZE TASKS
M. Bubser and W.J. Schmidt

The function of the dopaminergic innervation of the rat prefrontal cortex was investigated using delayed and non-delayed tasks in the T-maze and the 8-arm radial maze respectively. Selective lesions that depleted cortical dopamine and DOPAC but did not reduce cortical serotonin and did not change dopamine metabolism in subcortical structures (nucleus accumbens and corpus striatum), were produced by local infusion of 6-OHDA into the medial prefrontal cortex.
In each maze acquisition of delayed alternation was impaired in lesioned animals, whereas acquisition of uninterrupted tasks like spontaneous and reinforced alternation was not deficient. In a spatial reversal paradigm neither the acquisition nor the reversal phase were impaired.
The results of our experiments employing non-delayed tasks indicate that neither a deficit of spatial learning nor an increase of perseverative tendencies occurred after prefrontal lesion and these factors may therefore not account for deficits observed in delayed alternation.
The results are discussed in terms of an interference hypothesis (Simon H. et al., Nature 286 (1980)), and it is suggested that prefrontal dopamine serves to suppress interference mainly during the delay period of alternation tasks.

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HYPERDEFENSIVE RESPONSE IN THE MOUSE: A POSSIBLE MODEL OF BENZODIAZEPINE-RESISTENT ANXIETY. S. Cabib, S. Puglisi-Allegra and C. Belzung

Defensive behaviour toward non aggressive conspecifics exhibited by mice that have been previously exposed to repeated defeat experiences appears to be mediated through activation of dopamine receptors of the D2 type. In naive mice the selective D2 agonist LY171555 (LY) induces dose-dependently (0.5 to 5 mg/kg) defensive responses toward non aggressive conspecifics further supporting this hypothesis.
In order to investigate possible anxiogenic properties of the D2 agonist, its behavioural effects were compared with those produced by the benzodiazepine inverse agonist B-CCM in the elevated plus maze and in social interactions with non aggressive opponents. When tested in the elevated plus maze, mice injected with LY (.005 to 1 mg/kg) did not show any decrease either of the number of entries or of the time spent into the open arm. At the dose of 5 mg/kg an actual increase of these two measures was observed. By contrast, B-CCM (1 to 3 mg/kg) dose-dependently decreased both the number of entries and the time spent into the open arm without altering locomotion. These effects were completely antagonized by 5 mg/kg of chlordiazepoxide (CDZ) showing a selective involvement of benzodiazepine receptors in their modulation. Moreover, B-CCM, injected at the same doses, did not affect defensive behaviour of mice interacting with non aggressive opponents and the defensive responses of mice treated with 1 mg/kg of LY were not prevented by 5 mg/kg of CDZ.
These results show that DA D2-mediated hyperdefensiveness and anxiety modulated by benzodiazepine receptors are unrelated phenomena and suggest that this behavioural response may represent an interesting model of those forms of anxiety that do not respond to benzodiazepine treatment.
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ROLE OF EARLY EXPERIENCE IN THE MODULATION OF INDIVIDUAL RESPONSIVITY TO APOMORPHINE.
S. Cabib and F.R. D' Amato.

In previous studies we have shown that 15 days old mouse pups exposed for the first two weeks of life to clean bedding (15 min)(CB group) exhibited more apomorphine-induced climbing behaviour than pups never separated from the mother (CC group) or pups exposed to home-cage bedding during separation (HCB group). No difference was found between groups in 35 days old mice, one week after weaning. These results indicated that chronic stress-induced alteration of DA functioning in developing mice is no more evident in 35 days old subjects.
The data reported here were aimed to explore possible alterations of the organism/environment interaction in adult mice chronically stressed during development. 3 months old CB male mice tested in an elevated plus maze were more explorative than other groups, confirming the classical view that stress applied during development reduces emotional reactivity in adult life.
When submitted to repeated restraint stress (10 daily sessions of 120 min) male mice of the HCB and CC groups showed a significant increase of apomorphine-induced climbing behaviour in comparison with unstressed groups. By contrast, no difference was evident between stressed and unstressed mice of the CB group, suggesting that alteration of DA functioning induced by postnatal chronic stress affects adaptation to stress in adult life.
Taken together our results suggest that the effects of early experience on individual responsivity to pharmacological treatment may be not evident in basal conditions and revealed only under environmental pressure.

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STRESS AND BEHAVIORAL SENSITIZATION: MODULATION BY THE CORTICOTROPIN RELEASING FACTOR (CRF). M. Cador, B.J. Cole, L. Stinus, G.F. Koob, and M. Le Moal.
Repeated exposure to stress or psychostimulants such as d-amphetamine (AMPH) induce a progressive increase in behavioral response which has been correlated with an increased release of dopamine. This behavioral sensitization may lead to the emergence of pathological behaviors and has been suggested to provide a useful analogy to the longitudinal aspect of affective disorders. The polypeptide corticotropin releasing factor (CRF) is the primary hypothalamic releasing factor involved in mobilizing the pituitary-adrenal axis response to stress. CRF has also been localized in extra-hypothalamic regions of the CNS, where it is thought to play a crucial role in initiating behavioral response to stress. For these reasons, CRF has been proposed to be a coordinator of biological responses to stress. In a first experiment, we studied whether the blockade of CRF transmission may modulate stress-induced sensitization. In a second experiment, we studied whether administration of exogenous CRF may induce a sensitization to the behavioral effect of d-amphetamine.
Experiment I: Groups I and II were put through an immobilization stress paradigm (90 min/day/5 days) with prior icv infusion of either the specific CRF antagonist (α-helical CRF) or solvant. Group III was not stressed and received ICV saline infusion. Eight days later, response to d-amphetamine (0.75 and 3 mg/kg) was tested.
Experiment II: Three groups of animals received respectively for 5 days, a daily ICV infusion of saline, CRF (0.5 μg/2 μl) and CRF (2.5 μg/2 μl). Locomotor activity was recorded after each infusion. Eight days later behavioral response to d-amphetamine (0.75 and 3 mg/kg) was tested.
The results showed that i) behavioral effects of d-amphetamine are potentiated in stressed animals and ii) ICV administration of CRF antagonist prevent the development of this sensitization. Finally, iii) ICV administration of exogenous CRF induce a stimulation of locomotor activity which amplifies with the repetition of the injections. These animals also develop a sensitization to the behavioral effects of d-amphetamine. In conclusion, these experiments demonstrate that CRF participates in the establishement of behavioral sensitization.

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LONGITUDINAL STUDY ON AGING RAT IN RADIAL MAZE AND EFFECTS OF LONG-TERM TREATMENT WITH ACETYL-L-CARNITINE. A. Caprioli, O.Ghirardi, A. Giuliani, M.T. Ramacci and L. Angelucci.

Sprague Dawley rats aged 25 months were tested in the radial maze in the absence of external visual cues. They exhibited greater difficulties in learning compared with age-matched animals that underwent the same test when aged 4 and 13 months. A longitudinal study showed that these animals remembered previous experiences performing with a high number of correct choices since the very first sessions. The study on strategies indicated prevalent choices of adjacent arms at 4 months and of alternate arms at 25 months, indipendently of experience and performance. Therefore, the reduction possibly occurring in the sensorial capacities of the old rats was not such as to affect the correct test performance, since expert animals at 25 months scored almost as good performances as they did at 4 and 13 months. Thus, old animals can be said to remember previous experiences well, while exhibiting a reduced learning capacity of a new test. Since Acetyl-L-Carnitine (ALCAR) was shown to ameliorate the old rat's performance in the Morris water task, a test of spatial memory (Ghirardi et al., 1988), the effects of a long-term treatment with ALCAR on the aged rat's radial maze learning were also studied. ALCAR-treated old animals scored a higher number of correct choices than age-matched controls. High-level performances observed in treated old animals can be explained as a functional counterpart of ALCAR capability of retarding the loss of hippocampal neurons (Ricci et al., 1988), of reducing lipofuscin deposition (Amenta et al., 1989) and of opposing the loss of hippocampal axosomatic synapses (Badiali et al., 1987).
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ALTERED RESPONSES TO DIAZEPAM DURING THE MOUSE OESTROUS CYCLE. M.P. Carey and J.P. Fry

An exploratory model of anxiety in the mouse monitoring transitions made between the light and dark chambers of a novel environment, has been proposed to evaluate fearfulness and sensitivity to the anxiolytic action of diazepam (J.N. Crawley & F.K. Goodwin, Pharmac. Biochem. Behav. 13: 167, 1980). In a preliminary application of this test to female mice (Billing et al., J. Physiol. 377: 70P, 1986), we found altered responses to diazepam at certain stages of the oestrous cycle and have now extended this study to include other stages.

Tests lasted for 15 min and were initiated by placing the mouse in the dark chamber. Female mice were given a dose of diazepam (0.28 mg kg^{-1}, I.P., 60 min) which had been found in males to cause 50% of the maximal diazepam-induced increase in light/dark transitions. At this dose, diazepam significantly ($P<0.05$ compared to drug vehicle alone; Mann-Whitney U-test) increased transitions at oestrus and dioestrus but not at pro-oestrus or metoestrus I and II. Indeed, at metoestrus I, the test dose of diazepam significantly decreased the number of transitions, an effect which could be reversed by increasing the dose to 1 mg kg^{-1} and did not, therefore, appear to be due to a sedative action. Rather, the 0.28 mg kg^{-1} dose of diazepam at metoestrus I appeared to be having an anxiogenic effect, because latencies to emerge from the dark chamber increased while other exploratory measures, such as time, activity and rearings in the light chamber were found to decrease. Such changes were not seen upon administration of a range of low doses of diazepam to male mice.
Concentrations of diazepam and active metabolites in the brain after I.P. injection (as measured by radioimmunoassay) did not change during the oestrous cycle. Thus, the altered behavioural responses to diazepam during the oestrous cycle appear to reflect changes in sensitivity rather than changes in the distribution or metabolism of this drug.
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BEHAVIOURAL PROFILE OF PSYCHOMOTOR STIMULANTS AND REUPTAKE-INHIBITORS IN THE "LEARNED HELPLESSNESS" MODEL OF DEPRESSION.

A.V. Christensen, M. Geoffroy, and J. Scheel-Krüger

Rats were subjected to the "Learned Helplessness" model of depression i.e. A session of unescapable footshock, an interval of 4 days in which drugs were administered, and final shuttlebox test.
The testsession consisted of 10 FR1 and 15 FR2 non-signalled two-way escape trials. The shockfree intervals between trials lasted 20 sec. during which responding had no programmed consequences. In addition to the number of escape responses, the number of crossings in the intertrial intervals were recorded in search for a specific behavioural profile of antidepressants vs psychomotor stimulants which are considered to be false positive drugs in the model.
The behavioural profile of imipramin, nomifensine, buspirone, amphetamine, methylphenidate, apomorphine, cocaine, specific DA agonists (SKF 81297 (D-1), LY 171555 (D-2)), different uptake inhibitors (Lu 19-005 (DA + NA + 5-HT), talsupram (NA), citalopram (5-HT)), and finally the MAO-inhibitors moclobemide and isocarboxazide will be presented, and the relevance of the "Learned Helplessness" model for the experimental field of depression will be discussed.

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DSP-4- INDUCED DESTRUCTION OF BRAIN NORADRENERGIC NEURONS: INFLUENCE ON THE RESPONSE TO ANXIOLYTIC TREATMENTS. R.L. Commissaris and D.J. Fontana.

Previous studies have demonstrated that anxiolytic-like anti-conflict effects can be produced by either (1) acute PRE-TEST administration of traditional anti-anxiety compounds (barbiturates or benzodiazepines or (2) chronic POST-TEST administration of tricyclic (TCA) or monoamine oxidase inhibitor (MAOI) antidepressants. The present study determined the effects of noradrenergic neuronal destruction on these potentially distinct anti-conflict drug effects. After three weeks of training in the Conditioned Suppression of Drinking (CSD) conflict paradigm, water-restricted rats consumed 11-14 ml water/session (unpunished responding) and accepted 25-40 shocks/session (punished responding) during control (i.e., non-drug) test sessions. The noradrenergic neurotoxin DSP-4 (65 mg/kg, IP) or its vehicle (saline) was administered after training; CSD behavior was evaluated for 8 weeks post-treatment. DSP-4 treatment depressed punished responding slightly relative to saline controls. In separate groups of DSP-4 and saline pretreated subjects, the effects of acute PRE-TEST administration (10-min pretreatment) of phenobarbital (5-40 mg/kg) or alprazolam (0.3-2.5 mg/kg) were determined. The effects of chronic POST-TEST treatment with the TCA desipramine (DMI; 5 mg/kg, BID for 8 weeks) or the nonselective MAOI phenelzine (PHEN; 4.0 mg/kg, BID for 8 weeks) on CSD behavior were determined in additional groups of DSP-4 or saline pretreated subjects. DSP-4 pretreatment did not alter the anti-conflict effects of acute PRE-TEST treatment with phenobarbital or alprazolam. In contrast, DSP-4 treatment completely abolished the anti-conflict effects produced by chronic POST-TEST DMI or PHEN treatment. Thus, noradrenergic neuronal integrity is required for the anxiolytic-like effects of chronic POST-TEST antidepressant treatment, but not for the effects of acute PRE-TEST treatment with barbiturates and benzodiazepines (USPHS 42501).

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SEARCH AFTER NEUROBIOLOGICAL PROFILE OF INDIVIDUAL-SPECIFIC FEATURES OF WISTAR RATS.

A.R. Cools, R. Brachten, D. Heeren, A. Willemen and B. Ellenbroek.

The bimodal shape of variation in "fleeing" and "non-fleeing" rats of an outbred strain of Wistar rats has been found to represent two fundamentally different types of individuals, each of them marked by their own transsituational consistency in pharmacological and behavioural responses.
It will be demonstrated that the pharmacogenetic selection of apomorphine-susceptible (APO-SUS) and apomorphine-unsusceptible (APO-UNSUS) rats is a valid tool to disperse these individual-specific features as far as possible. First, these lines have allowed us to prove that the overall bimodal shape of variation in pharmacological and behavioural responses of individual outbred rats is in part genetically determined. Second, these lines have allowed us to prove that a bimodal variation in neurochemical features of the circuitry, in which the ventral striatum is embedded, underlies the overall bimodal variation in pharmacological and behavioural responses. Third, these lines have allowed us to demonstrate that a fundamental difference in organizing behaviour with the help of external and internal information has to be considered as a common factor giving rise to the individual differentiation found.
Given the notion that this individual differentiation appears to be valid across lines, substrains and strains of rats, the present study lays the foundation for understanding at least a part of the physiological basis underlying differences between the two fundamentally different types of individuals existing in normal populations of rodents.

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BEHAVIOUR MEDIATED BY 5-HT$_3$ RECEPTORS. S.J. Cooper

The discovery of specific 5-HT$_3$ binding sites in the brain, and the development of a range of highly selective 5-HT$_3$ antagonists has stimulated considerable interest in the functional significance of actions at this subtype of 5-HT receptor, and the potential therapeutic applications of these drugs. Three topics of current research interest will be considered: (i) behavioural effects of 5-HT$_3$ antagonists in several animal models; (ii) central sites of action of 5-HT$_3$ antagonists; (iii) interactions between 5-HT$_3$ antagonists and other drugs, particularly psychomotor stimulants and opioids. In addition, putative interactions between 5-HT$_3$ antagonists and central neurotransmitter systems will be discussed in relation to behavioural responses.

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MODULATION OF MU OPIOID ANTINOCICEPTION BY KAPPA OPIOID AGONISTS

R. M. Craft and L. A. Dykstra

The kappa opioid agonists U50, 488, bremazocine and ethylketazocine, and the mu agonist l-methadone were administered alone and in combination with morphine to squirrel monkeys responding under a shock titration schedule. Under the titration schedule, shock increased once every 10 sec from 0.01 to 2.0 mA in 30 steps. Five responses on a lever during the 10-sec shock period terminated the shock for 10 sec, after which the shock resumed at the next lower intensity. When administered alone, all opioids produced dose-dependent increases in median shock level (the intensity below which monkeys maintained shock 50% of the time) as well as decreases in rate of responding. When combined with a dose of morphine that increased median shock level (1.0 - 3.0 mg/kg), all kappa opioids dose-dependently antagonized the increase in median shock level and decrease in response rate produced by morphine. In contrast, the mu opioid l-methadone did not antagonize morphine's effects. In addition, low doses of morphine (0.03 - 0.32 mg/kg) did not antagonize the increase in median shock level produced by U50, 488. The present study corroborates previous evidence suggesting that the agonist effects of mu and kappa opioids in the shock titration procedure are mediated by different receptor types. In addition, the results demonstrate that several kappa opioids possess mu antagonist activity in this procedure, at doses below those that have kappa agonist activity.

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MECHANISMS OF STRESS EFFECTS ON IMMUNITY

Croiset, G*, C.J. Heijnen**, J.A.W.M. van Oers***, F.J.H. Tilders*** and D. de Wied*

The impact of emotional stimuli on the reactivity of the immune system was studied in rats using a one-trial learning passive avoidance test. This test uses the innate preference of rats for a dark environment. In this test an animal receives a 2 sec. lasting mild electric footshock in a dark compartment. A primary antibody response against Sheep Red Blood Cells (SRBC) was used as an in vivo immunological parameter: the number of antibody secreting cells (PFC) in the spleen was assessed using a plaque-forming cell assay (PFC test).

Depending on the nature of the environmental stimulus either an increase or a decrease in the immune response was observed. Exposure of rats to a novel situation (apparatus of the passive avoidance test) resulted in an increase of the primary antibody response. The opposite was observed in rats that were tested for passive avoidance behavior (inverse relationship between avoidance latency and number of antibody secreting cells).

An endogenous role for CRH and Vasopressin in immunomodulation was revealed by studies with antibodies. Intracerebroventricular pretreatment with monoclonal antibodies directed against CRH effectively prevented the rise in primary antibody response to a novel situation. Both local surgical denervation of the spleen and systemic β-adrenoceptor blockade prevented the increase of the immune response. This suggests that CRH stimulates the immune system through the sympatho-adrenal system.

Intracerebroventricular administration of antibodies against vasopressin resulted in an inhibition of passive avoidance behavior and consequently in an increase in immune response. The peripheral mechanism leading to a down-regulation of the immune response has not been elucidated. The role of the parasympathetic nervous system is currently under investigation and will be discussed.

These observations show that passive avoidance behavior is a good model for the study of the interaction of psychological, neuroendocrine and immune responses.

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SWITCHING-OFF OF THE CHOLINERGIC SYSTEM IN MEMORY.

S.E. Cruz-Morales, M.A. Díaz del Guante and R.A. Prado-Alcalá.

Anticholinergic drugs produce amnesia, which can be prevented when the magnitude of the reinforcers are increased during learning. It is not known whether this is a gradual or an "all-or-none" effect. To test these possibilities, rats were trained, in one trial, to avoid the darker compartment of a two-compartment box; retention was tested 24 hr later. Independent groups of rats were trained using one of the following footshock intensities: 3.0, 4.0, 4.1, 4.2, 4.4, 4.6 or 5.0 mA; half the groups were injected with 8 mg/kg of scopolamine (SCOP) and the other half was not treated. Isotonic saline or methylscopolamine (8 mg/kg) were injected to two additional groups, which were given 3.0 mA during training. All injections were administered 5 min posttraining (i.p.). SCOP produced amnesia in the 3.0 and 4.0 mA groups; all other groups showed near-perfect performance. These results suggest that once a certain level of training-related stimulation is reached, the cholinergic system is switched-off, and other neurochemical systems mediate the consolidation process. Supported by CONACYT (P228CCOX891608).

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ETHOPHARMACOLOGY AS A TOOL IN BEHAVIOURAL TERATOLOGY; SOME EFFECTS OF ANTICONVULSANT DRUGS. M.G. Cutler.

Evidence of delayed behavioural maturation, impaired learning and abnormal behavioural activity following prenatal or neonatal exposure to certain compounds (C.V. Vorhees et al., Science 205: 1220, 1979) precipitated concern about behavioural teratogenesis. Therefore guidelines requiring tests of developmental psychotoxicity have been implemented. Anticonvulsants need to be taken throughout pregnancy. These drugs may carry a risk to the unborn child (M.L. Friis, Acta Neurol. Scand. 67 suppl. 94: 39, 1983), depending on dose, genetic susceptibility and the stage of development during which exposure occurs. Developmental psychotoxicity tests are often confined to measures of sensory functions, learning and exploratory activity. We have used ethopharmacological methods to examine changes in social interactions produced by exposure of the developing young to chronic oral therapeutic doses of anticonvulsants, in mice and gerbils.

When given to pregnant animals, phenobarbitone (500 mg/l in drinking fluid) adversely affected reproductive performance of gerbils. In offspring gerbils and mice it caused developmental retardation and reduced growth. Sodium valproate (600 mg/l in drinking fluid) delayed development in gerbils but not mice. Neither drug impaired maternal care by the mouse dams. Gerbils and mice given phenobarbitone showed increased reactivity to and increased exploration in a novel environment. The effect of phenobarbitone in mice was less marked at 187.5 mg/l. Exposure from the time of conception produced larger effects than exposure after weaning. Mice treated with sodium valproate showed an increase in exploration, social investigation or aggression. Effects were more marked after prenatal and postnatal exposure than after treatment from the time of weaning. Sodium valproate given to gerbils from the time of conception increased exploration in adults but not in juveniles. Valproate given to gerbils for two weeks following weaning had no effects. Anticonvulsant drugs at therapeutic concentration have apparently adverse effects on development and modify social interactions later in life.

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SEXUAL BEHAVIOR ENHANCES DOPAMINE TRANSMISSION IN THE NUCLEUS ACCUMBENS AND THE STRIATUM OF THE MALE RAT.

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The extent to which central dopamine (DA) transmission is altered during sexual behavior was investigated in male rats. To monitor central DA activity *in vivo* microdialysis probes were implanted in the nucleus accumbens (n=6) and the striatum (n=6) of sexually experienced male rats. Two days later the rats were subjected to a test of sexual performance while DA transmission was monitored concurrently in the two brain areas at a 10-min sampling frequency. The experimental protocol consisted of an equilibration period in the home cage, a 40 min period in the mating chamber, a 10 min period in the mating chamber while a receptive female was placed behind a screen, a 30 min period of sexual interaction between the female and the sexually experienced male, and an 80 min period following the sexual performance.

Behaviorally, the male became very active when placed in the mating chamber, and this continued when the female was introduced behind the screen. During the actual sexual performance an average of 3.1 ejaculations were observed. Following the sexual interaction the males quickly became behaviorally inactive. Biochemically, a modest but significant increase (+30%) in DA obtained from the nucleus accumbens was observed when the male was placed in the mating chamber and when the female was behind the screen. During sexual interaction DA increased sharply (+80%) followed by a decrease towards pre-test values after the female was removed. The DA metabolites DOPAC and HVA showed patterns that were similar to DA during sexual behavior though the increases were less pronounced (+45% and +60 %, respectively) and slightly delayed. Changes in dialysate concentrations of DA, DOPAC, and HVA in the striatum were similar to those observed in the nucleus accumbens, though less pronounced. These results demonstrate that preparatory and consummatory aspects of sexual behavior in the rat are accompanied by enhanced DA transmission in the striatum and the n. accumbens. They provide a neurochemical basis for the well known effects of dopaminergic agents on sexual behavior in rats and humans.

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SOCIAL RECOGNITION: A SIMPLE TEST FOR MEASURING THE EFFECTS OF DRUGS ON MEMORY

R. Dantzer and R.M. Bluthé

The ability to recognize familiar from unfamiliar conspecifics is important for social animals. In rats, social recognition can be infered from the variations in duration of investigation of conspecifics since unfamiliar conspecifics are investigated longer than familiar ones. A reliable way to assess social investigation is to use juveniles as social stimuli since their presentation does not lead to any competing behaviour belonging to the sexual or the aggressive repertoire.

In adult male rats, social recognition has been found to be enhanced by mnemotonic drugs such as cholinergic agonists, nootropic drugs, benzodiazepine inverse agonists and vasopressin. The mechanims by which so many drugs can influence social recognition are unknown. In the case of vasopressin, two different mechanisms have been identified, one which is mediated by androgen-dependent vasopressinergic neurons in the lateral septum and another one which is likely to be mediated by circadian variations of vasopressin concentrations in the cerebrospinal fluid. In the first case, vasopressin would act as a transmitter in a neuronal circuit originating from the vomero-nasal organ, whereas in the second case it would act as a neurohormone which modulates arousal levels.

Although aged animals are still able to recognize conspecifics, their interest toward social stimuli is greatly decreased. This may be used as a baseline for a new class of drugs.

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QUISQUALATE NONCOMPETITIVELY BLOCKS KAINATE ACTION IN CULTURED CEREBELLAR GRANULE CELLS. W. Danysz, J.T. Wroblewski and E. Costa

In primary cultures of cerebellar granule cells kainate produced marked influx of $^{45}Ca^{2+}$, partially (30-40%) independent from the release of glutamate and secondary activation of N-methyl-D-aspartate (NMDA) receptors. Quisqualate was much less efficacious and more potent in this respect. Both kainate and quisqualate action was antagonized competitively by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and was only slightly attenuated in Na^+-free medium. Hence, both ligands apparently produce calcium influx independent from sodium influx-mediated depolarization. Action of 30 μM kainate was enhanced by quisqualate. On the other hand effect of 100 μM kainate was abolished in a non-competitive manner by Quisqualate but not ibotenate. Quisqualate-induced $^{45}Ca^{2+}$ influx was doubled by pretreatment (but not cotreatment) with concanavalin A (Con A), lectin which blocks desensitization of quisqualate responses in the hippocampal neurons (Mayer & Vicklicky, PNAS, 86(1989)p1411). However Con A failed to affect inhibition of kainate response by quisqualate. This suggest that quisqualate-induced calcium influx and the inhibition of kainate responses may be realized through different recognition sites.

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THE EFFECTS OF A CHOLINERGIC AGONIST AND CHOLINESTERASE INHIBITORS IN A CONDITIONED SUPPRESSION OF DRINKING PARADIGM

G.R. Dawson and S.D. Iversen

The passive avoidance test is widely used to assess the potential cognitive enhancing effects of compounds targeted for the treatment of Alzheimer's disease. The measure of learning in this test is the step-through latency (STL) from a safe, but brightly lit chamber, to a dark chamber in which the animal had received a brief electric shock 24 hours earlier. However, as Brammer (Neurosci & BioBeh Rev. 6 247-296, 1981) and Shulz et al. (Pharmacol Biochem & Behav, 25 979-983, 1986) point out there is substantial between-subject variability in STL in this test. We sought to reduce this between subject variability by designing a test in which: (i) the animals could be thoroughly habituated to the apparatus without introducing latent learning effects, (ii) a specific signal is given for the onset of the electric shock during acquisition and test (iii) an unambiguous measure of memory was used and (iv) the effects of the drugs on locomotor activity and motivation are minimized.

To this end we utilised a conditioned suppression of drinking paradigm in which water-deprived rats were placed in an operant chamber and allowed to drink a slightly sweet solution. In an 'off-the-baseline' conditioning session the drinking tubes were removed and the rats were given four pairings between a tone and an electric shock. On the test day the animals were again given access to the sweet solution. When they had made 150 licks the tone was reintroduced into the chamber. The measure of learning in this test is the latency to the first lick after the onset of the tone. Animals treated with vehicle during the off-the-baseline phase of the experiment were slow to resume licking. In contrast, animals treated with a 0.6 mg/kg dose of scopolamine during the off-the-baseline phase resumed licking a short time after the onset of the tone. This scopolamine-induced deficit was reversed by the cholinesterase inhibitors physostigmine (0.6 mg/kg) and THA (10 mg/kg), and the muscarinic receptor agonist AF102B.

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A COMPARISON OF THE EFFECTS OF CESIUM CHLORIDE, HALOPERIDOL AND ASCORBIC ACID ON THE BEHAVIOUR OF MICE. L. De Angelis

The therapeutic effects of lithium and rubidium encourage study of the other exogenous alkali, cesium. Contrasting data from animals' studies have indicated that cesium can have inhibitory or excitatory actions on CNS. Recently, possible antipsychotic effects of cesium have been suggested. Furthermore, evidence has been obtained from animals indicating that ascorbic acid plays an important role in potentiating the behavioural effects of a widely used antipsychotic drug, i.e. haloperidol. In view of the above data, the purpose of this study was to provide better information on cesium chloride, haloperidol and ascorbic acid by determining in mice the behavioural effects of these compounds administered alone or in combination. Cesium chloride (CsCl)(2.5 mmol/kg; 420 mg/kg ip); L (+) ascorbic acid (AA)(0.71 mmol/kg; 125 mg/kg ip); or their association were administered 45 min before the "open-field" test. Haloperidol (HAL)($0.27 \cdot 10^{3}$ mmol/kg; 0.1 mg/kg ip) was administered 30 min before the "open-field" test. The results of the present studies show that CsCl alone exerts a significant depressant effect, when compared with control mice. Moreover, the combination with an antidopaminergic drug i.e. haloperidol or ascorbic acid enhances the inhibitory effects of cesium, being the inhibition of the association more marked after HAL than AA administration. In conclusion, these data confirm and extend previous findings (Bose, R. and Pinsky, C. Psychopharmacology 1984, 84: 80) by demonstrating that CsCl may potentiate drug - induced anti-dopaminergic activity.

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CHARACTERIZATION OF THE OBJECT MEMORY TEST.
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The object memory test, developed by Ennaceur and Delacour (Psychopharmacol. 92:58, 1987), can be used to study incidental memory. No form of reward is involved, just the natural tendency of rats to explore novel objects in their environment. In order to evaluate the usefulness of the test in pharmaco-geriatric research the time course of incidental memory of wistar rats aged 2 months and 24 months was studied under conditions with a normal and a reversed light/dark cycle. Individually housed rats are first adapted to the test environment, a sound proof chamber. On the next day the home cage with the animal in it is placed on a motility measuring device and the sample object, a 25 ml glas beaker for half the animals and a 25 ml Erlenmeyer for the other half, is introduced in the center of the cage. The total time the animal makes physical contact with the object within a period of 4 minutes is taken as the exploration time. The object is then removed. After a variable interval (30, 60, 120 and 180 minutes) the sample object and a new object, the glas beaker and the Erlemeyer, are placed in the center of the cage. The exploration time for each object is measured during a 4-minute period. A longer exploration time of the new object compared to the sample object is indicative of memory of the latter. In the normal light/dark cycle condition, young animals remembered the sample object up to 3 hours whereas old animal's memory lasted only up to 1 hour. Also, total exploration time of the objects by old animals, compared to young ones, was consistently shorter. In the reversed light/dark cycle condition, memory for the sample object lasted 1.5 hours for young animals and, again, 1 hour for older animals. There was no difference in total exploration times between young and old animals under this condition. It is concluded that the object memory test could be useful in the search for substances which improve memory in old age and in cases of dementia.

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BRAIN CORTICOSTEROID RECEPTORS AND ADAPTATION
E.R. De Kloet

Circulating corticosteroid hormone (CORT) secreted by the adrenals enters nerve cells, binds to intracellular receptor proteins and controls the expression of specific gene networks. CORT binds to the glucocorticoid receptor (GR) and to the mineralocorticoid receptor (MR). GR has a widespread distribution in the brain with highest density in neurons involved in the stress response. MR is mainly restricted to limbic neurons and is abundantly co-localized with GR in hippocampal CA1 neurons.

Molecular studies suggest that co-localized MR and GR act coordinatively as a binary hormone response system. The hormone responsive genes encode the synthesis of neuropeptide precursors, and of enzymes underlying transmitter signalling and cell metabolism. These, together with the steroids, regulate excitability of the target neurons. In hippocampal CA1 neurons the action of MR maintains excitability, whereas GR suppresses excitability, if transiently raised by excitatory input. On the organismic level the function of central MR is constitutive and controls basal activities throughout the circadian cycle. Blockade of MR attenuates limbic inhibitory control and enhances stress-induced responses of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. The hormones of this axis are primarily involved in communicating adaptive changes in the organism. The stress-induced rise in CORT exerts via GR negative feedback and restores disturbances in homeostasis.

Individual differences are observed in limbic MR and GR. These differences also occur between genetically selected rat lines or can be induced experimentally. During ontogeny brief manipulations of the LHPA axis produce permanent changes in MR and GR, that result in altered stress-responsiveness and behavioural adaptation in later life.

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CHOLECYSTOKININ AND NEUROTENSIN INJECTED INTO THE VENTRAL TEGMENTAL AREA MODULATE CONCENTRATIONS OF DOPAMINE AND METABOLITES IN THE NUCLEUS ACCUMBENS IN VIVO USING MICRODIALYSIS PERFUSION. Ph. De Witte (1), K. Laitinen (2), I. Mefford (3) and J. Crawley (2).

Intracerebral microdialysis and HPLC with electrochemical detection were used to determine the in vivo concentration of extracellular dopamine and its metabolites in the nucleus accumbens after the microinjection of cholecystokinin (CCK-8) or neurotensin (NT) at doses of 10 pmoles, 1 nanomole and 10 nanomoles into the ventral tegmental area where both neuropeptides coexist in dopamine neurons. NT significantly elevated concentrations of dopamine and its metabolites at all the tested doses while CCK-8 significantly elevated dopamine metabolite concentrations only at a dose of 10 nanomoles without affecting extracellular dopamine level. These data suggest that NT, but not CCK-8, potently mediates the release of dopamine from the mesolimbic pathway via direct actions on the cell body.

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RU 33965: A NOVEL BENZODIAZEPINE RECEPTOR LIGAND WITH PARTIAL INVERSE AGONIST ACTIVITY.

R.M.J. Deacon, P. Budhram, A.B. Doyle, F.L. Parker, T.A. Thomson and C.R. Gardner.

Benzodiazepine receptor agonists such as diazepam are known to cause amnesia. A partial inverse agonist, however, might enhance cognitive processes while avoiding convulsions or induction of anxiety. RU 33965 (5,6--dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4] benzodiazepin-3-yl-cyclopropyl methanone), may be such a compound. It binds specifically to "central" benzodiazepine receptors with an IC_{50} of 70 nM. It is well absorbed in rodents (ED_{50} for displacement of [^{3}H]-Ro 15-1788 = 0.07 mg/kg ip, 0.11 mg/kg po in mice; 0.15 mg/kg ip, 0.45 mg/kg po in rats). A dose sufficient to cause maximal displacement at 30 min still showed >50% displacement after 4 h in both species. RU 33965 did not have convulsant effects alone in mice, but potentiated the effect of subconvulsant doses of pentylenetetrazol (ED_{50} = 0.25 mg/kg ip). This potentiation never reached 100% and was blocked by the antagonist Ro 15-1788. RU 33965 antagonised the discriminative stimulus properties of chlordiazepoxide in rats at 0.05-0.1 mg/kg po, but only generalised to a pentylenetetrazol stimulus at higher doses (20-50 mg/kg po). High doses (50 mg/kg ip) induced twitching of the suprahyoid muscles in anaesthetised rats, whereas much lower doses (ED_{50} = 0.67 mg/kg ip) antagonised the twitch depression caused by a classical benzodiazepine receptor agonist, RU 32007.

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INVESTIGATION OF POTENTIAL COGNITION ENHANCING PROPERTIES OF RU 33965, A BENZODIAZEPINE RECEPTOR PARTIAL INVERSE AGONIST.

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Benzodiazepine receptor partial inverse agonists may be of value in cognitive disorders. The partial inverse agonist RU 33965 (Deacon et al., this meeting) was investigated in animal cognition models. The learning deficit due to diazepam 3 mg/kg ip in a mouse one-trial passive avoidance test was alleviated by simultaneous administration of RU 33965. Scopolamine 0.7 mg/kg ip pre-train also produced a deficit in this test, and this was attenuated by RU 33965 at 1 and 2.5 mg/kg po. In a mouse multi-trial passive avoidance learning experiment, RU 33965 (0.2 mg/kg ip) reduced the number of electric footshocks required for criterion learning. Attenuation of a scopolamine (1 mg/kg ip) deficit was also observed (0.5, 2 mg/kg). In a 4 day mouse active avoidance test, RU 33965 (2 mg/kg ip) reversed a scopolamine-induced learning deficit on day 3. In the Morris water maze (rat) RU 33965 (0.2-10 mg/kg ip) reversed an atropine (5 mg/kg ip) deficit. At 1.5 mg/kg ip RU 33965 decreased the scopolamine-induced increase in errors in radial arm maze performance (rats). In contrast initial acquisition of a rat spatial delayed non-match to sample task was slightly impaired by RU 33965 at 0.5 and 2 mg/kg po. Scopolamine (0.1 mg/kg ip) decreased accuracy and was potentiated by RU 33965 2 mg/kg po. While the clinical predictivity of these animal models is not sufficiently established, there may be enough evidence from these studies to warrant trials of RU 33965 in man.

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SYMPTOMS SIGNS AND SYNDROMES OF AFFECTIVE DISORDERS. J.F.W. Deakin

Many behavioural models of depression and anxiety have evolved in attempting to detect new compounds with therapeutic activity. The models are validated by their sensitivity to drugs which are clinically effective and thus they depend on accurate clinical information. Some pitfalls of this dependence will be discussed. In general, however, validation is entirely utilitarian.

A distinct use of behavioural models is to investigate aetiological and therapeutic mechanisms of affective disorders and validity becomes a more precarious issue. Attempts have been made to increase face validity by modelling the aetiology and clinical features of depression. The genetic aetiology of affective disturbances (panic, manic depression) is undoubted but animal counterparts are generally lacking. Modelling psychosocial aetiology has improved with a move away from footshocks to more naturalistic stressors such as social isolation. However, the role of psychosocial stress in human affective disturbance is very uncertain. Only behavioural components of the clinical picture can be modelled in animals but they are not specific to depression or anxiety (e.g. insomnia, anorexia). Furthermore, depression and anxiety are not discrete conditions and there is heterogeneity within these conditions.

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SEROTONIN ANTAGONISTS IMPROVE PERFORMANCE IN TWO MODELS OF A DELAYED MATCH TO SAMPLE TASK IN SQUIRREL MONKEYS. V.J. DeNoble, L.M. Schrack, A.L. Reigel, and K.F. Strek.

Cognitive deficits resulting from neuropathological brain changes such as Alzheimer's Disease or normal aging are most likely due to alterations in multiple neurotransmitter systems. While the majority of preclinical studies has focused on the effects of acetylcholine, it has been shown that activation of the serotonergic (5-HT) nervous system interferes with passive avoidance retention in rats. In contrast, decreased 5-HT activity has been shown to improve learning and memory in similar procedures. In the present experiment, 5-HT antagonists were evaluated for their effects on performance in a delayed match to sample task (DMTS) in two groups of squirrel monkeys: one in which the baseline level of performance was low (<60% correct, N = 5; group 1) and another in which DMTS performance was high (>80% correct, N = 3; group 2), but impaired by exposure to hypoxia. Initial parametric tests exposing group 2 to various levels of oxygen deprivation were conducted to determine optimal conditions for performance deficits. Each monkey in both normoxia (group 1) and hypoxia (group 2) served as his own control and received an individualized range of doses for each test compound. For both groups ketanserin and mianserin, the 5-HT_2 selective antagonists, produced dose-dependent increases in DMTS performance at 0.1-1.5 mg/kg p.o. and 0.03-1.5 mg/kg p.o. respectively. Pirenperone was active in improving performance in group 1 at 0.001-0.2 mg/kg p.o. Cyproheptadine also produced increases in performance in both groups, however, the effects could not be replicated in group 1. The results of this study show that alterations of 5-HT are effective in preventing hypoxia-induced performance deficits and in improving normoxic performance levels, suggesting a major role for 5-HT in cognitive performance.

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COMPARISON OF DUP 996, AN ACETYLCHOLINE RELEASE ENHANCER,WITH PHYSOSTIGMINE, TETRAHYDROAMINOACRIDINE AND 3,4-DIAMINOPYRIDINE ON HYPOXIA-INDUCED AMNESIA IN RATS. V.J. DeNoble, K.F. Strek, K.R. Spencer, L.C. Johnson, L. Cook, M.J. Myers and R.M. Scribner.

DuP 996, 3,3-bis (4-pyrindinylmethyl)-l-phenylindolin-2-one, physostigmine (PH), tetrahydroaminoacridine (THA) and 3,4 diaminopyridine (3,4 DAP) were compared for their ability to protect against hypoxia-induced performance deficits in a passive avoidance (PA) task. The ability to retain PA response was found to decrease as the oxygen concentration decreased with the largest retention deficit occurring at 6.5% oxygen. DuP 996 (0.01-0.1 mg/kg s.c.), 3,4 DAP (0.1-20.0 mg/kg s.c.), THA (0.01-7.0 mg/kg s.c.) and PH (0.001-0.1 mg/kg s.c.) administered one minute after PA training produced dose dependent increases in retention latencies following exposure to 6.5% oxygen. In comparing each compound for side effects, DuP 996 induced tremor at 10 mg/kg s.c., PH at 0.3 mg/kg s.c. which was accompanied by hypersalivation and a decrease in lift strength. THA produced tremor at 6.0 mg/kg s.c. and 3,4 DAP at 50 mg/kg s.c. produced tremor, chromodacryorrhea and hypersalivation. In comparing the highest effective dose active in the hypoxia test with the minimum dose required to produce tremor, the safety ratios were DuP 996 (100), 3,4 DAP (5.0), PH (3.0) and THA (1.2), showing a greater safety margin for DuP 996 than the other cholinergic agents. These results suggest that DuP 996 may be of use in the treatment of diseases associated with cognitive impairment and has a greater safety margin than other cholinergic agents.

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DIFFERENTIAL EFFECTS OF FG 7142 AND CHLORDIAZEPOXIDE ON AVERSION INDUCED BY ELECTRICAL STIMULATION OF THE PERIAQUEDUCTAL GRAY OR THE MESENCEPHALIC LOCOMOTOR REGION

R. Depoortère, G. Di Scala; M. J. Angst and G. Sandner

In the rat, electrical stimulation of the dorsal part of the periaqueductal gray (PAG) produces aversive effects, since such stimulations induce escape reactions (violent running and explosive jumps) and prompt the stimulated animal to press a bar in order to interrupt the stimulation (switch-off behavior). We recently showed that stimulation of the mesencephalic locomotor region (MLR) - classicaly considered as involved in the control of locomotion and corresponding to the cuneiform and pedunculopontine tegmental nuclei - also produces aversive effects. PAG induced aversive effects are known to be decreased by benzodiazepine (BZ) receptor agonists. There is however no data concerning the effects of BZ receptor inverse agonists on PAG induced aversive effects, and no data at all on the effects of either BZ receptor agonists or inverse agonists on MLR induced aversive effects. The aim of the present study was hence to compare the pharmacological sensitivity to the BZ receptor inverse agonist FG 7142 and the agonist chlordiazepoxide (CDP) on the switch-off behavior induced by stimulation of the PAG or MLR.

Rats were trained to switch-off electrical stimulations applied to the PAG or the MLR. We investigated the effects of i.p. injections of FG 7142 (2.5, 5, 10 mg/kg) or CDP (5 mg/kg) on the switch-off latency i.e. the time elapsed between the onset of the stimulation and it offset by a press of the bar.

It was found that FG 7142 decreased whereas CDP increased the mean switch-off latency for electrical stimulation of the PAG, which is interpreted as a potentiating effect of FG 7142 and a reducing effect of CDP on the electrically induced aversive state. By contrast, neither FG 7142 nor CDP were found to affect the mean switch-off latency for MLR stimulations. These results suggest a difference in the pharmacological sensitivity to BZ receptor ligands between aversive states elicited by electrical stimulation of the PAG or MLR.

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ANXIOLYTIC-LIKE EFFECTS OF THE ADENINE DERIVATIVE BW A78U IN MICE AND RATS.

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BW A78U (9- (2-fluorobenzyl) -6- (methylamino) -9H -purine) is an adenine derivative with potent anticonvulsant activity. In the present study, possible anxiolytic effects of BW A78U have been investigated in mice and rats.

In mice, low doses of BW A78U had anxiolytic-like effects in the light-dark box choice situation: it increased the time spent in the lit box as well as the number of transitions between the two boxes. At higher doses (15 mg/kg, i.p.), BW A78U had sedative effects in a free exploratory situation: it reduced both the locomotion and the number of rearings.

In rats, BW A78U had also anxiolytic-like effects in a conditioned burying paradigm: it decreased the time spent by the animals burying the prod and decreased the number of escape movements away from the prod. However, unlike diazepam, it did not increase approach movements to the prod, and increased the time spent eating pica. Up to 10 mg/kg (i.p.), no sign of sedation, as decreased locomotion or decreased rearing activity was observed.

The present results show that BW A78U has anxiolytic-like effects in both mice and rats. It is unlikely that the mechanism of action of BW A78U involves the GABA-benzodiazepine receptor complex:

1. BW A78U only weakly binds to benzodiazepine receptors ((^3H)flunitrazepam binding, IC_{50} = 13.6 uM);
2. its anticonvulsant effects as well as sedative effects were not antagonized by Ro 15-1788 (a benzodiazepine receptor antagonist);
3. in the conditioned burying test, the behavioral profile induced by BW A78U slightly differed from the one induced by diazepam, a classical benzodiazepinic anxiolytic.

The structural characteristics of BW A78U suggest that this compound may interfere with adenosine neuromodulation.

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CLINICAL IMPLICATIONS OF THE ETHOPHARMACOLOGICAL APPROACH TO DRUG DEVELOPMENT

A.K.Dixon

Ethopharmacology applies ethological methods and concepts to the analysis of drug-induced changes in behaviour and is now widely employed in many drug development programmes. By studying the dynamics of the species-specific acts and postures which animals show under solitary and social conditions, ethologists have obtained clues as to the organization and function of many natural patterns of behaviour. This information provides a conceptual instrument which allows the putative mode of action of a drug to be formulated in behavioural terms suitable for clinical testing. Ethopharmacology is particularly concerned with drug effects upon social interactions. Man is endowed with behavioural patterns for interacting socially and disturbances in early social processes can lead to mental distress and even illness in susceptible individuals. Morever, impaired social behaviour is a prominent feature of many psychiatric illnesses and is often the main reason for clinical intervention. These facts imply that disturbed social behaviour is an intrinsic component of the pathological process rather than merely a consequence of the illness. It is, therefore, reasonable to develop drugs intended to improve social functioning in mentally ill patients. Obviously, clinical trials with such drugs should include objective measures of social behaviour. Human ethological methods appear suitable for this task and these techniques will be discussed.

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MODIFICATION OF OBJECT DISCRIMINATION REVERSAL LEARNING IN THE MARMOSET BY 5-HT_3 RECEPTOR ANTAGONISTS

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One of the most widely used assessments of cognitive skills in the primate is that of object discrimination reversal learning, where an animal is required to make a response in a manner opposite to a previously learned task. We have designed studies to investigate the effects of the 5-HT_3 receptor antagonists, ondansetron, zacopride, ICS 205-930 and granisetron on object discrimination learning in the marmoset.

Adult marmosets were tested using a Wisconsin General Test apparatus. They were required to select between two junk objects to a criterion of 6 consecutive correct responses (discrimination task), followed by object reversal learning (to the same criterion) in the same test session. Using this test procedure, the mean number of trials to criteria for both the initial discrimination task and the reversal task were found to be significantly decreased by ondansetron at doses of 1-100ng/kg s.c. given twice daily. At a higher dose of 10μg/kg s.c. given twice daily the number of trials to criteria were not significantly modified, whilst at 100μg/kg s.c. given twice daily some impairments in performance were recorded. Zacopride (10ng/kg), ICS 205-930 (10ng/kg) and granisetron (100pg/kg) also significantly improved cognitive performance of marmosets in the object discrimination reversal paradigm (maximally effective doses shown), and significantly reduced choice latency.

The data provide evidence that the 5-HT_3 receptor antagonists may represent a novel class of cognitive enhancing agents.

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THE ACTION OF 5-HT_3 RECEPTOR ANTAGONISTS IN RODENT AND PRIMATE BEHAVIOURAL MODELS

A.M. Domeney, B. Costall, D.N.C. Jones, P.A. Gerrard, R.J. Naylor and M.B. Tyers*

Since the identification of 5-HT_3 receptors in the brain, and the development of specific agonists and antagonists, much research has been carried out to determine the role of central 5-HT_3 receptors in the modulation of animal behavioural situations. These include models of mesolimbic dopamine excess, anxiety and cognition.

In rodent models of mesolimbic dopamine excess 5-HT_3 receptor antagonists, injected either directly into the nucleus accumbens or peripherally, reduce the hyperactivity response to acute intracerebral injection of amphetamine or to a 13 day intra-accumbens or intra-amygdala infusion of dopamine. Such inhibition can also be achieved in a primate dopamine infusion model.

5-HT_3 receptor antagonists also demonstrate anxiolytic activity in rodent and primate models of anxiety. In the marmoset 'human threat' test, 5-HT_3 receptor antagonists can be shown to reduce the number of postures resulting in response to a human observer standing in close proximity to the home cage. Posturing behaviour is also reduced by clinically effective anxiolytics such as diazepam and buspirone.

In a primate model of cognition 5-HT_3 receptor antagonists can be shown to improve the performance of marmosets in an object discrimination reversal protocol using the Wisconsin General Test Apparatus. Such cognitive enhancing activity can also be seen in rodent tests.

The data from animal studies suggests that 5-HT_3 receptors may play an important role in the control of mesolimbic dopamine excess, anxiety and cognition, and this may have clinical implications.

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EFFECTS OF ANTICHOLINERGIC DRUGS AND BENZODIAZEPINES INDICATE THE DIFFERENCES IN BRAIN MECHANISMS OF AGGRESSION AND TIMIDITY

P.Donát and M. Krsiak

Previous studies have shown that both aggressive as well as active defensive-escape (timid) activities are affected in a similar way by pheromones (Activ. nerv. sup. (Praha) 27(2):153-154, 1985) and testosterone in individually-housed male mice on interactions with non-aggressive group-housed opponents. Thus, one could propose that alternative behavioural strategies occurring on intraspecies conflict might be switched by external factors affecting unitary brain mechanism of agonistic behaviour.

However, anticholinergic drugs - scopolamine, atropine and trihexyphenidyl - strongly reduced aggressive activities, but were less potent to reduce timidity in individually-housed mice. These drugs showed dose-dependent effects, while methylscopolamine (with peripheral action) did not show it. These findings suggest that the inhibitory effects of anticholinergic drugs are mediated via CNS. The sensitivity of aggressive and non-aggressive mice to scopolamine does not seem to differ markedly, as comparable inhibitory effects were found in males showing timid behaviour (in interactions with sham-operated opponents) as well as aggression (in interactions with castrates). On the other hand, benzodiazepines - diazepam and nitrazepam - reduced timidity stronger than aggression.

Our results suggest, that different polysynaptic brain mechanisms seem to be involved in regulation of aggressive and defensive-escape components of agonistic behaviour.

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CNS EFFECTS OF CYTOKINES

A. J. Dunn

Several cytokines have been shown to have effects on the CNS, but most data concern interleukin-1 (IL-1). IL-1 and tumour necrosis factor (TNF) are pyrogenic in some species, and may alter body temperature by a direct effect on the anterior hypothalamus. Following the discovery that peripherally administered IL-1 is a potent activator of the hypothalamic-pituitary-adrenal (HPA) system, endocrine effects of IL-1 have been intensively investigated. The major effect of IL-1 appears to be mediated through hypothalamic secretion of corticotropin-releasing factor (CRF), although some direct pituitary effects are possible. TNF and IL-6 may also activate the HPA axis. IL-1 has also been shown to activate both noradrenergic systems in the brain, and the sympathetic nervous system and adrenal medulla. The brain effects are greatest in the hypothalamus, but are not confined to this structure. IL-1 and interferon can also alter electrophysiological responses in hypothalamic neurons, both directly and indirectly. ICV IL-1 also causes immunosuppression. There is some evidence that these effects can be dissociated, some appear to be dependent upon prostaglandin synthesis, and others on CRF secretion, whereas some depend on neither.

IL-1 also has behavioral effects. Peripheral administration increases the duration of slow-wave sleep, causes hypophagia, and taste aversion. ICV administration in very low doses (4 pg IL-1α, 10 pg IL-1β) causes reductions of exploratory behavior in mice, resembling those observed following stress or ICV CRF. Similarly in rats ICV IL-1α (1 ng), like restraint or ICV CRF, induces defensive withdrawal.

Whether or not IL-1 is present in the normal brain is unresolved. It does seem likely that IL-1 is synthesized in microglia under pathological conditions. Thus the physiological role of intracerebral IL-1 is in doubt.

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MECHANISMS OF FUNCTIONAL RECOVERY INDUCED BY INTRACEREBRAL TRANSPLANTS

S.B. Dunnett

Neural grafts can reverse many functional deficits associated with brain damage, whether of traumatic, toxic, neurodegenerative or genetic origin. In some model systems recovery can be partial or complete, whereas in other systems the grafts have limited effect or may actually cause further dysfunction.

In order to devise rational and effective transplantation strategies it is necessary to understand the mechanisms by which grafts exert their functional effects. Several alternatives have been proposed:

1. Non-specific consequences of surgery.
2. Acute diffuse neurotrophic and growth mechanisms.
3. Chronic diffuse release of deficient neurochemicals.
4. Bridge tissues for host regeneration.
5. Diffuse reinnervation of the host brain.
6. Reciprocal graft-host reconnection.

These alternative mechanisms are not necessarily exclusive in any particular model system, and all have been seen to apply in different model systems. Examples of each will be described, with particular emphasis on restoration of motor function with nigral and striatal grafts in the basal ganglia of experimental rats.

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THE EFFECTS OF CHRONIC TREATMENT WITH JO 1017 IN THE OLFACTORY BULBECTOMIZED RAT MODEL OF DEPRESSION.

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JO 1017 (2-(3,4-dihydrobenzyl) - 2 - dimethylamino - 1 - propanol, hydrochloride) is a novel antidepressant which selectively inhibits 5-HT uptake and has high affinity for 5-HT uptake sites radiolabelled by paroxetine and imipramine. **JO 1017** has been shown to be an effective antidepressant in phase 2 clinical trials in severely depressed patients. Gouret et al (1990) reported activities for **JO 1017** in behavioural despair tests in mice, in the rat learned helplessness test and in the potentiation of L-5-HTP- induced head twitches. Bi-lateral removal of the olfactory bulbs in the rat produces a series of behavioural changes which are characterized by hyperactivity in the open-field apparatus and deficits in passive avoidance responding. This model of depression will selectively detect antidepressant activity only following the chronic administration of the drug. In the present study, male Sprague-Dawley rats were bulbectomized or sham operated and allowed to recover for 14 days before drug treatment commenced. **JO 1017** was administered for 28 days (2, 4, 8 and 16 mg/kg I.P. twice daily) and behaviour in the open-field test was measured after the 14th day of treatment. An increase in ambulation scores was found in the olfactory bulbectomized (OB) rats treated with saline (201% ; $P < 0.0002$). **JO 1017** reversed the hyperactivity of olfactory bulbectomized rats at doses of 8 (70% ; $P < 0.012$) and 16 mg/kg (70.4% ; $P < 0.01$) I.P. twice daily and, thus, has antidepressant like activity in this procedure.

Reference. Biochemical and pharmacological evaluation of a novel antidepressant and serotonin uptake inhibitor (1990).
C.J. Gouret, , R. Porsolt, J. G. Wettstein, A. Puech, C. Soulard , X. Pascaud and J.L. Junien. Arzneim. Forsch. /Drug . Res. (in press).

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THE ROLE OF DOPAMINE IN THE OCCURRENCE OF SPONTANEOUS STEREOTYPIES IN A GROUP OF JAVA MONKEYS (M. fascicularis)

B.A. Ellenbroek, H. Th. van Aanholt & A.R. Cools

Stereotypies are among the most prominent motor symptoms of schizophrenia. They are usually defined as relatively normal motor acts which become abnormal due to the increase in frequency and the relative invariance of the movement. However, in schizophrenia the stereotyped behaviour is not necessarily restricted to motor acts, but can also occur in thought and speech. Therefore, studying the neuronal mechanisms underlying such stereotypies might give insight in the pathological processes underlying schizophrenia. In animals stereotypies are readily elicited by administration of dopamine agonists such as apomorphine or amphetamine (Wallach, Adv. Biochem. Psychopharmacol 12,(1974),241). In monkeys, the stereotypies induced by amphetamine usually consist of rocking (movements of the upper part of the torso while sitting). It has also been reported that normal behaviours such as autogrooming, or social behaviours, such as allogrooming may become stereotyped after amphetamine administration.

The disadvantage of the stereotypy models as discussed so-far is that these behaviours have to be induced in normal animals by pharmacological tools. In the course of developing a stable group of four Java monkeys (2 males and 2 females) for studying the social behaviour, we removed the β-male and replaced it by another male. After this change, three of the four animals (the two males and one female) developed "spontaneous" stereotypies. These spontaneous stereotypies offered a unique opportunity to study the role of dopamine in the occurrence of stereotyped behaviour. For that reason, the monkeys were treated with amphetamine, haloperidol or SCH 23390. The results show that SCH 23390 and haloperidol differentially attenuate the stereotypies, whereas amphetamine has a more complex action, i.e. increasing stereotypies in some monkeys while decreasing it in others.

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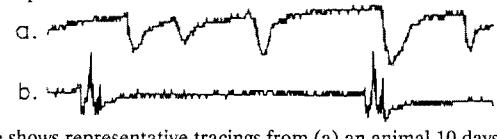
HALOPERIDOL INDUCES ORAL MOVEMENTS IN RATS WHICH HAVE EITHER A TARDIVE DYSKINESIA-LIKE FORM, OR A PRIMED DYSTONIA-LIKE FORM.

G. D. Ellison

Oral movements (OMs) in rats administered chronic neuroleptics were repeatedly observed by a human and also measured by a computerized video analysis system. Two distinct oral dyskinetic syndromes were discerned. If "typical neuroleptics" such as haloperidol (HAL) are continuously administered, rats gradually show an increase in smooth, OMs with one type of abnormal form (FFT analysis indicates a gradual shift in peak energy to 1-3 HZ; upon drug withdrawal, this effect dramatically increases, and increases in larger amplitude OMs are seen). This is presumably the rat equivalent of human tardive dyskinesia, where increases at the same energy spectrum are obseved.

A different type of OM pattern is observed when HAL is administered in weekly, large injections, similar to the "priming" studies used to induce dystonic reactions in monkeys. In this case OMs develop during chronic administration which are large in amplitude, rapid in slope of onset, and have a peak at 4-6 HZ. This is a dystonic-type reaction.

Atypical neuroleptics such as clozapine or raclopride do not induce these syndromes, but each show distinctively different effects on OMs which gradually develop. Drug regimen thus appears to play an important role in producing acute dystonic- and tardive dyskinesia-like syndromes in rats, and we will describe in detail the computerized system which permits these observations.



This figure shows representative tracings from (a) an animal 10 days into drug withdrawal following 8 months of continuous HAL, and (b) a comparable tracing from an animal given intermittent, weekly large HAL injections. The TD-like, smooth 1-2 Hz OMs on the top and the rapid, large gaping movements on the bottom are apparent.

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ASSESSEMENT OF POTENTIAL ANXIOLYTIC AND ANXIOGENIC DRUGS USING THE PENTYLENETETRAZOLE DRUG DISCRIMINATION TEST

M. W. Emmett-Oglesby and S. L. Abdel-Malek

Rats were trained to detect the anxiogenic drug pentylenetetrazole (PTZ), 20 mg/kg, and tested with novel drugs to determine their potential to mimic or antagonize the PTZ cue. These drugs include zolpidem (an agonist at omega receptors), CI-966 (a GABA uptake inhibitor), and WIN 53,365 and WIN 55,225 (mechanisms of action not established). Zolpidem (0.64-2.5 mg/kg) did not substitute for PTZ. However, this drug blocked the PTZ stimulus in a dose-related manner (0.32-5.0 mg/kg), although only partial blockade was obtained even at the highest dose that could be tested (31% PTZ-lever presses). CI-966 (0.5-4.0 mg/kg) did not block the PTZ stimulus. However, partial substitution for PTZ (65% drug-lever selection) occurred at 3-6 hours following the injection of CI-966 (16.0 and 32.0 mg/kg). WIN 53,365 neither substituted for, nor blocked, the PTZ stimulus. WIN 55,225 did not block the PTZ stimulus, and did not show dose-related substitution, although a single dose (100 mg/kg) produced 50% substitution for the PTZ cue. In summary, WIN 53,365 and WIN 55,225 do not appear to have potential anxiolytic activity. Indeed, only zolpidem could be considered to have potential as an anxiolytic, but this compound does not have the efficacy of many other anxiolytics previously tested in this discrimination. Although CI-966 has been shown to block PTZ seizures in mice, it failed to block the PTZ cue. These data are interesting because they suggest that the discriminative stimulus produced by PTZ is not related to its ability to produce convulsions. The partial substitution of CI-966 given in high doses is consistent with clinical reports that this compound may produce anxiogenic effects.

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THE EFFECTS OF 8-HYDROXY-2-(DI-N-PROPYLAMINO)TETRALIN (8-OHDPAT) ON ADJUNCTIVE DRINKING IN THE RAT

J.L. Evenden

8-OHPDAT, a $5HT_{1A}$ agonist, has marked effects on locomotor and exploratory activity, food intake and sexual behaviour. The present study examined the effects of the drug on excessive, adjunctive, drinking induced in rats by a fixed time 1 minute schedule of reinforcement with 45 mg food pellets. Under this schedule, after the delivery of the food pellet the rats indulge in a bout of drinking, followed by orientation towards and entry into the food tray in anticipation of delivery of the next food pellet. The drinking may amount to 15-20 mls in a 30 minute session. Administration of 8-OHDPAT 10 minutes prior to testing at doses of 0.1 and 1.0 mg/kg resulted, on the first day in suppression of drinking at both doses. However, by day 3, the effects of the low dose on drinking had disappeared. There was little tolerance to the effects of the high dose even after 16 days consecutive treatment. On removal of the drug, the drinking of the high dose group immediately returned to pre-treatment levels. Both doses of drug increased entries into the food tray. The dose of 0.1 mg/kg did so by increasing the number of anticipatory entries. The effects of the dose of 1.0 mg/kg suddenly appeared between treatment days 8 and 11, and showed a pattern of elevtated panel entries through each fixed time period. The effects of both doses were still apparent when drug administration was discontinued, and took 2 days to disappear. Many of the effects of 8-OHDPAT show rapid tolerance (see accompanying poster, Evenden & Lundgren). In the present study tolerance to one aspect of the drugs effects was accompanied by an abnormality in another behaviour with the result that the profile of the drug was quite different following repeated administration than on acute administration.

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TOLERANCE TO THE HYPOTHERMIC EFFECTS OF 8-HYDROXY-2-(DI-N-PROPYLAMINO)TETRALIN (8-OHDPAT) IN THE RAT

J.L. Evenden, K. Lundgren

8-OHDPAT, a $5HT_{1A}$ agonist, has well documented hypothermic effect in rats. This effect has variously been ascribed to both pre-synaptic and post-synaptic mechanisms of action. Repeated administration of the drug leads to a rapid tolerance to the effect, however, without obvious changes in pre- or postsynaptic $5HT_{1A}$ receptors or to 5HT neuronal biochemical parameters (Larsson et al, Neuropharmacology, in press). Recently, it has been found that a single injection of 1.0 mg/kg 8-OHDPAT induced a tolerance to the nypothermic effects of a threshold dose of 0.05 mg/kg 8-OHDPAT which lasted up to 3 weeks (Rényi, Ängeby Möller and Evenden, sub ms.). The present study complements those results. In the first experiment, rats were treated with doses of 8-OHDPAT from 0.1-3.0 mg/kg and it was found that tolerance to the hypothermic effects of a test dose of 0.06 mg/kg 24 hours later was equivalent over this 30-fold range. In the second experiment, tolerance induced by 1.0 mg/kg was significantly attenuated by a dose of 5.0 mg/kg (-)alprenolol, the $5\text{-}HT_{1A\text{-}1B}$ (and β-adrenoreceptor) antagonist. This dose of (-)alprenolol had no effects on body temperature itself nor any effects on the response to 8-OHDPAT when administered 24 hours prior to the hypothermia test. In the final experiment, rats were treated with saline or with an injection of 1.0 mg/kg 8-OHDPAT once per day for 1, 2, 3 or 4 days. The hypothermic effects of doses of 0.03-0.3 mg/kg 8-OHDPAT were tested 24 hours after each treatment regimen. As noted above, there was a marked attenuation of the hypothermic effects of 8-OHDPAT after 1 injection. After two 8-OHDPAT treatments the effects of the test doses of 8-OHDPAT were further reduced, and after 3 or 4 treatments, the effects of all but the highest dose were abolished completely. This dose, of 0.3 mg/kg 8-OHDPAT, was still capable of induced a significant hypothermic response and the tolerance appeared to have reached an asymptote. These results indicate that 8-OHDPAT produces a rapid tolerance, presumably mediated by the $5HT_{1A}$ receptor, but that the degree of tolerance may be limited.

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INDIVIDUAL DIFFERENCES IN RATS' SPONTANEOUS ACTIVITY: THE EFFECTS ON LATENT INHIBITION AND RESPONSIVENESS TO AMPHETAMINE. J. Feldon, R. Barkai and I. Weiner.

It has been recently suggested that individual differences in rats' spontaneous activity reflect differences in dopaminergic (DA) activity (Le Moal, EBPS Malta Meeting 1989). Latent inhibition (LI) i.e. poorer learning to a stimulus as a consequence of its prior nonreinforced presentation, has been shown to be highly sensitive to DA manipulations. More specifically, it is disrupted following DA activation (e.g. amphetamine administration) and enhanced following DA blockade (e.g. administration of neuroleptics). We therefore screened a group of 100 male Wistar rats for their spontaneous activity, and compared 20 rats with highest activity with 20 rats exhibiting lowest activity, in LI. The procedure used was the conditioned emotional response (CER) in rats licking for water, consisting of three stages: Preexposure - in which animals are either preexposed to the to-be-conditioned stimulus, tone (PE group) or not preexposed to the tone (NPE group); Conditioning - in which both groups receive tone-shock pairings; and Test - in which LI is assessed by the amount of supression in licking during tone preexposure. LI consists of the fact that the PE group exhibits less suppression than the NPE group. The results showed that high activity rats exhibited a robust LI effect whereas low activity rats showed a greatly attenuated LI. Three weeks later, high- and low-activity rats were tested for their response to 1.0 mg/kg d-amphetamine, after being habituated to the activity chamber. High-activity rats showed a significantly higher increase in activity following the drug injection as compared to low-activity rats. The latter result is in line with the reports of Le Moal's laboratory. The implication of the present results for the action of amphetamine (increased locomotion/disruption of LI) and of neuroleptics (decreased locomotion/enhancement of LI), are discussed.

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THE RELATIONSHIP BETWEEN NEUROPLASTICITY AND FUNCTIONAL RECOVERY: A MODEL AND ITS IMPLICATIONS. S. Finger.

It has been theorized that major reorganizational events, such as axonal sprouting, may underlie recovery of function. Often overlooked is the possibility that gross neuronal rearrangements are unlikely to be present simply to heal damaged brains, and that they can also contribute to dysfunction. This paper will argue against major anatomical reorganizations playing a consistently beneficial role in recovery of function. The point will be made that mechanisms such as collateral sprouting can be better understood as developmental processes that may or may not be adaptive.

It will be suggested that future research should be aimed not just at stimulating neural growth after brain injuries, but at inhibiting those changes which could be deleterious. In addition, greater emphasis should be placed on developing drugs that can minimize the size of the lesion after brain damage. Some behavioral findings with the central calcium channel blocker, nimodipine, will be presented in this context.

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CCK-8 MODULATES D-1 AND D-2 RECEPTOR MEDIATED LOCOMOTOR EFFECTS IN THE N. ACCUMBENS

Fink, H., Morgenstern, R. and Ott, T.

The neuropeptide CCK-8 co-exists within a subpopulation of mesolimbic dopamine neurons. It is well established that dopamine receptor subtypes, D-1 and D-2 receptors, are differently involved in the generation of behavioral effects.
We have studied the influence of CCK-8 on locomotor effects associated with independent D-1 and D-2 receptor stimulation.
To selectively stimulate mesolimbic D-1 and D-2 receptors SKF 38393 and LY 171555, respectively, were injected into the N. accumbens of awake rats. Locomotor activity was measured in the open-field test.
SKF 38393 inhibited locomotor activity dose dependently. LY 171555 induced a biphasic effect: Low doses stimulated, higher doses inhibited locomotor activity. The effects of both agonists were blocked by selective D-1 and D-2 antagonists, respectively.
CCK-8 injected into the posteromedial part of the N. accumbens suppressed hypolocomotion induced by SKF 38393 and hyperlocomotion induced by LY 171555. These effects produced by CCK-8 were prevented by the CCK-antagonists tifluadom and L 364,718.
Our results indicate that CCK-8 modulates both D-1 and D-2 receptor-mediated effects in the mesolimbic system. Thus, it can be suggested that CCK-8 is involved in controlling the expression of dopamine related locomotor effects.

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THE IMPORTANCE OF MEASURING NON-VERBAL ASPECTS OF COMMUNICATION IN PSYCHIATRY

H. U. Fisch

Despite the pioneering human ethological studies of Grant (1968, 1969) and the availability of techniques for measuring nonverbal behavior, psychiatry has paid little attention to these approaches. Therefore, psychiatry still faces basic methodological problems of behavioral evaluation and consequently encounters fundamental obstacles in objectively diagnosing mental diseases, measuring their severity and effects of treatment. The psychiatrist still has to rely to a large extent on his clinical judgment, i.e. his subjective assessment. In an attempt to standardize diagnosis and evaluation of treatment, rating scales have been used for more than 20 years. Rating is a rapid and useful tool for general clinical use. However, it is not a substitute for measurement because it directly transforms observations of behavior into psychological dimensions. In addition, conventional rating scales rely mainly on the patient's individual psychopathological symptoms rather than on parameters of social interaction. For treatment outcome, impairment of social interaction is more relevant than psychopathology. Etholoy may add a new dimension to psychiatry, because it may introduce a common conceptual framework for measuring and interpreting drug induced changes of social behavior in both animal and humans.

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NALTREXONE DISCRIMINATION IN MONKEYS AND PIGEONS TREATED CHRONICALLY WITH AN OPIOID AGONIST

C.P. France and J.H. Woods

Substitution studies in morphine (MS)-treated animals support the notion that discriminative stimulus effects of opioid antagonists under these pharmacological conditions are related to withdrawal. In the absence of independent evidence of dependence, the question remains as to whether antagonist discriminations in MS-treated subjects are between withdrawal and nonwithdrawal or between the presence and absence of agonist effects. Both MS-treated monkeys discriminating between saline and naltrexone (NTX) and MS-treated pigeons discriminating among MS, saline, and NTX responded as though they had received NTX when MS treatment was terminated. Monkeys continued to respond on the NTX lever for 28 days until MS treatment was reinstated, suggesting the stimulus associated with the saline lever was not simply the absence of withdrawal but probably was associated with effects of MS. Over 35 days of abstinence pigeons switched from the NTX key to predominantly the saline key, perhaps reflecting the dissipation of withdrawal. Substitution studies with MS and NTX over a period of several months in MS-abstinent pigeons resulted in: 1) decreased sensitivity to rate-decreasing effects of NTX; 2) increased sensitivity to rate-decreasing effects of MS; 3) no apparent change in the potency of NTX in attenuating discriminative stimulus effects of MS; 4) a loss of stimulus control for both MS and NTX; 5) and, perhaps, a qualitative difference in the discriminative stimulus effects of NTX between MS-treated and MS-abstinent pigeons. These studies provide vivid examples of how the relationship between withdrawal and a conditioned response, in this case responding on the NTX-associated manipulandum, is neither simple nor direct and is determined, in large part, by the training procedures employed.

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N-PIVALOYL-4-AMINOBUTYRIC ACID(PG-2): A NEW NEUROTROPIC DRUG
L.Galzigna,R.Pelloso and A.A.RIZZOLI

N-pivaloyl-4-aminobutyric acid(PG-2) overcomes the blood brain barrier and exerts a protective effect on cardiazol-and bicuculline-induced convulsions in the rat(Galzigna et al.,Arch. int.Pharmacodyn.& Ther.235,72,1978).
The present study shows that low doses(10 and 50 mg/Kg)of PG-2 facilitate and high doses(100 and 200 mg/kg) inhibit rat conditioned responses of active avoidance in a shuttle box.PG-2 also decreases, at doses of 50 to 200 mg/kg,the grooming behaviour and spontaneous behavioural effects,e.g. ambulation, rearing and defecation in an open field. A further anticonvulsant activity is observed with 50 to 100 mg/kg on strychnine-induced convulsions and additional effects,with the same doses, are the decrease of behavioural responses in a conflict stress. PG-2 seems to behave as a GABAergic agonist by potentiating the central GABAergic transmission and its general action seems to be anxiolytic toward psychic stress with no side effects of memory impairment.

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TRANSMITTER MECHANISMS IN THE MEMORY EFFECTS OF ANGIOTENSIN II
V.P. Georgiev

Angiotensin II (AT II) administered intracerebroventricularly at small doses (0.1-0.5 µg) shortly before or immediately after training improves memory processes in rats trained and tested for retention on active (Shuttle box) and passive (step through) avoidance tasks. This effect of AT II might be due to its interaction with AT II binding sites in brain, because it is antagonized by saralasin (an AT II receptor antagonist). Participation of brain DAergic, GABAergic and cholinergic neurotransmission in the mechanism of the memory-facilitating effect of AT II has also been suggested. Our data show an interaction between DA receptors and AT II binding sites (retention-improving effect of AT II was potentiated by DAergic agonists and abolished by DAergic antagonists), GABA receptors and AT II binding sites (the retention-facilitating effect of AT II was potentiated by muscimol and baclofen; bicuculline and picrotoxin abolished the influence of GABAergic agonists on this effect), as well as between Ach receptors and AT II binding sites (the cholinergic agonists galanthamine and oxotremorine potentiated the retention-improving effect of AT II, while scopolamine abolished it). The results about the influence of saralasin, DAergic, GABAergic and cholinergic drugs on the pre- and post-trial effects of AT II suggest a complex interaction between these systems in memory processes in brain structures involved in the regulation of memory consolidation.

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BEHAVIOURAL EFFECTS OF THE DITERPENE SCLAREOL GLYCOL ARE REALIZED THROUGH INTERACTION WITH TRANSMITTER MECHANISMS
J.V. Georgieva

Sclareol glycol (SG) (a semisynthetic diterpene of the labdane family, a direct activator of the catalytic subunit of the adenylate cyclase) was tested on some behavioural paradigms at doses well below the lethal dose. SG increased apomorphine stereotypy in mice and rats, decreased haloperidol catalepsy in rats, stimulated locomotor activity in mice, reversed reserpine-induced hypokinesia and increased hypokinesia induced by low dose of apomorphine; SG potentiated apomorphine hypothermia and reversed reserpine-induced hypothermia in rats. These effects of SG might be realized through interaction with DAergic transmission. SG at a low dose possesses proconvulsant properties (increases PTZ seizure susceptibility), and antagonized the anticonvulsant effect of diazepam. SG reduced the punished responses in Vogel punished drinking test in rats and abolished the effect of diazepam on this paradigm. These effects of SG might be realized through interaction with GABA-BDZ receptor-ionophore complex. Thus, the behavioural effects of SG are thought to be realized through activation of adenylate cyclase and through interaction with DA - and GABAergic transmitter mechanisms.

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DOPAMINERGIC EFFECTS ON PREPULSE INHIBITION OF RAT STARTLE PROVIDE A MODEL OF SENSORY GATING DEFICITS IN SCHIZOPHRENICS
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Schizophrenics have deficient sensory gating that can be quantified using measures of the blink reflex component of acoustic startle. In normals, startle is inhibited when the startling stimulus is preceeded (30-500 msec) by a weak acoustic prepulse. Schizophrenics exhibit less prepulse inhibition (PPI); that is, their startle is not gated by the prepulse. In rats, startle responses elicited by 120 dB sounds are inhibited by 80 dB prepulses. Dopamine (DA) agonists - apomorphine (APO), amphetamine, and quinpirole - disrupt PPI of acoustic startle in rats, paralleling results from schizophrenics. This effect appears to be mediated by D2 DA receptors: PPI is not affected by the D1 agonist SKF38393 except when combined with the D2 agonist quinpirole; the effects of APO and quinpirole are blocked by the D2 antagonist haloperidol; and the effect of APO is completely reversed by the D2 antagonist spiperone but not by the D1 antagonist SCH23390. The relevance of this model to schizophrenia is supported by the ability of low doses of the atypical antipsychotic clozapine to block the disruption of PPI induced by APO. The importance of DA projections to the nucleus Accumbens (NAC) in this effect is suggested: infusions of DA (0-40 µg) into the NAC decrease PPI dose-dependently; neurotoxin lesions of DA terminals in the NAC prevent the actions of amphetamine on PPI and potentiate the effects of APO; and the effects of intra-NAC DA on PPI are blocked by infusions of the GABA agonist muscimol (0-10 ng) into the NAC efferent terminal fields in the ventral pallidum. Thus, overactivity of D2 DA receptors in the NAC reduces PPI of startle in rats, mimicking the similar deficits in sensory gating of startle exhibited by schizophrenics. Such a loss of DA-mediated gating may lead to cognitive flooding and information overload in schizophrenics.

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ROLE OF DOPAMINE IN ADDICTION. A. Girdhar, S.M. Mansuri, R.K. Goyal and K.C. Dave.

Dopamine has been ascribed a significant role in the production of morphine dependence and withdrawal (Wood & Richard, 1982; Genget, et al., 1983). It is believed that morphine acts as an opiate receptor agonist (Carter and Bearden, 1982). Moreover Fetrai and Baggic (1982) have shown that lisuride, a dopamine agonist, can increase naloxone induced escape attempts in morphine-dependent rats by stimulation of dopamine receptors. Wood and Richard (1982) have suggested that in rats morphine appears to act exclusively at the pre-synaptic opiate receptors of dopaminergic nerve endings in the striatum and activiation of these receptors result in enhancement of dopamine synthesis.

In the present study, by two different methods attempts have been made to examine the mechanism of morphine dependence. Dopamine agonists L-dopa, apomorphine and d-amphetamine aggrevated the phenomenon of jumping and exploring during the phase of morphine withdrawal. The methods used in the present study were described by Way, et al., 1969 and Blesing et al., 1973. The results obtained in this study favour the involvement of dopamine and further suggest synthesis as well as release of brain dopamine increase during chronic morphinization and this is antagonized by pimozide and haloperidol.

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EFFECTIVENESS OF A LIQUID FORMULATION OF PRAZEPAM IN BENZODIAZEPINE WITHDRAWAL

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In a benzodiazepine withdrawal programme we investigated the effectiveness of a solution of prazepam in the form of concentrated drops (one drop = 0.5 mg of prazepam). Prazepam is an anxiolitic benzodiazepine it is a prodrug which through hepatic first-pass metabolism is completely transformed by dealkylation to N-desmethyldiazepam. The patients' drug was first changed to prazepam in equipotent dose to their previous benzodiazepine. Then the dosage was decreased every three days by half, under EEG in order to control withdrawal seizures. The design of the study was single-blind, the patient ignored when the dose was changed, the treatment being presented under a constant volume. In addition of the EEG controls, a daily assessment of the withdrawal symptoms was performed by scales (Hamilton Scale for anxiety and Lader Scale) and by clinical examination. Twelve inpatients, after giving their written informed consent entered the study, the daily dose range before withdrawal was between 200 mg and 20 mg in prazepam equivalent. Most of the patients (10) were completely free of benzodiazepine treatment at the end of the study, two of them kept low doses of prazepam required by their psychological status. In conclusion, we think that this liquid formulation of benzodiazepine is very suitable for a withdrawal programme permitting a very precise and slow decrease of doses in blind conditions.

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5,7-DHT LESIONS MODIFY THE EFFECTS OF 8-OH-DPAT, BUT NOT RITANSERIN, ON PUNISHED RESPONDING OF PIGEONS. S. Gleeson and J.E. Barrett

The hypothesis that reduced 5-HT neurotransmission underlies the anxiolytic effects of drugs such as buspirone has led to investigations of the effects on punished responding of the neurotoxin 5,7-DHT, which destroys 5-HT neurons. The results from such studies are equivocal, perhaps in part because of the wide variety of procedures employed. In the present experiments, we investigated the effects of bilateral intracerebroventricular injections of 5,7-DHT (400 ug/ventricle) on punished responding of pigeons, which has proved to be sensitive to the anti-anxiety effects of 5-HT compounds. Prior to 5,7-DHT administration, pigeons were trained to key peck under a multiple schedule of reinforcement in which responding also was punished during alternating components. Dose-response curves were determined for 8-OH-DPAT and for ritanserin in separate groups of pigeons before and after administration of 5,7-DHT. Prior to the lesion, 8-OH-DPAT substantially increased punished responding without altering unpunished responding. The effects of ritanserin were less pronounced, with more variability across subjects. Administration of 5,7-DHT resulted in increases in punished responding, although the effect generally was small and, in some cases, transient. After the lesion, 8-OH-DPAT increased punished responding at lower doses than before the lesion, and in some cases response rates at other doses were higher than before the lesion. Ritanserin, on the other hand, had more variable effects, producing either no increases in punished responding, or smaller increases than were obtained prior to the lesion. Although the anti-conflict effects of 8-OH-DPAT generally are thought to involve presynaptic mechanisms, the effects observed in the present study are more commonly seen in the case of postsynaptic receptors.

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MODULATION OF A 5-HT2-MEDIATED BEHAVIOR BY 5-HT1 RECEPTOR ACTIVATION R.A. Glennon, N.A. Darmani and B.R. Martin

The head-twitch response in mice appears to be a 5-HT2-mediated phenomenon; it has been previously demonstrated that the effect produced by various non-selective serotonin (5-HT) agonists is inhibited by 5-HT2 antagonists. We have now shown that the putative 5-HT2 agonist (±)DOI elicits head-twitch in a stereoselective manner with the R(-)-isomer being about twice as potent as its S(+)-enantiomer. The response produced by 2.5 mg/kg (±)DOI is antagonized by the 5-HT2 antagonists ketanserin (ID50 = 0.17 mg/kg) and spiperone (ID50 = 0.08 mg/kg). Interestingly, the non-selective 5-HT agonist 5-OMe DMT produced a less robust response than that of DOI suggesting that 5-OMe DMT may be only a partial agonist; an alternative explanation is that its agonist effects on 5-HT1 receptors may somehow modulate its 5-HT2 component of action. To test these possibilities, doses of 5-OMe DMT were administered in combination with DOI (2.5 mg/kg) and resulted in antagonism of DOI-induced head-twitch (ID50 = 1.5 mg/kg). Because this experiment does not differentiate between partial agonism and 5-HT1 activation, we conducted another study where a selective 5-HT1 agonist, with no reported 5-HT2 agonist or antagonist properties, was examined. Administration of the 5-HT1A agonist 8-OH DPAT in combination with (±)DOI also resulted in a dose-related antagonism of the head-twitch response (ID50 = 0.25 mg/kg). These results suggest that in addition to (or as an alternative to) any partial agonist or antagonist activity of serotonergic agents at 5-HT2 sites, this 5-HT2-mediated effect may be antagonized by 5-HT1 agonist activity.

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CHRONIC ANTIDEPRESSANT TREATMENT AND NEURO-TRANSMITTER FUNCTION. G.M. Goodwin.

For the last decade, pharmacologists have sought understanding of the action of antidepressant treatments not simply from the acute effects of antidepressant drugs such as inhibition of transmitter re-uptake, but also from the chronic effects of their administration in vivo to animals. This approach has had the important virtue of allowing comparisons between treatments of entirely different origin such as monoamine re-uptake inhibitors, monamine oxidase inhibitors and electroconvulsive shock (ECS). It has allowed the identification of apparently common actions, e.g. attenuation of function at beta-adrenoceptors and 5-HT1A receptors, and also important differences, such as enhanced dopamine function following ECS. Clinically, it has resulted in the introduction of lithium augmentation for the treatment refractory depression and it has prompted examination of novel treatments for depressive illness such as the 5-HTIA agonists. However, the paradigm has its limitations. Is downregulation itself actually the crucial functional change or does it simply flag other primary actions? Can the actions of old treatments really show us to new ones? How can the crucial interfact with human studies be made more interactive? These issues will be discussed in relation to both basic and clinical domains.

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BRAIN DAMAGE AND PROTECTION BY SYSTEMIC KAINATE AND KYNURENATE: A STUDY USING QUANTITATIVE $^{45}CaCl_2$ AUTORADIOGRAPHY

Jan Bert Gramsbergen

Systemic injection of the excitotoxin kainic acid (KA) in the rat, produces an experimental model for human temporal lobe epilepsy (Ben-Ari, Neuroscience 14: 375-403, 1985). Striatal KA lesions or quinolinic acid-induced seizures can be prevented by coinjection of the endogenous excitatory amino acid antagonist kynurenic acid (KYNA) into the brain (Foster et al, Neurosci Lett 48: 273-278, 1984). In addition, systemic KYNA attenuates infarction size after stroke (Germano et al, Ann Neurol 22: 730-734, 1987). Radioactive calcium has been used as a marker for nerve cell death, including intrastriatal KA lesions using $^{45}CaCl_2$ autoradiography (Gramsbergen et al, J Neurochem 50: 1798-1807, 1988).

In the present study, several days or weeks after receiving KA (12 mg/kg i.p.) and 24 hours after $^{45}CaCl_2$ (100μCi i.p.), wistar rats were killed by decapitation, and from their brains 30 μm thick coronal sections were cut at -20°C for quantitative autoradiography. Some rats received on the day they were treated with the excitotoxin, also KYNA (300 mg/kg i.p.; one dose 15 min prior and one or two doses after KA at 4 hours intervals). Two days after KA heavy labelling was found in the pyriform cortex, amygdala, subiculum and several thalamic nuclei. Most KA + KYNA treated rats had no seizures and did not accumulate calcium in those vulnerable brain areas. Histological examination of the same sections confirmed complete brain protection in those animals. In conclusion, systemic KYNA can block excitotoxic and epileptic brain damage, and $^{45}CaCl_2$ autoradiography is a very useful and relatively simple technique for studying neurotoxic, convulsive and neuroprotective compounds.

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EFFECT OF INTRACEREBROVENTRICULAR INJECTIONS OF SOMATOSTATIN AND CYSTEAMINE ON TWO LEARNING TASKS IN MICE : EVIDENCE FOR A TASK DEPENDENT EFFECT.

J.L. GUILLOU, J. MICHEAU and R. JAFFARD

Reduced brain somatostatin (SRIF) levels and receptor numbers have been reported in patients with Alzheimer's disease (AD); in addition neurofibrillary tangles and neuritic plaques have been identified in somatostatinergic neurons. Moreover recent studies have shown that in AD, the decrease in SRIF in the cerebrospinal fluid is correlated with the severity of cognitive dysfunctions (SOININEN et al., Neurosci. Lett., 1988, 85, 131-136). These findings have focused interest on a possible involvement of SRIF in cognitive processes. The present experiment was aimed at studying the effects of both SRIF and cysteamine (which transiently decrease SRIF availability) administration on learning and memory in BALB/c mice. Two tasks were used : a spatial concurrent discrimination (SCD) task performed in an automated 8-arm radial maze and a bar pressing task on CRF. SRIF (0.5 µg/0.5 µl) and cysteamine (50 µg/0.5 µl) were administered through chronic ICV cannula 30 min before each daily SCD training session and only before the bar pressing task acquisition session. SCD learning was significantly impaired by cysteamine. However cysteamine had no effect on the 24 hr delayed retention of the bar pressing task (in fact, slightly above controls). Conversely, SRIF administration produced a slight improvement of learning in the SCD task while no effect was observed in retention of the bar pressing task. Since these results indicated a task-dependent effect of the treatments, a regression analysis was performed which indicated negative correlation between performance in the SCD and bar pressing tasks ($r = -0.57$; $p = 0.0034$).

Taken together these results suggest that central SRIF plays a role in learning and memory processes but its involvement cannot be considered univoqually as "facilitative". Our findings indicate that high SRIF levels improve spatial reference memory performance (SCD) while decreased SRIF levels below physiological levels would be necessary to facilitate sensorimotor conditioning.

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SEX BEHAVIOR OF MALE AND FEMALE RATS AFFECTED BY 8OH-DPAT, A 5 HT1a AGONIST. S.M. Haensel*, J. Mos**, B. Olivier** and A.K. Slob*.

1. Middle-aged male rats, former studs, were tested for sex behavior. Two groups were formed after first test: "active" (1 or more ejaculations) and "inactive" (no ejacs). Sexual behavior was observed for 7 consecutive weekly tests. In one test 8OH-DPAT was injected 30 min before test (.2 mg/kg). Statistical analyses showed that the differences in ejaculations disappeared with DPAT; all males ejaculated. Thus: DPAT has aphrodisiacal properties in middle-aged male rats.
2. With DPAT male rats occasionally ejaculate during the first intromission, i.e. "premature ejaculation". This phenomenon was investigated in further detail. Male rats were pair-tested with an estrous female, 30 min after DPAT injection (.2 mg/kg). In 17% of the tests (n=30) there was an ejaculation with the first intromission, and in 13% it occurred with the second intromission. It was further discovered that the ejaculate was often deposited extravaginally. It was concluded that DPAT makes a number of male rats to ejaculate prematurely and extravaginally.
3. Female rats can show masculine sexual behavior during pair-tests with another female in heat. Testosterone (T) greatly enhances this behavior. Experienced ovexed female rats were tested with or without testosterone treatment, with or without DPAT. There were no significant effects of DPAT. It was concluded that DPAT does not have aphrodisiac properties in female rats.

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AKINESIA REVERSED BY NMDA ANTAGONISTS
W. Hauber and W.J. Schmidt

Antagonists of the glutamatergic transmission at the N-methyl-D-aspartate (NMDA) receptor exert to some extent similar behavioral actions like dopamine agonists as evidenced by rodent experiments conducted in our laboratory (see Schmidt et al. TINS 13,2,1990). For example, it has been demonstrated recently that systemic or intrastriatal administration of NMDA antagonists counteracts neuroleptic-induced catalepsy, an animal model of Parkinson's disease. Therefore, this class of compounds may have a therapeutic potential in the treatment of this disease. The present study was dedicated to investigate the anti-akinetic effects of NMDA antagonists in detail. In a novel simple reaction time task, rats were trained in a modified runway for rapid initiation of locomotion in response to a combined optic-acoustic stimulus. Reaction time, movement time and accelerative forces emitted by an animal were recorded from each locomotor initiation. Results indicate a dose related increase of reaction time, a prolonged movement time and a decreased initial acceleration during movement initiation following systemic administration of haloperidol. These effects were reversed by systemic coadministration of MK-801, a selective non-competitive NMDA antagonist. Haloperidol-induced movement initiation deficits in this task are in part comparable to bradykinesia seen in Parkinson's disease and their reversal by MK-801 is in line with recent evidence of an anti-parkinson potential of NMDA antagonists.

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INDIVIDUAL DIFFERENT RESPONSES OF RATS PRETESTED BY APOMORPHINE TO VARIOUS DRUGS
U. Havemann-Reinecke and B. Kücking

Apomorphine (APO, 0,5-5mg/kg s.c.) is well known to produce oral stereotyped behavior (in lower doses sniffing and in higher doses predominantly licking and gnawing aund locomotor activation. On the EBPS Meeting 1988 we presented results showing individual differences of male rats in response to APO (2mg /kg s.c.), which could be indivually reproduced in a second test 4 days later: 40% of the rats tested in an Opto-Varimex-Motility Meter showed predominantly sniffing accompanied by a pronounced locomotor activation (S(L,G)-rats). The other 60% of the rats tested showed predominantly licking and gnawing and less increase of locomotor activation (L(S,G)-rats). Both groups of rats significantly differed in all parameters measured in the Motility Meter and in their reaction to chronic treatment with morphine (MO) (Pharmacopsychiat 21:314-316 1988). We now present data demonstrating that these both types of rats are also differently sensitive to acute administration of MO(3,3mg/kg i.p.): The stereotyped behavior of the S(L,G)-rats, induced by APO, changed to licking after MO and that of the L (S,G)-rats to predominantly sniffing. Naloxone (1mg/kg i.p.) antagonized both effects. Furthermore these both types of rats pretested by APO were also differently sensitive to Haloperidol (HAL), but not to amphetamine. 0.2mg/kg of HAL did not antagonize the APO-induced stereotyped behavior of the S(L,G)-rats, but completely that of the L(S,G)-rats. To conclude, pretesting of rats with APO could probably give us informations an a preexisting different sensitivity to dopaminergic (DA) stimulation and inhibition, which could probably be relevant for different effectivness of other drugs as well, activating the DA system not by the DA receptor but via other mechanisms as f.e. the opioids do.
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Cholecystokinin octapeptide (CCK-8) and neurotensin (NT) act as neuroleptic-like agents depending on the site of injection in the mesolimbic system.
Ch. Heidbreder, M. Gewiss and Ph. De Witte.

Both CCK-8 and NT have been shown to display neuroleptic-like properties when injected in the mesolimbic system. We thus investigated the respective effects of CCK-8, NT, and haloperidol on the intracranial self-stimulation behavior (ICSS) after their direct administration into the lateral ventricle (ICV) into both portions of the nucleus accumbens (NAC) into the ventral tegmental area (VTA) as well as into the ventral subicular portion of the hippocampal formation (SUB). The ICV injection of CCK-8 induced a drastic decrease in the rate of ICSS. By contrast, the direct administration of CCK-8 into the medio-caudal part of the NAC induced an enhanced rate of ICSS while a similar injection into its rostral portion gave rise to a slight transient decrease of ICSS. When injected into the SUB, both CCK-8 and glutamate produced decreased ICSS rates. NT induced similar behavioral profiles to that observed after the ICV injection of CCK-8 or into both portions of the NAC. However, both peptides displayed asymmetric effects on ICSS when administered into the SUB or into the VTA. NT and CCK-8 were also shown to have a great deal in common with haloperidol when injected ICV. Nevertheless, they strongly differed from the classical antipsychotic when administered into both portions of the NAC. Finally NT closely resembled the behavioral profile of haloperidol in the VTA (i.e. an enhanced rate of ICSS) by contrast with CCK-8 suggesting both peptides may regulate ICSS most probably through different synaptic mechanisms and through different neuroanatomical pathways.

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ACTIVATION OF ENDOGENOUS OPIOID-MEDIATED MECHANISMS IN LABORATORY MICE BY EXPOSURE TO THE CALLS OF MURINE PREDATORS. C.A. Hendrie.

Several lines of evidence now suggest that exposure to stimuli associated with predators activates endogenous analgesia mechanisms. However, whilst it is now known that olfaction plays a role in the activation of endogenous analgesia mechanisms there is little information concerning the role of audition.

For these studies DBA/2 mice were assayed for tail-flick latency (TFL), exposed to 5 mins of tape recorded stimulus material (3 mins human voice followed by 2 mins of animal call) in a modified activity arena and re-assayed for TFL at various time points thereafter. Inititial screening of the calls of various species indicated that only the calls of the Barn Owl (Tyto alba) and the Tawny Owl (Strix aluco) induced significant analgesia. Further, the analgesia induced by the call of the Tawny Owl was found to be blocked by 5 mg/kg naloxone indicating its opioid nature.

These data clearly demonstrate that laboratory strains of mice are able to differentiate between the calls of various species and that physical stimulation is not a necessary pre-requisite for the activation of endogenous analgesia mechanisms under these circumstances.
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NEUROCHEMICAL CORRELATES OF NORMAL AND PATHOLOGICAL BEHAVIORS: MICRODIALYSIS STUDIES

L. Hernandez, P. Rada, G. Mark and B. G. Hoebel

In the last eight years our laboratories have been studying the neurochemical correlates of reinforced behaviors by means of brain microdialysis in freely moving rats (Hernandez & Hoebel, Pharmacol Biochem Behav 18:159, 1982; Hernandez et al., Life Sci 39:2629, 1986). The behaviors studied so far include feeding after food deprivation (Hernandez & Hoebel, Physiol Behav 44:599, 1988; Schwartz et al., Brain Res 479:349, 1989), feeding elicited by electrical stimulation of the hypothalamus (Hernandez & Hoebel, ibid), drinking induced by intracerebral injection of angiotensin, salt consumption induced by salt-free diet and antidiuretic drug injections, and self-stimulation (Hoebel et al., Ann NY Acad Sci 575:171, 1989). In all these experiments the emission of the consummatory behavior in the presence of the rewarding stimuli enhances dopamine turnover in the nucleus accumbens, and in some instances in the prefrontal cortex as well. We now report two experiments in which the emission of behavior decreases dopamine turnover instead of increasing it. First, when rats showed conditioned aversion to a novel flavor, extracellular dopamine decreased in the nucleus accumbens (Hoebel et al., in Obesity: Towards a Molecular Approach, G. Bray et al., eds, in press). Second, when a seizure was induced by amygdaloid kindling, dopamine turnover decreased in the nucleus accumbens, but increased in the prefrontal cortex. These results will be discussed in terms of the amygdala's role in taste aversion, epilepsy and the clinical phenomenon known as "forced normalization," i.e. relief of psychotic symptoms during temporal lobe epilepsy.

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DIFFERENTIAL HUMAN VIGILANCE PERFORMANCE AFTER ETHANOL INGESTION.

R. Hernández-Pozo and L. Rosas

A placebo design was used to assess the effect of ethanol ingestion on human vigilance performance. Twenty female university students with a low history of alcohol consumption participated in the experiment, they gave written consent and they were aware that they might receive an alcoholic drink. Half of the subjects were randomly assigned to a placebo group, and half to the alcohol group. Both groups drank liquid with 5 times tonic mixed with lemon powder and 1 time (1 ml. of pure ethanol per kg. of body weight) of 100 proof vodka for the experimental group, or the equivalent volume of tonic for the placebo group. In the vigilance task subjects touched a handle once a light was on, the light was turned on randomly within 1 minute after the subject responded on a switch. One day before the experiment subjects received a conceptual paper and pencil test, and a baseline of the reaction times in the vigilance test was taken. During the experiment, series of 10 latencies were taken: 0, 15, 30, 45 and 60 minutes after ingestion. A small increment in reaction times from their baseline was found for the placebo subjects. A stronger effect was found for the experimental group, the highest difference was recorded 30, 45 and 60 min. after ingestion. No relation was apparent among conceptual scores and latency differences between baseline and post ingestion data. Subjects with the highest scores in the conceptual test presented the lowest baseline latencies. Data suggest that the dose employed affected significatively vigilance performance, and that there is a high probability that individuals who tend to respond with short latencies, might exhibit high performance in conceptual tasks.

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EFFECTS OF COMMONLY USED AND ABUSED SEDATIVES ON HUMAN LEARNING AND PERFORMANCE

S. T. Higgins, W. K. Bickel, and J. R. Hughes

Originally developed with nonhumans, the repeated acquisition and performance of response chains procedure has been successfully adapted for use in human behavioral pharmacology studies. We will describe the use of this procedure in our studies comparing and contrasting the effects of commonly used sedatives across (1) different environmental conditions, (2) acute and chronic dosing arrangements and (3) different compounds.

In these studies, adult, male and female volunteers were administered varying doses of alprazolam, buspirone, diazepam, lorazepam, secobarbital and triazolam under double-bind conditions. Studies were conducted in both outpatient and inpatient laboratory settings. Acute and chronic dosing produced orderly dose-response relationships on the acquisition and performance of response chains baselines. Results were highly concordant with those from studies conducted with nonhumans (e.g., lower doses disrupt acquisition but not performance behavior).

Overall, our work with this procedure (1) demonstrates the generality of behavioral principles across human and nonhuman behavior, (2) permits integration of findings regarding drug effects on learning using operant procedures with those using more traditional "learning and memory" tasks, (3) illustrates the influence of environmental factors on the effects on drugs on human learning, and (4) demonstrates the utility of the repeated acquisition baseline in the assessment of the behavioral pharmacology and toxicology of commonly used and abused drugs.

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A DISCRETE-TRIAL TEST OF THE EFFECTS OF SECOBARBITAL ON CHOICE OF SOCIAL VERSUS MONETARY REINFORCEMENT

S. T. Higgins, W. K. Bickel, and J. R. Hughes

Drugs of abuse often increase human social interaction when taken acutely. Drugs of abuse (e.g., d-amphetamine) may also increase the relative reinforcing effects of social activities. Changes in choice or preference in a concurrent schedule arrangement are a well accepted measure of changes in the relative reinforcing function of a stimulus. In the present study, we examined the acute effects of secobarbital (100 & 200 mg/70 kg) and placebo on concurrent choice between social and monetary reinforcement.

Two mutually exclusive options were concurrently available to eight volunteers during 60 min. experimental sessions. Subjects chose every three minutes between conversing with another same-sex volunteer and providing speech monologues for monetary reinforcement. Secobarbital significantly increased choice of social over monetary reinforcement. Drug-produced increases in choice of the social option were associated with increases in total seconds of speech and the rate of social conversation. Secobarbital also increased subject ratings of friendliness, elation and energetic. These results extend to secobarbital effects observed previously with alcohol and d-amphetamine and suggest that these compounds may increase the relative reinforcing effects of social interaction.

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SOCIAL RECOGNITION IN RATS: MODULATION BY DRUGS.
Z. Hlinák, I. Krejčí

Changes in social investigatory behaviour have been designated to evaluate short-term memory process in rats. The test is based upon olfactory recognition. In this study the effect of various psychotropic drugs was examined. An adult male was exposed to an unfamiliar juvenile male for 5 min. The time spent by the adult in social investigation of the juvenile was recorded. Immediately after the exposure adult males were injected sc with saline or tested drugs. The males were again exposed either to the same or a novel juvenile 2 h later. At this time saline injected males no longer recognized the same juvenile. The time of social investigation of the novel juvenile was similar to that observed during the 1st exposure. In addition, a nonspecific habituation potency of adult males was estimated by the time spent in the sniffing of scent traces left on the floor.
MIF-I (1 mg/kg), its derivative alaptide (1 mg/kg), oxiracetam (30 mg/kg), nicotine (0.5 mg/kg) and takrine (2 mg/kg) reduced the time spent by adult males in investigation of the familiar juvenile during the 2nd exposure. Flunarizine (3 mg/kg) and pro-alaptide (10 mg/kg) were ineffective. However, the administration of pro-alaptide 1 h prior to the 1st exposure resulted also in reducing the social investigation time devoted to the same juvenile during the 2nd exposure.
The results suggest that various psychotropic drugs reducing the time of social investigation can be considered as enhancing the mechanisms involved in processing and short-term retention of chemosensory stimuli emitted by juvenile male.

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AFFINITY OF CAFFEINE FOR ADENOSINE RECEPTORS IS UNCHANGED IN RATS TOLERANT TO CAFFEINE-INDUCED STIMULATION OF LOCOMOTOR ACTIVITY: APPARENT pA_2 ANALYSIS.
S.G. Holtzman

The purpose of this study was to determine if the affinity of caffeine for adenosine receptors is altered in rats that are tolerant to the stimulant effect of caffeine on locomotor activity. An apparent pA_2 analysis was performed for the interaction between caffeine and 5'-N-ethylcarboxamidoadenosine (NECA), a metabolically stable adenosine analog, on the locomotor activity of control and caffeine-tolerant rats (n=12/group). Tolerance was produced by giving one group of rats scheduled-access to water bottles containing 1.0 mg/ml of caffeine; daily caffeine intake averaged 67 mg/kg. The control group was given scheduled-access to drug-free tap water. Locomotor activity was recorded for 30 min beginning 35 min after administration of caffeine (IP) and/or NECA (SC). NECA alone dose-dependently decreased the locomotor activity of both groups, but was 8-fold more potent in control than in tolerant rats (ED_{50}s: 0.005±0.001 and 0.040±0.006 mg/kg, respectively). Caffeine alone, 3.0-100 mg/kg, dose-dependently increased the locomotor activity of control rats but had little or no affect on activity of tolerant rats. When the two drugs were given concurrently, caffeine (1.0, 3.0, 10 mg/kg) produced dose-dependent shifts to the right of the NECA curve that were of comparable magnitude in both groups. Apparent pA_2 values for control and tolerant rats also were comparable: 5.11±0.12 and 5.05±0.17, respectively. Thus, in rats tolerant to caffeine-induced stimulation of locomotor activity 1) caffeine retains adenosine-antagonist activity, and 2) the apparent affinity of caffeine for adenosine receptors is unaltered.

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CHARACTERIZATION OF EXCITATORY AMINO ACID RECEPTORS.
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Excitatory amino acid (EAA) receptors are divided into several subtypes; the ionchannel coupled: NMDA, AMPA, and kainate receptors, which are named after the most potent and selective agonists in electrophysiological experiments. The glutamate receptor coupled to IP_3-formation is named the metabotropic receptor and has a different selectivity for compounds as compared to the ionchannel coupled receptors. However, quisqualate, glutamate, ibotenate and trans-ACPD are potent agonists for these receptors. During the last decade our knowledge of EAA receptors based on investigations of interactions between radioligands and the receptors has increased remarkably. Today, size and function of the ionchannel coupled receptors are mapped using radioligands such ad ^{3}H-glutamate, ^{3}H-CPP, ^{3}H-glycin, ^{3}H-D-serine, ^{3}H-TCP, ^{3}H-MK-801, ^{3}H-kainate, ^{3}H-AMPA, and ^{3}H-CNQX.

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USING COMPUTER MODELS TO PREDICT ANTAGONISTIC OR SYNERGISTIC DRUG INTERACTIONS
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We have previously reported a computer based method which assists in the planning and interpretation of multi-treatment experiments [Davies et al 1989]. We have now extended this method: drug treatments whose combined effects differ significantly from those predicted by a simple additive model can be identified and extracted for separate analysis.

To discriminate between drug combinations which interact in an inhibitory or facilitatory manner, from those which are purely additive is often difficult [Rushton and Steinberg 1967, Hughes et al 1990]. This can be made easier with a computer model which generates the surface predicted by a simple additive interaction; this surface is used as a basis with which the observed effects are compared. Deviations from the base model are displayed by the computer as different colours, or monochrome shades, to distinguish between drug combinations likely to interact in an inhibitory or facilitatory manner. Models will be presented using recent results from mouse behaviour.

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AMPEROZIDE, A NOVEL ANTIPSYCHOTIC DRUG, STIMULATES DOPAMINE (DA) RELEASE BUT NOT DA METABOSLIM IN THE STRIATUM AND THE NUCLEUS ACCUMBENS OF AWAKE, FREELY MOVING RATS AS STUDIED BY IN VIVO MICRODIALYSIS. J. Ichikawa and H.Y. Meltzer.

It has been generally accepted that the antipsychotic effect of neuroleptics is related to the blockade of DA D2 receptors in the forebrain regions. However, recent studies demonstrated that atypical antipsychotics, e.g., clozapine, amperozide, have a weaker affinity for DA D2 receptors compared to typical antipsychotics, e.g., haloperidol. We have already reported that clozapine enhanced DA release to a greater extent in the nucleus accumbens than in the striatum (Soc. Neurosci. Abstr. 15:109.5, 1989). In the present study, we investigated the effects of amperozide HCl on DA release and metabolism in the striatum and the nucleus accumbens using in vivo microdialysis. The dialysis probe was perfused with modified PBS buffer (pH 7.4) 24 hrs after implantation. After obtaining stable baseline efflux values, amperozide (2,5 and 10 mg/kg) was administered subcutaneously to the rats. Dialysates were collected every 30 min up to 180 min.

Amperozide preferentially stimulated accumbal DA release at doses of 2 and 5 mg/kg, whereas the largest dose (10 mg/kg) of amperozide produced DA release to the same extent in the striatum and the nucleus accumbens. However, none of the doses of amperozide produced an increase in the efflux of DOPAC in either brain regions.

In conclusion, amperozide differs from typical neuroleptics in that it produces: 1) a preferential increase in DA release in the nucleus accumbens, and 2) no increase in DA metabolism in either brain region.

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AMPHETAMINE EFFECTS ON JUMP-UP AVOIDANCE AND BRAIN DOPAMINE AS MEASURED BY HPLC IN VIVO DIALYSIS

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The effects of amphetamine (AMPH) on both avoidance response acquisition and striatal dopamine release were compared. Rats received 1 avoidance training trial a day for 2 consecutive days during which they were exposed to a 290uA footshock delivered to the grid floor of an automated shelf jump avoidance chamber 10 s following their placement within the chamber. Shock delivery coincided with shelf presentation, allowing rats to escape by jumping onto the raised shelf. Immediately following the escape response, animals received intraperitoneal (IP) AMPH or saline injection. Retention of the jump-up response was tested 24 hr later. Rats were tested to a criterion of 2 consecutive avoidances. Posttraining AMPH (1 mg/kg) facilitated acquisition of the avoidance response as indicated by enhanced performance during test as compared to saline-treated animals ($F(1,7)=10.53$ $p<.02$). In separate animals, changes in caudate nucleus dopamine, DOPAC and HVA levels were compared to baseline following IP injection of AMPH 48 hr after guide cannula implantation. Dialysate samples were collected for 3 hr after AMPH injection in 20 min intervals and analyzed using HPLC-ECD. The neurochemical results are complementary to the behavioral results, as 1 mg/kg IP-administered AMPH increased striatal dopamine levels to 430-513% of baseline. AMPH correspondingly decreased DOPAC and HVA by 38-45% and 60-79% respectively.

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VERAPAMIL AND DILTIAZEM SEEM TO REVERSE SOCIAL ISOLATION - INDUCED ANXIETY IN THE RAT

E.Jankowska , O.Pucilowski , W.Kostowski

Verapamil and Diltiazem are two structurally distinct Ca2+ entry blockers that reveal, in addition to their known antiarrythmic and hypotensive effects, some interesting psychotropic properties. Here we report their effect on rats' behavior in an elevated plus maze test of anxiety after 6 weeks of social isolation. Chronic stress situation, that occurs during 6 weeks of social isolation in rats, has been found to result in markedly higher anxiety level as measured by the plus maze test, i.e. to decrease the number of open arm entries and time spent therein. Diltiazem in doses of 5 and 10mg/kg/day, as well as Verapamil in dose of 10mg/kg/day, when given chronically i.g. to isolated animals resulted in marked increase of open arm entries and time spent therein, not affecting animals' locomotor activity. Non-isolated rats chronically treated either with Verapamil or with Diltiazem did not differ from the vehicle-treated controls in any aspect of behavior. Thus, it seems that both drugs may reveal some anxiolytic and\or stress-protective properties. However, unlike benzodiazepines, they do not increase anxiety level upon withdrawal of chronic treatment.

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INDUCTION OF TOLERANCE AND PHYSICAL DEPENDENCE BY LORAZEPAM, DESMETHYLDIAZEPAM AND BROTIZOLAM BY A FOOD-ADMIXED METHOD.

C.Jansen van't Land, J.W.van der Laan and G.de Groot.

Benzodiazepines are widely used as anxiolytics and hypnotics. However, they are known to induce physical dependence. The purpose of our study is to compare lorazepam (LRZ), desmethyldiazepam (DMD) and brotizolam (BTZ) with respect to their potency to induce tolerance and dependence.

The benzodiazepines were given during five weeks with food. LRZ in concentration range of 31.25-125 mg/kg and 125-500 mg/kg, DMD in a range of 2.5-10 g/kg and BTZ in a range of 125-500 mg/kg, all in food. We have used the continuous measurement of locomotor activity in home cages to obtain an estimation of the sedative activity during the treatment and of the intensity of the withdrawal-related hyperactivity as an observer-independent symptom. In addition, withdrawal intensity was measured using food intake and body weight data. Administration of the benzodiazepines via the food led to a decrease of nighttime locomotor activity during the first week. For all compounds tolerance developed after five weeks. The basis of this tolerance development may be a higher rate of metabolism resulting in lower serum levels, as was found for all compounds. However, tolerance development may have also a pharmacodynamic component.

Induction of withdrawal by terminating the administration of LRZ (31.25-125 mg/kg in food, i.e. 2.5-9.5 mg/kg body weight-/day) led to a strong decrease in the food intake and loss of body weight. Only using a higher dose range (125-500 mg/kg in food, i.e. 9.5-37.5 mg/kg body weight/day) resulted during withdrawal in an increased daytime activity. In the dose ranges used for DMD and BTZ during withdrawal only effects on body weight and food intake could be found. The data indicate that the relative potency of DMD and BTZ to induce primary dependence, as measured by the induction of withdrawal hyperactivity is lower than was revealed in a cross-dependency study (Van der Laan, Jansen van't Land, this congress). The relevance of pharmacokinetic factors to explain this difference between primary and cross-dependence will be discussed.

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MODELS OF NEUROLOGICAL DISEASES AND SYMPTOMS

P. Jenner

Models of neurological diseases are required to determine the nature of disease process, to detect the ability of drugs and toxins to induce neurological syndromes and to evaluate agents potentially able to reverse the symptoms of such illnesses. In the area of movement disorders experimental models of neurodegenerative and drug-induced syndromes are important tools in studying these disorders.

The pathological changes underlying neurodegenerative diseases can be induced by toxin administration. The selective destruction of substantia nigra in primates by MPTP induces motor deficits characteristic of Parkinson's disease. Focal injection of quinolinic acid into the striatum of rats mimics the pathology of Huntington's disease and may cause motor abnormalities. Administration of the amino acids BOAA and BMAA to primates may induce motor abnormalities and pathological changes characteristic of motor neurone disease through effects on excitatory amino acid systems. A variety of toxins can cause pathological changes in the cerebellum and induce ataxic syndromes.

The repeated administration of neuroleptic drugs to primates elicits the dystonic and dyskinetic phenomena produced by these compounds in man. Similar treatments of rats may produce pharmacological models of acute dystonia or tardive dyskinesia but there is dispute over the nature of the movements produced. A variety of substances focally injected into brain are also claimed to induce hyperkinetic movements but the published evidence is poor. However, the placement of σH drugs into the rat nucleus may elicit dyskinetic movements in rats.

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RAPID BEHAVIORAL SENSITIZATION TO THE D_2 DOPAMINE AGONIST RU24213

C. Jodogne and E. Tirelli

The behavioral effects of 2.5 mg/kg of the D_2 dopamine agonist RU24213 injected chronically (every other day over 14 days) were assessed using a time sampling observational technique (4 samples of 1 min separated by 9 min) in male OF-1 mice. This dose of RU24213 injected acutely facilitated exhibition of standing behavior (with or without sniffing), suppressed autogrooming and sleeping (position), and had a weak inhibitory effect on locomotion and rearing. A rapid tolerance to RU24213 was found for effects on standing (decreasing) and autogrooming (increasing), which approached saline values over the last three sessions. The levels of locomotion and rearing markedly increased by session three (sensitization). There was neither tolerance nor sensitization to the dopamine agonist for sleeping position, which remained almost completely suppressed. Marked oral stereotypies did not develop. It seems that, with chronic treatment, standing behavior was progressively converted into excitatory locomotion and rearing, and into normal autogrooming. These results for locomotion are in general accordance with those obtained in other studies using different D_2 agonists (e.g., Szechtman et al., Abstr. Soc. Neurosci. 15:406.8, 1989). We also discuss whether the diminishing effects of RU24213 on standing and autogrooming constitute a direct pharmacological tolerance parallel to the sensitization of locomotion and rearing or are indirect consequences of these changes.

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THE EFFECTS OF NMDA ANTAGONISTS ON THE ACQUISITION OF LEARNED FEAR IN MICE

Joly D. Sanger D.J.

The N-methyl-d-aspartate (NMDA) subtype of excitatory amino acid receptors has been implicated in the cerebral mechanisms involved in learning and memory. Recent studies have reported that NMDA antagonists including 2-amino-5-phosphonopentanoic acid (AP5) which is a competitive antagonist, and dizocilipine (MK-801), which non-competitively blocks the ion channel associated with the receptor, can interfere with learning in both appetitively and aversively motivated tasks. In order to investigate the effects of a variety of NMDA antagonists known to interact in different ways with the NMDA receptor complex, a simple fear conditioning method was used. Mice were injected with test compounds and, following a brief period of exploration, received footshock in the dark compartment of a two compartment box. 24 hr later, the passive avoidance of this compartment was assessed. The non-competitive NMDA antagonists, dizocilipine, phencyclidine and N-allylnormetazocine interfered with learning as did the competitive antagonist, CGS 19755, the non-specific glutamate antagonist, riluzole (PK 26124), and the anti-tussive drug dextromethorphan which also has NMDA antagonist properties. In contrast, ifenprodil and its analogue SL 82.0715, which are anti-ischaemic drugs which interact with NMDA receptors through an action at the polyamine modulatory site, had no effect on learning up to doses which greatly depressed locomotor activity. Similarly, the sigma site ligand, ditolylguanidine (DTG) was without effect. These results are consistent with previous studies showing that the behavioural effects of NMDA antagonists depend upon the site at which the compounds act within the NMDA receptor complex. Activity at the haloperidol-sensitive sigma site does not appear to be involved in the interference with learning.

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ARECOLINE AND ONDANSETRON REVERSE SCOPOLAMINE-INDUCED DEFICITS IN AN OBJECT DISCRIMINATION TASK IN THE MARMOSET

D.N.C. Jones, G.J. Carey, B. Costall, A.M. Domeney, P.A. Gerrard, R.J. Naylor and M.B. Tyers*

The muscarinic antagonist scopolamine is widely used experimentally to impair cognition in animals and man. We have studied the ability of the cholinomimetic arecoline and the 5-HT_3 receptor antagonist ondansetron to reverse a scopolamine-induced cognitive deficit in the marmoset.

Adult marmosets were tested using a Wisconsin General Test apparatus. They were required to select between two junk objects to a criterion of 9 out of 10 correct responses for object discrimination (acquisition), 24hr retention and 24hr reversal of the task.

Scopolamine (10-40μg/kg s.c.) caused significant ($P<0.05$), dose-dependent increases in the number of trials required by the marmosets to reach criterion for acquisition and caused significant ($P<0.05$) increases in choice latency.

Arecoline (100μg/kg s.c.) or ondansetron (1μg/kg s.c., given 3 times during the 24hr preceding scopolamine treatment), prevented the scopolamine-induced impairment of acquisition. Neither agent produced effects on object discrimination responding when administered alone.

These data provide further evidence for a role of 5-HT in the modulation of cognitive processes. The ability of ondansetron to reverse a scopolamine-induced memory impairment in the primate suggests a potential for the 5-HT_3 receptor antagonists to reduce cognitive deficits linked with cholinergic dysfunction.

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ACOUSTIC STARTLE INDUCED ULTRASONIC VOCALIZATION IN THE RAT - A NOVEL ANIMAL MODEL OF ANXIETY
M.Th. Kaltwasser

Adult rats emit 22 to 28 kHz calls in response to inescapable aversive stimuli. Since this ultrasonic vocalization is reduced by clinically active anxiolytics, it has been associated with the state of fear. High intensity acoustic stimuli which elicit a startle response also evoke ultrasonic calling. In this study, it was tested if the acoustic startle induced vocalization (ASV) may serve as a tool for detecting anxiolytics.
30 minutes after i.p. application of diazepam (5 mg/kg), flunitrazepam (0,5 mg/kg), ipsapirone (5 mg/kg), maprotiline (25 mg/kg) or vehicle rats were either subjected to 5 acoustic stimuli of 110 dB SPL or to 5 electric footshocks at an interstimulus interval of 20 s. Vocalization was recorded for 3 min following stimulation. Duration and number of calls were measured. The benzodiazepines and the 5-HT1A agonist significantly reduced the number of calls, whereas the NE-reuptake blocker enhanced vocalization independant of the kind of aversive stimuli.
The rat's perception of an acoustic stimulus is rather constant and controllable by the experimenter whereas the perception of an electric footshock is highly variable. Therfore, the ASV provides a simple and reliable animal model of anxiety.

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LACK OF CROSS TOLERANCE TO DOPAMINE AGONISTS IN COCAINE-TOLERANT RATS
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Mechanisms by which tolerance develops to the effects of cocaine were assessed by examining cross tolerance to specific drugs after the development of cocaine tolerance. Daily experimental sessions were conducted in which rats were trained to press a key with food reinforcement. Sessions consisted of five 10-min timeout periods (TO) during which key-press responses had no scheduled consequence, each followed by a 3-min period during which food was presented after each thirtieth response (FR 30 schedule). High response rates were maintained under the FR 30 schedule, whereas little responding occurred during TO. Effects of cocaine, and other dopamine uptake inhibitors, Win 35,428, GBR 12909, were assessed along with the effects of the direct agonist, apomorphine, the indirect agonist, *d*-amphetamine, the selective D2 dopamine receptor agonist, quinperole, the preferential D2 dopamine receptor agonist, (-)-NPA, and the selective D1 receptor agonist SKF 38393. Cocaine (10 mg/kg, i.p.) or saline was administered once daily prior to sessions for the next 100 sessions. Once subjects were tolerant to the effects of cocaine, daily cocaine injections continued, except before sessions during which the effects of the other drugs were assessed. Repeated administration of cocaine produced a small shift to the right in the cocaine dose-effect curve. The ED 50 values for cocaine changed from 13.3 to 21.7 mg/kg. Tolerance to cocaine conferred cross tolerance to its close structural analog, Win 35,428, but not to the other dopamine uptake inhibitor, GBR 12909. Cross tolerance was not conferred to several of the other compounds, including *d*-amphetamine, SKF 38393, quinperole, and (-)-NPA. The ED 50 value for apomorphine was not significantly changed; however, its effects were attenuated at the lower doses (0.03 to 0.3 mg/kg), whereas at higher doses its effects were relatively unchanged. Examination of the time course of effects of drugs to which the subjects became tolerant suggested a significant metabolic component to the tolerance produced. These results suggest that while tolerance can develop to the behavioral effects of cocaine, this tolerance is not functional in nature.

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THE EFFECT OF TIANEPTINE ON THE OLFACTORY BULBECTOMIZED (OB) RAT MODEL OF DEPRESSION. J.P. Kelly and B.E. Leonard.

Tianeptine is a novel antidepressant which has been shown to enhance serotonin reuptake into rat brain and human platelets (E. Mocaer, Clin. Neuropharm. 11: S32-S42, 1988). This contrasts with other antidepressant drugs which modify the serotonergic system by inhibiting serotonin reuptake. The objective of this experiment was to examine the effect of chronic tianeptine administration (10 mg/kg twice daily for 4 weeks) in the olfactory bulbectomized (OB) model of depression. This model has been shown to be effective in selecting antidepressants, irrespective of their presumed mode of action, following chronic administration (B.E. Leonard & M. Tuite, Int. Rev. Neurobiol. 22; 251-286, 1981).
Platelet serotonin uptake was measured 24 hours and 4 weeks after commencement of treatment. After 24 hours, a significant reduction (p) in Vmax was found in the OB control group (OB + V, 59 ± 13; n = 6), when compared to sham-operated group (S + T), there was some increase in Vmax (140 ± 35, n = 8), whilst there was a reversal of the deficit in the OB tianeptine group (OB + T, 113 ± 18; n = 12). After 4 weeks of treatment, a significant reduction in Vmax (p) was found in the OB + V group (74 ± 9, n = 10), when compared to the S + V group (110 ± 8, n = 9), which was reversed in the OB + T group (107 ± 15, n = 9). There was no difference in the S + T group (101 ± 12, n = 6) when compared to S + V.
Behavioural observations were made 2 weeks after tianeptine administration. These consisted of Open Field and results are expressed as median ± standard deviation. A typical increase in ambulation was found in the OB + V group (118 ± 44, n = 12) when compared to the S + V group (62 ±27, n = 11). A reversal of this ambulation was found in the OB + T group (94 ± 29, n = 13) and this value was essentially similar to that found in the S + T group (83 ± 29, n = 9). It can be concluded from these biochemical and behavioural observations that tianeptine is active in the OB rat model of depression. Supported by IRIS, Neuilly-sur-Seine Cedex, France.

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RODENT MODELS OF ANXIETY AND THE EFFECTS OF 5-HT_3 RECEPTOR ANTAGONISTS
M.E. Kelly, B. Costall and D.M. Tomkins

Classical anxiolytic agents such as the benzodiazepines have been detected using conflict models. More recently, alternative animal models have been devised which have also been shown to be effective in detecting known anxiolytic agents. These models include (i) the rat social interaction test (ii) the mouse black/white test and (iii) the rat elevated X-maze. In the present studies a group of drugs with potential anxiolytic activity, the 5-HT_3 receptor antagonists, including zacopride, granisetron and ICS 205-930, were compared to chlordiazepoxide and diazepam in the three test situations.

Chlordiazepoxide and diazepam increase the time spent by rats in social interaction (by up to 240%), they increase the time spent and exploratory behaviour in the light section of the mouse black/white box (by up to 80%) and increase the time spent by rats on the end section of the open arms of the X-maze (by up to 100%).

Under the same experimental conditions zacopride, granisetron and ICS 205-930 also increased the amount of time spent in social interaction (up to 240%), the amount of time spent and exploratory behaviour in the light section of the black/white box (by up to 70%) and the time spent on the end section of the open arms of the X-maze (by up to 200%).

In general the profile of action of the 5-HT_3 antagonists was similar to that of the benzodiazepines confirming the potential anxiolytic activity of this novel group of drugs. However, there were two important differences between the groups firstly the 5-HT_3 antagonists were more potent and secondly with this novel group of drugs there was no indication of sedation even at the highest doses used.

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EFFECTS OF CHOLINERGIC AGENTS IN A NEW TWO-TRIAL SWIM TEST OF EXPLORATION AND MEMORY FORMATION

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Adult male Sprague-Dawley rats were placed in a circular, black tank containing water at 23°C for two 5-min swims separated by 3 days. Injections were given before the first swim only. During the first swim control saline-injected animals initially swam quickly, remaining close to the edge of the pool. Thereafter swimming speed declined and the proportion of time spent in the central region of the pool increased. In the second swim a major change in behaviour compared to the first swim is a marked increase in the proportion of time spent in the central region during the first minute. Scopolamine hydrobromide (0.3 mg/kg s.c., 30 min) administered before swim 1 markedly reduced the decline in swimming speed and increase in time spent in the central region. Moreover the proportion of time spent in the central region during the first minute of swim 2 was markedly reduced compared to control and was similar to that of naive rats. Scopolamine methylbromide (1 mg/kg) did not produce such changes. Thus scopolamine disturbed exploration pattern and memory formation by a central action. The effects of muscarinic agonists (arecoline, oxotremorine, pilocarpine) and cholinesterase inhibitors (physostigmine, tacrine, SDZ ENA 713) administered to scopolamine-treated animals before swim 1 were examined. All compounds partly normalized the disturbance of exploration pattern. Significant increases in the index of memory formation were produced by pilocarpine and by SDZ ENA 713. Thus in this test cholinergic agents can be distinguished by their ability to normalize particular scopolamine-induced disturbances of behaviour.

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BEHAVIORAL EFFECTS OF CONTINUOUS COCAINE IN RHESUS MONKEYS: TOLERANCE AND DEPENDENCE

M.S. Kleven and W.L. Woolverton.

The behavioral effects of continuous infusion of cocaine for prolonged periods were examined in rhesus monkeys responding under fixed-ratio (FR) or fixed-interval (FI) schedules of food presentation. Operant behavior was sampled every six hrs for 30 min or 1 hr while saline or cocaine (4.0-32 mg/kg/day) were continuously infused through an intravenous catheter for periods of 7-90 days at each dose. Cocaine initially reduced FR responding and tolerance developed to doses as high as 32 mg/kg/day. Continuous infusion of cocaine also initially decreased the rate of FI 60 responding and tolerance developed to doses of cocaine as high as 8 mg/kg/day. When continuous infusions of cocaine were terminated after 50-80 days of exposure, FR responding was disrupted for up to 72 hrs in 3 of 4 monkeys, indicating that behavioral dependence upon cocaine had developed. These behavioral disruptions were reversed when cocaine (0.06-0.25 mg/kg, i.v.) was administered 5 min before a session in which responding was typically reduced, indicating a pharmacological basis of cocaine dependence. However, behavioral disruptions were not consistently observed in monkeys responding under the FI schedule when infusions of cocaine were terminated after 60-90 days of exposure.

In order to quantify the degree of tolerance development under the FR schedule, cumulative dose-response functions for acute cocaine were determined in a separate group of monkeys using a multiple schedule comprised of six 10-min epochs separated by time-out periods of 3 min. In this study, 2 weeks of exposure to cocaine (4.0 mg/kg/day) caused a 2-4 fold shift to the right in the cocaine dose-response function.

The results show that tolerance develops to the effects of cocaine on operant behavior when the drug is administered continuously. Further, rate and extent of tolerance development varied when reinforcement loss was comparable, indicating that schedule of reinforcement may itself be an important determinant of the rate and degree of acquisition of cocaine tolerance. The data also suggest that behavioral dependence upon cocaine develops only under conditions of continuous exposure to high doses for prolonged periods. (Supported by NIDA Grant DA-00250).

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DIFFERENTIAL EFFECTS OF CHRONIC COCAINE ON D1 AND D2 DOPAMINE RECEPTORS IN THE RAT

M. S. Kleven, B. D. Perry, W. L. Woolverton and L. S. Seiden

It is well known that repeated administration of cocaine results in sensitization to its behavioral effects. Since behavioral supersensitivity lasts for several months after drug treatment, it is likely that repeated exposure causes long-lasting changes in the CNS. Recently, changes in striatal and mesolimbic D2 dopamine (DA) receptors have been reported to occur immediately after repeated daily injections of cocaine; it is not known, however, whether these effects are long-lasting. In the present study, rats were treated with single injections of cocaine (10 mg/kg) or saline for 15 days and sacrificed either 20 min or 2 weeks after the last injection. D1 sites were labeled with [125I]SCH 23982 and D2 sites with [3H]spiperone in saturation studies. The density of D1 binding (Bmax) in frontal cortex was unchanged 20 min after the last daily injection, but was significantly decreased two weeks later (-38% of saline-treated group). D1 density in striatum was decreased both 20 min (-54%) and 2 weeks (-59%) after the injection regimen. Cocaine-induced decreases in D1 density in nucleus accumbens were observed to occur only 20 min after the last injection (-42%). In contrast to these effects on D1 sites, D2 density was significantly decreased in striatum (-29%) and frontal cortex (-34%) and increased in the nucleus accumbens (+200%) only 20 min after repeated cocaine. Computer-assisted analysis of the saturation isotherms revealed that chronic cocaine did not affect the affinity (K_d) of either radioligands for the D1 or D2 binding sites. These results show that repeated administration of cocaine caused transient decreases in D2 binding sites and longer-term decreases in D1 binding sites in striatum and frontal cortex. Furthermore, cocaine caused opposite, transient effects on D1 and D2 sites in nucleus accumbens. Since the cocaine-induced changes in D2 receptors were short-lived and behavioral supersensitivity is long-lasting, it is likely that alterations in the density of D2 receptors cannot account for sensitization. The relationship of observed longer-term changes in D1 receptors to altered behavioral effects of chronic cocaine remains to be determined. {Supported by grants from NIDA (DA-00085) and the Brain Research Institute, The University of Chicago}.

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A COMPARISON OF BENZODIAZEPINES AND 5-HT1A AGONISTS IN A PASSIVE AVOIDANCE TEST OF ANXIETY

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The effect of classical anxiolytic drugs such as diazepam and chlordiazepoxid is generally agreed to be mediated via the central benzodiazepine-GABA receptor complex. The effect of the new anxiolytic buspirone is possibly mediated via 5-HT_{1A} receptors. Receptor-receptor interactions have recently been postulated to be important for some pharmacological effects. Therefore the mechanisms of action were studied in a passive avoidance test of anxiety.

A passive avoidance procedure was used where the animals were placed on a lighted platform and allowed to enter a dark chamber. When entering the chamber a door was closed and the animal recived a 4 sec. electric shock of 0.3 mA through the grid floor. One learning trial was followed by a retention trial 24 hours later but in this case the drugs were delivered 30 minutes before the retention trial. Reference drugs like diazepam, flunitrazepam, chlordiazepoxide and meprobamat were found to be active in this paradigm as well as drugs like buspirone, melperone, setoperone and 8-OH-DPAT. The 5-HT_2 antagonist amperozide was also found to be active in passive avoidance. On the other hand antidepressants seem not to be active in this test. Four drugs (diazepam, chlordiazepoxide, buspirone and 8-OH-DPAT) were subjected in blocking experiments with flumazenil (Ro-15 1788) and unselective 5-HT antagonists. The benzodiazepines were blocked by flumazenil but the 5-HT_{1A} agonists were not. However, the anticonflict effect was not blocked by pindolol neither for the benzodiazepines nor for the 5-HT_{1A} agonists.

These results dispute that effects in this passive avoidance paradigm are mediated via 5-HT_{1A} receptors or alternatively that pindolol does not act as an antagonist at 5-HT_1 receptor sites.

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BEHAVIOUR MEDIATED BY 5-HT_2 RECEPTORS

Wouter Koek, Anne Jackson and Francis C. Colpaert

A variety of behavioral procedures are used as in vivo assays for studying drug interactions at central 5-HT_2 receptors. Novel compounds, selective for serotonin receptor (sub)types, constitute useful tools to examine the validity of these assays. One relatively simple behavioral model is provided by the head-twitch response in rodents, which can be elicited by the serotonin precursor, l-5-HTP, and can be antagonized by a variety of 5-HT antagonists, including 5-HT_2-selective antagonists. However, drug potencies in blocking l-5-HTP-induced head-twitches have not always been found to correlate closely with affinities for 5-HT_2 receptors. Although most of the putative 5-HT_3 antagonists appear to be ineffective, the head-twitch response can be antagonized also by compounds considered to be selective for 5-HT_{1a} receptors. Several 5-HT_2 selective agonists (i.e., DOM, DOB, DOI) have been employed as training drugs in drug discrimination studies. Consistent with the involvement of 5-HT_2 receptors, their discriminative stimulus effects have been observed to be blocked by 5-HT_2 antagonists, and to be mimicked by a series of 5-HT_2 agonists with relative potencies correlating significantly with their 5-HT_2 affinity. Some test drugs, however, produce partial generalization, which merits further analysis, particularly in view of the suggestion that agonist activity at 5-HT_2 receptors may be involved in the effects produced by hallucinogenic drugs. One of the clinical applications that have been suggested for 5-HT_2 antagonists is the treatment of anxiety. Although ritanserin has been reported to show anxiolytic actions in humans, its effect in preclinical animal models using mammalian species are limited. However, punished responding in pigeons, which has been suggested to provide a sensitive model for detecting potential anxiolytic activity of nonbenzodiazepine compounds, was reliably increased by ritanserin.

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EXCITATORY AMINO ACIDS: A BEHAVIORAL ANALYSIS.

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Excitatory amino acid receptors are classified according to their sensitivity to N-methyl-d-aspartate (NMDA), kainate, or quisqualate. Of these receptors, the NMDA receptor is the most extensively characterized, because of the availability of selective, competitive antagonists. The NMDA receptor constitutes part of a complex involving an ion channel at which phencyclidine (PCP)-type drugs act as noncompetitive antagonists, and additional sites, such as the glycine-sensitive site. Previously, NMDA antagonism was found to be associated with PCP-like behavioral activity. To further examine this relationship, the ability of a variety of compounds to attenuate behavioral effects of NMDA was compared with their ability to produce PCP-like behavioral effects, in mice, rats, pigeons and monkeys. NMDA-induced lethality, convulsions, suppression of operant responding, and discriminative stimulus (DS) effects were antagonized by competitive NMDA antagonists and by PCP-type drugs, with relative potencies correlating with their potencies to produce PCP-like DS and other behavioral effects. However, the magnitude of the NMDA-antagonist and PCP-like agonist activity that was observed depended on the type of antagonist used, the effect measured, and on other factors (e.g., route of administration, species). Some putative glycine antagonists attenuated in vivo effects of NMDA without producing PCP-like behavioral effects. To further characterize the behavioral activity of these compounds, their ability to mimick the DS effects of drugs other than PCP (e.g., pentobarbital) was examined. Together, the results suggest that the extent to which antagonists at the NMDA receptor complex produce PCP-like behavioral effects might depend in part on the specific component of the complex with which they interact.

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Involvement of the nucleus accumbens in oro-facial behaviour in the rat

Paul Koene, Eric Prinssen and Alexander R. Cools

Oro-facial dyskinesia (OFD) is one of the unwanted side-effects of long-term L-dopa treatment in Parkinson patients. Dopamine plays a central role in most hypotheses that are proposed to clarify the cause of these effects.
Effects of systemic administration of dopaminergic receptor agonists and antagonists are well investigated in rats in relation to oral behavior. D1-agonists cause an increase in rhythmic jaw movements (RJM) and grooming, while D2-agonist increase general activity and stereotypic behavior, but reduce oral behaviors. Both D1- and D2-agonists combined produce stereotypic behaviors.
Dopaminergic stimulation of a discrete subregion of the striatum plays a critical role in oral behavior in rats. Previously, our lab has shown that a subregion of the feline caudate nucleus, i.e. r-CRM - the feline counterpart of the ventral striatum - is involved in OFD (Spooren and Cools, this volume). In ketamine anaesthetized rats with a spinal C1 transection, local administration of D1- and D2-agonists in the ventral striatum produced excessive amounts of RJM. Accordingly, we studied the effects of local administration of the D1-agonist SK&F38393 (5µg/0.5µl) and the D2-agonist LY171555 (10µg/0.5µl) in the nucleus accumbens on the overt behaviour of freely-moving rats (n=34).
Concerning oral behavior, SK&F caused an increase in tremorous mouth movements and tongue protrusions, while LY caused a decrease in tremorous mouth movements and an increase in tongue protrusions and yawning. SK&F and LY increased vacuous chewing movements, but antagonized each other after combined administration. SK&F did not affect grooming, while LY caused a decrease in the duration of grooming. Stereotypic behavior was induced by both drugs separately, but became intensive 30 minutes after combined administration. Concerning grooming behaviour these findings are in contrast with the results of systemic administration of these agonists. In conclusion, D1- and D2- receptors in the nucleus accumbens are involved in the modulation and/or generation of oral behavior in the rat.

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THE EFFECT OF NALTREXONE ON RESUMED ETHANOL CONSUMPTION AFTER ABSTINENCE IN RHESUS MONKEYS

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Alcohol addiction is characterized by frequent remissions of alcohol abuse after periods of complete abstinence. Prevention of this phenomenon is of major interest in the treatment of alcohol addiction. We found that after periods of abstinence (1, 2, or 7 days) free-choice drinking rhesus monkeys (n=8) (net ethanol intake on the average 4 $ml.kg^{-1}$ per day) resumed ethanol consumption immediately at reappearance of ethanol supply (a 16 and a 32 % v/v, ethanol in water solution, in addition to a bottle with normal drinking water) at a temporary increased level. Withdrawal distress was not observed. We suggest that the increased motivation for ethanol after a period of abstinence in the rhesus monkey can be compared to what is seen at the onset of remission.
Endogenous opioids have been postulated to play a role in positive reinforcement of behaviour and in motivational processes. We compared the effect of a single injection with naltrexone (.02; .06; .17; .50; 1.0; 1.5 $mg.kg^{-1}$) on the drinking behaviour in the monkeys a) during continuous alcohol supply to b) after a 2 day abstinence of alcohol supply. Ethanol intake after abstinence was significantly decreased with 75% by naltrexone at a dose of .17 $mg.kg^{-1}$ and higher in comparison to placebo; water consumption was not affected. During continuous supply naltrexone also reduced ethanol intake significantly but at a higher doses (.50$mg.kg^{-1}$ and higher) and in lesser degree (48%). Water consumption also was temporarily reduced. These results indicate that during the immediate remission in alcohol drinking after abstinence, endogenous opioids were more specifically and more pronounced involved than in regular drinking. Possibly this represent a specific interaction with a state of increased motivation.

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THE EFFECTS OF 5-HT$_{1A}$ RECEPTOR AGONISTS IN ANIMAL MODELS OF ANXIETY AND DEPRESSION. W. Kostowski, W. Dyr and P. Krzascik.

The current study examined the effects of three agonists of 5-HT$_{1A}$ receptors: buspirone, 8-OHDPAT and NDO-008 in animal model of anxiety (elevated plus-maze) and two models of depression (behavioral despair in rats forced to swim and footshock-induced suppression in open field activity in rats).

Both buspirone and NDO-008 produced anxiogenic-like action in the plus-maze test (i.e. reduced exploration of open arms), particularly in high doses (1-4 mg/kg) while anxiolytic-like action occurred over a very narrow dose-range.

All 5-HT$_{1A}$ agonists tested in this study counteracted the footshock-induced behavioral depression and, to a certain extent, increased animals activity in forced swim tests.

These results suggest that 5-HT$_{1A}$ agonists possess intrinsic antidepressant activity probably unrelated to anxiolytic action. The mechanism of anxiogenic-like action in the elevated plus-maze paradigm seems to be, at least partly, related to sedative effect.

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PASSIVE AVOIDANCE BEHAVIOUR OF RATS IN AN ARENA FREELY ACCESSIBLE FROM THE HOMECAGE.
I. Krejčí, Z. Hliňák

In the standard procedure of passive avoidance behaviour of the step-through type the animal avoids the shock-compartement because it has greater aversion to this area. However, even the "safe" compt. has some aversive meaning; if the animal had a free choice, it would probably avoid the whole apparatus. The present experiments were undertaken to obtain more information about the states of motivation that determine the animal behaviour in this situation. To this end an experimental set-up was used allowing rat to enter the arena from its homecage. In one of the compts. of the arena the rat receives a footshock. This procedure allows to estimate if the animal avoids the whole arena or predominantly the shock-compt.
During the first 5 trials rats could enter and explore the arena for 5 min. During trial 6 the experimental animals received a footshock (300 μA, 0.4 s) in the shock-compt. Following items of behaviour were recorded: latency to enter the arena; number of entries into the compts.; time spent in the arena; number of entries into the shock--compt.
In post-shock trials rats continued to enter the arena but the exploratory activity was diminished. Rats almost completely avoided the shock-compt. The rate of extinction was slow, occuring apparently due to receiving repeated information about the safety of the different parts of the arena rather than due to a decay of memory.
Scopolamine (250 μg/kg, sc.) given before the shock abolished the avoidance behaviour.

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ANTIDEPRESSANT SUBCLASSIFICATION BASED ON THE ELECTROCORTICOGRAM OF THE RAT.
F.Krijzer, R.van der Molen, B.Olivier, F.Vollmer.

Clinical data show different types of antidepressant drugs e.g. sedative (amitriptyline), anxiolytic (mianserine) or stimulating (nomifensine). Here we present a subclassification of antidepressants based on the quantitative analysis of the ECoG of the rat.
The ECoG is differentially recorded between the frontal and parietal cortex. During an experiment the rats are placed in drums within a sound attenuated Faraday cage. During the ECoG recordings the drums turn slowly to control the vigilance state. The ECoG is recorded during the 6 minutes immediately before and starting at 20 and 45 minutes after i.p. drugtreatment. For each recording period a mean powerspectrum is calculated. Powerspectral changes after drug or saline are expressed as percentage of the pretreatment powerspectrum using a 2 Hz wide moving window resulting in a t-profile for each postdrug period per drugdose. The weighted mean of the t-values of all t-profiles of a drug lead to a so called drug profile.
Drug profiles of the antidepressant drugs desmethylimipramine, nortryptyline, viloxazine, imipramine, clovoxamine and nisoxetine are all characterized by a decrease of the power over the whole frequency range from 0 to 100 Hz. The drugprofiles of the antidepressants fluvoxamine, mianserine, zimeldine, rolipram, clorgyline, iprindole and tranylcypromine show a power decrease in the frequency bands from 7 to 18 Hz and from 55 to 100 Hz and a power increase from 19 to 53 Hz. The latter is characteristic for anxiolytics (17 to 63 Hz). The drugprofiles of nomifensine and bupropion show a power increase from 0 to 14 Hz, from 25 to 50 Hz and from 60 to 100 Hz and a power decrease from 14 to 25 Hz. The power increase from 60 to 100 Hz is characteristic for psychostimulants.
Thus three subgroups of antidepressants can be distinguished based on changes of rat ECoG. This preclinical subclassification seems to fit well with the clinical subclassification. This drug profiling technique can be used to detect potential new psychoactive drugs.

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ETHOPHARMACOLOGY AND SEARCH FOR NOVEL CALMING AGENTS
M. Kršiak

Ethologically oriented laboratory experiments are typically based on evoking natural motor acts and postures. Aggressive and defensive-escape acts and postures occurring on intraspecies conflict in mice seem to be especially convenient for testing calming activity of drugs. We wondered whether there is a drug which would be able to eliminate aggressive and defensive-escape agonistic activities in mice without inhibiting locomotion or producing other adverse effects.
To answer this question, we analyzed a data-base containing effects of over 60 drugs from various pharmacological classes tested in wide dose ranges in aggressive and timid singly-housed male mice under a uniform procedure at our laboratory in Prague and at Dr. Šulcová's laboratory in Brno (Department of Pharmacology, University of T.G. Masaryk) during the last 18 years.
Although some drugs (e.g. fluprazine) reduced attacks to near abolition without inhibiting locomotion, none of the many drugs tested was able to inhibit escapes totally at non-sedative doses. Such a highly potent non-sedative potentially anxiolytic drug remains to be discovered. No drug has been able to inhibit both aggressive and timid activities without affecting locomotion or producing other adverse effects. Consequently, such a potent 'broad-spectrum' non-sedative tranquilizant also remains to be discovered. Ethopharmacology thus opens new vistas and ways in searching for novel calming agents.

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HYPOTHALAMIC RESPONSES IN THE RAT: A MODEL TO STUDY THE PHARMACOLOGY OF OBSESSIVE-COMPULSIVE DISORDERS?

M.R. Kruk, A.M.M. Van Erp, W. Meelis.

Drug treatment of Obsessive-Compulsive Disorders (OCD) is difficult. OCD patients perpetuate certain actions out of context, compulsively, irrespective of consequences. Rappoport (1989) suggested that OCD arises by desinhibition of brain-mechanisms involved in the execution of patterns which can be described in ethological terms such as 'fixed' action patterns. Re-uptake inhibitors potentiating the effects of 5HT are of clinical use in OCD. The brain mechanisms involved in OCD are not fully understood. We suggest that these mechanisms can be studied in the rat.

Specific behavioural responses elicited in specific areas of the hypothalamus can be described as 'action patterns' of a compulsive nature. Hypothalamic responses can be elicited 'out of context'. They are not affected by factors which do affect 'natural' behaviour profoundly. We studied hypothalamic attack, teeth-chattering, and self-grooming.

Most drugs do not affect hypothalamic responses at all, although they do affect comparable 'natural' behaviour profoundly. However, 5HT-re-uptake inhibitors such as Fluvoxamine, and the agonists TFMPP, Fluprazine and Quipazine do suppress hypothalamic responses. By contrast Mianserin, 8OHDPAT and Ipsapiron have no effect. Propranolol has a stereo-specific effect due to its serotonergic properties. Other anxiolytic ß-blockers have no effect. Parallel dose-effect relations of TFMPP, Quipazine, Fluprazine and Propranolol on hypothalamic responses suggest a common mechanism, involving a 5HT-receptor.

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MORPHINE TOLERANCE INDUCED BY DRUG-FREE PROCEDURES: EFFECTS OF EXPERIENCE AND HANDLING ON TIME-EFFECT RELATIONS OF MORPHINE IN THE RAT.

M.R. Kruk, A.M.M. Van Erp, J.H. Van den Bosch, C.J. Visser.

Biologically important stressors may cause analgesia. Chronic stressors may cause cross-tolerance to the analgetic properties of morphinomimetics. Fanselow was one of the first to point out that catching and injecting may emulate predation in a rat, resulting in changed pain perception and sensitivity for analgetics. Such findings do complicate experimental design, but also suggest a way to study mechanisms involved in behavioural pain modulation.

We studied the effects of normal lab procedures such as catching, handling, gentling and i.p. injections of saline on the time/effect relation of Morphine analgesia. Pain sensitivity was measured as the latency to tail-withdrawal from water of 55 °C. Tail withdrawal latency was measured every 10 minutes for 2 hours. Rats subjected daily to this procedure on 5 subsequent days, following a daily injection of 10 mg/kg i.p. Morphine developed tolerance for the analgetic properties of Morphine. Rats injected with saline, did not show a change in pain sensitivity. However, when challenged with 10 mg/kg i.p. Morphine on day six, control group and Morphine treated group were equally tolerant. The effect is caused by an interaction of injection and pain determination procedures, since these effects are absent if rats are subjected to a daily saline injection or daily tail withdrawals only. Procedure-induced 'tolerance-like' effects can also be shown after one single acute pre-injection with saline. Tolerance induced by procedure depends on details in the handling procedure and on the time elapsed between control injection and drug injection, and is rather easy to obtain. Prior Naloxone 0.6 mg/kg i.p. does not reverse these 'tolerance-like' effects.

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THE EFFECTS OF STYRENE EXPOSURE ON NEUROBEHAVIORAL FUNCTIONING IN RELATION TO BRAIN AND BLOOD LEVELS

Beverly M. Kulig

The purpose of the present series of studies was to evaluate the use of behavioral methods in the assessment of the effects of organic solvents using styrene (STY) as a model compound and to examine the body burden and target organ levels at which effects occur.

Acute effects were studied in rats exposed by inhalation to STY at 0, 100, 350 and 1225 ppm for 18 hrs/day and tested for changes in learned performance using discrete-trial discrimination procedures. Results indicated that STY produced changes in response speed at concentrations as low as 100 ppm. As exposure continued, however, the degree of STY-induced deficits particularly in the highest concentration group was significantly attenuated. Toxicokinetic studies indicated parallel reductions in both brain and blood during the 3 day exposure period. Effects of chronic exposure were evaluated in rats similarly exposed for 24 weeks. Animals were tested at predetermined intervals using a battery of tests designed to evaluate changes in spontaneous activity, gripstrength, coordinated movement, peripheral nerve conduction velocity and learned discrimination behavior. Results indicated that STY produced mild changes in motor function during exposure, however, these effects did not persist into the post-exposure period. Effects on learned performance again showed tolerance during the early stages of exposure. As exposure continued beyond 12 weeks, however, the highest concentration group tended to make significantly more short-latency responses. Although the magnitude of this effect was small, it did persist into the post-exposure period and was accompanied by a significant rise in STY brain levels. In conclusion, these experiments demonstrate the utility of behavioral methods in evaluating organic solvent effects and the need for toxicokinetic studies for the purposes of neurotoxicity risk assessment.

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SIMULTANEOUS MEASUREMENT OF CONDITIONING OF APOMORPHINE EFFECTS ON BEHAVIOUR AND ON CORTICAL EEG ACTIVITY IN RATS. K. Kuschinsky, W. Kropf and J. Krieglstein.

In previous studies, it was found that apomorphine-induced stereotyped behaviour can be conditioned when repeatedly paired with CS. Since apomorphine, an agonist at dopamine receptors, produced characteristic alterations in the EEG pattern (as recorded by a telemetric device) with an increase in power in the alpha-1 band (7.00-9.50 Hz), the possible conditioning of this effect was studied as well and correlations with conditioned behavioural effects were evaluated.

Conditioning for seven times with apomorphine (0.5 mg/kg s.c.) led to a significant increase in the number of short-lasting periods with enhancement in the power of the alpha-1 band in the presence of the CS alone when the results obtained from the conditioned group were compared with those of a "pseudoconditioned" group with no positive pairing of apomorphine with the CS.

In addition, extinction experiments were performed in which the CS were repeatedly uncoupled from apomorphine administration. Extinction occurred rapidly, and during the fourth extinction session, the level of conditioned alpha-1 activation had decreased to the level of pseudoconditioned rats.

In general, there was some parallelism between stereotyped behaviour and increase in the alpha-1 band insofar as this EEG alteration was positively correlated with any type of stereotypy observed (sniffing, licking, and gnawing) but could not be correlated with a specific pattern of stereotyped behaviour. This applied both to unconditioned and conditioned responses. The results demonstrated that a characteristic alteration in the EEG pattern produced by apomorphine can be conditioned and is expressed with similar time-courses as the behavioural patterns. Supported by a grant (Ku 395/4-1) of the Deutsche Forschungsgemeinschaft.

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EFFECTS OF GALANIN AND NEUROPEPTIDE Y ON EXTRACELLULAR NOREPINEPHRINE IN THE PARAVENTRICULAR HYPOTHALAMUS: A MICRODIALYSIS STUDY. V.E. Kyrkouli, B.G. Stanley and S.F. Leibowitz.

Galanin (GAL) and neuropetide Y (NPY), neuropeptides which coexist with norepinephrine (NE), specifically stimulate food intake when injected into the paraventricular hypothalamus (PVN) of satiated rats. Evidence suggests that these peptides have different effects on the release of endogenous NE in the PVN.
To test this, GAL (0.3 nmol) or NPY (78 pmol) was injected into the PVN of satiated rats. Using a small, removable microdialysis probe, consecutive samples of dialysate (40 μl/20 min) were collected for 80 min before and 120 min postinjection. Extracellular levels of NE and of the DA and 5-HT metabolites, DOPAC and 5-HIAA, were measured by HPLC-EC. Galanin reliably increased extracellular NE from 3.0 to 7.2 pg ($p<0.01$, by ANOVA). This effect occurred within 20 min after the injection and lasted for about 80 min. There was no change in the other metabolites measured. In contrast to GAL, PVN injection of NPY failed to increase, and actually tended to reduce, local NE levels. Specifically, extracellular NE decreased to approximately 50% of its baseline levels 40 min after PVN injection of NPY. This suppression did not reach statistical significance, although it was observed in 80% of the animals tested. These effects, consistent with evidence from pharmacological brain cannula-mapping and electrolytic lesion studies, suggest the existence of two types of peptide-amine interactions in the PVN. These are: a cooperative interaction, whereby GAL stimulates the release of NE and through this amine regulates feeding; and an antagonistic interaction, whereby NPY and NE may actually suppress each other's action. This and other evidence suggests a physiological function of these substances in the control of natural feeding behavior.
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DOSE-RELATED EFFECTS OF AF64A ON SPONTANEOUS AND LEARNING TASKS IN MICE. Y. Lamberty, A.J. Gower, J. Gobert, I. Hanin and E. Wülfert.

AF64A selectively and irreversibly inhibits high-affinity choline transport and is used as an animal model for Senile Dementia of the Alzheimer type. This study was designed to characterize the effect on spontaneous behaviour and learning of AF64A, 4 to 7 nmoles, injected into the third ventricle of female NMRI mice. The tests, which included motor activity, sensory-motor reflexes, hole board exploration, Y-maze alternation, plus-maze behaviour, spatial learning in a Morris water maze and passive avoidance were completed over a period of 5-6 weeks and the brains then removed for biochemical and histological examination. The results in the learning tasks showed: 1) a place learning deficit in the Morris maze, significant for all days at 5, 6 and 7 nmoles but only on the last day for 4 nmoles; in a quadrant preference test at the end of learning none of the AF64A groups showed any spatial bias; 2) a cue learning deficit at 6 and 7 nmoles; 3) a passive avoidance deficit for all doses. The results of spontaneous behaviour showed: 1) significant dose-related increases in locomotor activity; 2) no effect on sensori-motor reflexes; 3) marked significant dose-related decreases in the number of head dips in the hole board; 4) a significant effect on spontaneous alternation showing a definite rotational tendency and a greater number of arm entries; 5) abnormal plus-maze behaviour with marked preference for open arms. Thus, AF64A not only impairs learning ability in mice but also has marked effects on spontaneous behaviours, some of which could be due to hyperactivity. Histologically, at 6 and 7 nmoles widespread necrosis occurred but at lower doses, the effects were limited to ventricular dilatation.
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EARLY SOCIAL ENVIRONMENT AND BENZODIAZEPINE EFFECTS ON ADULT HOTPLATE RESPONSE, LOCOMOTOR AND EXPLORATORY BEHAVIOUR IN MICE
G. Laviola, G. Loggi and E. Alleva.

There is now substantial evidence for a role of social environment on GABA/benzodiazepine systems functioning. In the present experiment, outbred Swiss CD-1 mouse litters were reduced at birth to six pups, according to three conditions: MM (all males), MF (three males and three females), FF (all females). At weaning (day 21) all mice were housed in groups of six according to sex. When adults (day 70), one mouse from each litter was injected either with saline (0.9% NaCl), or with a benzodiazepine agonist chlordiazepoxide (CDP) at 2.5 or 5.0 mg/kg dose, or with a specific benzodiazepine antagonist RO15-3505 (RO) at 3, 10 or 30 mg/kg dose. Following an adequate test-treatment interval, animals were assessed in sequence for fore-, and hind-paw licking latencies in a hot-plate apparatus (set at 55+1 °C), for locomotor activity in a Varimex apparatus, and finally for latency to approach a novel object. Moreover frequency of contacts to the novel object was scored during a 2-min session. For the latency to forepaw licking, drug effects, and influence of postnatal social environment were limited to the male group (hyperalgesia was observed in MM-males upon 5.0 mg/kg CDP, and analgesia in MF-males following 10 mg/kg RO). For latency to hindpaw licking, drug effects were limited to females. Latencies were significantly shortened in MF-females receiving CDP (5.0 mg/kg), while RO induced a prominent, dose-dependent analgesia in FF-females. Activity levels were decreased at the 2.5 mg/kg CDP dose and enhanced at the 3.0 mg/kg RO dose. For the latency to approach a novel object, a sex difference emerged in baseline levels, since males exhibited shorter times than females. Drug effects and influence of postnatal social environment were limited to the male group. In fact, MF-males receiving either a 5.0 mg/kg CDP dose, or a 3.0 mg/kg RO dose explored more often the object than MM-males. Overall, these results indicate that drugs acting at GABA/benzodiazepine receptor can bi-directionally modulate responses to painful stimulation, locomotor activity levels, or exploratory behaviour. In addition, variations in early social environment can exert long-term effects on drug-induced behavioural changes.

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DOPAMINE AND BEHAVIOUR
M. LE MOAL and H. SIMON

An interesting question is to understand why so many laboratories are still involved in research on dopamine and that 25 years after its discovery in the central nervous system. In parallel it becomes more and more difficult to obtain from thousands of papers a clear perspective about the so-called "functional role" of these neurons which contribute to a unique neuronal system regulating most of the forebrain regions. From many respects physiology is enlightened by anatomical and biochemical considerations. Dopamine neurons project onto thirty regions; these neurons are inter-regulated by many feedbacks so that a given region can control dopamine neurons in another region; liberation and synthesis are finely tuned according to the homeostatic needs; at these levels molecular processes regulate genome synthesis of proteins, enzymes and allow memories; D_1 and D_2 correspond to different ways of communications, cooperate and are modulated by other neurotransmitters. The feature of this neuronal network contradicts the classical parallel-distributed mode of information processing. These neurons do not have function in the proper physiological sense; they enable the regions onto which they project to function; they are in permanent change and allow imbalance between these regions; these adjustments are the biological bases of the behavioural adaptation.

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CAFFEINE AND AUTOMATICITY: EFFECTS ON HUMAN INFORMATION PROCESSING PARADIGMS

W.H. Loke

The present study examined the integration of the automaticity theory and Yerkes-Dodson law using a three-factor design--Automaticity (automatic and nonautomatic behaviors), Drug (caffeine--high arousal and placebo--low arousal), and Task Difficulty (low and high levels of difficulty). A specific significant three-way interaction was predicted; that is, caffeine facilitates low difficulty nonautomatic performance relative to placebo but decreases high difficulty nonautomatic performance relative to placebo, and caffeine does not affect automatic performance across levels of task difficulty relative to placebo.

Two interpretations of the automatic/nonautomatic distinctions were used to select three experimental paradigms, permitting a cross-situational comparison of the predicted Drug X Difficulty X Automaticity interaction. The tasks were consistent mapping (automatic) versus variable mapping (nonautomatic) in a visual search task (Exp. 1), frequency monitoring (automatic) versus free recall (nonautomatic) in a memory task (Exp. 2), and Stroop versus non-Stroop (Exp. 3).

Some of the results of Exp. 2 were consistent with the predicted three-way interaction, but the results of the other experiments were not. The nonsignificant results could be explained as either due to methodological differences in the two tasks or as evidence for more than one form of automaticity. Potential differences in methodology include less extensive practice (than previous studies) and smaller ranges of task difficulty. However, acceptance of the observed different patterns of results in the two paradigms suggests different mechanisms for automaticity and the need for further theoretical analyses.

Thus, the present study supports the proposed integration of the theory of automaticity and the Yerkes-Dodson Law. Equally important, the present study demonstrates the viability of using pharmacological agents to test concepts of automaticity and other mechanisms of information processing.

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STRAIN DIFFERENCES IN THE BEHAVIORAL, ENDOCRINE AND NEUROCHEMICAL RESPONSES TO NOVELTY: WILL THE REAL RAT PLEASE STAND UP! S.A. Lorens, R.J. Handa, N. Hata, T.M. Cabrera, E. Bingaman-Rodriguez, M.K. Cross and M.E. Hamilton.

Young (4-5 mo) Sprague-Dawley (SD) and Fischer 344 (F344) male rats were acclimated (12 h light-dark cycle; lights on at 07:00 h) for 3 weeks. The animals were handled daily for 5-7 days, then were sacrificed (09:00-11:30 h) immediately after being removed from their home cages (HC groups) or 20 min after being placed in a novel open field (OF). HC animals also were sacrificed at 4 h intervals throughout the light-dark cycle. The number of squares entered, rears, and nose pokes emitted by the SD rats were 100+% greater than by the F344 rats. Conversely, the plasma corticosterone (CORT) and prolactin levels in the the F344 OF rats were 50% higher than in the SD OF animals. Differences in basal trough (08:00 h) levels (HC groups) were not observed. The F344 HC rats, however, showed higher (40%) peak (20:00 h) plasma levels of CORT, and 100-400% higher plasma ACTH concentrations throughout the diurnal cycle. The dopamine (DA; 33 and 50%, respectively) and DOPAC (25%) concentrations in the hypothalamus and medial frontal cortex (MFC) were significantly higher in the F344 than in the SD rats. Only the F344 OF rats evidenced a significant increase (81%) in MFC DOPAC content. In contrast, norepinephrine levels in the MFC and amygdala were significantly higher (20 and 33%, respectively) in the SD groups. Differences in regional CNS serotonin levels were not observed. The distinct behavioral responses of the two strains to novelty appear to be related to fundamental differences in CNS monoamine metabolism and neuroendocrine regulation. Will the real rat please stand up!

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FUNCTIONAL CONSEQUENCES OF SELECTIVE CNS SEROTONIN DEPLETION: A COMPARISON OF METHODS. S.A. Lorens, N. Hata, R.J. Handa and T. Cabrera.

5,7-Dihydroxytryptamine (5,7-DHT; 50 or 200 ug icv), d,l-3,4-methylene-deoxymethamphetamine (MDMA; 10 or 40 mg/kg, s.c., b.i.d. x 4 d), and d,l-fenfluramine (FEN; 5 or 20 mg/kg, s.c., b.i.d. x 4 d) selectively and dose-dependently reduce CNS 5-HT and 5-HIAA levels, as well as ^{3}H-paroxetine binding, when measured 2 and 8 weeks post-treatment. These effects are not uniform throughout the CNS, but 5,7-DHT is the most effective. 5-HT neurons recover from the effects of FEN, MDMA and low but not high doses of 5,7-DHT. The rate of recovery differs in distinct CNS regions and varies as a function of drug and dose. The effects of FEN do not appear to be due to the accumulation of "neurotoxic" levels of FEN and/or its metabolites. If this were true then the effects of the 20 mg dose a) should be greater than those of the 5 mg dose, and b) should approach the reductions in 5-HT and 5-HIAA levels and decreases in ^{3}H-paroxetine binding produced by the 200 ug dose of 5,7-DHT. Repeated high doses of MDMA and FEN do not lead to dysfunctions in a) exploratory behavior, b) motor coordination or stamina, c) thermal pain sensitivity, d) morphine analgesia, e) the acquisition of a one- or two-way conditioned avoidance response (CAR), f) extinction processes, or g) spatial memory. 5,7-DHT (200 ug i.c.v.) does not alter the behavioral or corticosterone response to stress (20 min in a novel environment), and does not affect thermal pain sensitivity, CAR acquisition, or spatial memory. Thus, the functional effects of sustained CNS 5-HT depletion depend on the method used to reduce CNS 5-HT levels. Although sensitive to drugs which affect 5-HT synaptic transmission, the CNS can compensate for the loss of 5-HT axons.

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MONOAMINE, ENDOCRINE AND IMMUNE SYSTEM RESPONSES TO STRESS IN YOUNG AND OLD F344 MALE RATS. S.A. Lorens, R.J. Handa, N. Hata, M. Guschwan, L. Van de Kar, J. Goral and J. Clancy, Jr.

Regional forebrain dopamine (DA) but not norepinephrine (NE) or serotonin (5-HT) metabolism is significantly reduced in old non-stressed rats. Conditioned fear (20 min CER paradigm) increased medial frontal cortex, nucleus accumbens and amygdaloid DA turnover in both young (7 mo) and old (22 mo) rats; decreased medial frontal NE content only in young rats; and, increased medial frontal cortical and hypothalamic 5-HT turnover only in old animals. These observations suggest age-related differences in the response of central NE and 5-HT systems to stress.

No age-related differences were observed in basal (morning trough) plasma corticosterone levels. However, the corticosterone response to a) ether stress, b) following 20 min exposure to a novel open field, and c) to conditioned fear was significantly higher in old rats. Hippocampal corticosterone type I but not type II receptors were decreased by 47% in 17.5 mo old rats. Thus, age-related changes in hippocampal corticosterone receptor types do not occur in unison, and the exacerbated corticosterone response to stress precedes the reported down-regulation of hippocampal type II receptors in aged rats.

Immune function was impaired in the old non-stressed rats, and further compromised by exposure to conditioned fear. The old non-stressed rats showed and increased percentage of splenic large granular lymphocytes, reduced splenic natural killer cytotoxicity, and impaired Con-A stimulated splenic T lymphocyte proleferation. Compromised immune function also was observed in the young rats subjected to fear conditioning, but not to the same extent as in the old rats.

Thus, aging male F344 rats evidence major alterations in central monoamine, endocrine and immune functions, and an increased sensitivity of these systems to stress.

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BEHAVIORS MEDIATED BY 5-HT1 RECEPTORS. I. Lucki.

5-HT_1 receptors were defined originally by sites in rat brain labeled by the ligand ^{3}H-5-HT (Peroutka and Snyder, 1979). Subsequently, multiple subtypes of 5-HT_1 receptors were identified in rat brain, termed 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptors. Although these receptors were classified originally using radioligand binding techniques, these receptors are now known to be structurally dissimilar, heterogenously localized in rat brain, and associated with distinct biochemical, electrophysiological, and behavioral responses in rats.

Different types of behavioral studies that distinguish functional effects associated with the stimulation of 5-HT_1 receptor subtypes will be reviewed. First, selective 5-HT agonists elicit different unconditioned behaviors in rats that are associated with different 5-HT_1 receptor subtypes. Second, rats have been trained to discriminate the stimulus properties of selective 5-HT agonists that distinguish among 5-HT_1 receptors using drug discrimination procedures. Third, 5-HT_1-selective agonists produce different effects on conditioned behaviors that are predictive of the actions of classes of psychotherapeutic drugs. These latter effects are important for determining the role of 5-HT_1 receptor subtypes in the behavioral actions of anxiolytic and antidepressant drugs.

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ANTIDEPRESSANT-LIKE EFFECT OF 8-OHDPAT IN MICE
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The 5HT-1A agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OHDPAT) has an antidepressant-like effect of dose-dependently (0.3-10 mg/kg sc; 1h previously) increasing the mobility of male CD1 mice in the Porsolt test (Luscombe et al, Br. J. Pharmac. 95, 784P (1989)), a model of depression.

This response appears to be mediated by 5HT-1A receptors since it was inhibited by oral pretreatment with both the 5HT-1A receptor antagonists spiroxatrine (1 mg/kg) and high dose (±)-pindolol (30 mg/kg), and by the 5HT-1A partial agonists buspirone (30 mg/kg) and gepirone (30 mg/kg). In contrast, the 8-OHDPAT (3 mg/kg)-induced antidepressant-like effect was not inhibited by pharmacologically relevant oral doses of antagonists at other central neurotransmitter receptors: ketanserin (3 mg/kg; 5HT-2 receptor), prazosin (10 mg/kg; α-1 adrenoceptor), idazoxan (30 mg/kg; α-2 adrenoceptor), (±)-pindolol (3 mg/kg; β-adrenoceptor), SCH 23390 (1 mg/kg; dopamine D-1 receptor), (±)-sulpiride (100 mg/kg; dopamine D-2 receptor) and naloxone (30 mg/kg; opiate receptors).

The 5HT-1A receptors involved in the antidepressant-like effect of 8-OHDPAT may have a different neuronal location to the presynaptic 5HT-1A receptors which mediate 8-OHDPAT-induced hypothermia in mice. Thus, once daily pretreatment of mice for 10 days with either 8-OHDPAT (3 mg/kg sc) or tricyclic antidepressants (amitriptyline, 30 mg/kg po; desipramine, 30 mg/kg po; dothiepin, 100 mg/kg po) attenuated the hypothermia but not the antidepressant-like effect of 8-OHDPAT. Lesion studies will help determine if the 5HT-1A receptors involved in the antidepressant-like response of mice to 8-OHDPAT are postsynaptically located.

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ANXIOLYTIC EFFECT OF DOTHIEPIN AND DOXEPIN, BUT NOT OTHER ANTIDEPRESSANTS, IN THE ELEVATED PLUS-MAZE IN RATS
G. P. Luscombe, S. E. Mazurkiewicz and W. R. Buckett

The elevated plus-maze is a model of anxiety able to detect the anxiolytic activity of benzodiazepines. We have evaluated a wide range of tricyclic and atypical anti-depressants in this model, including some which are reported to be of value in treating the symptoms of anxiety in patients suffering from depression with anxiety.

Male Sprague Dawley rats administered vehicle rarely entered the open arms of the elevated plus-maze (accumulated control mean (±SEM) = 0.8 ± 0.1 open arm entries in 10 min). Drugs were administered orally at a minimum of four doses 1h prior to placing in the centre of the maze (n=6 rats/dose). Open arm entries were dose-dependently increased by the benzo-diazepines, chlordiazepoxide (10 mg/kg, 9.2 ± 0.7 open arm entries, $P<0.001$ vs. vehicle) and diazepam (10 mg/kg, 6.2 ± 0.5, $P<0.001$), and the tricyclic antidepressants, dothiepin (10 mg/kg, 6.8 ± 0.5, $P<0.001$) and doxepin (10 mg/kg, 5.2 ± 0.3, $P<0.001$). In contrast, open arm entries were only weakly increased following pretreatment with amitriptyline (30 mg/kg, 2.2 ± 0.4, $P<0.05$) and unaltered by two other tricyclic antidepressants, imipramine (30 mg/kg, 1.0 ± 0.2, NS) and desipramine (10 mg/kg, 1.3 ± 0.2, NS). The monoamine oxidase inhibitor anti-depressant, phenelzine, did not increase open arm entries (30 mg/kg, 0.7 ± 0.2, NS). Atypical antidepressants were also without effect on the number of open arm entries: nomifensine (10 mg/kg, 0.8 ± 0.2, NS), mianserin (30 mg/kg, 1.2 ± 0.3, NS) and trazodone (30 mg/kg, 0.7 ± 0.2, NS).

The anxiolytic activity of dothiepin and doxepin in the elevated plus-maze supports their reported clinical efficacy in alleviating anxiety in anxious-depressed patients.

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BEHAVIOURAL EFFECTS OF LEVOPROTILIN GIVEN REPEATEDLY IN RATS
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Levoprotiline, (-)-enantiomer of oxaprotiline, devoid of an inhibitory activity on NA uptake, has a potent clinical antidepressant action. In this study the behavioural effects of levoproti-line given repeatedly (14 or 28 days, twice daily) in Wistar rats were examined. For comparison (+)-oxaprotiline inhibiting the NA uptake was studied.

Repeated treatment with levoprotiline increased the locomotor activity and the exploratory behav-iour (open field-test). The immobility time in behavioural despair test was reduced. Levoproti-line increased the locomotor hyperactivity in-duced by d-amphetamine and the stereotypy induced by d-amphetamine or apomorphine. Similar effects (but weaker in some tests) were observed in rats treated repeatedly with (+)-oxaprotiline.

Similarities and differences between levoproti-line and other antidepressants will be discussed.

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ANIMAL MODEL OF COCAINE WITHDRAWAL: POST-COCAINE ANHEDONIA AND ITS REVERSAL BY BROMOCRIPTINE

A. Markou and G.F. Koob

Cocaine use frequently occurs in episodic, prolonged binges. Following such a cocaine binge, the user suffers from depressive symptoms, mixed with irritability, anergia and anhedonia ("crash", cocaine withdrawal). The present studies represent an attempt to develop an animal model of post-cocaine anhedonia, a major symptom of cocaine withdrawal in humans. Male Wistar rats were prepared with lateral hypothalamic electrodes and jugular catheters. Following prolonged periods (3, 6, 12, 24, and 48 hr) of cocaine self-administration, self-stimulation current-thresholds were determined. Validation studies indicated that changes in thresholds reflect a change in the sensitivity to the stimulation (reward effect) and not a performance effect. Thus, self-stimulation thresholds appear to measure an animal's "hedonic-anhedonic" state. Following the termination of cocaine self-administration, animals had elevated thresholds, reflecting an "anhedonic" state. The magnitude and the duration of these elevations were functions of the dose self-administered. A separate group of rats self-administered cocaine continuously for 24 hr. Four hr post-cocaine, rats were injected with 0, 1, 2 or 4 mg/kg bromocriptine, a dopamine agonist. Two hr later, self-stimulation thresholds were assessed. Bromocriptine reversed the post-cocaine anhedonia in a dose-related manner without affecting controls. These studies indicate that a post-cocaine elevation in reward thresholds (anhedonia, a symptom of cocaine withdrawal), can be measured reliably in rats. Furthermore, the results indicate that bromocriptine-like drugs may be able to ameliorate some of the effects of cocaine withdrawal on mood and motivational state; and that this animal model of cocaine withdrawal could be useful in the discovery and development of new pharmacological treatments for cocaine withdrawal.

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A DISSOCIATION OF THE ROLES OF THE CINGULATE CORTEX AND HIPPOCAMPUS IN THE ACQUISITION OF A CONDITIONAL RULE.

H.M. Marston, T.W. Robbins, B.J. Everitt and C.N. Ryan.

The effects of (i) excitotoxic lesions of the septal region, which would be expected to destroy the cholinergic septo-cortical projections, (ii) excitotoxic lesions of the hippocampal formation and (iii) an aspirative lesion to the cingulate cortex, on the rate of acquisition of a conditional visual discrimination, were compared.

Septal lesions were made by infusing either 0.5 ul quisqualic acid (0.12 M) or vehicle at four sites bilaterally. Hippocampal lesions were made by infusing ibotenic acid (0.06 M) at 11 sites bilaterally. Aspirations were made to the cingulate cortex 1 mm anterior to bregma extending rostrally to the frontal pole and 1 mm laterally from the midline.

Post mortem biochemical analysis revealed that the consequence of lesions to the septum were of three types; those with reductions in the level of choline acetyltransferase (ChAT) primarily in the cingulate cortex (S-C group; 58% Cing, 18% Hipp), those where the reductions were primarily in the hippocampus (S-H; 23% C, 55% H) and those which sustained major reductions in both structures (S-CH; 47% C, 60% H). Histological examination of the hippocampal ibotenate group revealed extensive damage in the intended regions, with the exception of some cells in the dentate gyrus. The aspirative lesions of the cingulate cortex successfully avoided damage to the corpus callosum with only limited damage to adjacent cortical regions.

The behavioural paradigm involved a discrimination between fast and slow flashing lights. Following presentation of the discriminative stimulus two levers were introduced into the operant chamber. A response had then to be made either to the left or right, depending upon the frequency of the stimulus. The animals with hippocampal lesions showed no difference in the ability to acquire the task when compared with controls. The S-H group also demonstrated normal learning. In contrast, the S-C and S-CH groups were significantly impaired in the acquisition of the task. Animals with cingulate ablations were also impaired in acquiring the task.

The results suggest that the cingulate cortex rather than the hippocampal formation in the rat plays a major role in the acquisition of conditional rules. Furthermore, the cholinergic projection from the septal region to the cingulate cortex may be required for optimal performance of this function.

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THE EFFECTS OF BUSPIRONE, GEPIRONE, IPSAPIRONE AND THEIR COMMON METABOLITE 1-PP IN THE LEARNED HELPLESSNESS PARADIGM

P. Martin and A.J. Puech

The 5-HT1A agonists, buspirone, gepirone and ipsapirone, have been shown to possess antidepressive-like properties in several animal models of depression including the learned helplessness paradigm (LH) as well as in clinical studies.
These compounds are rapidly and extensively metabolized to 1-PP in rat and man and can be detected in the brain after the administration of these 5-HT1A agonists. Whether 1-PP might affect the action of the parent substances needs to be determined. In the LH, these 5-HT1A agonists exhibit a biphasic action: at low doses they show an antidepressant-like effect but this action is progressively reversed as the doses are increased. In order to establish whether 1-PP affects the reversal of helpless behavior induced by the 5-HT1A agonists at higher doses in rats, we have investigated its role in the LH. Thus, 1-PP has been evaluated alone (0.06 to 4 mg/kg/day) or in combination with 8-OH-DPAT (0.06 and 0,25 mg/kg/day), a selective 5-HT1A agonist which is not metabolized to 1-PP. In addition, buspirone, gepirone and ipsapirone, at higher doses have also been examined in the presence of proadifen (50 mg/kg/day) which inhibits oxidative metabolism. Drugs were injected ip each day, i.e., 6h after inescapable shocks on day 1 and then twice a day in the morning and at 18h-19h. On days 3, 4 and 5, the number of escape failures for the rats was recorded in a shuttle-box avoidance task.
Our results show that: i) daily injections of 1-PP did not reverse helpless behavior; ii) the reversal of helpless behavior by 8-OH-DPAT was antagonized by daily co-administration of 1-PP (0.5 mg/kg); iii) in rats pretreated by proadifen, the highest doses of the three 5-HT1A agonists do induce a reversal of helpless behavior.
These results strongly suggest that up to a certain concentration 1-PP can impair the effects of the parent compounds buspirone, gepirone and ipsapirone in the LH.

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MK-801 EXERTS BENZODIAZEPINE-LIKE EFFECTS IN A SITUATION OF SUPPRESSED AGGRESSIVENESS IN MALE MICE

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MK-801, an antagonist of the NMDA receptor -associated ion channel has been attributed with behavioural effects similar to those of benzodiazepines i.e. the compound exerts anxiolytic effects. The present experiment compared the effects of MK-801 and chlordiazepoxide upon the behaviour of aggressive male mice in a situation which suppresses aggressive and social behaviour. It would be expected that both compounds would increase aggressiveness and social behaviour and at the same time reduce those activities consistent with approach-avoidance. Male OF-1 mice were paired with females for four weeks. After a series of habituation trials the male mice were given chlordiazepoxide (0.0-30.0mg/kg) or MK-801 (0.0 -0.3mg/kg) in a randomised order i.p. 30 mins prior to pairing with an unfamiliar group housed male in a neutral environment. The time spent in, and the frequency of occurrence of the following behavioural categories were measured: Nonsocial, Social, Sexual, Offence, Offensive Ambivalence, Distance Ambivalence, Defensive Ambivalence, Freeze and Escape. Both chlordiazepoxide and MK-801 enhanced aggressiveness (Offence, Offensive Ambivalence) and decreased approach-avoidance activity (Distance Ambivalence). Chlordiazepoxide increased Social and Sexual behaviour at the highest dose. The highest dose of MK-801 however reduced Offence, Offensive Ambivalence and Distance Ambivalence, and resulted in stereotypy and ataxia. These data would support the conclusions of previous studies that MK-801 may exert benzodiazepine-like effects.

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RITANSERIN IN STATES OF ADDICTION: A PHARMACOLOGICAL APPROACH

T.F. Meert and P.A.J. Janssen

Ritanserin is a potent serotonin 5-HT2 receptor antagonist with slow wave sleep increasing effects. Clinically, ritanserin is characterized as a thymosthenic with energy enhancing and mood regulatory properties. These clinical properties result in a better coping with daily live and may support subjects withdrawing from drugs of abuse.
By itself, ritanserin lacks any abuse potential. The drug possesses no cueing properties in the drug discrimination test procedure in rats and does not interact with the stimulus properties of d-amphetamine, cocaine, opiates, alcohol and benzodiazepines. However, in rats given the free choice between 3 % alcohol and water, after a week of alcohol drinking and a week of alcohol withdrawal, ritanserin produced a dose-related reduction of alcohol intake and alcohol preference without affecting total fluid consumption. Significant daily reductions were present from a dose of ≥ 0.63 mg/kg, given subcutaneously once a day. At 10.0 mg/kg ritanserin, a nearly 50 % reduction in alcohol consumption was measured. Functionally, ritanserin virtually abolished the alcohol preference shown by the control rats. Furthermore, experiments using 0.1 mg/ml cocaine instead of alcohol, revealed that ritanserin also reduced cocaine intake and cocaine preference. At 10 mg/kg ritanserin, cocaine intake was reduced by 30 %. Also here, the reduction in cocaine drinking was accompanied by an increase in water intake.
These results on alcohol and cocaine, two drugs of abuse with a different mechanism of action, indicate that the 5-HT2 antagonist ritanserin affects addiction by a general mechanism of action, probably related to its thymosthenic properties.

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CLINICAL APPLICATIONS OF EXCITATORY AMINO ACID ANTAGONISTS. B.S. Meldrum and A.G. Chapman.

Animal studies have emphasized two major areas of potential clinical application for excitatory amino acid antagonists, namely epilepsy and cerebroprotection against acute stress such as cerebral ischaemia and trauma. However the possibility of other applications (anxiety, spasticity, schizophrenia) should not be neglected.

In epilepsy the best prospect lies with competitive NMDA antagonists which have been shown to be potent anticonvulsants in a wide range of animal models. Prolonged oral activity has recently been demonstrated in rodent and primate models for two unsaturated analogues of 2-amino-5-phosphonovalerate (CGS 37849, CGS 39551) and for CPP and its unsaturated analogue CPPene. NMDA antagonists acting at the glycine site possess anticonvulsant properties but compounds with appropriate pharmacokinetics have not yet been identified.

Marked cerebroprotection has been demonstrated with NMDA receptor antagonists (of all types) in focal cerebral ischaemia (MCA occlusion in rodents and cats). Protection is also seen in neonatal hypoxia/ischaemia in the rat, and in some models of cerebral trauma. Problems in designing appropriate clinical trials concern the behavioural and other side effects of NMDA antagonists and the duration of the therapeutic time window.

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5-HT RECEPTOR AGONISTS, ANTAGONISTS AND SUBTYPES

D.N. Middlemiss and M.D. Tricklebank

The classification of 5-HT receptors into three main subtypes, 5-HT_1-like, 5-HT_2 and 5-HT_3 by Bradley et al., in 1986 has formed the framework for the understanding of the actions of a number of selective agonists and antagonists at these sites. However, a more complex view of 5-HT receptor subtypes is now emerging with 5 subtypes of 5-HT_1-like, 2 of 5-HT_2, 3 of 5-HT_3 and recently a new subclass, 5-HT_4, postulated.

Several 5-HT receptor subtypes are linked either positively or negatively to the adenylate cyclase (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and 5-HT_4), or phosphatidylinositol (5-HT_{1C}, 5-HT_2) second messenger systems, whereas the 5-HT_3 receptor subclass is thought to be associated with an ion gated channel. Radioligand binding studies have shown a differential distribution of these sites in the CNS with the highest density of receptors in the hippocampus (5-HT_{1A}), substantia nigra (5-HT_{1B}, 5-HT_{1D}), choroid plexus (5-HT_{1C}), cortex (5-HT_2), entorinal cortex (5-HT_3) and superior colliculi (5-HT_4). Definitive evidence for three 5-HT receptor subtypes, 5-HT_{1A}, 5-HT_{1C} and 5-HT_2, has been provided by receptor cloning techniques. Considerable effort is currently being devoted to the development of "subtype-selective" agonists and antagonists. Selective 5-HT receptor agonists have been defined for the 5-HT_{1A} (eg 8-OH-DPAT, ipsapirone), 5-HT_{1C} (MCPP), 5-HT_{1D} (sumatriptan), 5-HT_2 (DOI) and 5-HT_3 (m-chloro-phenylbiguanide) subclasses. Selective antagonists have been identified for the 5-HT_2 (ketanserin) and 5-HT_3 (MDL 72222, ICS 205-930, ondansetron) subtypes although 5-HT_1-like receptors can be blocked by methiothepin and certain β-adrenoceptor antagonists (eg propranolol, pindolol). The affinity, selectivity and potency in vivo of these 5-HT receptor tools will be reviewed.

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ATTENUATION OF NICOTINE INDUCED CONDITIONED TASTE AVERSIONS BY GR38032F

E.A. Mitchell and J.A.Pratt

Conditioned taste aversions (CTA) to some psychotropic drugs can be attenuated by lesions of the area postrema; an area rich in 5-HT_3 receptors (G. J. Kilpatrick et al, Br J Pharmac 95:871P, 1988). Since nicotine can produce strong CTA in rats (R. Kumar et al, Br J Pharmac 79: 245-253, 1983), the aim of this study was to investigate whether the 5-HT_3 antagonist GR38032F could block nicotine induced CTA.

CTA responses to nicotine (0.1 & 0.4mg/kg sc) and GR38032F (0.001-0.1mg/kg ip) were investigated in male Sprague Dawley rats (n=8/group) using a 2-trial conditioning procedure. Rats were presented with either a sodium saccharin (0.1%) or a sodium chloride solution (0.9%) for 15 min and immediately afterwards injected with drug or saline. The subsequent simultaneous presentation of the drug- and the vehicle-paired flavours provided the main measure of CTA. This was defined as when the intake of drug-associated flavour, calculated as a percentage of total fluid intake, was significantly below 50%. In a further set of experiments, the putative blocking drug GR38032F (0.001-0.1mg/kg ip) was administered 45mins prior to the nicotine injection in the conditioning trials. Following treatment with nicotine (0.1 & 0.4mg/kg) the percentage fluid intakes associated with the nicotine-paired flavour were 31.2 ± 3.8% and 31.7 ± 3.6% respectively ($p<0.01$ vs 50%). For example, mean intakes of nicotine (0.1 mg/kg)- and vehicle-paired flavoured solutions were 4.5 ± 0.9ml and 11.4 ± 1.1ml respectively. Conversely, GR38032F did not produce CTA. Pretreatment with GR38032F (0.001-0.1mg/kg) attenuated the CTA to 0.01mg/kg nicotine (mean % fluid intakes; 36.9 ± 5.8%, 36.3 ± 3.4% and 39.0 ± 5.8% respectively). Similarly the CTA to 0.4mg/kg nicotine was attenuated by 0.1mg/kg GR38032F. Thus GR38032F appears to attenuate nicotine induced CTA but not in a dose dependent manner.

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REPEATED ACQUISITION PROCEDURES.

J.M. Moerschbaecher.

It has been 27 years since Boren first described repeated acquisition as a technique to study drug effects on learning. Since that time this technique has been widely used in the characterization of drug effects on the acquisition, performance, and the retention of discriminations in both animals and man. It has been demonstrated that procedures using this technique are exquisitely sensitive to drug effects on behavior in several ways. First, selective drug effects on rate versus accuracy of responding have been demonstrated using these procedures. For example, phencyclidine has been shown to disrupt accuracy of responding at doses which have no effect on response rate. Secondly, differential drug effects on the acquisition versus the performance of a discrimination have been repeatedly demonstrated. In these studies it has generally been found that learning is affected at lower doses than those which are required to effect performance. Thirdly, these procedures have revealed that acquisition and performance are differentially sensitive to various drug classes. For example, differences exist in terms of the effects of various opioid agonists on learning. It has also been shown that such differential effects may not be attributed to other intervening variables, such as the anorectic effects of a drug. Another compelling advantage of the repeated acquisition technique is that it is easily modified in order to compare the effects of a drug among species. More recently, the technique has been modified to study drug effects on retention. A requirement basic to demonstrating a drug effect on memory is that the drug acts in a delay-dependent manner. Both delay- and dose-dependent effects on retention have been demonstrated using the technique of repeated acquisition. In summary, using this technique it has been demonstrated that inherent differences exist among various classes of drugs in terms of their effects on complex behavioral processes.

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THE 5-HT SYNDROME AND HYPOTHERMIA INDUCED BY FLESINOXAN, A 5-HT$_{1A}$ AGONIST, COMPARED TO 8-OH-DPAT, BUSPIRONE AND IPSAPIRONE IN THE RAT.

H.E.Molewijk, J.A.M.van der Heyden, B.Olivier.

Activation of central 5-HT receptors is known to induce a so-called 5-HT syndrome. Furthermore, activation of 5-HT$_{1A}$ receptors is associated with lower lip retraction and hypothermia. The effects of flesinoxan on these measures were compared to those of the 5-HT$_{1A}$ agonist 8-OH-DPAT and the partial 5-HT$_{1A}$ agonists buspirone and ipsapirone.

At 15, 30, 45 and 60 minutes after sc injection of drugs or saline to male Wistar rats, the behaviour was observed. Rectal temperature was measured after the last observation. Flesinoxan (1-3-10 mg/kg), 8-OH-DPAT (0.1-0.3-1 mg/kg), buspirone (1-3-10 mg/kg) and ipsapirone (1-3-10 mg/kg) were dissolved in saline.

Like 8-OH-DPAT, flesinoxan produced a 5-HT syndrome consisting of lower lip retraction, flat body posture, hindlimb abduction, spreadpaws, arched back, forepaw treading and headweaving at all doses tested. Flesinoxan was about 10-fold weaker in generating these behaviours and hypothermia than 8-OH-DPAT.

Buspirone and ipsapirone only produced part of the 5-HT syndrome elicited by flesinoxan and 8-OH-DPAT. Although they elicited lower lip retraction, flat body posture, spreadpaws and arched back, they did not induce hindlimb abduction, forepaw treading or head weaving. Hypothermia induced by buspirone and ipsapirone occurred at higher doses and was less intense compared to flesinoxan and 8-OH-DPAT. No wet dog shakes were observed after these four drugs, indicating the absence of 5-HT$_2$ agonism.

In conclusion, flesinoxan behaves as an in vivo functional 5-HT$_{1A}$ agonist comparable to 8-OH-DPAT. For most behavioural items and hypothermia flesinoxan is more potent than the partial 5-HT$_{1A}$ agonists buspirone and ipsapirone.

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THE PROTECTIVE EFFECT OF DOPAMINE AGONISTS ON EEDQ-INDUCED INHIBITION OF APOMORPHINE-INDUCED CLIMBING BEHAVIOUR IN MICE.

N.A. Moore, G. Rees, S.R. Howarth

The peptide coupling agent N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) can produce an irreversible inactivation of both D-1 and D-2 dopamine receptors and it has previously been shown that pretreatment with selective dopamine agonists and antagonists will prevent this inactivation. In the present study we have looked at the ability of a number of dopamine agonists to prevent the inhibition of apomorphine-induced climbing behaviour following EEDQ treatment. Female albino TO mice (20-25g) were used in all the studies. The mice were pretreated with either vehicle or various dopamine agonists 15 min prior to the EEDQ (10mg/kg i.p.) treatment. Twenty four hours later the animals received apomorphine (2.5mg/kg s.c.) and climbing behaviour was assessed by placing the animals in cylindrical wire mesh cages and counting the number of paws the animals had on the bars at 5min intervals for up to 1hr.

In vehicle treated animals EEDQ treatment totally abolished the climbing response produced by apomorphine 24 hrs later. The mixed D1/D2 agonist, apomorphine (0.625-10mg/kg) prevented the EEDQ-induced inhibition of the climbing behaviour. The selective D1 agonist, SKF38393 or the selective D2 agonist, quinpirole when administered alone had very little effect on EEDQ-induced inhibition of climbing; however, when administered together a combination of SKF38393 and quinpirole partially prevented the inhibition of climbing produced by EEDQ. Bromocriptine (10 - 40mg/kg), and lisuride (1.25-10mg/kg) had no effect on the inhibition of the response, whereas pergolide (1.25 - 10 mg/kg) pretreatment prevented the EEDQ-induced disruption of the climbing response. This data would, therefore, suggest that unlike bromocriptine and lisuride, pergolide interacts with both D-1 and D-2 receptors.

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INACTIVATION OF D-1 AND D-2 DOPAMINE RECEPTORS DISRUPTS APOMORPHINE-INDUCED CAGE CLIMBING AND HYPOTHERMIA: SELECTIVE PROTECTION BY SCH23390 AND CLEBOPRIDE.

N.A. Moore, M.S. Axton, and S.R. Howarth

A number of groups have shown that the peptide coupling agent N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) can produce an irreversible inactivation of both D1 and D2 dopamine receptors (Meller etal, in: Central D1 dopamine receptors, Plenum Press, 1988). In the present study we have looked at the effect of EEDQ on apomorphine-induced cage climbing and hypothermia in mice. Female albino TO mice (20-25g) were used in all the studies. At various intervals after EEDQ treatment animals received apomorphine and climbing behaviour was assessed by placing the animals in cylindrical wire mesh cages and counting the number of paws the animals had on the bars at 5 min intervals for up to 1hr. Body temperature was measured immediately prior to and 30 min after apomorphine administration.

EEDQ (10mg/kg) totally abolished the climbing response and hypothermia produced by apomorphine (0.625 - 10 mg/kg i.p.) 24 hrs after the EEDQ treatment. The disruption of the climbing response and hypothermia lasted for up to 48 hrs; after this time the responses gradually returned. Pretreatment with the selective D1 antagonist, SCH23390 (2mg/kg), 15 min prior to the EEDQ administration had no effect on either the inhibition of apomorphine-induced climbing or hypothermia measured 24hrs after the EEDQ. The selective D2 antagonist, clebopride (20mg/kg) partially reversed the inhibition of the hypothermic response and climbing behaviour. Concomitant administration of SCH23390 (2mg/kg) and clebopride (20mg/kg) partially protected the hypothermic response and totally restored the climbing behaviour. These results demonstrate that both D-1 and D-2 receptor protection is necessary to restore climbing behaviour, whereas only D-2 receptor protection is necessary to prevent the disruption of apomorphine-induced hypothermia.

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THE EFFECTS OF SCOPOLAMINE ON ACQUISITION AND REVERSAL LEARNING IN A CIRCULAR SPATIAL MAZE TASK.

Paula Moran

The exact nature of scopolamine effects on spatial learning and memory in rodents has not been agreed upon. Divergent results may be attributable to different motivational and motor requirements of the paradigms used. The following experiments assess the effect of scopolamine treatment in a spatial learning task adapted from Barnes (J Comp Physiol Psychol 1: 74, 1979).

In this task the animal is required to escape from a test platform (diameter 1.2 m) to a darkened box hidden under one of 18 holes (10 cm diameter) around the perimeter of the apparatus. In the first experiment, male Sprague-Dawley rats were treated with scopolamine HBr (0.3 mg/kg SC) prior to six acquisition trials. Dependent variables included numbers of errors (visits to non-goal holes), frequency of errors per position, and latency to find the goal box. In the second experiment animals were pretrained on the task and administered scopolamine prior to a 'reversal' trial where the goal box location was changed. Subsequent trials involved learning the new goal box location.

Control animals rapidly learned to locate the hidden goal box over 6 trials. Scopolamine treatment initially increased both error number and latency over these trials, but by trial 6 scopolamine treated rats performed at control levels. In the second experiment, relocation of the goal box induced a significant increase in error number, with a rapid decrease to prereversal levels on subsequent trials. Scopolamine treated animals made significantly more errors than controls during the initial trials of the 'reversal' experiment. However, by the fourth relearning trial they performed similarly to controls. Analysis of errors in both experiments suggests that the increases in error number in scopolamine treated animals can be accounted for by perseveration of 1) the initial choice in the acquisition phase and 2) the previously correct response in the relearning phase.

This task may be considered to be spatially analogous to the Morris water maze in its design, but without the high level of stress induced by water submersion and swimming, and similar to the radial arm maze in its motoric requirements without the necessity for food deprivation. These results suggest that it may be of use in the evaluation of drug effects on spatial memory without the possible confounding effects of food deprivation and swim stress.

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NOVEL LONG-ACTING BENZODIAZEPINE RECEPTOR LIGANDS WITH POTENTIAL VALUE FOR THE TREATMENT OF EPILEPSY

J.-L. Moreau, E.P. Bonetti, W. Hunkeler, F. Jenck, J.R. Martin and W.E. Haefely

In the search for anticonvulsants virtually devoid of the side-effects of classical benzodiazepines (motor impairment, sedation, tolerance, physical dependence), two long-acting novel benzodiazepine receptor ligands have been identified. These compounds, Ro 41-7812 and Ro 42-8773, were totally devoid of proconvulsant activity in pentylenetetrazole (PTZ) and audiogenic seizures (AS) tests in mice and rats. In squirrel monkeys, both compounds were devoid of any appreciable sedative or motor impairing effects up to a dose of at least 200 mg/kg p.o. In mice and rats, impairment of horizontal wire test or rotarod performance was not detectable up to 100 mg/kg p.o. In fact, both compounds potently antagonized flunitrazepam-induced sleep in monkeys and diazepam- or meclonazepam-induced motor impairment in mice and rats. Ro 41-7812 was devoid of anticonvulsant activity against PTZ- or maximal electroshock (MES)-induced seizures but exhibited partial prevention of AS and NMDA-induced convulsions. Ro 42-8773 exhibited slight anticonvulsant activity against PTZ- or MES-induced convulsions and completely suppressed AS and NMDA-induced convulsions. Thus, despite a predominantly antagonist pharmacological profile, these two benzodiazepine receptor ligands nonetheless possess weak intrinsic activity which seems to be sufficient for clear anticonvulsant activity. Given such a profile, such compounds might prove of value in the treatment of epilepsies.

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Spatial learning and memory: methods, scope and limitations.

R.G.M.Morris

Given the need to move around to find food or escape from prey, it is not surprising that evolution should have led to the development of various ways in which animals can learn about their spatial environment and navigate accurately through it. Whether certain types of spatial learning, particularly allocentric spatial mapping in mammalian species, entails different psychological processes from other kinds of learning remains unclear. It is, however, a sophisticated type of memory well suited to neuropsychological and pharmacological analysis.

Traditionally, laboratory studies have used mazes in which the imposition of "detours" or other manipulations can be used to unravel the manner in which environmental information is represented. For example, Olton and Samuelson's (1976) radial-maze has been used very effectively to investigate short-term aspects of spatial memory. However, the open-field watermaze (Morris, 1981) offers certain advantages over traditional techniques: (a) learning can be very rapid (eg 1 trial); (b) the animals do not need to be deprived of food or water to be motivated to learn; (c) the motor-generators for swimming are in the brainstem and thus relatively unaffected by either brain lesions to higher structures or many classes of drugs; and (d) there are no walls within the apparatus "imposing" particular directed movements upon the animals. Furthermore, a wide range of behavioural procedures can be conducted in the one piece of apparatus in order to unravel potentially dissociable components of spatial memory.

This talk, together with a short video presentation, will illustrate these aspects of watermaze methodology with reference to relevant published work from my own and others' laboratories. Examples will be given of work on the effects of hippocampal formation lesions and selective blockade of NMDA receptors. Image-analysis and computing equipment, and professional software for obtaining objective information about performance (eg latency, distance, directionality, and other published analysis functions etc.) will be illustrated and displayed at the meeting.

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SEROTONIN, SEX AND AGGRESSION IN MALE RATS.

J.Mos, B.Olivier.

Modulation of serotonergic neurotransmission may have profound behavioural consequences. Serotonin is involved in many different behaviours like feeding, sleep, anxiety, aggression and sexual behaviour. The latter two behaviours were studied in male rats and the effects of various serotonergic compounds were recorded using ethopharmacological tools.

5-HT_{1a} agonists like 8-OH-DPAT, buspirone and ipsapirone non-specifically decrease aggression in various animal models, but facilitate sexual performance as measured by decreased ejaculation latencies. Mixed $5\text{-HT}_{1a/b}$ agonists like eltoprazine and RU24969 and the more specific 5-HT_{1b} agonist TFMPP reduce aggression specifically, but inhibit sexual performance. Quipazine, a non-selective $5\text{-HT}_{1/2}$ agonist and 5-HT_3 antagonist, reduces aggression non-specifically and also inhibits sexual behaviour. The 5-HT reuptake blocker fluvoxamine had no effect on sexual behaviour, but reduced aggression in a non-specific way.

In general, all serotonergic agonists (direct or indirect) reduced aggression, albeit qualitatively different. Mixed effects, varying from inhibition to facilitation, were observed when these drugs were tested in similar dose ranges in sexual behaviour. The results suggest that different sites of actions may underly this discrepancy and that broad concepts like general inhibition by 5-HT are not useful for the study of brain-behaviour relationships.

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EFFECT OF METHOCTRAMINE AND HIMBACINE ON PILOCARPINE-INDUCED CHEWING AND PHYSOSTIGMINE-INDUCED YAWNING

P.C. Moser

Himbacine and methoctramine are two of the most selective muscarinic M2 receptor antagonists currently available. This abstract describes the effects of these two compounds on pilocarpine-induced purposeless chewing and physostigmine-induced yawning.

Chewing and yawning behaviours were induced in male Sprague-Dawley rats with pilocarpine (1 mg/kg SC) and physostigmine (0.1 mg/kg SC) respectively. Purposeless chews were counted between 10 and 15 min post pilocarpine. Yawns were counted between 0 and 30 min after physostigmine.

Methoctramine inhibited chewing over the range 0.03 - 0.3 mg/kg SC (56% maximum inhibition; $P < 0.02$) but higher doses were less effective. Methoctramine also inhibited yawning, but higher doses were required than against chewing (1, 3 and 10 mg/kg SC; 15, 82 and 100% inhibition respectively). Lower doses (0.1 and 0.3 mg/kg) had no significant effects. Methoctramine ICV (30 µg) also significantly inhibited chewing (60%, $P < 0.02$). In contrast to methoctramine, himbacine (0.1 - 3 mg/kg SC) dose-dependently potentiated yawning behaviour (saline 9.1 ± 1.0 yawns, himbacine (3 mg/kg SC) 24.3 ± 3.1, $P < 0.01$; all values mean ± SEM). Himbacine (3 mg/kg SC) alone induced only a low incidence of yawning. Purposeless chewing was unaffected by himbacine (0.3 - 300 µg ICV).

The inhibition of chewing by methoctramine supports the suggestion that it is mediated by the M2 receptor (Stewart et al, Psychopharmacology 97: 228, 1989) although the inability of himbacine to inhibit chewing suggests otherwise. The potentiation of physostigmine-induced yawning by himbacine is probably due to inhibition of the cholinergic autoreceptor, which is of the M2 (cardiac) subtype (Richards, Br J Pharmacol, *in press*). The inability of methoctramine to potentiate yawning may reflect its insufficient selectivity between the autoreceptor and the receptor mediating yawning.

The very different profiles of the two compounds in these tests suggests that they do not act at the same site and that the autoreceptor and the postsynaptic receptor mediating chewing behaviour are not the same, despite the current classification suggesting both are of the M2 subtype.

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GENERALISATION OF L-DEPRENYL, BUT NOT MDL 72974, TO THE D-AMPHETAMINE STIMULUS IN RATS

P.C. Moser

Previous data suggests that many of the pharmacological properties of L-deprenyl, a selective MAO-B inhibitor, result from its metabolism to L-amphetamine and methamphetamine (Fozard et al, N S Arch Pharmacol 331: 186, 1985). These effects included sympathomimetic activity in the pithed rat and drug induced rotation in unilaterally 6-hydroxydopamine lesioned rats. The present experiments were carried out to examine the effects of L-deprenyl in rats trained to discriminate D-amphetamine from saline. Also tested was MDL 72974, a selective MAO-B inhibitor lacking the sympathomimetic activity of L-deprenyl (Zreika et al, J Neural Transm [P-D sect] 1: 243, 1989).

Male Sprague-Dawley rats were trained to discriminate D-amphetamine sulphate (0.8 mg/kg IP) from saline using standard operant techniques, as previously described (Bourson et al, Br J Pharmacol 98: 1312, 1989).

L-deprenyl (1 - 10 mg/kg IP) dose-dependently and completely generalised to the amphetamine stimulus. At 3 and 10 mg/kg 88% of the rats that responded (7/8 in each case) did so on the amphetamine lever although there was some reduction in response rate at these doses (amphetamine: 30.7 ± 4.4 presses/min, mean ± SE, $n = 6$; L-deprenyl 3 mg/kg: 20.1 ± 2.3, $P < 0.05$ Student's t-test; 10 mg/g: 15.2 ± 1.1, $P < 0.01$). In contrast, MDL 72974 (3 and 10 mg/kg IP) showed no generalisation to amphetamine (0/5 and 1/5 respectively), although it reduced response rate at 10 mg/kg (amphetamine: 24.1 ± 1.9, $n = 5$; MDL 72974: 6.5 ± 1.7, $P < 0.001$).

The lack of generalisation of MDL 72974 to the amphetamine stimulus, at a dose substantially above that required to maximally inhibit MAO-B (Zreika et al, as above), demonstrates that MAO-B inhibition is not responsible for the generalisation of L-deprenyl to amphetamine. These results therefore show that the formation of L-amphetamine from L-deprenyl can reproduce the subjective effects of amphetamine in rats at a dose of L-deprenyl widely used for selective MAO-B inhibiton. MDL 72974 may consequently have certain advantages over L-deprenyl. However, in the context of the applicability of the amphetamine stimulus to the study of drug abuse in humans it is interesting to note that L-deprenyl is reported not to have amphetamine-like effects in man (eg Birkmayer et al, Clin Neuropharmacol 5: 195, 1982).

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DIFFERENCES IN THE MECHANISM OF β-ADRENOCEPTOR DOWNREGULATION BROUGHT ABOUT BY IMIPRAMINE AND ECT: POSSIBLE ROLE FOR INTERACTION WITH PROTEIN KINASE C. I. Nalepa and J. Vetulani

To find out how kinase C is involved in β-downregulation (β-DR), we investigated how chronic imipramine (IMI) and ECT affect cyclic AMP (cAMP) responses in rat cortical slices to stimulation with forskolin (FOR), isoproterenol (ISO) and noradrenaline (NA) in the absence and presence of a protein kinase C activator, TPA. In control rats TPA potentiated the cAMP responses to ISO (by over 100%) and to NA (by 38%). Chronic IMI depressed the cAMP accumulation induced by NA (by 47%) and - less effectively - by ISO (by 34%; NS). Chronic ECT significantly depressed the cAMP response to NA (41%) and, less, to ISO (35%; NS). The potentiating effect of TPA on cAMP response to ISO was retained in IMI-treated (60%) and even accentuated in ECT-treated (207%) rats; the TPA effect on NA-induced cAMP response was blunted in IMI (33%, NS), but augmented in ECT-treated rats (86%). In IMI-treated rats the β-DR (depressed cAMP accumulation) was still evident in the presence of TPA; in ECT-treated rats the TPA-induced stimulation was so high that no significant β-DR could be observed. No procedure (IMI, ECT, TPA) affected the response to FOR. Thus, β-DR is not related to the direct influence on adenylate cyclase, and β-DR developing during chronic IMI treatment differs from that caused by chronic ECT. Possibly, a part of the downregulatory action of IMI is related to the TPA-irreversible inhibitory effect of the drug on protein kinase C, while ECT does not affect the activity of the enzyme.
In vitro TPA does facilitate the cAMP responses but it also inhibits the NA-induced accumulation of inositol phosphate (IP). IMI did not affect cAMP response to NA, but inhibited the NA-induced IP formation and antagonized the facilitating effect of TPA on cAMP response to ISO and NA. The data confirm that IMI does not act directly on β-adrenoceptor complex, but may directly affect mechanisms involved in NA-induced mobilization of phosphatidyl inositol system and act as a protein kinase C inhibitor. A possibility exists that IMI specifically inactivates a subtype of kinase C linked with phosphorylation of α-adrenoceptor.

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CHRONIC AMPHETAMINE PRODUCES SENSITIZATION TO THE PROPHAGIC EFFECTS OF MORPHINE, BUT NOT OF U50488H, MICROINJECTED INTO THE VENTRAL TEGMENTAL AREA IN RATS. P. Nencini, J. Stewart

Chronic administration of AMPH leads to sensitization to the prophagic effects of systemic injections of both morphine (MORPH) and the selective kappa opiate agonist, U50488H (50). Since both MORPH and dynorphin have been reported to stimulate feeding when administered into the ventral tegmental are (VTA), we evaluated whether this area is the site where AMPH produces sensitization to the feeding effects of opiates. Rats were given daily IP injections of either saline of AMPH (3 mg/kg) and the amount of powdered food ingested during the 5 h following the injections was measured. After 9 days of AMPH or saline administration, twice weekly tests were begun of the effects of either saline, MORPH (1 to 10 nmol) or U50 (10pmol to 10 nmol) injected into the VTA; AMPH administration was continued on intervening days. MORPH produced a statistically significant greater increase in food intake in the AMPH group than in the saline group. No statistically significant effects were produced by U50. However, when U50 was administered systemically to the same animals, food intake increased, and the effect was significantly greater in the AMPH-pretreated group. Thus the sensitization to the feeding effects of MORPH and U50 produced by chronic AMPH administration appears to involve different systems; the mesolimbic dopamine system appears to mediate sensitization to the effects of the predominately mu receptor agonist, MORPH, but not of the kappa receptor agonist, U50.

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INDIVIDUAL DIFFERENCES IN RESPONSE TO DOPAMINERGIC DRUGS AS RELATED TO AGGRESSION. P. Netter.

It has been demonstrated that application of dopamine (DA) agonists may cause shock-induced fighting in rats (Mason, 1984) or anger in humans (Goodwin, 1970). Furthermore, higher DA levels have been observed in individuals of higher spontaneous aggression (Barr et al., 1979). Since aggression, like anxiety, may impair cortical functions known to be influenced by DA, we investigated 1) whether human subjects high in trait aggressivity would benefit from the DA antagonist haloperidol as opposed to low aggressives with respect to psychomotor performance and emotional state and 2) whether the DA agonist levodopa would impair their performance and increase their irritability more than that of low aggressives. **Methods**: In a double blind balanced cross-over design a single oral dose of 3 mg haloperidol (H), 125 mg madopar (M) and a placebo were administered at 1 week intervals to 24 healthy male volunteers divided according to a questionnaire score into high and low aggressive subjects. They were tested on Critical Flicker Fusion (CFF), Choice Reaction Time (RT), and rating scales measuring emotional states (drowsiness, concentration, energy, irritability), and physiological responses were recorded concomitantly. **Results**: Analyses of covariance and correlations between aggression scores and baseline corrected drug effects yielded the following results: 1. Aggressive subjects were more impaired in RT performance and felt less irritated by H than non-aggressive subjects. 2. M induced deterioration in RT performance selectively in aggressives concomitantly decreasing their drowsiness and feelings of relaxation.
The role of possible differences in DA baseline levels underlying the differences in aggression for the differences in response to dopaminergic drugs will be discussed.
References: Mason, S.T. (1984) Catecholamines and behaviour. Cambridge; Goodwin, F., Murphy, D.L., Brodie, H.K.H., Bunney, W.E. (1970). Biol. Psychiatry, 2, 341-366; Barr, G.A., Sharpless, N.S., Gibbons, J.L. (1979). Brain Res., 166, 211-216
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EFFECTS OF ATIPAMEZOLE, AN α_2-ADRENOCEPTOR ANTAGONIST, ON BEHAVIOUR AND MEMORY IN RATS
S.A. Nieminen, E. MacDonald, P.J. Riekkinen Jr., J. Sirviö, M.M. Airaksinen

A specific α_2-adrenoreceptor antagonist, atipamezole, was studied in Wistar rats. The effects of drug on memory in appetitive spatial discrimination maze and in the Morris water maze, on the behaviour in the open field and in the plus maze tests, on the metabolism of biogenic amines and on quantitative EEG were recorded. Atipamezole (0.6 and 3.0 mg/kg sc) alleviated forgetting in the appetitive spatial discrimination maze task, in the open field test and in the elevated plus maze it slightly decreased the motor activity and improved the EEG in the lesioned rats. In the water maze, after small doses of atipamezole, the rats remained immobilized for 30-60 seconds before starting to swim, while after higher doses (6.0 and 10.0 mg/kg) they did not want to swim at all. In the rat brain atipamezole increased the release of NA and also other amines, since the major metabolites of NA, 5-HT and DA.
The mechanisms of modulation of the complex behavioural processes are still unknown, but the results indicates that noradrenergic compounds can be used in modulating memory retrieval. Atipamezole may not only act by blocking cortical α_2-receptors, but it can also increase firing of locus coeruleus cells. The coerulo-cortical noradrenergic projection has been proposed to be involved in attention, learning and memory. On the other hand, increased release of other neurotransmitters by atipamezole, suggest that the effects are partly mediated via serotonergic, dopaminergic or other systems.

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EFFECTS OF SEROTONERGIC AGENTS ON OBJECT-BURYING: INVESTIGATION AS AN ANXIETY MODEL.
K. Njung'e and S. L. Handley.

Mice readily bury harmless objects. Broekkamp et al. (Eur J Pharmac 126: 223 1986) suggested this modelled anxiety since burying was reduced by anxiolytics and 5-HT uptake inhibitors without affecting immersion-grooming. We have examined drug effects on marble burying (MB) in female MF1 mice (placed individually for 30 min with marbles on 2cm sawdust), using locomotor activity (LA) in a circular runway to indicate non-specific effects. Burying was not affected by yohimbine or ß-CCE. Diazepam .1mg/kg increased both MB and LA. Compounds selectively reducing MB included diazepam (2.5-5 mg/kg), MCPP, TFMPP, DOI, zimeldine, citalopram, fluvoxamine, indalpine, fenfluramine. RU-24969 increased LA at active doses. 8-OHDPAT, gepirone, buspirone, 5-MeODMT, ketanserin, methysergide, cyproheptadine decreased MB only at doses decreasing LA. Ipsapirone, pindolol, ritanserin, ICI 169 369, ondansetron, ICS 205-930, pCPA were inactive. The zimeldine effect was present after 10 but not 14 daily doses. Neither re-exposure to, nor pre-housing with marbles affected MB. In a 2-compartment box, mice spent 49% of time in the side with marbles. Thus increased 5-HT activity potently inhibited MB but the lack of habituation or aversiveness suggests burying behaviour does not model anxiety.

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THE POSTCONDITIONING DRUG TEST: A POTENTIAL USEFUL PROCEDURE FOR ACQUISITION OF CONDITIONED PLACE AVERSION.
Ph. Oberling, B. Rocha, G. Sandner and G. Di Scala.

In a companion poster (Conditioned place aversion with lithium chloride. Does a test under LiCl potentiate learning? Rocha and al.), a potent procedure for learning of conditioned place aversion (CPA) with LiCl was described. Briefly, testing the animals under LiCl potentiated the effects of previous pairings with the same drug so as to elicit a strong CPA during a subsequent postconditioning drug-free test. The purpose of the present study was to determine whether such an effect was particular to LiCl or if it could be applied to other aversive drugs. Two drugs, FG 7142 and Naloxone, respectively a GABA-BZ receptor inverse agonist and an opioid antagonist were chosen. Rats were submitted to two pairings sessions with either FG 7142 (15 mg/kg, i.p.), Naloxone (5 mg/kg, i.p.) or LiCl (31.8 mg/kg, i.p.). All the animals were tested twice. On the first test day following the last conditioning day, half of the rats were tested under the drug previously used during the conditioning sessions (postconditioning drug test). The other half was tested in a drug-free state (postconditioning test). This protocol was reversed on the second test day. Two pairings with either one of the drugs did not produce CPA. However, the procedure with two pairings followed by a postconditioning drug-test led to a marked place aversion during the subsequent postconditioning test, for all three drugs.
The results show that the potentiation of CPA learning by a postconditioning drug-test is not specific to LiCl, since the same effect was obtained with FG 7142 and Naloxone. Therefore, the procedure described above seems a valuable method to elicit CPA.

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FLESINOXAN: BEHAVIOURAL PROFILE OF A NEW 5-HT_{1A} AGONIST.

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Flesinoxan* was initially developed as a centrally acting antihypertensive agent. It soon became evident that flesinoxan is a potent and selective 5-HT_{1A}-agonist and has anxiolytic and antidepressant activity in a number of animal tests. Flesinoxan exerts anxiolytic activity, comparable to that of 8-OH-DPAT, ipsapirone and buspirone in ultrasonic pup vocalization, but has no or only marginal effects in anxiolytic tests like the four-plate, light-dark exploration and open field.
In a conflict procedure in pigeons flesinoxan, like the other 5-HT_{1A} agonists, displays a potent anticonflict effect, comparable to that of the benzodiazepines (Barrett et al., J.Psychopharmacol. 3:64, 1989).
In an EEG-profiling test flesinoxan has a primarily anxiolytic profile on the cortical EEG of rats (Krijzer, Neuropsychobiol. 18: 51, 1987).
Drug discrimination experiments show that flesinoxan produces a clear 5-HT_{1A}-cue in rats, with cross generalization towards 8-OH-DPAT.
Antidepressant activity of flesinoxan is found in the forced-swim test and is comparable to 8-OH-DPAT and ipsapirone. After 14-days treatment flesinoxan induces a downregulation of β-receptors in rat cortex, a parameter which has been suggested as a common denominator of antidepressant drugs.
Further studies have shown that flesinoxan facilitates sexual performance, comparable to other 5-HT_{1A}-agonists and has, although behaviourally nonspecific, anti-aggressive activity in several aggression paradigms.
Flesinoxan induces lower lip retraction, a typically 5-HT_{1A}-receptor mediated behaviour (Berendsen et al., Pharmacol. Bioch. Behav. 33; 821, 1989). All data suggest flesinoxan as a full agonist of the 5-HT_{1A}-receptor with a behavioural repertoire strongly indicative for potential activity in human anxiety disorders and depression.
* (+)-N-[2-[4-(2,3-dihydro-2-hydroxymethyl-1,4-benzodioxin-5-yl)-1-piperazinyl]ethyl]-4-fluorobenzamide hydrochloride)

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MORPHINE-INDUCED HYPERACTIVITY IN RATS IS ENHANCED BY THE SELECTIVE D2 DOPAMINE ANTAGONIST RACLOPRIDE AND BLOCKED BY DOPAMINE AGONISTS

M.F. O'Neill, C.T. Dourish and S.D. Iversen.

Previous studies have indicated that drugs of abuse (nicotine, heroin, morphine, alcohol) share a common mechanism of action via the release of dopamine (DA) from mesolimbic neurons (DiChiara and Imperato, Proc. Natl. Acad. Sci. 85: 5274-5278, 1988). Thus, the stimulant action of nicotine is blocked by selective D1 and D2 receptor antagonists (O'Neill *et al*, J. Psychopharm. 3: 67P, 1989). Furthermore, the stimulant effects of nicotine and dopamine agonists on locomotion were additive (O'Neill *et al*, unpublished results). The present study examined whether morphine-induced hyperactivity is mediated by a common dopaminergic mechanism to that of nicotine.

Rats were habituated for 90 minutes to test cages fitted with infra-red photobeams linked to a BBC microcomputer to monitor locomotor activity. Morphine (0.3-10.0mg/kg i.p.) increased activity, the dose response curve being bell-shaped with 3.0mg/kg producing maximal levels of locomotor stimulation. The hyperactivity induced by 3.0mg/kg morphine was blocked by the D1/D2 antagonist fluphenazine (0.3mg/kg), the D1 dopamine agonist SKF 38393 (10.0mg/kg) and the D1/D2 agonist apomorphine (0.2mg/kg). In contrast morphine-induced locomotor stimulation was unaffected by pretreatment with the D1 antagonist SCH 23390 (0.01mg/kg) and enhanced by the D2 antagonist raclopride (0.1mg/kg). These unexpected results contrast with our previous findings on nicotine-induced hyperactivity (see above). The data suggest that nicotine and morphine engage different dopamine receptor mechanisms for the expression of their locomotor stimulant actions.

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BLOCKADE OF 8-OH-DPAT-INDUCED PLACE PREFERENCE BUT NOT PLACE AVERSION BY DA ANTAGONISTS OR PCPA

M.Papp & P.Willner

This study examined the effects of the 5HT-1A agonist 8-OH-DPAT in the place conditioning paradigm. Male rats were confined for 8 daily trials on alternate sides of a chamber containing two distinct arms. 8-OH-DPAT was administered prior to confinement either on the initially non-preferred side (preference experiments) or on the initially preferred side (aversion experiments). Changes in side preference as a result of conditioning were examined in a drug-free post-conditioning test.

Low doses of 8-OH-DPAT (0.125 and 0.25mg/kg) caused a shift towards the drug-associated side, comparable in size to the effect of 1.5mg/kg amphetamine. A higher dose (1mg/kg) induced place aversion. Pimozide (0.5mg/kg), sulpiride (40mg/kg) and PCPA (200mg/kg) had no significant effects when given alone, but in combination with 0.125mg/kg 8-OH-DPAT, abolished the 8-OH-DPAT-induced place preference. However, the 8-OH-DPAT-induced place aversion was unaffected by either pimozide or PCPA.

These results confirm that low and high doses of 8-OH-DPAT have opposing behavioural effects, and further support the hypothesis (Muscat et al, 1989, Psychopharmacology 99, 402-408) that 'presynaptic' doses of 8-OH-DPAT disinhibit DA activity by inhibiting the activity of serotonergic projections.

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THE EFFECTS OF PHENCYCLIDINE (PCP) ON RHESUS MONKEY PERFORMANCE IN AN OPERANT TEST BATTERY (OTB)

M.G. Paule, R.R. Allen and M.P. Gillam

In efforts to determine the effects of PCP administration on various complex behaviors, saline injections or one of seven doses of PCP ranging from 0.003 to 0.3 mg/kg, were given iv to adult male Macaca mulatta, 15 min prior to the beginning of daily (M-F) 50-min behavioral test sessions. The tasks in the multiple schedule OTB (food-reinforced) and the specific brain function(s) they are thought to model are: Progressive Ratio (PR), motivation; Conditioned Position Responding (CPR), color and position discrimination; Incremental Repeated Acquisition (IRA), learning; Delayed Matching-to-Sample (DMTS), short-term memory and attention; and Temporal Response Differentiation (TRD), time perception. Endpoints monitored included response rates, accuracies, and percent task completed. PCP at 0.3 mg/kg eliminated responding in 8/8 subjects. Group data for 6 animals that performed all 5 tasks showed that doses up to 0.1 mg/kg had no significant effects on performance in any of the 5 tasks, however, at 0.13 mg/kg, there was a significant disruption of behavior in the PR, IRA, DMTS and TRD tasks. CPR responding was significantly disrupted at a dose of 0.18 mg/kg. Thus, the sensitivities of these tasks to disruption by PCP were PR=IRA=DMTS=TRD>CPR. The pattern of sensitivity to PCP is quite different from those for several other psychotropic agents tested in similar fashion. This suggests a common PCP-sensitive factor in performance in the motivation, learning, short-term memory and attention, and time perception tasks that are equisensitive to disruption by PCP. Color and position discrimination is the least sensitive of these behaviors to the disruptive effects of PCP.

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AN EXTENSION OF THE SCALING HYPOTHESIS: SPECTRA OF SINGULARITIES AS A SENSITIVE DESCRIPTION OF THE GEOMETRICAL AND DYNAMICAL STRUCTURE OF RAT LOCOMOTOR PATHS

M.P. Paulus and M.A. Geyer

A previously proposed scaling hypothesis states that the characteristics of the sequential structure of rat locomotor behavior may be described by a scaling exponent that relates the measures of interest to the resolution with which these measures are obtained. Two scaling exponents have been used to differentiate psychoactive drugs, an α exponent describing how the number of events scale with their duration and a d exponent relating geometrically the measured length of the path to the length of the measuring instrument. These approaches allow a global description of behavioral sequences. To differentiate subsets of behavioral sequences, an extension of these scaling exponents leads to a local scaling hypothesis. Assuming that local sub-sequences of behavior scale with the change of the resolution, a spectrum of scaling indices is constructed that describe how many subsets can be found by increasing the resolution geometrically, i.e. increasing the resolution with which the rat locomotor paths are tracked, or temporally, i.e. following the rat for longer sequences in time. Rats tested in a Behavioral Pattern Monitor show characteristic path structures changing specifically with drug and dose. The locomotor paths of 46 animals treated with D-amphetamine (0.0-2.0 mg/kg) were recorded for 60 min. Amphetamine does not change the overall geometric structure of the paths but increases the dynamical entropy significantly. The singularity spectra reveal, however, that with increasing doses of amphetamine the subsets of sequences with low and high scaling exponents are decreased whereas subsets with slightly higher scaling exponent than the global d are increased. The change in the dynamical structure of the paths is not due to a loss of low entropic sequences but rather a gain in higher entropic sequences than the global metric entropy. These measures enable an extremely sensitive description of the structure of behavioral sequences, providing a quantitative bio-assay to assess the behavioral effects of drugs.

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MODIFICATION OF LIPOPOLYSACCHARIDE(LPS)-INDUCED FEVER BY PAVLOVIAN CONDITIONING USING α-MSH AND LiCl

H.P. Pfister, R. Brown, D.F. Bull, A.J. Husband and M.G. King

Recent investigations have demonstrated the susceptibility of various components of the immune system to behavioural conditioning, using a conditioned taste aversion (CTA) paradigm. In the series of experiments reported here we have established CS-CR contiguity using saccharine as the CS and α-MSH or LiCl as the UCS.

The results show clearly that the antipyretic effect of α-MSH can be conditioned utilising the CTA paradigm outlined above. The conditioned rise in body temperature (by LPS in the control group) is, although significant, smaller in on re-exposure day magnitude when compared to the pharmacological effect on the first exposure. Similarly, the reduction of the conditioned α-MSH effect, on re-exposure, is also diminished when compared to the α-MSH effect obtained on the first exposure. The saccharine consumption data supported the predicted reduction in saccharin consumption on re-exposure. The data of the additional control groups included strengthens the conclusions drawn from the above data.

In a preliminary experiment utilising LiCl as the UCR we have observed a significant conditioned fall in temperature following the CS only on re-exposure.

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NEUROLEPTIC-INDUCED RESPONSE DECREMENT IN THE ABSENCE OF EFFECTS ON REWARD. G. Phillips, P. Willner and R. Muscat

The impairment of performance by neuroleptic drugs typically increases during the course of an experimental session. These within-session decrements are often referred to as 'extinction-like', reflecting a belief that they arise from a blockade of the rewarding properties of response-contingent stimuli. We report here a series of studies in which within-session response decrements were independent of reward.

In an initial experiment, pimozide (0.25 mg/kg) caused a typical within-session decrement in rats trained under random interval (RI)-30s or 300s reinforcement schedules of food reward, but tested under time-out conditions (ie. house lights off and no feedback for responding). In a second experiment, raclopride (100 μg/kg) caused a within-session decrement following prolonged extinction. Response rates were sensitive to the presence of cues previously associated with reward, but the effects of raclopride were independent of the presence or absence of reward-associated cues.

The involvement of DA in reward has typically been ascribed to the DA projections to the nucleus accumbens. In rats performing on a RI-30s schedule, sulpiride (0.625 and 2.5 μg) caused within-session response decrements when administered to the dorsal caudate nucleus. However, in the accumbens, sulpiride suppressed performance equally throughout the session.

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INDIVIDUAL DIFFERENCES AND SELF-ADMINISTRATION: PREDICTIVE FACTORS AND BIOLOGICAL CORRELATES.

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Individual vulnerability to the reinforcing effect of drugs is one of the main factors influencing the prognosis of addiction. Differences in vulnerability to develop drug-intake are shown also by rats of the same strain. In the present study we will suggest that in animals individual vulnerability to develop amphetamine self-administration is predictable. Thus, vulnerable rats have both a greater behavioural and biological response to novel environment exposition, i.e. a greater locomotor reactivity and a greater corticosterone release. Moreover, to a greater sensibility to the reinforcing effect of amphetamine is associated a greater locomotor response to the drug. For istance, when the locomotor reactivity to amphetamine of individual animals is increased by repeated injections of the drug (amphetamine sensitization) also their sensibility to develop amphetamine self-administration is increased.

These predictive traits have been utilized for the study of the biological basis of the vulnerability to drug self-administration. A possible role of the interactions between corticosterone and dopamine for a predisposition to develop amphetamine self-administration is discussed.

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EVIDENCE FOR DIFFERENT GLUCOCORTICOID RECEPTORS IN HUMAN BRAIN

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Two types of glucocorticoid receptors exist in the rat's brain: Type I, binding primarily endogenous glucocorticoid (like cortisol, CORT) and mineralocorticoids; Type II, binding preferentially synthetic glucocorticoids, such as dexamethasone (DEX). However, the existence of similar glucocorticoid receptor subtypes in the human brain has not been proved. In recent studies we found different effects of CORT and DEX on human sleep. While rapid eye movement (REM) sleep was suppressed by CORT and DEX, slow wave sleep (SWS) was increased by CORT but suppressed by DEX. The present experiments aimed to affect sleep selectively via Type I and Type II receptors by aldactone (potassium-canrenoat), CORT and DEX. Aldactone was expected to antagonize effects of cortisol via Type I receptors. DEX was expected to antagonize Type I effects via suppression of pituitary secretory activity and to directly affect sleep via Type II receptors. In each experiment, 10 healthy male students were tested under double-blind conditions according to within-subject cross-over designs. In experiment I, either placebo or CORT (100 mg) were infused during sleep after a 4-day pretreatment with either DEX or placebo. Pretreatment with DEX was supposed to facilitate effects of cortisol. In experiment II, subjects received placebo, 8 mg/h CORT and aldactone (200 mg, at 8.00 a.m. and 5.00 p.m.). CORT treatment after pretreatment with DEX did not differ from CORT treatment alone; it decreased REM and increased SWS. However, DEX pretreatment as well as aldactone, markedly reduced SWS ($p<0.01$). While DEX decreased REM sleep, aldactone left REM sleep unaffected. The pattern of results supports the conclusion, that in humans the cortisol-induced increase in SWS is mediated via Type I-like central glucocorticoid receptors, whereas REM sleep is affected via Type II receptors.

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EFFECT OF LONG-LIFE DIETARY RESTRICTION ON AGE-RELATED CHANGES IN PSYCHOMOTOR BEHAVIOR IN THE RAT

N. Pitsikas, P. Garofalo, A. Zanotti° and S. Algeri

Life-long dietary restriction may delay or antagonize age-related deficits of cognitive abilities of the aged rat. The purpose of our study was to evaluate the eventual beneficial effect on these behaviours of restricted diet (hypocalorid diet; 50% of lipids and 35% of carbohydrates replaced with vegetal fibers as compared to the standard diet). Two different studies were performed: in a cross-section model, were compared the cognitive functions of rats of different age and diet, a longitudinal model in which was followed in the same animals the evolution of the cognitive abilities and was assessed the influence of different diet on them. Motor activity was tested in a series of equilibrium tests as round or square bridge. Locomotor activity and drive for exploration were assessed in a 16-holeboard apparatus. Discrete memory measured as retention of a noxious stimulus was measured by an avoidance procedure. Spatial learning, long-term and short-term memory were evaluated in the Morris water maze. The results of our studies suggest us that: 1. Motor ability, locomotion and exploration were deteriorated in the aged animal and this impairment was not affected by the diet; 2. Discrete memory ability expressed as retention of an adversive stimulus in an avoidance procedure was impaired in the senescent rats. However, the hypocaloric diet antagonize this age-related deficit; 3. Spatial learning abilities of the senescent rat were impaired as compared to their young counterparts in the Morris water maze task. On the contrary, the performance of the aged animals fed a hypocaloric diet was not different than that displayed by the young animals; 4. A longitudinal study however, reveals that short-term but not long-term memory of the senescent rats was impaired, while, hypocaloric diet seems to antagonize this cognitive deficit.

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EFFECT OF ORG. 2766 AN ACTH (4-9) ANALOG ON RECOVERY AFTER BILATERAL TRANSECTION OF THE FIMBRIA FORNIX IN THE RAT

N. Pitsikas, B.M. Spruijt°, S. Algeri and W.H. Gispen°

Facilitation of recovery after a peripheral or brain damage induced by neuropeptides is a common feature in the literature. In one previous our study it has been seen that deficiency in spatial learning induced by unilateral lesion of the septo-hippocampal pathway was reversed by subchronic treatment of the ACTH (4-9) analog Org. 2766.
The aim of the present experiment was to evaluate whether this ACTH (4-9) analog exerts a trophic effect on a brain damage more extended such as the bilateral transection instead of the unilateral of the fimbria fornix of the rat. The Morris water maze, a test sensitive to hippocampal damage and the Passive Avoidance which does not require spatial orientation were chosen as the test apparatus of this study.
The results of our behavioral observations indicate us the following:

1. Subchronic treatment with Org. 2766 attenuates the behavioral deficit shown in the performance of the rat bearing bilateral lesion in a spatial memory task.

2. Interestingly, performance of lesioned animals in a shock motivated task was not affected by this neuropeptide.

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AN INVOLVEMENT OF ACCUMBENS 5HT1A-RECEPTORS IN REGULATION OF RAT MOTOR ACTIVITY. A. Plaznik, R. Stefanski, W. Palejko, W. Kostowski

Limbic serotonergic (5HT) innervation has been implicated in many central pathologies including emotional and motor disturbances. The role of accumbens (NAS) 5HT in controlling central nervous system functions is underlined by the fact of an involvement of this brain structure in processing and transmitting cortical output to the brainstem locomotor centers (G.J. Mogenson, M. Nielsen, Behav Neural Biol 42: 38-51, 1984). In the present study we have analysed the behavioral function of limbic 5HT1A-receptor system using the method of local stimulation of this receptor sub-population within the NAS region.
It was found that intra-NAS injections of 5HT1A-receptor agonists: buspirone and NDO-008 reduced dose-dependent and short-latency depression of rat motility, thus mimicking the effects of 5HT and quipazine within this area. The opposite behavioral changes were produced by noradrenaline and dopamine administration. The effect of buspirone was partly antagonized by non-selective 5HT1A-receptor antagonist cyanopindolol. These findings indicate that 5HT1A-receptors might be responsible for the inhibitory influence of accumbens serotonin in the regulation of rats' locomotor behavior.

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ROLE OF MESOLIMBIC DOPAMINERGIC ACTIVITY IN MEMORY PROCESSES IN RATS

G.E. Ploeger and A.R. Cools

Recently, it has been shown at our laboratory that the ventral striatum (VS) is involved in switching behaviour by using external available cues. As we wondered whether the VS could also play a role in memory processes, in which retention and/or retrieval occurs with the help of available cues, we studied the effects of direct manipulation of the dopaminergic activity within the VS in two different kinds of cue-directed memory tasks, viz. the social memory test (task 1) and the Morris water maze (task 2).

In task 1, an adult male rat had to recognize an individual young rat, when exposed to it twice with an interexposure interval of different length. Recognition was shown to vanish with prolonging of the interval. Direct injection of the dopaminergic agonist DPI (0.1-1.5 µg) into the VS, immediately after the first exposure, was found to facilitate the recognition of the young rat at a long interval.

In task 2, rats were trained to find a hidden platform at a fixed location from different starting positions, thereby forced to use extra-maze cues for correct localisation. Then, the platform was moved to the opposite side and the rats were tested on their reaction to this change. Immediately after the last training trial, DPI (0.5 µg) was injected into the VS. In the first trial after platform relocation, time spent in the previously correct quadrant was equal for both DPI and control groups, whereas the DPI group spent more time searching around in the remainder of the pool. At the second trial, however, they both showed the same latency for detecting the platform. So, retention of the old location as well as refinding the new location of the platform at the second trial remained intact. On the other hand, DPI apparently retarded finding a shifted platform, the location of which was not yet cued. Whether this effect is direct or indirect (by preventing the use of other, non cue-directed search strategies) remains open for further investigation.

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NAN-190 ANTAGONIZES THE BEHAVIOURAL BUT NOT THE HYPOTHERMIC OR CORTICOSTERONE RESPONSE TO 8-OH-DPAT IN THE RAT

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5-HT_{1A} receptor antagonistic properties of 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine (NAN-190) were studied in rats: its effect on the 8-OH-DPAT-induced behavioural syndrome, hypothermia and corticosterone (CORT) secretion, i.e. responses mediated by 5-HT_{1A} receptors, were examined. NAN-190 (1-8 mg/kg) antagonized dose-dependently behavioural effects of 8-OH-DPAT (in both non-reserpinized and reserpine-pretreated animals); however, when administered in doses of 0.5-4 mg/kg, it did not affect the hypothermic or the hormonal response to 8-OH-DPAT. Importantly, NAN-190 (1-8 mg/kg) alone produced hypothermia and increased the serum CORT concentration. The latter effects of NAN-190 were not reduced by (-)-pindolol or spiperone. Moreover, the NAN-190-induced CORT secretion was not affected by ketanserin, prazosin or yohimbine.

The above results indicate that NAN-190 acts as a 5-HT_{1A} receptor antagonist only in the model of the 8-OH-DPAT-induced behavioural syndrome. The lack of effect of NAN-190 on the hypothermic or CORT response to 8-OH-DPAT most probably results from its own action which mimics the effects of 8-OH-DPAT. Mechanism responsible for the NAN-190-induced hypothermia and CORT secretion is still unknown though stimulation of 5-HT_{1A} receptors (either effect), 5-HT_2 ones and α_1- and α_2-adrenoceptors (CORT response) seems to be excluded.

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FURTHER BEHAVIORAL CHARACTERISTICS OF THE GENETIC RAT MODEL OF DEPRESSION WITH CHOLINERGIC SUPERSENSTIVITY*

O. Pucilowski, D.H.Overstreet, A.H.Rezvani and D.S. Janowsky

The Flinders Sensitive Line of rats (FSL) has been selectively bred for increased sensitivity to cholinergic drugs. The similarly bred resistant line (FRL) does not differ from the parent strain (Sprague-Dawley) rats. Behaviorally, FSL rats show greater immobility in the forced swim test and a more profound behavioral deficit following exposure to a mild footshock. They have also a shorter REM latency, like depressed humans, and it has been suggested that the FSL rat may be suitable as the animal model of depression. We present the evidence that FSL rats have more pronounced fear-related behavioral responses. Male FSL and FRL rats were compared in three tests: neophobia in unfamiliar open field, water-competition test and apomorphine-induced fighting (defensive irritable aggression). FSL rats were significantly ($p<0.01$) less active in brightly illuminated open field (lower number of peripheral and central square crossings, longer freezing time or central object exploration). They spent significantly ($p<0.01$) less time drinking than their FRL partners in the water competition test. Both groups did not differ in water intake when tested individually. There was a significant positive correlation between the number of central square entries or object exploration in the open field and the drinking time in the competition test. FSL rats displayed high level of aggression (boxing, biting attack, vocalization) when injected with 10 mg/kg of apomorphine, whereas FRL rats did not fight at all. Fear or anxiety appears to be a significant component in all three behavioral test employed in the present study. We conclude that the FSL rat can be considered as an animal model of depression with a marked anxiety component.

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NICARDIPINE, BUT NOT VERAPAMIL, ATTENUATES HYPOTHERMIC EFFECT OF OXOTREMORINE OR ETHANOL IN GENETICALLY BRED HYPERCHOLINERGIC RATS*

O. Pucilowski, D.H. Overstreet, A.H. Rezvani and D.S. Janowsky

Flinders Sensitive Line (FSL) of rats has been selectively bred for increased sensitivity to cholinergic agonists. Routinely, these rats are screened for hyperresponsiveness to the hypothermic effect of oxotremorine (0.2 mg/kg sc). We have recently found that FSL rats are also more responsive to ethanol-induced hypothermia. Since calcium channel inhibitors (CCIs) reportedly can attenuate some central depressant actions of ethanol we decided to study the effect of two CCIs, nicardipine and verapamil, on the hypothermic action of ethanol and oxotremorine in FSL rats. Each CCI was injected ip in a dose of 10 µM, either immediately after ethanol (3 g/kg ip as 20% sol. v/v) or 30 min prior to oxotremorine. 15 min before oxotremorine challenge 2 mg/kg of methylatropine was injected ip to block the peripheral effects of the drug. The colonic temperature was measured for subsequent 2 h at 30 min intervals and the hypothermic effect was expressed as the total area under the temperature decrease curve integrated according to the Simpson's rule. The hypothermic effect of both ethanol and oxotremorine was significantly ($p<0.01$) decreased by nicardipine. Verapamil, however, failed to influence oxotremorine hypothermia and even tended to augment ethanol-induced hypothermia (the effect was not significant though). It is concluded that, out of two CCIs studied, only nicardipine can provide effective protection against hypothermic effects of ethanol and oxotremorine. This activity of nicardipine seems to be related neither to its known anticholinergic nor to calcium channel blocking activity as it does not differ in this respect from verapamil.

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GENOTYPE-DEPENDENT DIFFERENCES IN DOPAMINE-MEDIATED BEHAVIOURS. S. Puglisi-Allegra, S. Cabib

A number of studies have suggested that intraspecific differences in the behaviourial response to dopamine (DA) agonists may depend on genetic differences in density of DA receptors of the D2 type. Apomorphine (APO) (1 and 3 mg/kg) induces stereotyped climbing and enhances locomotion in mice of the C57BL/6 (C57) strain while it has no effect on climbing behaviour and reduces locomotor activity in DBA/s (DBA) mice. The genetic analysis of the behaviourial response to 3 mg/kg of apomorphine shows that with regard to climbing the additive-dominance model fits adequately while for locomotor activity data the best fitting model involves epistatic parameters. The D2 DA receptor agonist LY 171555 at doses ranging from 0.5 to 5 mg/kg induces hyperdefensive response toward non aggressive opponents and a slight cataleptic response in mice of the C57 strain while it induces a dose-dependent cataleptic response but no hyperdefensive response in DBA mice. A correlation study conducted in an outbred population (CD1) demonstrates lack of either positive or negative correlation between the two behaviourial effects of the D2 agonist. These results suggest that genetic factors modulating the behaviourial effects of DA agonists depend on the behaviourial measure taken in examenination. Low doses of APO (0.1 to 0.5 mg/kg) do not affect climbing behaviour either in DBA or in C57 mice showing lack of strain-dependent differences for the behaviourial effects of APO at these doses. However, when the doses of APO are injected 24 hrs after the last session of chronic stress, a significant increase of climbing is observed in mice of the DBA strain while C57 mice show a significant decrease of this behaviour. A classical genetic analysis confirms that genotype plays a major role in the modulation of the behaviourial effects of low doses of apomorphine following chronic stress. Taken together, these results support the view the pharmacogenetic approaches looking mainly for single-gene effects and trying either to control environmental influences or to ignore them cannot evaluate the complexity of individual differences in the behaviourial response to drugs.

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BEHAVIOURAL EFFECTS OF RO 41-9067: A NOVEL DA D2 RECEPTOR AGONIST. S. Puglisi-Allegra, S. Cabib and C. Belzung

The behavioural effects of a novel putative D2 DA receptor agonist, RO 41-9067 (RO), were investigated in the mouse and compared with those of the more classic D2 selective agonist LY 171555 (LY). Both LY and RO (0.1 to 5 mg/kg) dose-dependently increased defensive behaviour exhibited by naive mice interacting with non aggressive conspecifics. At lower doses (0.01 to 1.2 mg/kg) both compounds decreased locomotor activity in mice tested in an automatized apparatus, an effect usually observed following administration of low doses of the mixed D1/D2 agonist apomorphine (APO). Finally coadministration of the D1 selective agonist SKF 38393 (10 mg/kg) and high doses (5.6 and 6 mg/kg) of RO or LY produced the hyperactive response classically induced by high doses of APO in the mouse.

These results indicate that LY and RO induce similar behavioural effects when tested in mice and suggest that at high doses these compounds activate postsynaptic D2 receptors while, at low doses, they selectively activate DA autoreceptors of the D2 type.

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BEHAVIOURAL AND NEUROCHEMICAL ADAPTIVE CHANGES AFTER CHRONIC ALPRAZOLAM TREATMENT

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The mechanisms underlying tolerance to the benzodiazepines (BDZ) are of both clinical and theoretical importance.Alterations in both BDZ and GABA receptors have been proposed as possible mechanisms for tolerance to the BDZ following chronic treatment(Rosenberg,H.C.and Chiu,T.H.Eur.J.Pharmacol. 70(1981)453-460).In order to investigate the mechanisms after chronic BDZ treatment we administered alprazolam 5mg·kg^{-1}ip. in groups of 20 male Wistar rats for 1,2 and 14 days with or without washout period (24hrs).Rats were placed on open arm exploration observed for 5 min and on open field locomotion (O.F.L) for 20 min.Control groups administered with vehicle were similarly treated.Rats were immediately decapitated and dopamine(DA),DOPAC,HVA,serotonin(5-HT),and 5-HIAA were estimated using HPLC in striatum,fr.cortex,hypothalamus and hippocampus.The behavioural results in the two first series of experiments(without washout)showed a decrease in locomotion ($p<0,05$) after 2 days alprazolam treatment and an increase ($p<0,05$) after 14 days.There were no significant changes on O.A.E .According to our biochemical results ,there was a significant decrease in 5-HT turnover in all brain regions tested ($p<0,05$-$0,005$) and a decrease in DA turnover($p<0,01$) with the exception of fr.cortex when alprazolam was administered acutely.Chronic treatment resulted in a loss of this decrease even from the second day but there was a significant increase in 5-HT turnover in hippocampus($P<0,05$) after 14days treatment with 24 hrs washout.Our behavioural and biochemical results indicate adaptive receptor changes even from the second day of a short-acting BDZ administration.

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CHRONIC NALTREXONE FACILITATES ACQUISITION OF COCAINE SELF-ADMINISTRATION IN RATS.

Nick F. Ramsey and Jan M. Van Ree

Endorphins have been implicated in addiction to various drugs (1). To explore the significance of these opioid peptides in cocaine addiction, experiments have been done using intravenous cocaine self-administration behavior in rats,a reliable experimental model of cocaine addiction. It has been shown that the opiate antagonist naltrexone attenuates the acquisition of cocaine self-administration when injected systemically prior to testing (2). Thus opioid systems may be involved in the rewarding action of cocaine. To elucidate this involvement further we designed experiments in which rats were pretreated with naltrexone (10 mg/kg/day) or placebo for twelve days,followed by two non-treatment days to minimize direct interference of the drug when testing for acquisition of cocaine self administration. During five consecutive days the rats were placed in operant chambers in which lever presses were followed by infusion of a cocaine solution through an implanted cannula in the jugulary vein. Graded doses of cocaine (0.015, 0.03 and 0.06 mg/infusion) and saline were tested. Chronic naltrexone increased cocaine intake. This facilitating effect was present at the intermediate dose only, a selectivity also seen with the attenuating action of acute naltrexone pretreatment on cocaine intake (2). These data support the idea that opioid systems in the brain are involved in cocaine self-administration.Furthermore,alterations of these systems by chronic blockade of opioid receptors may facilitate acquisition of experimental cocaine addiction.

1. Van Ree, J.M. (1987).Reward and Abuse: Opiates and neuropeptides. In: Brain Reward Systems and Abuse (J.Engel and L.Oreland, eds) Raven Press NY, pp 75-88.
2. De Vry, Jean, Inge Donselaar and J.M. Van Ree. (1989) Food deprivation and acquisition of intravenous cocaine self administration in rats: effect of naltrexone and haloperidol. J.Pharmacol.Exp.Ther.,251(2), pp 735-740.

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CHP MODULATES THE DOPAMINERGIC RESPONSE TO d-AMPHETAMINE: A MICRODIALYSIS STUDY

T.M. Rauch and A. Levy

Histidyl-proline-diketopiperazine (CHP) is a biologically active peptide related to TRH, ubiquitously distributed in the brain. CHP administration has been reported to decrease striatal dopamine (DA) in brain homogenates and inhibit tyrosine hydroxilation (TH) in-vivo. However, CHP has also been reported to augment stereotypic behavior induced by d-amphetamine, possibly by increasing the release of DA (for review see: Prasad, C. in: The Basal Ganglia II, Plenum, 1987, p. 155).

In the present microdialysis study, extracellular levels of DA and its metabolites (DOPAC and HVA) were monitored in the striatum of rats to reconcile these conflicting reports and study the dopaminergic mechanism of CHP action. Pretreatment with CHP (0.5 mg/kg, s.c.) (n=5), or the equivalent volume of saline in a control group (n=5), was followed 30-min by 5 mg/kg of d-amphetamine (i.p.). Dialysate samples were collected and analyzed by HPLC-EC. Statistical analysis (ANOVA) of the results revealed a significant difference between the two pretreatments ($p < .05$) for DA levels post d-amphetamine, but not for DOPAC or HVA. No difference was found between baseline DA values. No synergistic effect of CHP was observed on extracellular DA induced by d-amphetamine. On the contrary, following the initial response to amphetamine, striatal DA in CHP treated rats was significantly lower than in saline treated animals across time. Since there were no variations in DOPAC or HVA between the two groups across time, it is unlikely that CHP interferes with d-amphetamine induced inhibition of DA reuptake. Our data and previous findings suggest that CHP might have two opposing effects on DA activity. Attenuation of the dopaminergic response to d-amphetamine might be best explained on the basis of striatal DA depletion, possibly via TH inhibition.

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DIFFERENCES BETWEEN NORMAL HEIFERS, AND HEIFERS WITH STEREOTYPIES IN PLASMA LEVELS OF ENDOGENOUS OPIOID PEPTIDES. I. Redbo, F. Nyberg*, K.G. Jacobsson.

Animals living in restricted, barren environments often develop stereotypies. These have been interpreted as coping strategies with negative effects of stress, and are attributed to endorphins. Naloxone, can reduce stereotypies in pigs, horses and bank voles suggesting a role for endogenous opioids. Our hypothesis was that animals with stereotypies would have an enhanced opioid activity. To test the hypothesis we catetherized six heifers, three of which had the stereotypy tongue-rolling while the other three were free of stereotypies. Blood sampling was initiated the third day after the catetherization. At 20-min intervals blood samples were taken and the behaviour of the animals registered. The plasma was analyzed by radioimmunoassays for a) MEAP (Met-enkephalin-arginyl-phenylalanine) and b) Leu-enk-arg6 containing peptides. The two groups of heifers in this study had significantly different plasma levels both according to MEAP and Leu-enk-arg6 activity. The stereotypy group had significant higher plasma levels of Leu-enk-arg6, but significant lower levels of MEAP. There was a negative correlation between MEAP and Lou over the entire sampling period. No specific behaviour, including stereotypies, was correlated with changes in plasma levels of MEAP or Leu-enk-arg6. The stereotypy-heifers had significant increases in Leu-enk-arg6 and a corresponding decrease in MEAP in the period after feeding. Heifers with stereotypies may have had a different and enhanced enzyme secretion, that acts by rapid cleavage of MEAP. However, stereotypies are not accompanied by changes in plasma opioids.

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THE USE OF THE WISCONSIN GENERAL TEST APPARATUS IN THE ASSESSMENT OF COGNITION IN PRIMATES. R.M. Ridley and H.F. Baker

The Wisconsin General Test Apparatus can be used for assessing cognition in non-human primates and humans. It has been of major importance in establishing localization of cognitive function within cortex and, more recently, in exploring primate models of amnesia and dementia. The extent to which the various types of tasks available assess different facets of memory, according to present theories of human memory, will be discussed in this presentation. For example, it will be argued that competence in general task performance is a form of semantic rather than procedural memory and that when information about stimulus attributes, reward associations or rules of responding is stored long-term then that knowledge is semantic. Procedurally, tasks can be classified as trial-independent, trial-dependent and trial-unique. Trial-independent tasks assess mainly the acquisition of semantic knowledge. Performance of trial-dependent and trial-unique tasks requires use of semantic rule-of-the-task and memory for stimulus events from a previous trial or stimulus presentation. Considerable difficulties exist in describing this latter component as short-term memory, working memory, episodic memory or recognition. Subtle differences in procedures, e.g. the total number of stimuli used, may have profound effects on the type of memory required for task performance. Tasks can also be divided into those which assess memory for stimulus attributes and stimulus-reward associations (first order representations - which things are) and memory for stimulus-response associations (2nd order representations - what things imply). Evidence is presented that the cortex/amygdala and the hippocampus are differentially involved in the two functions.

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RELATIONSHIP BETWEEN ELECTROCORTICAL AROUSAL AND MEMORY DEFICITS IN AGED RATS - EFFECTS OF ATIPAMEZOLE ALPHA-2 ANTAGONIST

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Anatomical and electrophysiological properties of noradrenergic neurons projecting from the locus coeruleus to the forebrain suggest that this system plays a role in learning and memory. Dysfunction of noradrenergic system may also underlay some aspects of age-related cognitive deficits. The present studies were undertaken to investigate whether atipamezole an alpha-2 antagonist which increases the turnover of noradrenaline, would alleviate age-related deficits in electrocortical arousal (high voltage spindles) and learning/memory (passive avoidance task and water maze task).

The incidence of high voltage spindles was high in a subpopulation of aged rats (24 months) that was impaired in passive avoidance retention (PA), but the rest of the aged rats had only few HVSs. A different sub-group of aged rats was impaired in morris water maze (MWM) retention. No relationship was found between HVSs and MWM performance. Atipamezole (3 mg/kg, sc.), markedly decreased the incidence of HVSs in aged rats. Pre-retention test injections of atipamezole (3 mg/kg, s.c.) improved PA performance. However, daily post-train injections (3 mg/kg, s.c.) failed to improve either acquisition or long-term retention (7 days interval) of MWM task. Atipamezole (3 mg/kg, s.c.) had no effect on the PA or MWM behavior in young rats. The present results suggest that the noradrenergic pathology is involved in the EEG and passive avoidance retention deficits found in old age. Furthermore, they suggest the usefulness of alpha-2 antagonist in the treatment of age-related deficits of cognitive functions.

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APOMORPHINE BLOCKADE OF PREPULSE INHIBITION OF ACOUSTIC STARTLE RESPONSE AS A SCREEN FOR NEUROLEPTIC DRUGS

G.C. Rigdon and K. Viik.

In normal rats and humans the amplitude of the acoustic startle response to strong sensory stimuli is greatly reduced by a weak (non-startling) stimulus presented prior to the startle stimulus. This prepulse inhibition phenomena is significantly reduced in schizophrenic patients (Braff et al., Psychophysiol. 15:339, 1978). Studies by Geyer and coworkers (Psychopharm. 94:507, 1988) have demonstrated that apomorphine administration to rats abolishes prepulse inhibition in a manner similar to that seen in schizophrenic patients. The effect is attenuated by haloperidol. We have attempted to validate this test as a screen for potential neuroleptic agents by testing the typical neuroleptic drugs, haloperidol and chlorpromazine; the atypical neuroleptic drugs, clozapine and risperidone; and the non-neuroleptic psychopharmacological agents, diazepam, buspirone and imipramine for their ability to disrupt apomorphine's effects on prepulse inhibition. Test drugs were administered i.p. 30 min prior to testing and apomorphine 0.5 mg/kg s.c. was administered 10 min prior to testing. In vehicle treated subjects, apomorphine blocked prepulse inhibition. Haloperidol (1 mg/kg), chlorpromazine (5 mg/kg) and risperidone (5 mg/kg) attenuated the apomorphine effect. Clozapine (40 mg/kg) did not attenuate the apomorphine effect. The non-neuroleptic agents did not disrupt apomorphine's effects on prepulse inhibition at behaviorally relevant doses. These results suggest that apomorphine blockade of prepulse inhibition may provide a selective screening procedure for compounds with neuroleptic activity, however, the test's sensitivity may be questionable since the atypical neuroleptic, clozapine, was ineffective at the dose tested.

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EFFECT OF CHOLINERGIC MANIPULATIONS ON ATTENTIONAL FUNCTION IN THE RAT. T.W. Robbins, J.L. Muir and B.J. Everitt.

Previous studies have suggested a role for the cholinergic system in attentional processes. Relatively specific destruction of cholinergic cells in the nucleus basalis of Meynert (nbM) induced by infusing quisqualic acid into the basal forebrain impairs rats' ability to localise brief visual targets in a 5-choice serial reaction time task. Latency to respond correctly was also lengthened post-operatively and showed little recovery over several months.

The extent to which these deficits can be attributed to cholinergic dysfunction was investigated in two further experiments employing this attentional paradigm. The first study examined the effect of pharmacological manipulation of the cholinergic system using hemicholinium (HC-3), a high affinity choline uptake blocker, infused into the lateral ventricle. The behavioural deficits observed following administration of HC-3 were markedly similar to those following quisqualate-induced lesions of the basal forebrain. Furthermore, these deficits were reversed by administration of the anti-cholinesterase, physostigmine. The second study investigated the effects of infusing the GABA agonist, muscimol, in the vicinity of the cholinergic neurons of the nbM. Preliminary results suggest a similar pattern of deficits to those following ICV HC-3. Taken together, the results of these experiments indicate a role for the basal forebrain cholinergic projection to the cerebral cortex in attentional processes.

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CONDITIONED PLACE AVERSION WITH LITHIUM CHLORIDE. DOES A TEST UNDER LITHIUM CHLORIDE POTENTIATE LEARNING ?

B. Rocha, Ph. Oberling, G. Di Scala and G. Sandner.

In the context of conditioned place aversion (CPA), we investigated the relevance of testing the animals under drug influence.

In a first experiment, the influence of the number of pairings was tested. Rats were submitted to a classical place conditioning procedure with LiCl (31.8mg/kg, i.p.): the day following the last conditioning day, rats were tested in a drug-free state (postconditioning test); the next day they were retested under LiCl (postconditioning drug-test). It was found that the number of pairings (1 to 4) determined the magnitude of the CPA during the postconditioning test. Only four pairings led to a significant CPA. Contrastingly, the CPA expressed during the postconditioning drug-test was independent on the number of pairings.

In a second experiment, we investigated the putative role on acquisition of a postconditioning drug-test. To this end, the postconditioning drug-test was performed before the postconditioning test. Whereas two pairings in a classical procedure did not produce CPA, the modified procedure elicited a strong aversion during the postconditioning test. Control experiments showed that with this modified procedure: 1) neither a postconditioning drug-test under saline, nor a home-cage injection of LiCl elicited CPA during the subsequent postconditioning test; 2) CPA was stronger than following three pairings in a classical procedure.

It is suggested that testing the animals under drug influence: 1) is not similar to testing them in a drug-free state; 2) may facilitate acquisition of the conditioned place aversion induced with LiCl.

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5-HT_3 ANTAGONISTS INHIBIT THE ANALGESIC RESPONSE TO DEFEAT IN MALE MICE: EVIDENCE FOR A PERIPHERAL ACTION

R.J.Rodgers & J.K.Shepherd

The onset of non-opioid defeat analgesia in male mice is potently blocked by the 5-HT_3 antagonist odansetron (Rodgers et al. 1990, Neuropharmacol., 29: 17-23). The present study investigated the effects of three more 5-HT_3 antagonists on basal nociception and defeat analgesia: MDL73147 (1H-indole-3-carboxylic acid,trans-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl ester methanesulphonate), MDL72222 (1 H,3 ,5 H-tropan-3-yl-3,5-dichlorobenzoate) and MDL72699, a peripherally-acting quaternary derivative of MDL72222. Male DBA/2 mice (Bantin & Kingman, Hull) were group-housed and maintained under a reversed LD cycle in a temperature-controlled room (24±1°C). All testing was conducted under dim red light during the dark phase of the cycle. Tail-flick latencies were recorded before drug administration, and after, drug uptake (basal) or defeat. For defeat studies, DBA/2 intruder mice were introduced into the home cage of an aggressive male BKW resident, and removed upon display of defeat. MDL73147 (0.03-10 mg/kg), MDL72222 (0.01-10 mg/kg) and MDL72699 (0.01-10 mg/kg) had no significant intrinsic effects on tail-flick latency. Defeat analgesia, apparent in all vehicle-treated mice ($p<0.001$), was attenuated by MDL73147 (0.3-10 mg/kg) and MDL72222 (0.01-10 mg/kg). Similarly, the quaternary ligand MDL72699 significantly attenuated the analgesic response, although with a much narrower effective dose-range (0.50-1.0 mg/kg).

These data are consistent with previous reports concerning an inhibition of defeat analgesia with the 5-HT_3 antagonist odansetron, and lend support to the involvement of 5-HT_3 receptor sub-types in the mediation of this form of adaptive pain inhibition. Furthermore, present findings with MDL72699, would indicate a peripheral component in the observed effects of the 5-HT_3 antagonists tested in this paradigm.

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ETHOPHARMACOLOGY, SEROTONIN RECEPTORS AND STRESS ANALGESIA

R.J. Rodgers

Field studies have long suggested that, when faced with danger, animals of many species are capable of inhibiting normal responses to injury. Laboratory studies have provided unequivocal support for the concept of environmentally-triggered analgesia, and have pointed to a primary defensive function. Early methods employed stimuli such as electric shock to induce analgesia, whereas recent work has focussed on more ecologically-valid paradigms. For example, social conflict in male mice is associated with 2 forms of pain inhibition; one opioid, the other non-opioid. Behavioural and pharmacological studies have implicated anxiety in the non-opioid reaction and our most recent work has provided evidence of a major role for serotonin (5-HT) receptor mechanisms.

Findings indicate that non-opioid, defeat-induced analgesia is blocked by drugs that have agonist activity at the 5-HT_{1A} site and which have anxiolytic effects in animal models (e.g. buspirone, ipsapirone, gepirone and 8-OH-DPAT). The 5-HT_{1A} antagonist (-)-pindolol enhances analgesia while, at sub-threshold doses, it potently blocks the effects of ipsapirone. Stereospecificity of 5-HT_{1A} receptor involvement in non-opioid analgesia has been shown by a selective inhibitory effect of the agonist (-) MDL72832. While further studies are necessary, 5-HT_3 antagonists (GR38032F, MDL72222, MDL73147) also inhibit defeat analgesia, and our most recent data suggest a possible peripheral mechanism of action. These new insights into the substrates of intrinsic analgesia systems may ultimately yield fresh approaches to the problem of pain management in the clinic.

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GROOMING BEHAVIOUR: ROLE OF THE HYPOTHALAMIC PARAVENTRICULAR NUCLEUS.

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The hypothalamus has been suggested to play a role in the integration of behavioural and autonomic responses to various stimuli. Behavioural responses evoked by electrical stimulation have shown a spatial organization within the hypothalamus. The neural substrate of this organization is subject of our study.

Excitatory, non-lesioning doses of kainic acid injected into the hypothalamic paraventricular nucleus (PVH) and dorsal hypothalamic area (DHA) have been reported to induce grooming behaviour. This grooming behaviour was measured as a percentage of the total observation time and kainic acid effects on grooming behaviour were compared with the effects of sham injections using each animal as its own control. The results show a clear effect only after injection within the PVH and adjacent dorsal hypothalaic area (DHA).

To investigate the characteristics of this type of grooming behaviour, total time recordings up to 30 min. after injection were made and the time sequence and frequency of different elements of grooming behaviour (eg. face washing, fur grooming, scratching and paw licking) were analysed in detail using PC-Protocol (ProGamma, Groningen, The Netherlands).

Grooming behaviour elicited by kainic acid stimulation of PVH/DHA neurons appears to show an elongation of grooming bouts, which mainly consist of face washing and fur grooming. Scratching can also be induced, but appears later in the time sequence.

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COMPARISON OF THE EFFECTS OF SCOPOLAMINE AND TACRINE IN THE MORRIS WATER MAZE AND DELAYED NON-MATCHING TO SAMPLE TASK.

D.C. Rogers, T.M. Ballard, A.J. Hunter and R.G. Hill

The 'cholinergic' hypothesis suggests that age-related decline in memory and cognitive deficits associated with Alzheimer's dementia are associated with degeneration of central cholinergic systems. Models of these deficits in rats have utilised centrally acting muscarinic antagonists such as scopolamine which have been shown to disrupt performance on a wide range of cognitive tests. We have investigated the effects of scopolamine in two separate tasks, the water maze and delayed non-matching to sample (DNMTS). Additionally, we have studied the action of tacrine, a potent cholinesterase inhibitor which has been shown to improve performance in T-maze active avoidance and passive avoidance learning in rats, as well as producing reversal of scopolamine-induced deficits.
The dose of scopolamine required to disrupt the performance of rats in the water maze was considerably greater than that seen in the operant boxes. In the water maze, well trained rats were required to learn a new platform position and the minimum effective dose of scopolamine that disrupted this task was 0.2mg.kg^{-1}. By contrast, the minimum effective dose of scopolamine required to disrupt performance of rats trained to press for reward in a DNMTS task in the skinner box was 0.06mg.kg^{-1}. This differential sensitivity of the task to scopolamine may be due to the fact that the tasks have different memory requirements or may reflect actions of the drug on non-mnemonic processing. For example, the disruptive consequences of brief lapses of attention are far greater in the operant task than in the water maze. In addition, although decline of DNMTS performance under scopolamine in a delay-dependent manner may be interpreted as a deficit in short-term memory, the increase in delay may simply magnify and disruption of attention to relevant stimuli.
Tacrine (2.5mg/kg) had no significant effect on the scopolamine induced deficits in the water maze. This suggests that the amount of ACh made available by tacrine is unable to overcome the receptor blockade produced by this dose of scopolamine. Reversal of the deficits caused by low doses of scopolamine in DNMTS has been reported and the effects of tacrine on this task will be presented. Thus, the differential sensitivity of tests to scopolamine may have implications for reversal studies with cholinesterase inhibitors.

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SIGMA RECEPTORS AND BEHAVIOR - EFFECTS OF THE SELECTIVE SIGMA LIGAND DTG

N. Rückert and W.J. Schmidt

Sigma receptors are described by Martin et al. 1976 based on their work with the psychotomimetic benzomorphan SKF 10047, a sigma agonist that produces amnesia, dysphoria and in rats dose related increases in locomotion and sniffing. Here, some behavioral effects of 1,3 Di-o-tolyl-guanidine (DTG) are presented:
Male Sprague Dawley rats were tested 10 min after i.p. injection of 2, 4, and 8 mg/kg DTG.
In the spontaneous alternation task using an 8-arm maze, DTG (4 and 8 mg/kg) reduced the average number of arm entries. In the reinforced and delayed alternation task with baited arms, DTG prolonged the time to collect all food pellets. Working memory errors were not changed. The motor depressant effect of DTG was also evident in the dose dependent decrease of sniffing (2 to 8 mg/kg) as well as locomotion in the 8-arm maze.
DTG (8 mg/kg i.p.) was ineffective in place preference conditioning.
In contrast to sigma agonists DTG reduced motor-behavior without any symptoms of amnesia
Still unclear is the relation between sigma receptor and the NMDA complex. We found also an antagonistic effect from DTG to MK-801 induced behavior.

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MOLECULAR SUBSTRATES OF BEHAVIOUR. R.W. Russell

This century began with very basic questions about relations between behaviour and other properties of living organisms. By mid century research in comparative biochemistry had led to the hypothesis that there exists a fundamental chemical ground-plan to which all animals conform and that superimposed on this ground-plan are numerous specific and adaptational variations that characterize differences between and within species. New technologies and new concepts have made it possible to study the roles of molecules in this ground-plan as they participate in events from genetic memory stores in macromolecules to the behaviour of the total, integrated organism. Molecules that affect behaviour may enter the body from external sources, as well as be synthesized within the body. Effects of molecules from either source can only be a result of interactions between them and receptor sites on other biologically important molecules. A molecule binds to its specific receptor initiating an extensive series of events that may lead eventually to effects on behaviour. This concept of the nature of living organisms has led to the view that some forms of behaviour are linked more directly to their biochemical substrates than others. Where the linkage is direct, changes in biochemical events are reflected in specifc changes in behaviour. However, when the linkage is diffuse, changes in biochemical events may affect a variety of behaviours and in some instances, the effect may not be observable unless there already exists an abnormal state of the organism. Both clinical and experimental studies have shown how specific and how critical this cascade of events from molecules to behaviour is in the capability of living organisms to adjust to their physical and psychosocial environments. Biochemical lesions such as the failure to synthesize an important enzyme may lead to disorders of the kind seen in children suffering from phenylketonuria. Inadequate sources of the molecule choline may be involved in the etiology of such aging processes as Alzheimer's disease. Basic to most knowledge about interactions between biochemical events and behaviour is experimentation with animal models in which biochemical events are systematically altered using drugs as tools for research.

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EFFECTS OF COMBINED CHOLINERGIC AND NORADRENERGIC LESIONS ON RAT MEMORY

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Alzheimer's disease (AD) is characterized behaviourally by severe mnemonic loss and neurochemically by reduced cortical cholinergic (ACh) activity originating from the nucleus basalis of Meynert (NBM); noradrenergic (NA) deficiencies have also been reported. However, few studies have manipulated both neurotransmitters in animal models. We trained rats on two variants of an operant matching to position (memory) task, with and without delays (0 - 64 s). They were then divided into four further groups and given neurochemical lesions as follows: (1) NBM, (2) dorsal noradrenergic bundle (DNAB), (3) NBM + DNAB combined, (4) sham controls. Subsequent depletion levels of choline acetyl transferase (ChAT, a marker for ACh) and NA in the cortex, compared to sham, were: NBM, 51% (ChAT); DNAB, 90% (NA); NBM + DNAB, 48% (ChAT) and 92% (NA).

NBM lesions produced a weak disruption of performance which disappeared within days. DNAB lesions had no effect, and the combined NBM + DNAB lesions produced scores similar to the NBM only group. The initial mean percent correct scores were: control, 74%; NBM, 68%; DNAB, 75%; NBM + DNAB, 66%.

The ACh antagonist scopolamine (0 - 0.5 mg/kg, IP) had a profound effect on performance. Moreover, there was evidence to suggest a selective lesion x drug x delay interaction. Methyl scopolamine had no effect.

These results suggest that (a) NBM lesions do not, in rats, produce the severe and permanent mnemonic deficits seen in AD, (b) other cholinergic pathways may be involved, and (c) the noradrenergic loss detected in AD patients may contribute only slightly, if at all, to mnemonic function.

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THE ROLE OF SEROTONERGIC AND ADRENERGIC MECHANISMS IN INHIBITION OF ISOLATION-INDUCED AGGRESSION IN MALE MICE

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Inhibition of isolation-induced aggressive behaviour has been suggested as a test model for anxiolytic effect. Male mice were individually housed for 3 weeks and then trained to attack a group-housed intruder mouse. Only mice reaching attack latencies of less than 10 sec were included in further experiments. Drugs were given s.c. and pretreatment time was 30 min. Test time was 180 sec.

Full (8-OHDPAT) and partial (buspirone, ipsapirone, NAN 190) 5-HT1A agonists inhibited the aggressive behaviour completely. 5-HT1B (TFMPP) and 5-HT2 (DOI) agonists as well as 5-HT1 ((-)alprenolol, pindolol, tiaspirone, spiroxatrine),5-HT2 (ritanserin) and 5-HT3 (ondansetron) antagonists had weak or no effect. The 5-HT-uptake inhibitor citalopram had only effect when given together with 1-5-HTP (5-HT precursor). Prazosin (α1 antagonist) and clonidine (α2 agonist) inhibited completely, and clenbuterol (β agonist) inhibited partly. St587 (α1 agonist), idazoxan (α2 antagonist) and talsupram (NA-uptake inhibitor) was without effect. Ketanserin (mixed 5-HT2 and α1 antagonist) and clozapin (atypical neuroleptic with strong α1 antagonism in vivo) were also effective. Selective dopamine D1 and D2 antagonists (SCH 23390 and YM 09151-2) had no effect.

It is concluded that 5-HT1A receptors as well as α-adrenoceptors are involved in the inhibition of aggressive behaviour in male mice.

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TOLERANCE AND CROSS TOLERANCE TO THE BEHAVIOURAL EFFECTS OF ω (BENZODIAZEPINE) RECEPTOR LIGANDS

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The pharmacological profile of benzodiazepines consists of anticonvulsant, anxiolytic, muscle-relaxant, and memory disrupting effects. Other compounds which act at similar binding sites (ω receptors) share some or all of these effects. There is much evidence to show that tolerance develops rapidly to the depressant effects of benzodiazepines but that the extent to which tolerance occurs to anticonvulsant and anxiolytic effects depends on features of the test situation and the particular compound under investigation. Little tolerance develops to the depression of operant behaviour in rats produced by the imidazopyridine hypnotic, zolpidem, under conditions where tolerance is seen to the similar effects of midazolam and zopiclone. Cross tolerance is seen between benzodiazepines and zopiclone but not between benzodiazepines and zolpidem. Similarly complex results have been reported in investigations of tolerance to anticonvulsant effects. Tolerance does not seem to develop at the same rate to the anticonvulsant activity of different benzodiazepines and studies of other ω receptor ligands, including zolpidem and alpidem, indicate low rates of tolerance development. Such demonstrations of differential tolerance and cross tolerance with different compounds acting at ω sites presumably implicate different modes of interaction with these receptors.

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THE MANY-FACETED RADIAL ARM MAZE TASK : FACILITATION AND IMPAIRMENT OF PERFORMANCE THROUGH THE NORADRENERGIC SYSTEM.
S.J. Sara, C. Dyon-Laurent and V. Devauges.

The role of noradrenaline in attention and behavioral plasticity was studied using both the 8 and 12 arm version of the radial maze. The alpha 2 autoreceptor antagonist idazoxan, which enhances release of noradrenaline, has no effect on the acquisition or performance of the 8 arm maze. Destruction of noradrenaline terminals in the cortex and hippocampus by treatment with the selective neurotoxin, DSP4 likewise had no effect in the 8 arm task. If the room in which the experiment is carried out is changed, the animals respond with a marked disruption of performances. Treatment with idazoxan facilitates adaptation to the change in relevant environmental cues. Noradrenaline-lesioned animals show the same performance decrement as controls but they are not facilitated by idazoxan. Thus intact noradrenaline axon terminals are necessary for the drug to be effective, suggesting that the mediating mechanism of action of idazoxan is through release of noradrenaline in forebrain structures.
In the 12 arm version of the task, which puts a high demand on with-in trial working memory, idazoxan produces a marked impairment in performance of the tasks.
Thus, it appears that increase in release of noradrenaline can enhance performance in tasks requiring shifts in attention to relevant cues. On the other hand, when the task taxes spatial working memory to its limit, as in the 12 arm maze, enhancement of noradrenaline release impairs performance. Since spatial working memory is believed to be highly dependent upon the septal-hippocampal cholinergic system, we are presently investigating to what extent this impairment by idazoxan might be due to inhibition of release of acetylcholine.

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BEHAVIORAL ASPECTS OF ASPARTATE-INDUCED AQUISITION DEFICIT IN VARIOUS EXPERIMENTAL PARADIGMS. V.A. Sazhin, A.V. Yanitzkaya and G.V. Kovalev

After chronic treatment for 10-day period D, L-aspartate in the doses 10 and 100 mg/kg i.p. impaired aquisition of passive avoidance reaction in 2-month rats. In the dose 100 mg/kg, but not 200 mg/kg, it retarded also learning of active avoidance reaction (AAR) of adults rats in shuttle box. Although in 1,5-month extinction period animals treated with amino acid (200 mg/kg) displayed significantly improved retention of AAR compared to both control and aspartate (100 mg/kg) - treated groups maintaining equivalent decreased performance level. Aspartate in the doses 100 and 200 mg/kg disrupted aquisition in 8-arm radial maze increasing markedly time to complete the maze, but did not alter total number of errors and time of water maze aquisition.
After acute administration aspartate only in the dose 100 mg/kg decreased immobilization periods in forced swimming test, but its acute "antidepressant" effect was eliminated after daily injections for 10 days. Chronically aspartate in the dose 100 mg/kg induced fear reaction of rats in elevated plus-maze, in the dose 200 mg/kg decreased locomotor and exploratory activity in open field test. Hence aspartate is predominantly proposed to alter emotional and locomotor behavioral patterns subsequently deteriorating aquisition in various experimental paradigms with negative and positive reinforcements.

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EFFECTS OF DRUGS ON ACQUISITION AND PERFORMANCE IN THE MORRIS WATER MAZE.
J. Scheel-Krüger, E. Widy-Tyszkiewicz and R. Krieger

In recent anatomical studies from our laboratory was found that an intact glutamate transmission from cortex towards the anterior dorsal striatum contributes to internally guided behaviour in the Morris Water maze test.
Furthermore both glutamate and dopamine within the nucleus accumbens were involved in the process of selecting behavioural strategies utilizing contextual retrieval of external cues, the hippocampal - nucleus accumbens link.
These results have now been extended and compared with results obtained after the systemic injection of dopamine D-1, D-2 antagonists haloperidol (0,1 -0,5 mg/kg), raclopride (0,025-0,075 mg/kg), Sch-23390 (0,01-0,05 mg/kg), clozapine (1-7,5 mg/kg), scopolamine (0,1-0,5 mg/kg), the M-1 antagonist dicyclomine (1-5 mg/kg), morphine (1-2,5 mg/kg), the μ agonist sulfentanil (0,25-1 μg/kg) and naloxone (0,25-1 mg/kg in 19° and 23° water).
None of the drugs impaired performance in well-trained rats, whereas acquisition was found impaired by haloperidol, raclopride, Sch23390 and scopolamine. Surprisingly acquisition was improved to various degrees by clozapine and dicyclomine. The effects of sulfentanil and naloxone depended on the experimental conditions.
However, the performance was impaired after subchronic treatment of high doses of Sch23390 (0,1-0,25 mg/kg) without influence on memory, seen after discontinuation of Sch23390.

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NONHUMAN PRIMATE SCRATCHING AND ANXIETY: A PHARMACOLOGICAL STUDY
G. Schino, A. Troisi, G. Perretta and V. Monaco

Several lines of indirect evidence indicate that scratching is an anxiety-related behaviour pattern in nonhuman primates. A number of behavioural studies have reported that scratching tends to occur in situations of tension, conflict, or stress. However, to our knowledge, no study has provided direct evidence that the frequency of scratching is affected by substances that reduce levels of anxiety. The aim of the present study was to assess the effects of lorazepam, an anxiolytic drug, on scratching behaviour in group-living macaque females. The subjects were six adult long-tailed macaques (Macaca fascicularis) living in a captive social group of 35 monkeys. Each subject was observed during two 2-hour sessions after intramuscular administration of lorazepam (0.2 mg/kg) or saline. Behavioural measures included frequency of scratching, locomotor activity, and frequency of approaching to dominant males.

Confirming our predictions, lorazepam significantly reduced the frequency of occurrence of scratching ($p<0.05$). Locomotor activity was not significantly affected by drug treatment. The female subjects' approaches to dominant males increased significantly ($p<0.02$) while on lorazepam. Taken together, these two latter results suggest that lorazepam exerted its effects on scratching behaviour through its anxiolytic properties. In fact, the increase of approaching behaviour is likely to reflect a reduction of female subjects' anxiety toward a potential source of danger (i.e. the dominant males), and the lack of changes in locomotor activity allows us to exclude a sedative effect of the drug. In conclusion, this study provides a pharmacological validation of the notion that scratching is is an anxiety-related behaviour pattern in nonhuman primates.

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NEURO-ANATOMICAL CORRELATE OF THE ANXIOLYTIC EFFECTS OF THE 5-HT_{1A} RECEPTOR LIGANDS 8-OH-DPAT, IPSAPIRONE AND BUSPIRONE IN THE RAT.

R. Schreiber and J. De Vry

The pyrimidinyl piperazines buspirone, gepirone and ipsapirone (IPSA) are second generation anxiolytics with high affinity for 5-HT_{1A} receptors in the brain. These receptors are located both presynaptically (predominantly in dorsal and medial raphe nuclei, DRN and MRN), and postsynaptically, predominantly in the limbic system. In a rat model based on conditioned anxiety (Benz et al., submitted), systemic and central (icv) application of the piperazines and the selective 5-HT_{1A} ligand DPAT dose-dependently and completely inhibits the electric shock induced ultrasonic vocalisation (USV) anxiety response. DPAT and IPSA inhibit USV (0.1-10 and 0.1-30 µg/rat, respectively) when applied locally in the DRN. Both compounds appear to be less potent when applied in the MRN. Depletion of brain 5-HT by means of icv application of 5,7-DHT partially inhibits USV, suggesting that a reduction in 5-HT function has an anxiolytic effect and that the anxiolytic effects obtained with 5-HT_{1A} ligands may involve a presynaptically 5-HT_{1A} receptor-mediated reduction in 5-HT neurotransmission (T. Sharp et al. Br J Pharmacol 96:283, 1989). In 5-HT lesioned rats, however, IPSA administered i.p. retains its ability to inhibit USV completely and in non-lesioned rats, IPSA, buspirone and DPAT, applied bilaterally in dorsal hippocampus (CA4 layer) inhibit USV (CA4 application about 10 times less potent than NRD application). Application of DPAT and IPSA in lateral septum appeared to be less potent as compared to hippocampal application. No tolerance to the anxiolytic response of IPSA was obtained after quadruple application (in 24 hrs) of the compound in either DRN or CA4. Together, these data suggest that both pre- and postsynaptic 5-HT_{1A} receptors are involved in the anxiolytic effects of 5-HT_{1A} ligands.

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NEURO-ANATOMICAL CORRELATE OF THE ANTIDEPRESSANT-LIKE EFFECTS OF IPSAPIRONE AND 8-OH-DPAT IN THE RAT FORCED SWIMMING TEST.

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DPAT [8-hydroxy-2-(di-n-propylamino) tetralin] and the pyrimidinyl piperazines ipsapirone (IPSA), buspirone and gepirone are second generation anxiolytics with high affinity for the 5-HT_{1A} receptor in the brain. These receptors are located presynaptically on the cell bodies of 5-HT containing neurons in the brain stem raphe nuclei (so-called somatodendritic receptors; predominantly in the dorsal raphe nuclei, DRN), as well as postsynaptically, predominantly in the limbic system. Recently, antidepressive effects of 5-HT_{1A} receptor ligands have been suggested in different animal models. In the rat forced swimming test DPAT was found to reduce the immobility response and this antidepressant-like effect was suggested to be presynaptically (DRN) 5-HT_{1A} receptor mediated (L. Cervo et al., Eur J Pharmacol 158:53, 1988). Triple i.p. application (in 24 hrs) of DPAT dose-dependently and almost completely reduced immobility (ED_{50}: 1.6 mg/kg). Single i.c.v. or local application in the DRN resulted in a parallel shift of the systemic dose-response curve to the left (ED_{50}: 5.1 and 3.9 µg/rat, respectively). Triple i.p. or single i.c.v. application of IPSA resulted in an inverse U-shaped dose-response curve; with maximum effects of about 30 and 20% immobility reduction at 3-10 mg/kg and 10 µg/rat, respectively. Local application of IPSA in the DRN dose-dependently reduced immobility (40% effect at 60 µg/kg, the maximal applicable dose). Lesion of the brain 5-HT system by means of i.c.v. application of 5,7 DHT shifted the dose-response curve obtained with DPAT and IPSA to the right (DPAT: ED_{50}: 0.8 and 1.7 mg/kg in sham and lesioned rats, respectively; IPSA: maximal effect at 10 mg/kg: 44 and 18%, respectively). These data suggest that the antidepressive-like effects of DPAT and IPSA are partially mediated at the presynaptic (DRN) level, but that a postsynaptic component may contribute to these effects.

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BEHAVIOURAL AND PHYSIOLOGICAL ASPECTS OF THE AGING PROCESS IN THE NERVOUS SYSTEM OF RATS.

T. Schuurman[1], C.E.E.M. van der Zee[2], W.H. Gispen[2] and J. Traber[1]

Young (2-4 months), middle old (6-12 months) and old rats (18-30 months) were subjected to a variety of behavioural tests in order to study the effects of brain aging on behaviour. The tests included learning and memory, social behaviour, open field, sensorimotor and locomotion tests. Learning and memory function of aged rats was severely impaired as assessed in both simple tasks (one way passive avoidance learning) and more complex tasks (maze learning). Diminished intraspecies social interactions and reduced exploratory behaviour of aged animals in a novel environment suggest that besides impaired information processing or cognitive processes also motivational deficits account for the decreased performance in learning tasks. Furthermore, impaired sensorimotor functions of aged rats as measured in a balance-rod, traction and pole-climbing test may contribute to the differences in learning behaviour between young and old individuals. Finally, an analysis of the walking patterns (footprints) of old rats suggests that the central coordination of the movements of the hindlegs during walking is disturbed in old age. Besides central aging mechanisms, reduced nerve conduction velocity in the sciatic nerves might also account for abnormal walking patterns.
Conclusion: The aging process affects besides cognitive behaviours, also motivational processes, sensorimotor and motor functions. Further physiological, biochemical and histological examinations of the nervous system are necessary to elucidate underlying mechanisms for these age-related behavioural deficits.

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EFFECTS OF NIMODIPINE ON LEARNING AND MEMORY, OPEN FIELD BEHAVIOUR AND WALKING PATTERNS OF AGED RATS

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Nimodipine is a dihydropyridine calcium-entry blocker which easily crosses the blood brain barrier. In neurons nimodipine can block Ca^{2+}-channels of the L-type, thereby reducing the transmembrane influx of Ca^{2+}-ions into the cell. Effects of this drug on the CNS and behaviour have been described before (Hoffmeister et al., Drug Research 32:347-360, 1982). There is growing evidence that increased intracellular Ca^{2+}-ion concentrations play an important role in the aging process of the brain (Landfield and Pitler, Science 226:1089-1092, 1984). Therefore, we investigated whether nimodipine could reduce age-related behavioural deficits in old rats.

Old rats (16-27 months of age) treated with nimodipine escaped faster from a water maze and made fewer errors than age-matched controls. Exploratory behaviour of aged rats placed into a novel environment (open field) was increased after subchronic nimodipine treatment.

Furthermore it was shown that long-term nimodipine-treatment inhibits the progressive impairment of sensorimotor functions during the aging process. The onset of age-related abnormal walking patterns was significantly delayed by chronic nimodipine administration. The reduction of the nerve conduction velocity in the sciatic nerves of old rats was prevented by nimodipine.

It is concluded that the centrally active Ca^{2+}-antagonist nimodipine improves learning in aged rats, stimulates exploratory behaviour and inhibits the progressive loss of sensorimotor functions and degenerative processes in the nervous system.

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INDIVIDUAL DIFFERENCES IN RESPONSE TO AMPHETAMINE: BEHAVIORAL AND NEUROCHEMICAL CHARACTERISTICS

D.S. Segal and R. Kuczenski

There is a relatively wide range of individual differences in responsiveness to amphetamine (AMPH). However, most animals administered transitional doses of AMPH (1.5/2.5 mg/kg) displayed two types of individual response profiles: one with continuous locomotion, characteristic of lower AMPH doses; the other, a multiphasic pattern including a prolonged focused stereotypy phase, typically associated with higher AMPH doses. Pharmacokinetic factors do not appear to underlie the distinct behavioral profiles associated with the two subgroups. Therefore, these differences may reflect intrinsic variation in neurochemical mechanisms regulating responsiveness to AMPH.

Consistent with this interpretation is the observation that with repeated AMPH administration, the two prominent features of the sensitization are dissociable between the subgroups. That is, the emergence of stereotypy was confined to the animals which had exhibited continuous locomotion in the initial response to AMPH, whereas the progressive increase in poststereotypy locomotion was displayed only by those animals which engaged in focused stereotypies in their initial response to AMPH. These results suggest that the profile of stimulant sensitization includes distinct components which can be altered independently.

The wide variation in individual behavioral response to single and repeated injections of AMPH indicates the need for concomitant behavioral and biochemical characterization of the AMPH response in individual animals to elucidate underlying mechanisms. Therefore, in recent studies we have used in vivo microdialysis techniques to measure monoamines during AMPH-induced behaviors in rats. Our results suggest that variations in the behavioral and DA response profiles are not well correlated, indicating that changes in DA alone cannot account for the individual response differences.

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CHANGES OF 3,4-DIHYDROXYPHENYLACETIC ACID AND 5-HYDROXYINDOLACETIC ACID IN HYPOTHALAMUS AND STRIATUM AT DIESTRUS-2 IN RELATION TO STRESS AND TO DIFFERENCES OF CONDITIONED AVOIDANCE PERFORMANCE.

A.Sfikakis, Z.Papadopoulou, A.Sakellariou, M.Sfikakis.

The purpose of this study was to determine possible metabolic changes of brain dopamine (DA) and 5-hydroxytryptamine (5-HT) in relation to the neurogenic stress of the shuttle box avoidance assay and in relation to differences of conditioned avoidance performance. Rats were submitted to the avoidance test only on diestrus-2 after at least 4 consecutive 4 day-oestrous cycles. They were sacrificed immediately after one 30min shuttle box avoidance session of 60 trials. Serum progesterone was measured by RIA and hypothalamic and striatal DA, 3,4-dihydroxyphenylacetic acid (DOPAC), 5-HT and 5-hydroxyindolacetic acid (5-HIAA) were measured by HPLC with electrochemical detection.

Comparison of rats submitted to the shuttle box avoidance assay with their littermates controls revealed a significant increase of progesterone, of hypothalamic 5-HIAA, DA and DOPAC and of striatal 5-HIAA but no difference in striatal DA and DOPAC. In relation to avoidance performance hypothalamic DOPAC was higher in low performers compared to high performers but not different from rats with lack of acquisition. Hypothalamic 5-HIAA was higher in rats with lack of acquisition in comparison to high performers while striatal 5-HIAA was similar in the three groups. The results suggest that stress induced activation of DA and 5-HT in hypothalamus, but not in striatum, is negatively related to avoidance performance.

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MOTIVATIONAL EFFECTS OF 5-HT1 RECEPTOR AGONISTS: PLACE CONDITIONING AND IN-VIVO MICRODIALYSIS STUDIES

T.S. Shippenberg, R. Spanagel and A. Herz

Serotonin (5-HT) systems have been implicated in the modulation of mood and motivation. The receptor types and neural substrates mediating such effects are unknown. This study used the conditioned place preference paradigm and in-vivo microdialysis to examine the motivational effects of 5-HT1 agonists and the role of the mesolimbic dopamine (DA) "reward" pathway in mediating such effects. Rats exhibited a marked preference for a stimulus paired with sc injections of the 5-HT1a agonists 8-OH-DPAT. Preferences were also observed with morphine and amphetamine (AMP). In contrast the 5HT1b agonist CGS-12066B was without effect. 6-OHDA lesions of the n. accumbens (NAC) abolished morphine and AMP-induced conditioning. Pilot studies indicate that this treatment does not alter 8-OH-DPAT-induced place preferences. Microdialysis studies revealed that behaviorally effective doses of 8-OH-DPAT decreased NAC DA release whereas morphine and AMP increased release. 8-OH-DPAT also decreased dialysate levels of 5-HT and 5-HIAA. These data indicate that 8-OH-DPAT, like morphine and AMP, functions as an appetitive reinforcer in rats. However, 8-OH-DPAT, in contrast to prototypic drugs of abuse, does not appear to exert this effect via stimulation of the mesolimbic DA "reward" pathway.

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INDEPENDENCE OF CONDITIONED PLACE PREFERENCES AND ACTIVITY IN RATS. M. Shoaib, I.P. Stolerman and T. Hewett

Changes in activity may interfere with measurements of conditioned place preferences (CPP) produced by addictive agents. The aim was to establish a CPP procedure for studies on nicotine, using morphine as a standard addictive agent. The present study used a box with two distinctive compartments to examine the role of conditioned locomotor activity in CPP produced by morphine. The validity of recordings from photocells was tested by comparing them with direct observations. After three 15-min exposures to the apparatus, rats received morphine (0.1-10.0 mg/kg SC) and were confined in one compartment for 30 min. On alternate days they received saline and were confined in the other compartment according to a counterbalanced design (n=8). After 4 drug and 4 vehicle sessions, they were given access to both compartments in 15 min trials.

Correlations between observed and automated data were high and reliable [$r(10)=0.87$-0.93; $P<0.001$]. Increasing doses of morphine produced consistent increases in preferences for the drug-paired compartment, with a maximal effect achieved at a dose of 3.2 mg/kg. Morphine produced dose-related increases in locomotor activity that became greater across successive conditioning trials. During tests for CPP, activity measured in drug- and saline-paired compartments was similar; there was no evidence for conditioned changes in activity that might have influenced the measures of CPP. Neither chequered and grey rather than black and white visual cues, nor floors with different textures instead of wire grids, influenced the results with morphine (10 mg/kg). The results highlight the advantage of using an automated apparatus in which effects of morphine on locomotor activity do not contribute to the expression of CPP. Such procedures may be useful for testing motivational properties of nicotine and other agents (research supported by Medical Research Council).

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IS THE ANTIAGGRESSIVE ACTION OF HALOPERIDOL IN LABORATORY ANIMALS A MODEL FOR ITS ANTIPSYCHOTIC EFFECTS IN HUMANS?

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The effects of a dose of Haloperidol (0,4 mg/kg, i.p.) administered acutely or chronically for 9, 15 or 30 days were determined on agonistic behaviour in male mice. 174 OF1 albino male mice commercially acquired, arriving in the laboratory at 42 days of age, and housed under standard conditions with a reverse light schedule, were used in this study. Half were individually housed in transparent plastic cages for 30 days and employed as experimental animals, the remainder were housed in groups of six to be used as 'standard opponents'. The latter were temporally rendered anosmic by intranasal lavage with zinc sulphate solution. 10 minute diadic interactions were staged between a singly housed and an anosmic mouse in a neutral arena. The encounters were videotaped and the accumulated times allocated by subjects to 11 broad behavioural categories estimated. Categories were compared using Mann-Whitney U tests. When tested 30 minutes after injection, the antiaggressive effects of Haloperidol are evident after 9, 15 and 30 days of treatment whereas its motor consequences (marked increase in immobility) develop a clear tolerance to repeated administration of the drug. Such a disparity between the temporal course of the antiaggressive and the motor properties is reminiscent of the differential course showed by antipychotic and extrapiramidal effects of neuroleptics in clinical use. This finding points to the possibility of using the antiaggressive action of neuroleptics in the laboratory animals as a model for their antipsychotic effects. It also strongly suggests that decreases of aggression caused by Haloperidol are not purely a consequence of its decremental effect on motor behaviour since the temporal course of these phenomena is clearly divergent under certain circumstances.

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THE SOCIAL INTERACTION TEST: A NEW PARADIGM TO PINPOINT DIFFERNTIAL DRUG EFFECTS. M. Soffié and M. Bronchart.

The social interaction test consists of analysing the behavioural repertoire in pairs of rats after a separation period of 15h. The procedure was as follows: pairs of rats were reunited and observed during 500 sec. (for details see Soffié and Bronchart, Psychopharmacology, 1988, 95: 344-350). The type of behaviour was noted every 5 sec. according to the folllowing six categories: (A) environmental interaction regrouping all behavioural patterns not directed towards the animal itself or towards its partner such as exploration, locomotion and rearing: (B) individual grooming; (C) social investigation (principally sniffing); (D) social grooming; (E) agonistic interactions and (F) immobility. Several drugs were tested; cholinergic and noradrenergic blockers, anxiolytic, anxiogenic and antidepressant drugs.

Results obtained with young adult rats show a behavioural profile specific for each drug tested. Moreover for most of them a dose relationship was found. Some of the drugs were also tested in aged and/or presenescent rats. Preliminary results suggest a difference in drug sensitivity during ageing (i.e. hyposensitivity for the cholinergic blocker, scopolamine and supersensitivity for the $\alpha 2$ noradrenergic agonist clonidine). This behavioural paradigm therefore appears promising and useful in psychopharmacology. (Supported by Region Wallonne-IRSIA-UCB grant/100).

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IDENTIFICATION OF THE OPIOID RECEPTOR TYPES MEDIATING THE β-ENDORPHIN-INDUCED DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS. R. Spanagel, A. Herz and T.S. Shippenberg

Several studies have demonstrated that dopaminergic (DA) neurotransmission in the mesolimbic system is modulated by opioid agonists. A stimulation of DA metabolism is observed following central administration of the endogenously occurring opioid peptide β-endorphin. However, the receptor type through which β-endorphin acts to exert its effects in vivo remains unclear. Therefore we examined this issue by use of in vivo microdialysis in both the freely behaving and anesthetized rat. Microdialysis probes were inserted into the nucleus accumbens and perfusates were analyzed for DA and its metabolites: dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) using a reversed phase HPLC-system with electrochemical detection for separation and quantification. The detection limit for DA was 10 fmol/50 µl dialysate. Intracerebroventricular (ICV) administration of β-endorphin resulted in a dose dependent increase in DA and metabolites. Pretreatment with the selective δ-antagonist ICI 174,864 significantly attenuated the β-endorphin-induced increase in DA release whereas pretreatment with the selective µ-antagonist CTOP resulted in an abolition of the β-endorphin effect. The receptor specifity of both antagonists is indicated by the findings that CTOP pretreatment abolished µ-agonist- (DAMGO) induced DA release but dit not modify that produced by the δ-agonist DPDPE, whereas ICI 174,864 abolished the δ-agonist- (DPDPE) induced DA release, but not that of DAMGO. These data demonstrate that the blockade of either µ- or δ- opioid receptors is sufficient to antagonize the stimulatory effects of β-endorphin on DA release. Further they provide apparent support for the hypothesis that β-endorphin may exert its central effect upon DA release via an interaction with an opioid receptor complex composed of both µ-and δ-receptors.

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DIRECT EVIDENCE THAT THE FELINE CAUDATE NUCLEUS HAS FUNCTIONALLY AND ANATOMICALLY DIFFERENT INPUT AND OUTPUT CHANNELS

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Previous studies have shown that the feline caudate nucleus (CN) can be subdivided into at least two sub-regions i.e. the rostromedial CN (CRM) and rostrodorsal CN (r-CRM). The CRM, susceptible to apomorphine (APO) and haloperidol (HAL), is involved in switching arbitrarily from one behaviour to another. This function is funneled via the well-known striato-nigro-collicular pathway. In contrast, the r-CRM is unsusceptible to APO and HAL but susceptible to DPI, an agonist of a sub-class of dopamine receptors. Bilateral injections of DPI into the r-CRM induce oro-facial dyskinesia (OFD) i.e. tic-like contractions of the facial eye, ear and cheek muscles and tongue protrusions. OFD is also elicited from the sub-commissural part of the Globus Pallidus (scGP), a first order output station of of the r-CRM but not the CRM, by inhibition of GABA or stimulation of acetylcholine (ACH). On basis of these data it has been hypothesized that 1) OFD is a feature of the r-CRM, but not the CRM, and that 2) OFD is funneled via the scGP. To provide direct evidence in favour of these hypotheses, the present study was conducted. Accordingly, cats were bilaterally equipped with cannulae directed at the CRM or r-CRM and scGP. After recovery, the cats received intra-CRM and r-CRM injections of DPI (5 and 10 ugr/5ul), the latter in combination with intra-pallidal injections of muscimol (50 and 100 ngr/1ul) or its solvent. Subsequently, behaviour was analyzed. OFD, quantified in terms of tongue protrusions, could only be elicited from the r-CRM, and not from the CRM. Furthermore, OFD elicited from the r-CRM could be attenuated by muscimol injections into the scGP. These data show that OFD is funneled from the r-CRM to the scGP. Additional retrograde tracing experiments have provided direct evidence that the r-CRM and CRM have their own input and output channels. Taken together these data show that the CRM and r-CRM have distinct input and output channels that are differentially involved in behaviour.

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BENEFICIAL EFFECTS OF ORG2766 IN AGING AND FIMBRIA FORNIX LESIONED RATS
Berry M. Spruijt

Effect of chronic treatment with the $ACTH_{4-9}$ analog Org2766 on social attention was studied longitudinally in aging rats. During treatment social attention remained at the same level in Org2766-treated animals, whereas control animals showed a gradual decrease in reactivity upon changes in behavior of another rat. One month after the treatment was ceased this effect was still present; moreover, these animals performed better in a spatial learning task, as was assessed in a Morris maze, four weeks after the last injection.

In addition, the nerve conduction velocity of the major caudal nerves and the sciatic nerve were measured; aged peptide-treated animals preserved their conduction velocity. The present study shows beneficial long-lasting effects of Org2766 in aging rats on social attention, spatial orientation and on a parameter essential for nerve functioning. Neurotrophic properties of Org2766 have already been described in peripheral nerve regeneration paradigms and neuronal development. The findings in aged rats were elaborated in a lesion paradigm involving hippocampal denervation and spatial orientation deficits. The beneficial effects of Org2766 were tested in animals lesioned in the fimbria fornix. The lesion dramatically affected the performance of a spatial learning task, however, animals treated with Org2766 after the lesion for two weeks showed a remarkable improvement in their performance.
Summarizing, both the performance of aged animals and of fimbria fornix lesioned young rats in a spatial orientation task improved after a chronic treatment with Org2766.

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SOCIAL RELATIONSHIP-INDUCED PLACE PREFERENCE BEHAVIOR IN RATS. C. Spyraki*, G.G. Nomikos

The present study examined the role of social relationship as the unconditioning stimulus in the place conditioning paradigm. In experiment I, dyads of rats consisted of two male or two female rats were randomly assigned to one of two distinct environments. Placement occurred for 60 min. every other day for 8 days. The alternate days each rat was placed single in the other side. The place preference of each rat was assessed over a 20 min. test period. Male and female rats showed significant preferences for the compartment that was associated with the presence of another rat of the same sex. In experiment II, couples of male or female rats were confined to the less preferred side, as that was determined by a preconditioning test. The conditioning phase was as in experiment I. The postconditioning test revealed that only the male rats increased their preference for the compartment where the placements of the dyads occurred. In experiment III, couples of male and female rats were given 8 60 min-exposures to one of two sides. At the postconditioning test the rats did not show any preference for either the novel or the side that was associated with the existence of the couples. In experiment IV, dyads of rats consisted of a dam and one of its pups. The mothers were multiparae and they varied across the postpartum period 1st, 2nd and 3rd week after delivery. Each dyad was placed for one hr over 5 days in the same side. The postconditioning test showed that mothers in the 3rd postpartum week significantly increased their preference for the compartment associated with the presence of their pup over the novel compartment. The results demonstrate that rats show a conditioned place preference for a compartment in which they have previously interacted with another rat of the same sex or with their offspring.

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Sex-differences in stress-induced behavioral inhibition.
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Stress-induced behavioral disturbances have widely been used as animal models of depression. Stress-induced suppression of activity has been a disputable topic for a long time within the 'learned helplessness' (LH) paradigm [S.F. Maier et al. In: The psychology of learning and motivation, edited by G. Bower. New York: Academic Press. 1979, Vol.13, pp 155-218].
In three experiments we investigated the behavioral consequences of exposure to IS in male and female Wistar rats. We studied changes in activity during IS in free moving subjects in a skinnerbox (Exp.1a), and 24 hours later in a shuttlebox (Exp.1b). The shuttlebox was choosen to study behavior in an environment which shows strong similarities to contextual stimuli present in the skinnerbox. Further we studied behavior 24 hours after IS in the elevated plus-maze (Exp. 2) and in the hole-board (Exp. 3). In Exp.1a both sexes showed a strong suppression of activity during IS. In Exp.1b suppression of activity compared to no-shock control subjects was shown in both sexes. In Exp.2 IS resulted in suppression of 'total number of arm entries' and 'rearings' in males but not in females. In addition 'time on open arms' was reduced in both sexes after IS, which seemed stronger in males than in females. Exp.3 showed that IS reduced ambulation and rearing in the hole-board only in males, whereas the time spent on head-dipping was reduced in both sexes.
A sex-difference in emotional reaction to stress might contribute to the observed sex difference in stress-induced behavioral inhibition. The strong behavioral inhibition tendency observed in males, strongly interferes with the acquisition of the subsequent escape response by this sex as studied within the LH-paradigm. These findings therefore predicts a stronger susceptibility for male compared to female rats, for engaging in 'learned helplessness'.

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STRESS-INDUCED ANALGESIA: IMPLICATIONS FOR STUDYING LEARNED HELPLESSNESS IN BOTH SEXES. H.L. Steenbergen, R.P.W. Heinsbroek and N.E. van de Poll

Exposure to inescapable shocks (IS) has been shown to produce deficits in subsequent shock-avoidance/escape procedures in rats ['learned helplessness' (LH); S.F. Maier et al. J Exp Psychol: General 105: 31-46, 1976]. Another consequence of exposing rats to footshocks is to elicit antinociceptive effect which has been termed stress-induced analgesia (SIA). In both LH and SIA, the 'uncontrolability' has been described as an absolute essential factor. It was recently reported that LH could also be induced in female Wistar rats, though the impact is less intense than in males [H.L. Steenbergen et al. Physiol Behav 45:781-878, 1989] On the other hand, SIA has been reported to be displayed significantly less in female rats than in males [M.-T. Romero et al. Physiol Behav 44:257-265, 1988].
In our experiment free moving male and female Wistar rats were exposed to IS of either relatively low (0.5 mA) or high (1.0 mA) shock-intensity. Subsequent shuttlebox escape training was conducted using also the former mentioned shock-intensities (0.5/1.0 mA). IS exposure most prominently affected escape performance in males than in females compared to no-shock control (C) subjects. Especially males previously exposed to 1.0 and trained on 0.5 shock-intensity, showed the most prominent disturbed escape performance. SIA was further studied using the tail-withdrawal test for measuring pain responsiveness. IS resulted in a transient analgesia in both sexes compared to C-subjects. The effects of IS were no longer present 24 hours later after a short re-exposure to the compartment in which IS or C treatment was administered the day before. It is proposed that previous exposure to IS results in SIA in both sexes, and probably somewhat stronger in males than in females. Although it is unclear to what extent sex-differences in LH studies are determined by differences in SIA.
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AN INVOLVEMENT OF ACCUMBENS GABA-B RECEPTORS IN THE REGULATION OF MUSCLE TENSION. R. Stefański, A. Plaznik and W. Kostowski

The role of Gaba-ergic mechanisms within the nucleus accumbens septi (NAS) in the regulation of muscle tension was investigated in rats using behavioral tests: bar test, inclined wire-mesh platform test, rota-rod test and Wirth's test of catalepsy. The results show that baclofen dose-dependently decreased muscle tone both when injected into the NAS (1.0 and 2.5 μg), and intra-peritoneally in a dose of 20 mg/kg. In the Wirth's test intra-peritoneal injections of haloperidol (5.0 mg/kg) produced catalepsy, while baclofen (20 mg/kg) was ineffective in this respect. Intra-accumbens microinjections of muscimol (GABA-A receptor agonist), midazolam (benzodiazepine receptor agonist), nicardipine (calcium channel inhibitor) as well as peripheral injections of haloperidol (0.1 and 1.0 mg/kg) and midazolam (2.0 and 10.0 mg/kg) failed to modify the myotonus in the wire-mesh test, thereby ruling out the involvement of GABA-A receptors, benzodiazepine receptors, as well as dopaminergic and calcium channel mechanisms in the regulation of muscle-hypotonia. These data suggest that the relaxant effect of baclofen may be mediated through GABA-B receptor sites within the NAS. The possible involvement of dorsal-versus ventral-striatum balance in the GABAergic activity in the symptomatology of the Parkinson disease, is discussed.

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IMMUNOMODULATORY TREATMENT INHIBITS THE BEHAVIOURAL EFFECTS OF BENZODIAZEPINE RECEPTOR AGONISTS AND ANTAGONISTS. A. Sulcová, O.Gulda.

There is evidence that treatment with benzodiazepine receptor (BZr) ligands influences the immune system. The aim of this study was to investigate whether treatment with immunomodulatory agents can also change the behavioural pharmacology of BZr ligands.

We studied the interactions between immuno-adjuvant agents and benzodiazepine ligands in an experimental model of mice agonistic behaviour. Dyadic interactions between singly housed male mice with non-aggressive group housed partners were used to quantify drug effects on anxiety, defensive escape and sociable behaviour. The behavioural effects of benzodiazepine ligands and immuno-adjuvent agents were assessed singly and in all combinations of immuno-adjuvent and benzodiazepine ligands.

The anxiolytic effect of 4 mg/kg Diazepam was evident from the inhibition of defensive escape behaviour and the stimulation of sociable activities in timid singly housed mice. The anxiogenic effect of 5mg/kg of the ß-carboline FG 7142, an inverse BZr agonist, was evident from the increase in defensive escape behaviour and the decrease of sociable activities in timid isolates.

When given *alone*, the immunomodulatory drugs Levamisol (1mg/kg), MDP (5mg/kg) and AdDP (2mg/kg) did not change the behaviour of timid isolates. However, when given *in combination* with BZr ligands these immunomodulators all *antagonized* the anxiolytic effect of Diazepam as well as the anxiogenic effect of the inverse agonist FG 7142.

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U-78875, A BENZODIAZEPINE ANXIOLYTIC WITH POTENT ANTAGONIST ACTIVITY. A.H.Tang, S.R.Franklin, P.M.Ho, D.P.Blakeman, W.B.Im, V.H.Sethy, and T.T.Oien.

U-78875 (U; 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-(1-methyl-ethyl)-imidazo<1,5-a>-quinoxalin-4(5H)-one) has a high affinity for the benzodiazepine (BZ) receptors in rat brain membrane. It displaced the binding of ^{3}H-flunitrazepam with a Ki of 1.56 nM. Like the BZ antagonist, flumazenil, U did not affect the binding of ^{35}S-TBPS (TBPS shift ratio = 1.07). U was very weak in enhancing GABA-mediated $^{36}Cl^-$ uptake into rat cerebrocortical synaptoneurosomes, but antagonized the enhancing effect of diazepam on ^{36}Cl uptake and TBPS binding.

In behavioral tests, U has both BZ agonist and antagonist properties. At i.p. doses of 1-3 mg/kg in rats, it increased lever-press responding which had been suppressed by shocks (Geller's conflict test). Punished water-licking in the Vogel's procedure was also increased at the same doses. In rats chronically implanted with cortical electrodes for EEG recording, U (1-10 mg/kg) produced an increase of EEG power density at frequencies above 12 Hz, and a decrease of EEG power at the lower frequencies. The EEG effect was antagonized by flumazenil (10 mg/kg), which by itself produced little EEG change.

In the mouse one-trial passive avoidance task, U produced no locomotor depressant or amnesic effect, but completely antagonized the effects of diazepam (10 mg/kg) in this test. U was much weaker than diazepam to impair rotorod performance and did not suppress conditioned avoidance in rats. On the other hand, the depressant effect of diazepam in these tests was completely antagonized by U. U is being developed as a novel anxiolytic in man.

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THE CCK-B/GASTRIN ANTAGONIST L-365,260 INCREASES PALATABLE DIET CONSUMPTION IN FREE FEEDING RATS.
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On the basis of receptor binding and functional studies CCK receptors have been classified into two subtypes: peripheral type, CCK-A and gastrin/brain type, CCK-B. The selective CCK-B/gastrin antagonist L-365,260 has previously been shown to increase food intake and postpone satiety in food deprived rats (Dourish *et al,* Science 245:1509, 1989). The present study investigated the effects of CCK octapeptide sulphated (CCK) and L-365,260 on the consumption of a palatable wet mash in rats, a procedure which uses animals that are not food deprived. Individually housed male SD rats were presented daily with a palatable sweet mash (powdered food mixed with water and sweetened condensed milk) for a 60 min period. The animals were not food deprived but immediately before presentation of the mash their normal food pellet diet was removed.

The amount of mash consumed during 60 min was determined for each animal. After 7 days the quantity of the palatable diet consumed had reached an asymptotic level with approximately 12g being eaten. In studies investigating the effects of CCK on mash consumption animals were injected ip with CCK (1-8μg/kg) and the amount consumed during the next 30 min determined. In studies using L-365,260 the rats were given a period of 40 min access to the palatable diet (presatiation) after which the mash was removed and weighed. The rats were injected subcutaneously with L-365,260 (10pg/kg - 10μg/kg) or its vehicle (1ml/kg : 2%v/v ethanol in 0.5%w/v Methocel) and after 30 min the weighed palatable diet was reintroduced into the cages. The amount of food consumed during the following 60 min was determined. CCK (1-8μg/kg) produced a dose dependent decrease in mash consumption. Significant increases in food intake were produced by L-365,260 at doses of 100pg/kg - 1μg/kg. The results of this study confirm that L-365,260 increases food intake in partially satiated rats and illustrate that this hyperphagic action can be observed in animals which have not been food deprived. These findings provide further evidence that blockade of CCK-B/gastrin receptors postpones the onset of satiety in rats.

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INTERACTION OF BUSPIRONE WITH "ANXIOGENIC" DRUGS IN A SAFETY SIGNAL WITHDRAWAL PARADIGM OF CONFLICT BEHAVIOR. M.H. Thiébot, L. Dangoumau, D. Charrier and A.J. Puech.

A suppression of operant responding for food reward sensitive to anxiety-related drugs was induced in rats by the withdrawal of a conditioned signal for safety with no presentation of conditioned signal of punishment (and no punishment). This behavioral suppression was lessened by several benzodiazepines and by the agonists at 5-HT1A receptors, buspirone (0.25-2 mg/kg ip) and gepirone (0.125-1 mg/kg sc) but not by 8-OH-DPAT nor by the antagonist at 5-HT3 receptors ICS 205-930. The blockade of lever pressing induced by the safety signal withdrawal was further enhanced by picrotoxin, caffeine, CGS 8216 and FG 7142 in keeping with an "anxiogenic" effect of these compounds. Buspirone (1 mg/kg), but not 8-OH-DPAT (0.015-0.03 mg/kg sc) nor ICS 205-930 (0.01 mg/kg sc), antagozined the enhanced behavioral blockade induced by picrotoxin (1 mg/kg ip). Buspirone also counteracted the effects of caffeine (16 mg/kg ip) and CGS 8216 (2 mg/kg ip) during the period associated with the safety signal withdrawal, but CGS 8216-induced reduction of baseline performances was not modified. Thus, buspirone seemed to specifically interact with a particular state associated with the safety signal withdrawal and the 3 "anxiogenic" drugs. The effects of FG 7142 (8 mg/kg ip) however, were not reversed by buspirone but conversely, FG 7142 completely antagonized the anxiolytic-like effects of buspirone.
These results indicated that acute buspirone reliably released the suppression of operant responding induced by the safety signal withdrawal and counteracted the effects of several (but not all) "anxiogenic" compounds in this procedure. This suggested that this kind of inhibition might be subserved by different neurobiological processes and that the behavioral blockade induced by the safety signal withdrawal might be a better index of uncertainty-induced anxiety than the inhibition generated by signal of punishment.
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POLITICS IN THE DEVELOPMENT OF BEHAVIORAL PHARMACOLOGY. T.I. Thompson

Scientific research is supported largely by public funds. There is an implicit contract among researchers, our governments and taxpayers concerning the support for research. This contract provides scientists with a good deal of latitude in exploring basic science ideas so long as, at least periodically, researchers are willing to directly address important problems facing our societies. Research in behavioral pharmacology affords a unique opportunity to bring basic science knowledge to bear in helping solve important human problems, while concurrently generating significant new basic scientific knowledge. Substantial contributions have already been made by behavioral pharmacology in the area of drug abuse and behavioral teratology and toxicology. Within the next decade, behavioral pharmacology will begin to make more significant inroads in clinical behavioral pharmacology of mental health problems, and in treating behavior disorders among people with developmental disabilities. Programmatic research in which basic science is embedded within the context of resolving human problems is the best mechanism for assuring long term support for excellence in behavioral pharmacology.
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OXYTOCIN BLOCKS CONDITIONED TOLERANCE TO ETHANOL. E. Tirelli, P. Klingbiel and C. Jodogne

It is generally accepted that oxytocin (OXY) attenuated tolerance to ethanol (ETH); OXY has also been shown to disrupt learning and memory (Szabo et al., Front. Horm. Res. 15:128, 1987). On the other hand, it is known that tolerance is more pronounced when assessed in the presence of ETH-associated cues rather than in their absence. Such an environment-specific tolerance (EST) has been explained in terms of associative learning and considered as a conditioned tolerance (Le et al., Science 206:1109,1979). From this arises the possibility that the effect of OXY on tolerance to ETH is exerted via an inhibition of learning processes. In this study we used a conditioning paradigm, with the testing room as CS, to examine the effect of OXY on EST to the hypothermic effect of ETH. Twice daily, for four days, four groups of OF-1 mice received two i.p injections two hrs. apart. The two CS-paired groups were given either SAL + ETH (2g/kg) or OXY (0.005 mg/kg) + ETH in the testing room, and SAL twice in the colony room after measurements. The CS-unpaired groups received SAL twice in the testing room, and SAL + ETH in the testing room. EST to the hypothermic effect of ETH was found in the SAL + ETH paired group tested in the ETH associated context, and this group was more tolerant than the SAL + ETH unpaired one. This EST was diminished in OXY + ETH paired group whereas OXY was without effect in the unpaired condition. According to Le et al. (1979), EST occurs because a compensatory hyperthermia conditioned to ETH-paired cues attenuates the ETH effect. In a second experiment, using the same design as in Exp. 1, except that the four groups received only SAL on day 5, hyperthermia was absent in the OXY + ETH paired group. Our results suggest that OXY exerts a selective inhibition on the development of this conditioned tolerance.

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ACTION OF RITANSERIN AND DOI ON THE ELEVATED X-MAZE
D.M. Tomkins, B. Costall and M.E. Kelly

The 5-HT_2 antagonist ritanserin (Van Neuten et al., Drug Dev. Res. 8: 187, 1986) has been shown to treat generalised anxiety disorder and phobic anxiety. However, experimental evidence is conflicting: little anxiolytic activity is observed in classical conflict models and both anxiolytic and anxiogenic effects are seen in neophobia-based models. We investigated the effects of ritanserin alone or in combination with the 5-HT_2 agonist, DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) using a novel protocol for the elevated X-maze (Costall et al., Br. J. Pharmacol. 96: 312P, 1989).

Male hooded Lister rats received: vehicle + vehicle (VEH), VEH + DOI (0.1mg/kg i.p.), ritanserin (0.1mg/kg i.p.) + VEH, or ritanserin + DOI. These were then placed on the maze and the time spent (T) and number of entries (E) onto the end sections of the maze arms were assessed for 10 min and the results expressed as a ratio of open/total (O/T) x 100.

Control animals showed a marked preference for the closed arms as indicated by the O/T ratios of 221±31 and 182±21 for E and T respectively. Treatment with VEH + DOI caused slight but insignificant reductions in both these measures. In contrast, treatment with ritanserin + VEH significantly increased O/T E and O/T T to 323±20 ($P<0.05$) and 270±28 ($P<0.05$). DOI significantly reversed these effects.

The action of ritanserin in our model of the elevated X-maze is consistent with anxiolysis. This agrees with the findings of Critchley & Handley (Psychopharmacol. 93: 502, 1987). The reversal of the anxiolytic effect by DOI would indicate an action via 5-HT_2 receptors.

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IS NONVERBAL BEHAVIOUR DURING INTERVIEW A VALID INDEX OF IMPROVEMENT IN DEPRESSED PATIENTS ?

A. Troisi, A. Pasini, G. Bersani, A. Grispini, and N. Ciani

In a previous study, we found that depressed patients' response to tricyclic treatment could be predicted on the basis of the ethological profile at baseline (Troisi et al., J. Affective Dis. 17:129-136, 1989). In the present study, analizing data from the same 22 subjects, we aimed at ascertaining whether nonverbal behaviour during interview is a valid index of improvement. Patients' nonverbal behaviour was recorded during the initial interview (i.e. before drug administration) and during the final interview (after 5 consecutive weeks of antidepressant treatment, 50-100 mg/day of amitriptyline). At the end of the study, patients were divided into two treatment outcome groups (responders and nonresponders) on the basis of their final Hamilton depression score. A repeated measures analysis of variance was performed on each of eight behavioural categories.

A significant therapy effect was found for Submission (p=0.01) and Affiliation (p=0.03). However, no significant interaction effect was found between group and therapy, indicating that an increase in submissive and affialiative behaviours was shown by both responders and nonresponders. Two alternative explanations for these results are plausible. First, that etological profile reflects personality traits rather than mood state. If this is the case, while useful for predicting drug response, etological profile is not a valid index of improvement. Secondly, that nonresponders' judgement of their subjective well-being was not accurate, which produced inconsistency between nonverbal information and verbal content. If this were the case, nonverbal behaviour should be trusted over verbal content.

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EFFECTS OF TOTAL AND PARTIAL BILATERAL FIMBRIA-FORNIX LESIONS ON SPATIAL LEARNING AND RETRIEVAL ABILITY OF RATS - EFFECTS OF A NORADRENERGIC ALPHA-2 AGONIST, GUANFACINE

A. VALJAKKA, R. MIETTINEN, R. LAMMINTAUSTA, S. NIEMINEN AND P. RIEKKINEN

The whole fimbria-fornix (FF) or only the lateral part of fimbria of male Wistar rats were aspirated bilaterally. Rats were trained in a Water maze spatial learning task. Rats in the partial FF-lesion group recieved either guanfacine (0.1 mg/kg, i.p.) or vehicle 30 min before daily testing. After a recovery period of 3 weeks rats with total FF-lesion were unable to learn the Water maze spatial learning task. In the vehicle group partially FF-lesioned rats learned the Water maze task more slowly than control lesioned animals when tested 2 months after the lesioning. However, the guanfacine treated lesioned rats did not differ from the non-medicated control animals. In the spatial probe memory test performed one week after the learning period only the FF-lesioned rats treated with guanfacine were impaired as compared to undrugged control rats. The open-field testing revealed that the exploratory activity of the totally FF-lesioned rats was decreased as compared to the control group. Biochemical assays of hippocampal amines and staining for AChE in the dorsal and ventral part of hippocampus were made for partial FF-lesion-group. The only difference observed was a decreased concentration of serotonin (31 %) in the hippocampus of lesioned animals.

These results would suggest that guanfacine administered during the learning period slightly improved the spatial learning ability of partially FF-lesioned rats.

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BEHAVIOURAL STUDIES ON THE ROLE OF EXCITATORY AMINO ACIDS IN THE NUCLEUS ACCUMBENS OF THE RAT

Ruud van den Bos, Gustavo A. Charria Ortiz* and Alexander R. Cools

Previously it has been shown that the nucleus accumbens is involved in the ability to switch to cue-directed behaviours using the swimming test as experimental paradigm (Van den Bos and Cools, Life Sciences 44: 1697-1704, 1989). The nucleus accumbens receives afferents from structures like the amygdala, hippocampus and prefrontal cortex, that are thought to use the excitatory aminoacids (EAA) glutamate and/or aspartate as neurotransmitter. It was therefore decided to study the ability of these EAA to affect switching to cue-directed behaviour.
The quisqualate-agonist AMPA (10-250 ng/0.5 ul) increased the number of different cue-directed behaviours, whereas NMDA (250-1500 ng/0.5ul), an agonist at the NMDA-type of receptor was ineffective. The NMDA-antagonist AP-7 (100-500 ng/0.5 ul) on the other hand increased the number of cue-directed behaviours, albeit in a manner different from AMPA. The non-specific antagonist kynurinic acid (250-500 ng/0.5 ul) was ineffective.
The data show that glutaminergic drugs anyhow influence the ability to switch to cue-directed behaviours, but that differences may exist between the different subtypes of receptors. The data will be discussed in relation to the above mentioned inputs as well as to the previously found data with dopaminergic drugs.

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THE EFFECTS OF SEROTONERGIC DRUGS IN A BEHAVIOURAL MODEL OF DEPRESSION.

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Behavioural despair is often regarded as an animal model of depression in man. Thus, antidepressant drugs can be identified in animals by their ability to reduce behavioural despair. The forced swim test in rats is such a model: the animals acquire an immobile posture in water after being forced to swim in a restricted space. The active escape period (active swimming) can be prolonged by clinically effective antidepressants. The forced swim test described here involves a pre-exposure of the rats to the stressful swimming in water of 25 °C 24 hours prior to testing, immediately followed by administration of the drug, which is administered again 30 minutes before testing. Both these factors, pre-exposure and multiple administration, are crucial factors for the detection of antidepressant activity. If either the animals are not pre-exposed to stress or drugs are administered only once before testing, no effect on the acquired immobility is observed. In this test all types of antidepressant drugs, including tricyclics, MAO-inhibitors and atypical antidepressants can be identified. Enhancing serotonergic neurotransmission through blockade of the re-uptake of this neurotransmitter has resulted in several clinically effective antidepressants like trazodone, fluvoxamine and fluoxetine. Here we describe the effects of several drugs affecting different subtypes of the 5-HT receptor in forced swimming in rats. Thus the 5-HT_{1A} agonist 8-OH-DPAT strongly reduced the duration of immobility over the entire 6 min observation period at doses as low as 0.03 mg/kg s.c. A similar effect was observed for the 5-HT_{1A} agonists ipsapirone and flesinoxan. The mixed 5-HT_{1B}/5-HT_{1C} agonist TFMPP did not affect swimming activity up to doses of 3 mg/kg s.c. Of the 5-HT antagonists tested, only the mixed 5-HT_2/5-HT_{1C} antagonists mianserine and methiotepine reduced immobility at doses of 1.8 and 8 mg/kg s.c., respectively. No effect was observed after the selective 5-HT_2 antagonist ketanserin (> 10 mg/kg s.c.) and the 5-HT_3 antagonist GR 38032F (> 10 mg/kg s.c.). The data obtained here suggest that stimulation of 5-HT_{1A} receptors or blockade of 5-HT_{1C} receptor may predict antidepressant activity in man.

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THE ANTIPSYCHOTIC ACTIVITY OF BEFIPERIDE IS DUE TO ITS SEROTONIN-AGONISTIC PROPERTIES.

J.A.M.van der Heyden, B.Olivier, J.Schipper, M.T.M.Tulp.

Befiperide is a new drug predicted to possess antipsychotic activity on basis of behavioural models. Befiperide does not block DA receptors and does neither produce catalepsy nor adaptive changes of the DA system after chronic administration. The in vitro receptorbinding profile of befiperide reveals the highest affinity for the 5-HT_{1A} (K_i=22nM) and 5-HT_2 (K_i=45nM) receptor. Since befiperide strongly lowers 5-HIAA content and decreases the 5-HTP accumulation after decarboxylase inhibition in the rat brain, this interaction is most likely of an agonistic nature. Several serotonergic drugs were studied to unravel the mode of action of befiperide in conditioned avoidance behaviour (CAR). All drugs tested in combination with befiperide did not affect CAR themselves at the doses tested. The 5-HT reuptake blocker fluvoxamine did not affect the inhibitory effect of befiperide on CAR. TFMPP, a 5-HT_{1B}/5-HT_{1C} agonist showed a potentiating effect. The 5-HT_{1A} agonists 8-OH-DPAT and ipsapirone both attenuated the effect of befiperide. The latter effect does not necessarily point to a 5-HT_{1A} antagonistic effect of befiperide, since a similar inhibitory effect of 8-OH-DPAT was found for the effects of haloperidol and higher doses of TFMPP on conditioned avoidance behaviour. The latter two drugs do not posses 5-HT_{1A}-antagonistic activity. Propranolol, a β-blocker with 5-HT_{1A} and 5-HT_{1B} antagonistic properties antagonized the effect of befiperide, as did the non-selective 5-HT antagonist methysergide. Surprisingly, propranolol also attenuated the inhibitory effects of haloperidol. The 5-HT_2 antagonist ketanserine showed no clear inhibitory effect, whereas the mixed 5-HT_{1C}/5-HT_2 antagonist mianserine was very active in this respect. The latter drug also attenuated the haloperidol-induced inhibition. As with most behavioural interaction studies, these data do not allow any differentiation between receptor-mediated or functional antagonism. They do support the involvement of 5-HT activity in the antipsychotic effects of befiperide and suggest an important role for the 5-HT_{1A} and 5-HT_{1C} receptor types in antipsychotic activity.

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EVIDENCE THAT ONDANSETRON, A SELECTIVE 5-HT ANTAGONIST, REDUCES COCAINE'S PSYCHOMOTOR STIMULANT[3] EFFECTS IN THE RAT.

G.A. van der Hoek and S.J. Cooper

The stimulant and reward effects of cocaine appear to depend upon mesolimbic dopamine (DA). Novel means to antagonize cocaine's effects are of considerable interest; the present study focuses on the selective 5-HT_3 receptor antagonist, ondansetron. Previous work has demonstrated that ondansetron modulates mesolimbic DA activity (e.g. B. Costall et al. Br. J. Pharmacol. 92: 881-94, 1987). In the present study, rats were placed in an open field and several behavioural categories were subject to a microstructural analysis. The animals were tested after cocaine (10 or 17.8 mg/kg i.p.), and with or without ondansetron (30 ug/kg). The observation period was 30 min, and six groups were tested (n = 8 per group).

Cocaine consistently increased the bout frequencies (bf) for locomotion, rearing to the side and in the centre, and sniffing. Across these four categories there was a 90% increase in bf at 10 mg/kg, and a 153% increase at 17.8 mg/kg. Bout durations (bd) were not similarly affected. By itself, ondansetron did not affect bf, but it did reduce substantially the cocaine's effects. Thus, in the presence of the 5-HT_3 antagonist, cocaine (17.8 mg/kg) produced only a 87% increase in bf across the four cateogries. For grooming, cocaine reduced the bd measure; ondansetron reversed the effect. In conclusion, several of the characteristic psychomotor stimulant effects of cocaine were attenuated by ondansetron.

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WITHDRAWAL HYPERACTIVITY AFTER CHRONIC TREATMENT WITH LORAZEPAM. CROSS-SUPPRESSION STUDIES WITH OTHER BENZODIAZEPINES.

J.W.van der Laan and C.Jansen van't Land

This study regards the further development of a model for the induction of physical dependence of lorazepam in the rat.Rats were made dependent by offering lorazepam via the food in increasing concentrations of 31.25 till 500 mg/kg food. The concentration of lorazepam in serum increased linearly the dose over the whole dose range tested. After administration over about 5-6 weeks dispositional tolerance developed by an increased metabolism of the liver. This dispositional tolerance may explain the development of tolerance for the sedative and muscle relaxing effects of this compound. However, tolerance development may have also a pharmacodynamic component.

Induction of withdrawal by terminating the administration of lorazepam led to several withdrawal symptoms, namely a strong decrease in the food intake, loss of body weight and a strong increase in daytime locomotor activity. The decrease in food intake and body weight appeared to be dose related in the lowest range tested, viz. 31.25- 125 mg/kg in food. The increase in daytime locomotor activity occurred only with a minimal dose of 125 mg/kg in food. Locomotor activity was maximal 2-3 days after withdrawal and returned to the basal level after 5-6 days.

Since it could be expected that withdrawal symptoms of lorazepam could be suppressed by other benzodiazepines such as brotizolam, flunitrazepam and desmethyldiazepam, the relative potency of these compounds has been tested. Dose ratios equivalent to the ED_{50} of lorazepam are:

	LRZ	BTZ	FNZ	DMD
Locomotor activity	1	1.5	1.5	14
Food Intake	1	2	2.5	23
Loss of body weigth	1	2	2	25

It was concluded that lorazepam is the most potent benzodiazepine among the compounds tested. Lorazepam is roughly a factor 2 more potent than brotizolam and flunitrazepam and a factor 20 more than desmethyldiazepam.

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SUPPRESSION OF CLONIDINE-STIMULATED ULTRASONIC VOCALIZATIONS OF RAT PUPS BY FLESINOXAN AND OXAZEPAM.

A.M.van der Poel, E.Molewijk, J.Mos, B.Olivier.

Ultrasonic vocalizations (UV) emitted by rat pups when separated from the mother, have been used to test anxiolytic properties of drugs (Gardner, J Pharmacol Meth 14:181, 1985). Benzodiazepines and non-benzodiazepine anxiolytics like buspirone and ipsapirone have been shown to suppress UV (Mos & Olivier, In: Behavioural Pharmacology of 5-HT, 361, 1989). Clonidine, though claimed to be anxiolytic in humans (Hård et al., J Neural Transm 73:217, 1988), potently stimulates UV (Kehoe, In: Symp Molec Cell Biol New Series, 97: 307, 1988). In order to analyze this seemingly paradoxic effect of clonidine, the effects of concurrent administration of the 5-HT_{1A} agonist flesinoxan (0.03, 0.1 and 0.3 mg/kg) and oxazepam (0.3, 1 and 3 mg/kg) were studied.

Rat pups, aged 9-11 days, were placed singly in a circular perspex cage (dia 19 cm) with a metal floor held at 37 °C. Onset and end of each call were timed for 5 min using a customized computer system. Pups were injected IP with saline, flesinoxan or oxazepam 35 min before the test, 5 min later followed by injection of 0.3 mg/kg clonidine IP.

Clonidine increased the time spent vocalizing by simultaneously increasing the number of call bouts, bout duration and call duration. Both flesinoxan and oxazepam dose-dependently suppressed clonidine-stimulated UV, though each in a slightly different way. Following pretreatment with flesinoxan pups almost completely ceased vocalizing due to concurrent reduction of call and bout duration. Following pretreatment with oxazepam UV was diminished due to reduction in number of bouts and call duration, but bout duration and intervals between calls were increased. The suppression of the effects of clonidine on UV by anxiolytics suggests that clonidine is anxiogenic in rat pups of this age.

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LONG-LASTING BEHAVIOURAL CHANGES AFTER A SINGLE FOOTSHOCK STRESS SESSION.

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It is well known that chronic or repeated stress can affect subsequent behaviour. We report that even a single footshock session induces long-lasting behavioural changes.
Male Wistar rats were stressed by inescapable and uncontrollable foot shocks (15 minutes; 10 shocks of 6 sec. duration; V.I. schedule; 1 mA) or non-stressed (15 minutes in shock chamber without shocks). The rats were subsequently tested in a large brightly lit circular open field.
The locomotor activity of shocked rats (S) was decreased to 50% of the activity level of control rats (NS) when tested 1 day after the stress. The S-groups showed an even greater reduction in locomotion, when tested for the first time 7,14 or 21 days after the stress (25%, 16%, 25% of NS activity level, respectively). This difference disappeared at re-testing.
The behavioural response of S-rats to a sudden change in environmental stimuli was also investigated (1). During 3 minutes a noise signal was given in an observation cage lit by red dim light (pre-test). The noise then was suddenly switched off (SWO) and the behaviour was scored for another 3 minutes.
Locomotion of S-rats was decreased in response to the SWO to 11% of pre-test level. NS-rats only showed a reduction to 77% of pre-test locomotion. The immobility response of S-rats to the SWO was of longer duration than for NS-rats.
After the repeated open field test, a clear behavioural differentiation was again observed when a noise test was performed. Repeated testing was only possible, when the test conditions were varied.
In conclusion: A single exposure to an aversive stimulus e.g. footshock results in long-lasting behavioural changes, which may relate to some aspects of depression.

1) Steenbergen J.M. et al. (1989) Physiol. Behav.45:729-733.

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GROOMING ELICITED BY ACTH1-24 INJECTED IN THE PARA-VENTRICULAR NUCLEUS OF THE HYPOTHALAMUS OF THE RAT.

A.M.M. Van Erp, M.R. Kruk, J.G. Veening *, and B.M. Spruijt **.

Intracerebroventricular (ICV) injection of neuro-peptides elicits grooming in the rat. The neural organization of this response is not yet elucidated. Electrical stimulation (EHS) in a periventricular region of the rat hypothalamus also elicits grooming. Fibres in this area show ACTH-like immunoreactivity.

We found that injection of ACTH 1-24 (0.3 μg/0.3 μl) in the same PVH area (PVH-ACTH) elicits intense grooming. This suggests that grooming induced by ICV injection of ACTH 1-24 is due to the activation of periventricular fibres in the hypothalamus. It also suggests that EHS-grooming may be mediated by fibres showing ACTH-like immunoreactivity.

Timing and patterning of the grooming response depends on the exact site of ACTH injection. In the centre of the 'grooming area' the response is fast and accompanied by yawning and stretching. Around this area yawning and stretching are absent. At greater distances the onset of grooming is delayed.

ICV-ACTH, EHS, and PVH-ACTH elicit slightly different responses. Yawning and stretching *precedes* PVH-ACTH-grooming. ICV-ACTH-grooming is *followed* by yawning and stretching and accompanied by excited locomotion. EHS elicits no scratching and *reduces* 'spontaneous' scratching. EHS grooming is frequently interrupted by short pauses. PVH-ACTH does not elicit excited locomotion. ICV-ACTH apparently elicits locomotion by acting on ACTH-sensitive mechanisms outside the PVH. The periventricular hypothalamus is apparently involved in the organization of different grooming components.

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ABSENCE OF STRESS-INDUCED ANALGESIA AND MORPHINE TOLERANCE IN RATS DEFEATED BY 'UNCONTROLLABLE' HYPOTHALAMIC ATTACK.

A.M.M. Van Erp, M.R. Kruk, T.A.P. Roeling, W. Meelis.

Stressors and biological relevant factors may cause analgesia and tolerance for analgesics. Defeat causes naloxone-reversible analgesia in mice. Moreover, repeated exposure to defeat results in tolerance to the analgetic effects of defeat. Miczek (1983) showed complete cross-tolerance between tolerance to the analgetic effects of morphine and tolerance to the analgetic effects of defeat in mice. In rats the analgetic effects of defeat are less clear, and the role of opioids is controversial. It has been suggested that loss of control over the social environment is the crucial factor in this kind of stress-induced, opioid-mediated analgesia.

Defeat caused by attack behaviour elicited by hypothalamic stimulation was used to test this 'loss of control' hypothesis. Hypothalamic attack is a particularly vicious attack, which is almost impossible for a victim to control. Rats are defeated after two or three of such attacks. They adopt a defensive posture and emit 22 KHz ultrasound, but this does not prevent new attacks. The immediate analgetic effects of this complete 'loss of control' are small and short. Moreover, the effects are not reversible by naloxone. Hypothalamic defeat does not change the analgetic properties of morphine. Time-effect relations of morphine analgesia directly following hypothalamic defeat, or one, two or three weeks after defeat are not different from control. These findings suggest that opioids may have a different role in victim analgesia in rats and mice, and that loss of control over the social environment may not be the main factor in defeat analgesia.

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SIMILARITY OF BEHAVIORIAL AND BIOCHEMICAL CONSEQUENCES OF CHRONIC TREATMENT WITH IMIPRAMINE AND VASOPRESSIN.

J. Vetulani, P. Popik, I. Nalepa.

Several data suggest that vasopressin may play a role in depression and that administration of this peptide or its derivative for a prolonged period of time may have beneficial effect in some depressed patients. In this study we compared the effect of chronically administered arginine vasopressin (AVP) with that of a classical antidepressant drug imipramine (IMI) in a behaviourial and a biochemical test, known to yield results suggesting clinical antidepressant efficacy: anxiolytic action related to novel situation and β-adrenoceptor down-regulation.
Rats were treated with IMI, 10 mg/kg b.i.d. i.p. or AVP, 1.5 μg/rat s.c. for 7 or 14 days. At the end of experiments the rats were tested in the social interaction test [File, S.E.Hyrde, J.R.G.: Br. J. Pharmacol. 62, 19 (1978)], and then were killed and tested for the responsiveness to noradrenaline and isoproterenol of cyclic AMP generating system in cerebral cortical slices.
IMI or AVP given alone for 7 days did not affect the average active interaction time, but the interaction increased in rats receiving both the agents together. Treatment with IMI, AVP, or their combination for 14 days significantly prolonged the time of interaction. This result might be interpreted as suppression of fear, but other interpretations, e.g., increased sociability are also possible. No significant differences in cyclic AMP response to isoproterenol were observed, but IMI, AVP, and their combination given for 14 (but not 7) days significantly depressed the stimulatory effect of noradrenaline by 35-45%.
The present results indicate that AVP given for a sufficient period of time (not less than 2 weeks) increases social interaction and produces β-adrenoceptor downregulation to an extent similar to that induced by an intensive (b.i.d.) treatment with IMI. The mechanism of biochemical action is probably related to the interference of the treatment with α-adrenergic potentiation of β-adrenergic response. Thus AVP may not only share with IMI clinical effects, but also may similarly alter the rat behavior and produce similar accompanying biochemical changes.

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THE ANALEPTIC EFFECTS OF PYLADOX (RGH-2202)

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The putative analeptic properties of Pyladox, a new, non-hormonal TRH analogue tripeptide (L-6-oxo-piperidine-2-carbonyl-L-leucyl-L-proline amide; RGH-2202), were investigated in various animal models. In a combined surgical anesthesia paradigm (8 ug/kg atropine, 200 ug/kg diazepam, 80 ug/kg droperidol, 10 mg/kg ketamine and 130 ug/kg fentanyl administered i.v. simultaneously) in rats intravenous Pyladox shortened sleeping time in a dose-dependent manner in contrast with TRH, whose effect was not dose-dependent. Moreover Pyladox, but not the parent compound, abolished recovery excitation observed at the control animals. Pyladox pretreatment also shortened hexobarbital sleeping time, nevertheless the analogue unexpectedly did not possess the ability of TRH to reduce the duration of ethanol-induced narcosis in mice.
In an experimental cranial trauma model in mice i.v. Pyladox pretreatment dose-dependently reduced the head injury induced disturbance of consciousness measured by the loss of righting reflex and the recovery of spontaneous movement. In another series of experiments the animals received i.v. injection of either 4 mg/kg Pyladox or 4 mg/kg TRH or vehicle within 10 minutes postinjury, and their neurological status was evaluated 1 hour later. Both Pyladox and TRH significantly decreased the incidence of hindlimb paraparesis, and markedly reduced the proportion of severely impaired mice.
The results are suggesting that Pyladox, owing to its more pronounced analeptic properties and better side-effect profile than those of TRH, may be a unique therapeutic agent for treating patients with disturbances of consciousness, in hypnotic and narcotic intoxication, postoperative recovery, and post-traumatic reconvalescence.

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CHEMISTRY AND ELECTROPHYSIOLOGY OF EXCITATORY AMINO ACIDS

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L-Glutamate and related excitatory amino acids were found to depolarize and excite neurones in the mammalian central nervous system (CNS) more than 30 years ago. This raised the possibility that one or more excitatory amino acids (as they have come to be called) play a transmitter role in the CNS. To establish such a function, however, specific antagonists for these excitatory amino acids needed to be developed. The eventual realization of this goal led not only to the recognition that excitatory amino acid receptors are the predominant type of excitatory transmitter receptors in the mammalian CNS, but also that such receptors are of multiple sub-types subserving different functions. Four such sub-types giving rise to electrophysiological responses are now known, namely, those defined by the preferential agonists N-methyl-D-aspartate (NMDA), (S)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate and L-2-amino-4-phosphonobutyrate (L-AP4). L-Glutamate activates each of these sub-types. A further sub-type is linked to inositol 1,4,5-triphosphate (IP_3) and diacylglycerol turnover and is activated by L-glutamate, quisqualate, ibotenate and trans-ACPD. A range of useful agonists and antagonists of each receptor type, and possible functions of these receptors, will be summarized.

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DIRECT DOPAMINE AGONISTS AND LATENT INHIBITION.

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Latent inhibition (LI) refers to a decrement in learning to a stimulus as a consequence of its prior nonreinforced presentation. It is considered to reflect learning to ignore irrelevant stimuli. We have shown that LI is abolished by low but not high doses of the dopamine (DA) releasing drug, amphetamine. In order to investigate further the role of the Da system in the abolition of LI, we tested the effect on LI of direct DA agonists: apomorphine (mixed D1/D2 agonist), SKF-38393 (specific D1 agonist) and quinpirole (specific D2 agonist). The procedure used was the conditioned emotional response (CER) in rats licking for water, consisting of three stages: Preexposure - in which animals are either preexposed to the to-be-conditioned stimulus, tone (PE group), or not preexposed to the tone (NPE group); Conditioning - in which LI is assessed by the amount of suppression in licking during tone preexposure. LI consists of the fact that the PE group exhibits less suppression than the NPE group. Apomorphine at doses of 0.03, 0.3 and 1.5 mg/kg failed to alter LI. Likewise, SKF-38393 at doses of 1.0, 5.0 and 10.0 mg/kg and quinpirole at doses of 0.1, 0.3 and 1.0 mg/kg left the LI effect intact. Both drugs affected conditioned suppression. SKF-38393 at a dose of 1.0 mg/kg decreased suppression in both the PE and NPE groups, and at a dose of 10.0 mg/kg increased suppression in both groups. Quinpirole at the dose of 0.3 mg/kg decreased overall suppression. We conclude that the abolition of LI is not due to a direct stimulation of DA receptors. These results have implications for the role of the DA systems in learning to ignore irrelevant stimuli and for animal models of psychosis.

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THE NON-COMPETITIVE NMDA ANTAGONIST MK 801 DECREASES EFFICIENCY IN A DRL 10-S SCHEDULE IN RATS

H. Welzl, S. Berz, K. Bättig

Non-competitive NMDA antagonists such as ketamine, PCP, and MK 801 are known to influence a variety of sensory, motor, and cognitive functions. For example, they are known to increase locomotor activity at low doses whereas higher doses decrease activity; further, they attenuate spatial learning (e.g. Alessandri et al., Behav Neural Biol 52:194, 1989). In the present study, we investigated how MK 801 affects performance in a DRL 10-S schedule. MK 801 injected systemically at low doses (0.20mg and 0.25mg/kg) 30 minutes before a test session increased response rate (lever presses for food reward) and decreased performance efficiency (number of reinforcements/number of responses per 30-minute session). A higher dose of MK 801 (0.30mg/kg) suppressed response rate substantially. Low doses of MK 801 shifted the median of the inter-response times (IRT) distribution to the left, with an additional peak appearing at the shortest IRT interval.
The introduction of a stimulus light into the operant chamber that signalled the end of an uninterrupted 10-S interval and, thus, availability of a reward, increased the efficiency in control animals. In these animals, low doses of MK 801 only slightly increased response rate and decreased efficiency. Further, no shift in the median of IRTs could be seen. These results suggest that low doses of MK 801 (a) increase response rate and (b) affect time estimation in a DRL 10-S paradigm leading to a shortening of IRTs. (Supported by NF grant No. 3.184-0.88).

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EFFECT OF PRECURSOR LOADING ON THE SYNTHESIS RATE AND RELEASE OF DOPAMINE AND SEROTONIN IN THE STRIATUM AS DETERMINED BY BRAIN MICRODIALYSIS IN CONSCIOUS RATS. B.H.C. Westerink and J.B. de Vries.

The effect of systemic administration of tyrosine and phenylalanine on the extracellular levels of tyrosine and dopamine were determined by microdialysis in the striatum of awake rats. In addition, the effect of the precursors on in vivo DOPA formation (during continuous infusion of a decarboxylase inhibitor), was determined. The latter model is considered to reflect the in vivo tyrosine hydroxylase synthesis. Both precursors (in a dose of 250 mg/kg, i.p.) increased the dialysate levels of tyrosine 6-fold, but only phenylalanine administration stimulated the DOPA-formation. However, both precursors did not affect the release of dopamine. When the precursor administration was repeated in rats in which the release of dopamine was stimulated by haloperidol pretreatment, again no effect was seen on the release of dopamine.

Systemic administration of tryptophan (100 mg/kg i.p.) induced a 3-fold increase in the formation of 5-hydroxytryptophan (during continuous infusion of a decarboxylase inhibitor), and caused an increase in the release of serotonin to about 150% of controls.

Finally we investigated whether feeding behavior of rats is able to influence neurotransmitter formation and release. Rats trained to consume their daily food in a period of 2 h were implanted with a microdialysis probe. Scheduled eating induced a small increase in the extracellular levels of tyrosine (135% of controls), but the release of dopamine or the formation of 5-hydroxytryptophan was not affected. It is concluded that under normal conditions the striatal release of dopamine or serotonin, is not dependent on the availability of the respective precursors.

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INCREASED RELEASE OF MESOLIMBIC DOPAMINE FOLLOWING CHRONIC UNPREDICTABLE MILD STRESS

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Stress is known to be implicated in the etiology of depression. In rats, chronic mild unpredictable stress (CMS) reliably decreases the consumption of highly palatable weak sucrose solutions; this deficit may be reversed by antidepressant drugs (Willner et al, 1987, Psychopharmacology 93, 358-364). As the mesolimbic dopamine system is known to be critically involved in responsiveness to rewards, we have examined aspects of mesolimbic dopamine function following CMS.

In all experiments, decreases in the consumption of 0.7% sucrose were seen, prior to neurochemical analysis, in animals subjected to CMS. In expt. 1, CMS (7 weeks) caused large increases in the levels of DA and 5HT and their metabolites in samples of limbic forebrain (accumbens, olfactory tubercle) but not caudate nucleus (CN). There was also a significant decrease in D2 receptor binding. Expt. 2 confirmed increases in DA, 5HT and metabolites in limbic forebrain (but not CN or septal area), after 3 weeks CMS, but receptor binding was unchanged. In expt. 3, CMS (2 weeks) increased electrically-stimulated DA release in the accumbens (but not CN), monitored in vivo by fast cyclic voltammetry (Stamford et al, 1982, Brain Res. 424, 282).

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NEW PHOSPHONIC ANALOGUES OF EXCITATORY AMINO ACIDS IMPROVE MEMORY IN RATS. K. Wiśniewski, M.M. Winnicka

Receptors for the excitatory amino acids (EAA) have been suggested to play a critical role in learning in both developing and mature central nervous system. The influence of five phosphonic analogues of EAA: 2-amino-3-phosphonopropionic acid (AP3), N-methyl AP3, N-dimethyl AP3, 2-amino-4-phosphonobutyric acid (AP4), and N-methyl AP4 on locomotor activity in the "open field" test, apomorphine stereotypy and recall of information in passive avoidance situation was tested.

All tested aminophosponic acids have not any influence on locomotor activity, rearings and bar approaches in the "open field" test.

Except for N-methyl AP3 other aminophosphonic acids significantly enhanced apomorphine stereotypy in the dose 100 μg per rat given intracerebroventricularly (icv), and AP4 and N-methyl AP4 also in the dose 200 μg.

Although all aminophosphonic acids significantly enhanced recall of information in passive avoidance situation in the icv dose 100 μg per rat, only N-methyl AP3 caused this effect also in higher doses 200 and 250 μg.

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COGNITIVE EFFECTS OF ANGIOTENSIN II AND ITS FRAGMENTS IN RATS. K. Wisniewski, J.J. Braszko

There are two types of centrally mediated effects of angiotensin II (Ang II). One type results from the well known receptor mediated activity causing an increase of blood pressure, thirst and release of certain hormones like vasopressin and ACTH. The second type is independent of specific angiotensin receptors and results in the increase of central psychomotor activity. The present data deal with the non-receptor mediated behavioural effects of Ang II and its fragments: Ang III, Ang II (3-8), Ang II (4-8) and Ang II (3-7). All the peptides, with the exception of Ang II and Ang III, are practically devoid of influence on thirst and blood pressure. All the peptides, without exception, stimulate dopamine controlled behaviour (e.g. stereotypy). All the peptides except for Ang II (4-8), have shown learning and memory enhancing properties.

The results support our earlier notion about lack of a relationship between central "classic" and psychotropic effects of angiotensin and strongly imply an involvement of central dopaminergic system in the psychotropic activity of Ang II and its fragments.

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DISCRIMINATIVE STIMULUS EFFECTS OF FLUMAZENIL IN PIGEONS. J.M. Witkin and J.L. Katz

Flumazenil (Ro 15-1788) is a selective benzodiazepine antagonist in mammals with little intrinsic efficacy of its own. White Carneaux pigeons appear to be uniquely sensitive to this compound. Flumazenil produces behavioral effects in pigeons at doses two orders of magnitude lower than those in mammals (Witkin and Barrett, Life Sci, 44:1587, 1985). We further examined the behavioral pharmacology of flumazenil in pigeons trained to discriminate flumazenil (0.1 mg/kg im) from vehicle. After drug injection, 30 consecutive keypeck responses on one of two illuminated disks produced food. The ED50 of flumazenil under these conditions was 0.005 mg/kg. Discriminative effects of flumazenil were only modestly decreased by midazolam. Nonetheless, flumazenil produced a dose-dependent blockade of the discriminative stimulus effects of midazolam; 0.1 mg/kg shifted the midazolam dose-effect function ten fold to the right. Full flumazenil-like responses (generalization) were produced by the inverse agonists Ro 15-4513, and Ro 15-3505; these compounds also blocked the discriminative stimulus effects of midazolam in pigeons. In contrast, FG 7142 did not generalize to flumazenil although it was an effective midazolam antagonist. β-CCE partially generalized to flumazenil but fully blocked the discriminative effects of midazolam. Preliminary results indicated that the partial agonists Ro 16-6028 and ZK 95,962 also partially generalized to flumazenil. The convulsants Ro 5-3663, picrotoxin and pentylenetetrazol generally did not generalize to flumazenil nor did the benzodiazepine antagonist CGS 8216 or the agonists midazolam or chlordiazepoxide. The discriminative stimulus effects of flumazenil in pigeons appear to be related to actions of only certain partial agonists or inverse agonists of the benzodiazepine receptor. This activity may differ somewhat from its benzodiazepine antagonist actions.

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TOLERANCE TO MORPHINE-INDUCED "ANOREXIA" IS NOT MEDIATED BY PAVLOVIAN CONDITIONING

D.L. Wolgin and H.D. Benson

In order to determine whether tolerance to the suppression of food intake induced by morphine is mediated by Pavlovian conditioning, rats were administered the drug and given access to sweetened milk in the presence of a distinctive compound cue on alternate days. On the intervening days, the rats were given injections of saline and tested in the presence of a second compound cue. Control rats were injected with saline and tested in the presence of both cues. Following 24 drug-cue pairings, during which tolerance developed in the experimental subjects, two tests of the Pavlovian conditioning hypothesis were conducted.

In the first test, saline was administered in the presence of the cues previously associated with morphine. Although tolerant rats ingested more milk, they did not drink more than saline controls, suggesting that the increased intake was not compensatory. In the second test, morphine was administered in the presence of the cues previously associated with saline. This manipulation did not result in a significant loss of tolerance. These results suggest that tolerance to morphine-induced "anorexia" is not mediated by Pavlovian conditioning.

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THE PROCESSING OF REWARD-RELATED STIMULI IN THE VENTRAL STRIATUM DEPENDS MAINLY ON D1 RECEPTOR ACTIVATION.

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Stimulation of the dopamine system in the nucleus accumbens of rats with dopamine or D-amphetamine enhances the effects of reward-related stimuli, as shown using an acquisition of new response procedure with conditioned reinforcement (CR). In the present study the role of D1 and D2 receptor systems in this behaviour was investigated. Thirsty rats were trained to associate a light/noise compound stimulus (CR) with water prior to a test phase in the absence of water in which responses on one (CR lever) of two novel levers produced CR, but on the other (NCR lever) had no effect. The D1 receptor agonist SKF38393 (0.01-10ug) dose-dependently and selectively increased responding on the CR lever, while infusion of the D2 receptor agonist LY171555 (0.01-3ug) had no effect. The effects of intra-accumbens AMPH (18ug) were dose-dependently blocked by immediately antecedent intra-accumbens infusions of the D1 receptor antagonist SCH23390 (0.1-1ug) or the D2 receptor antagonist raclopride (0.5-5ug). Raclopride also decreased responding on the NCR lever suggesting that this drug decreased general activity in the animals. There was no evidence of synergistic effects of combined infusions of the D1 and D2 agonists. Intra-accumbens administration of either the agonists or the antagonists at doses that affected responding on the CR lever did not affect drinking in thirsty animals. This suggests that the effect of these drugs is not the result of an influence on primary motivation. The results indicate that processing of reward-related stimuli in the nucleus accumbens may depend mainly on D1 receptor stimulation. Lesions of the ventral pallidum induced by ibotenic acid completely abolished response acquisition with conditioned reinforcement as well as the potentiating effect of intra-accumbens D-amphetamine. These results indicate the importance of the ventral striatopallidal system in reward-related processes.

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COMPARISON BETWEEN THE DISCRIMINATIVE STIMULUS PROPERTIES OF A LOW AND HIGH DOSE OF 8-OH-DPAT. C.E. Ybema, J.L. Slangen, B. Olivier* and J. Mos*.

Rats were trained to discriminate either 0.1 mg/kg (i.p.) or 2.5 mg/kg (i.p.) of 8-OH-DPAT from saline in a two lever operant drug-discrimination task.

Once trained, animals in both groups displayed a dose-related decrease in discriminitive performance upon administration of lower doses of the training-drug 8-OH-DPAT. The time-dependency was demonstrated in both groups, by separately testing the dose of 8-OH-DPAT used in training, at different injection-test-intervals (ITI). The maximum effect was at an ITI of 15 and 60 minutes for the groups trained to the low and the high dose of 8-OH-DPAT, respectively. In generalization-tests, the 5-HT1a agonists ipsapirone and flesinoxan substituted for 8-OH-DPAT in both groups, whereas buspirone only partially generalized to the 8-OH-DPAT-cue in both groups. The mixed 5-HT1a/5-HT1b agonist eltoprazine generalized completely to the cue of 2.5 mg/kg of 8-OH-DPAT, but produced only 33.3% drug-lever-selection in the group trained to 0.1 mg/kg of 8-OH-DPAT. Neither the α2 agonist clonidine nor the 5-HT reuptake-inhibitor fluvoxamine showed stimulus-generalization in animals trained to 2.5 mg/kg of 8-OH-DPAT. The α2 antagonist idazoxan was inactive in blocking the cue of 2.5 mg/kg of 8-OH-DPAT.

In antagonism-studies, pindolol dose-dependently blocked the cue of 0.1 mg/kg of 8-OH-DPAT, but pindolol given before the administration of 2.5 mg/kg of 8-OH-DPAT only slightly reduced the percentage of animals selecting the drug-appropriate lever.

Taken together, the results suggest that the discriminative stimuli of 0.1 mg/kg and 2.5 mg/kg of 8-OH-DPAT may be qualitatively different.

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BINDING AND BEHAVIOURAL PROPERTIES OF NAN ANALOGUES SUITABLE FOR IODINATION

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NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-pthalimido)-butyl]piperazine) has 100-fold higher affinity for central 5-HT_{1A} receptors than for other 5-HT receptor subtypes and binding sites for other neurotransmitters. We report on a number of NAN-190 derivatives, some incorporating an iodine atom for possible use as SPET ligands. The compounds were tested in radioligand binding assays using [^{3} H]-5HT and [^{3}H]-8-0H-DPAT and K_i values for the subtypes of $5HT_1$ sites determined. They were then examined in vivo for activity in the $5HT_{1A}$ receptor mediated hypothermic response in mice and the 5HT behavioural syndrome in rats.
NAN-190 (5mg/kg, s.c.) induced hypothermia in mice which facilitated the effects of 8-OH-DPAT; it did not induce the 5HT behavioural syndrome in rats but antagonised its induction by 8-OH-DPAT (0.5mg/kg, s.c.). Iodination at the 2 position of the phenyl ring in NAN-190 did not change the properties of the compound compared to NAN-190. The benzamido analogue of NAN-190 induced hypothermia and the behavioural syndrome but did not antagonise 8-OH-DPAT induced responses, suggesting increased agonist effects at the $5HT_{1A}$ receptor. Iodination of the benzamido benzene ring caused a loss of affinity for the $5HT_{1A}$ receptor. The O- and M-iodo substituted compounds did not induce hypothermia or the behavioural syndrome or antagonise the effects of 8-OH-DPAT. The p-iodo substituted benzamide-NAN induced both hypothermia and a low intensity behavioural syndrome and reduced the amount of behavioural stimulation produced by 8-OH-DPAT. These data indicate that the NAN group of compounds demonstrate a spectrum of partial agonist activity and should not be uncritically viewed as antagonists at the 5-HT1A receptor.

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TOLERANCE AND CROSS-TOLERANCE TO THE BEHAVIORAL EFFECTS OF OPIOID AGONISTS A.M. Young

Tolerance to the behavioral effects of repeatedly administered opioids is multiply determined. Studies of tolerance to the effects of opioid agonists on simple operant behaviors suggest that the magnitude and pattern of tolerance is determined jointly by the opioid employed for repeated treatment, its dose and frequency, and the environmental conditions under which tolerance is developed and assessed. The magnitude of tolerance to the rate-altering effects of morphine varies directly as a function of the maintenance dose employed for repeated treatment and is similar to that developed to the analgesic effects of morphine under comparable treatment regimens. Patterns of cross-tolerance suggest that tolerance to the rate-altering effects of morphine is opioid-specific. Among **mu** opioids, tolerance appears to vary as a function of agonist efficacy, inasmuch as repeated treatment with a full agonist can confer greater tolerance to the rate-altering effects of compounds with low intrinsic efficacy than to the effects of compounds with high efficacy. Tolerance to discriminative stimulus control by **mu** opioid agonists is also dose-dependent, reversible, pharmacologically specific, and dependent on the efficacy of the challenge agonist.

Other lines of evidence suggest that development of tolerance to the behavioral effects of opioids is also modulated by respondent and operant conditioning processes. Tolerance to the analgesic effects of morphine, for example, can be brought under conditional control of the testing environment. Development of pharmacologically-specific tolerance to the disruptive effects of opioids on well-developed operant behavior is enhanced by the opportunity to perform the operant in the presence of drug during tolerance development. Behavioral contingencies also modulate tolerance to the discriminative stimulus effects of opioids, with tolerance developing most readily under training conditions that limit transfer of control to lower doses. (DA03796 and K02 DA00132)

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EFFECTS OF PHOSPHATIDYLSERINE IN BEHAVIOURALLY IMPAIRED AGED RATS AND RELATED CHANGES IN SEPTAL CHOLINERGIC NEURONS

A. Zanotti, M.G. Nunzi, P. Polato, D. Guidolin and G. Toffano

In aged rodents, impairments in spatial memory have been associated with age-dependent derangements of cholinergic neurons of the basal forebrain. We evaluated, both behaviourally and morphologically, the effects of Phosphatidylserine (BC-PS) in a subpopulation of aged rats that proved impaired in a spatial task. Aged (22-24 months) impaired and non-impaired rats were selected after one week's training in the Morris Water Maze. Chronic BC-PS treatment (50 mg/kg os for 12 weeks) improved performance in aged impaired rats. Passive avoidance retention was also increased. At the end of behavioural testing rats were perfused; serial coronal sections obtained throughout the septal area were alternatively processed for immunocytochemical detection of Choline Acetyltransferase (ChAT)-positive or NGF receptor (NGFr)-positive neurons and then analyzed for total immunoreactive area (TIA) by using a computer-assisted image analysis. ChAT and NGFr TIAs were found to be markedly reduced in the aged control rats as a group (-34% and -25% respectively). However, values of ChAT and NGFr TIAs appeared to be higher in aged non-impaired compared to aged impaired rats, thus correlating with the cognitive impairment exibited in the Morris Water Maze. BC-PS treatment increased both ChAT anf NGFr TIAs in aged impaired rats. This study extends previous findings that BC-PS can improve age-associated cognitive deficits in rats, probably through restoration of cholinergic function.

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ANTICIPATORY ANXIETY IN MICE, A NEW ANIMAL MODEL FOR ANXIETY.

T.J.J.Zethof, J.A.M.van der Heyden, B.Olivier.

In many animal models of anxiety the effects of some form of aversive stimulus on behaviour is measured. This aversive stimulus can be a footshock coupled to water drinking as in the Vogel test or coupled to exploration as in the 4-plate test. In the light/dark anxiety model the natural aversion of rodents to avoid the brightly lit places is used. Treatment with anxiolytic drugs should ideally facilitate punished (suppressed) behaviour without affecting unpunished behaviour.
In a recently described model (Borsini et al., Psychopharmacol 98:207,1989) it was observed that mice removed last compared to those removed first from the same cage had a higher rectal temperature (hyperthermia). This phenomenon was interpreted as a state of anxiety due to the expectation of an unknown event: anticipatory anxiety. We tried to replicate this attractive and simple model.
We used male NMRI mice, weighing 25-35 g. The animals were handled for at least 5 days prior to the temperature measurement. The hyperthermic response was found to be determined only by the order in which the animals were removed from the cage. Reversing the order of measurement produced the same hyperthermic response. The effect was also not dependent of whether the number of animals per cage was reduced or maintained constant. The hyperthermic responses could repeatedly be measured in the same group of animals.
The rise in rectal temperature of mice removed last was prevented by prior treatment with diazepam in a dose dependent way. Several other non-anxiolytic drugs (imipramine, haloperidol) did not affect the hyperthermia. We essentially replicated the findings of Borsini et al. and suggest that this model represents a new tool for studying the psychobiological basis of anxiety, in particular the "alarm reaction" due to emotional stimuli.

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DRUG DISCRIMINATION AS A TOOL IN DRUG ABUSE RESEARCH

J.B. Appel.

Drug discrimination (DD) has been useful in elucidating both the basic and clinical pharmacology of abused substances because: 1) the procedure requires organisms to attend to drug-induced changes in their own physiological (internal) state since these changes signal the availability of reinforcement and, 2) abused substances produce particularly potent (and reinforcing) changes in this state. Thus, it has been possible to classify and differentiate drugs on the basis of their discriminable properties; correlate the stimulus effects of drugs with both binding affinities (in animals) and reports of "hallucinations" (in humans); and, most importantly, determine the mechanisms underlying the *in vivo* effects of various opiates (Woods), hallucinogens (Glennon) and PCP- like agents (Balster). Unfortunately, DD has been less successful in describing the actions of CNS stimulants (e.g., cocaine) and "designer" drugs (e.g., MDA and MDMA).

The principle problem with DD or, more accurately, its use, concerns the fact that results (e.g., extent of generalization of a compound to other agonists) often depend on particular parameters (e.g., training drug dose) and procedures (drug-saline vs. drug-drug) as well as the specificity of the agents and techniques used to test hypothesized receptor or neuronal mechanisms. However, in this respect DD is no different from other useful assays (e.g., receptor binding).

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MDA: HALLUCINOGEN ? STIMULANT ? BOTH ? OR NEITHER ?

J.B. Appel, J. Broadbent, E.K. Michael, J.H. Ricker, and C. A. Metosh.

The hallucinogen- and stimulant- like effects of MDA were studied in groups of rats trained to discriminate either (-) MDA (1.25 mg/kg), (+) MDA (1.25 mg/kg), (+) LSD (0.16 mg/kg), or (+) amphetamine (1.0 mg/kg) from saline. The (-) MDA cue generalized completely to both (+) LSD and DOM, and partially to mescaline and, possibly, cocaine; (+) MDA did not generalize completely to *any* of these compounds. The (-), but not the (+) MDA cue was blocked by the 5-HT_2 antagonist pirenpirone: the DA antagonists Sch-23390 and (-) sulpiride disrupted responding but did not appear to alter the (-) or the (+) MDA cue.

When animals were trained to discriminate prototypic hallucinogens or stimulants from saline, neither LSD (0.16 mg/kg) nor (+) amphetamine generalized more than partially to either (-) or (+) MDA.

These results, in combination with those reported previously, indicate that, at the doses tested, (-) MDA is more similar to hallucinogens and is probably more serotonergic than (+) MDA; neither isomer of MDA seems to have robust, stimulant-like properties.

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DISCRIMINATIVE STIMULUS PROPERTIES OF PHENCYCLIDINE AND OTHER NMDA ANTAGONISTS

Robert L. Balster

The pharmacological specificity of the phencyclidine stimulus has been systematically examined. Complete substitution occurs with aryicyclohexylamine analogs of PCP, MK-801, certain sigma-agonist benzomorphans, some dioxolane derivatives, as well as with drugs from a few other novel drug classes. The relationship of this pattern of cross-generalization results to actions at the PCP receptor have clearly implicated this receptor as the cellular basis for PCP discrimination. Despite considerable effort, a reliable antagonist of the PCP stimulus has not been found. Cross-generalization studies with other drug classes show that the PCP stimulus is quite specific for PCP-receptor agonists, with the following exceptions. Some drugs selective for the high-affinity sigma binding site have PCP-like discriminative stimulus effects. In addition, there is some overlap in the stimulus effects of PCP-like drugs and classical CNS depressants such as the barbiturates and alcohol. More recently, some similarities have been found between the discriminative stimulus effects of PCP-like drugs and competitive N-methyl-D-aspartate (NMDA) antagonists, possibly reflecting PCP's proposed noncompetitive NMDA antagonist effects. Nonetheless, the growing evidence for differences as well in the discriminative stimulus effects of competitive and noncompetitive NMDA antagonists may have important implications for medication development in this area. (Research supported by NIDA Grant DA-01442)

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DISTINCTIVE DISCRIMINATIVE EFFECTS OF ETHANOL H. Barry, III Pharmacological classifications view ethyl alcohol as a hypnotic sedative, closely similar to general depressants, such as barbiturates, ether, and chloral hydrate, also related to anti-anxiety agents such as benzodiazepines. Social classifications view alcoholic beverages as producing less consistent differences from the nondrug condition than do the barbiturates and benzodiazepines. Studies of discriminative effects of ethanol in laboratory rats agree with the pharmacological classifications. The seemingly stimulant or exhilarating effects of ethanol are due to stronger depression of disinhibitory than excitatory functions. Several studies indicate discriminative effects of ethanol in rats at lower doses than the minimum sufficient to cause observable changes in behavior. Ethanol has distinctive discriminative effects, demonstrated by discriminability of this drug from barbiturates or benzodiazepines. After rats have been trained to discriminate a drug from its vehicle, the ethanol response is induced in tests with barbiturates and benzodiazepines, but the barbiturate or benzodiazepine response is not consistently induced in tests with ethanol. This asymmetrical generalization suggests that some attributes of the ethanol stimulus resemble barbiturates, some resemble benzodiazepines, some resemble the nondrug condition. Barbiturates and benzodiazepines resemble the ethanol attributes that differ from the nondrug condition. Ethanol may resemble barbiturates, benzodiazepines, or the nondrug condition. This model of discriminative drug effects agrees with the social model of alcoholic beverages as producing less consistent differences from the nondrug condition than do barbiturates or benzodiazepines.

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OPIOID DRUG DISCRIMINATION IN HUMANS
George E. Bigelow and Kenzie L. Preston

Drug discrimination procedures have been adapted and utilized with human volunteers to study the comparative clinical pharmacology of opioid agonists, antagonists, and mixed agonist-antagonists, as well as to study features of the drug discrimination procedure itself. Studies have been conducted in a residential laboratory with experienced opioid-abuser volunteers serving as subjects. In some studies participants have been currently nondependent opioid postaddicts; in other studies they have been opioid-dependent due to concurrent therapeutic methadone maintenance treatment. Opioid discriminations have been rapidly learned, typically with only two exposures to each training drug. Discriminations have been trained using either a three-choice procedure (agonist vs antagonist vs placebo, or agonist vs mixed agonist-antagonist vs placebo) or a two-choice procedure (agonist vs placebo). Subjects were then tested under double blind conditions with a range of doses of the training drugs and a range of doses of various opioid mixed agonist-antagonists. The mixed agonist-antagonists butorphanol and nalbuphine were discriminated as antagonist-like by dependent subjects. The mixed agonist-antagonists butorphanol, nalbuphine, pentazocine, and buprenorphine were discriminated as agonist-like by non-dependent subjects in a two-choice procedure but not in a three-choice procedure. Subjective reports usually, but not always, corresponded to behavioral discrimination performance. It is concluded that the drug discrimination methodology is adaptable to and readily learned by humans, that the methodology is of substantial value in making subtle distinctions among compounds with overlapping profiles of activity, and that the three-choice procedure permits more precise differentiations among drugs.

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ANXIETY AND THE DISCRIMINATIVE STIMULUS INDUCED BY PENTYLENETETRAZOLE IN THE PIG. M.P. Carey, J.P. Fry and *D.G. White

At subconvulsant doses, pentylenetetrazole (PTZ) causes anxiety in man and produces an interoceptive stimulus in animals, as revealed by pharmacological conditioning procedures. Previous studies on the discriminative cue induced by PTZ in animals have been inconclusive in their determination of the anxiogenic, as opposed to the proconvulsant nature of this stimulus. Using a novel conditioning procedure, we have evaluated the PTZ cue by examining the discriminatory response of pigs conditioned with PTZ to a behavioural conditioned anxiogenic stimulus. Large White pigs (initial weight 15-20 kg) were trained to select two levers in a modified Skinner box, with the levers set to provide food reward in an alternate fashion. The ratio of presses to food reward for each lever was gradually increased to 20 (FR 20). Pigs were then trained to select one lever following injection of PTS (7.5-10 mg kg^{-1}, i.v.), and select both levers alternately following injection of the 150 mM NaCl vehicle alone. Pigs typically satisfied our criterion of successful PTZ/NaCl discrimination within 50-55 sessions.

In a situation distinct from the PTZ/NaCl discrimination training, a conditioned emotional response (CER) was induced in these pigs by pairing the presentation of a tone stimulus with the application of a mild, non-injurious electric shock. Subsequent presentation of the conditioned tone stimulus during a NaCl test session in the Skinner box caused a switch in responding from alternation of lever selection to selection of the PTZ lever alone. On removal of the conditioned stimulus the animals reverted to alternate responding.

Generalization between the PTZ cue and a CER was antagonized by diazepam (0.5 mg kg^{-1}, p.o.). In some pigs, a generalization to environmental stimuli (novel floor, home intruder etc.) known to disturb pigs was also seen, further suggesting that the discriminative cue induced by PTZ corresponds to an anxiety state.

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STATE-DEPENDENCY AS A POSSIBLE MECHANISM OF BENZODIAZEPINE DRUG ACTION. F.C. Colpaert.

The experiments used a food-reinforced fixed-ratio 10 procedure to analyse state-dependency (StD) with benzodiazepines in rats. Saline-to-chlordiazepoxide (CDP) as well as CDP-to-saline state changes yielded robust transfer failures of the acquired response at CDP ED_{50} doses of 29 and 5.0 mg/kg, respectively. Ro 15-1788 antagonized the CDP state; diazepam substituted for CDP in producing the state, while all non-benzodiazepine compounds tested failed to do so. Neither food deprivation nor extensive overtraining on CDP were able to prevent that the response failed to transfer when rats were trained with CDP and tested with saline. The doses at which CDP and diazepam produced anti-conflict effects were similar to those at which transfer failure occurred in saline-to-drug state changes. It is proposed that StD can act as a mechanism of benzodiazepine drug action. The mechanism may be involved in the anxiolytic and mnesic effects of the benzodiazepines and can conceivably underlie dependence on these drugs.

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NEURO-ANATOMICAL CORRELATE OF THE DISCRIMINATIVE STIMULUS EFFECTS OF THE 5-HT_{1A} RECEPTOR LIGANDS 8-OH-DPAT AND IPSAPIRONE IN THE RAT.

J. De Vry and R. Schreiber

Male Wistar rats were trained to discriminate either DPAT [(8-hydroxy-2-(di-n-propylamino) tetralin), 0.1 mg/kg], a selective 5-HT_{1A} receptor agonist, or 5-OMe-DMT [(5-methoxy-N,N-dimethyltryptamine), DMT, 1.25 mg/kg], a mixed 5-HT_{1A}/5-HT_{1B}/5-HT_2 receptor agonist, from saline (i.p., t-15 min) in a FR-10 food-reinforced two-lever operant procedure. The DPAT cue generalized to DPAT (ED_{50} in mg/kg: 0.04) and the selective 5-HT_{1A} ligand ipsapirone (IPSA, 1.5) and partially to DMT. The DMT cue generalized to DMT (0.35), DPAT (0.07) and IPSA (4.2). These results suggest that both cues are 5-HT_{1A} receptor mediated, although the latter one may involve additional 5-HT receptor subtypes. Local application of DPAT into the dorsal raphe nucleus (DRN) of DPAT and DMT trained rats resulted in dose-dependent and complete generalization (1-10 µg/rat); suggesting that the DRN mediates at least partially the discriminative effects of DPAT. IPSA, applied locally in the DRN (10-30 µg), failed to generalize to the DPAT cue; although possible generalization of higher doses was not tested due to solubility problems. However, bilateral application of the same dose range of IPSA and DPAT into the dorsal hippocampus (CA4) induced partial and complete generalization to the DPAT cue, respectively. It is suggested that both presynaptic (somatodendritic) raphe and postsynaptic hippocampal 5-HT 1A receptors are involved in the discriminative effects of 5-HT_{1A} ligands.

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INTRACRANIAL STIMULATION AS THE REINFORCER FOR STUDYING NEUROPEPTIDES DISCRIMINATION. Ph. De Witte, M. Gewiss and Ch. Heidbreder

Rats were trained to discriminate vehicle injection from intraperitoneal injections of a cholecystokinin (CCK) neuropeptide analog. Intracranial stimulation in the hypothalamus served as the reinforcer according to a FR 10 schedule of bar pressing. Dose-response quantitative generalization was obtained and qualitative generalization to the vehicle occurred after injecting unsulfated CCK-8, CCK-4, neurotensin or bombesin, apomorphine and amphetamine. Total generalization to the CCK-8 analog cue was obtained with gastrin 2-17, somatostatin, haloperidol and chlorpromazine. The previous injection of an antiemetic drug such as chlorhydrate of trimethobenzamide did not eliminate the discriminative properties of a subsequent injection of the CCK-8 analog. Our data thus tend to show that IP injection of CCK-8 analog produces effects similar to those of IP neuroleptics. In these experiments, the use of direct electrical stimulation in a rewarding brain center producing short and highly powerful repetitive rewards without satiety offers the advantage to train animals having a normal body weight without food deprivation.

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DISCRIMINATIVE PROPERTIES OF AVERSIVE ELECTRICAL STIMULATIONS OF THE MESENCEPHALIC LOCOMOTOR REGION: A PARAMETRIC STUDY

R. Depoortère, G. Di Scala and G. Sandner.

In the present work, we examined if the 2 lever food reinforced operant procedure classicaly used for the dicriminative properties of drugs would be suitable for the study of the discriminative properties of aversive brain stimulations. We chose to stimulate the mesencephalic locomotor region (MLR) - a brain area classicaly considered as involved in the control of locomotion and which corresponds to the cuneiform and pedunculopontine tegmental nuclei in the rat - since we have recently shown that these electrical stimulations are aversive.

14 Wistar rats were maintained at 85% of their free feeding weight and trained to press one lever in the presence of the stimulation (train of electrical pulses (0.5 s on, 2.5 s off), frequency: 50 hz; pulse duration: 0.1ms; average intensity: 90 µA) and press the other lever when non stimulated. 11 rats acquired the discrimination task after an average of 60 training sessions.

After acquisition of the discrimination, rats were subjected to stimulus generalization sessions, in which we studied the effects of varying stimulation strength on the lever choice. Only one of the following stimulation parameters was changed at a time: intensity, frequency or pulse duration. It was found that for each of the stimulation parameter, the decrease in the incidence of stimulus generalization was ordely related to the decrease of stimulation strength.

In conclusion, our results show that it is possible to study the discriminative properties of aversive brain stimulations using the 2 lever food reinforced operant procedure. This opens the perspective of pharmacological studies, in particular with anxiogenic/aversivogenic and anxiolytic/antiaversive drugs, in order to investigate cross generalization between perceptual states induced by pharmacological treatment and stimulation of discrete brain structures.

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A COMPARISON OF THE STIMULANT-LIKE EFFECTS PRODUCED BY VENTRAL TEGMENTAL AND NUCLEUS ACCUMBENS MORPHINE INJECTIONS.

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Morphine can produce psychomotor stimulant-like effects by acting at opiate receptors within both the ventral tegmental area (VTA) and the nucleus accumbens (NAS). The former effects are dopamine (DA) dependent whereas the latter effects are DA-independent. In the present study the ability of morphine injected into each of these sites to produce amphetamine-like stimulus properties and locomotor stimulation was compared. Rats were trained to discriminate 1.0 mg/kg amphetamine (AMPH) from saline using a two lever successive discrimination procedure with food pellets available on a VI-30 sec schedule. Separate groups were then tested for generalization during extinction sessions after bilateral injections of morphine sulphate (2.5, 5.0 and 10.0 µg/side) either into the VTA or the NAS. Intra-VTA morphine produced significant increases in AMPH-lever responding at each dose (range of means = 39 - 54%) relative to tests with intra-VTA saline. In contrast, these doses of morphine had no effects on AMPH-lever responding when they were injected into the NAS. However, intra-NAS AMPH injections (2.5, 5.0 and 10.0 µg/side) did increase drug lever responding (range of means = 42 - 56%), confirming that DA release in this area plays a role in mediating the stimulus properties of AMPH. In a second experiment, intra-VTA morphine (2.5, 5.0 and 10.0 µg/side) produced large increases in locomotor activity in food-deprived, and AMPH-sensitized rats whereas injections of the same doses into the NAS produced only slight increases in activity. Intra-NAS AMPH produced strong hyperactivity indicating that the NAS injections were administered to regions which mediate the locomotor stimulant actions of AMPH. Together, these findings indicate that activation of opiate receptors within the VTA produce psychomotor stimulant-like effects that mimic to some degree the actions of systemic AMPH. Although activation of opiate receptors in the NAS may produce mild excitatory effects on activity, such activation appears to differ at least quantitatively and perhaps qualitatively from the stimulant effects produced by amphetamine or VTA morphine injections.

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DRUG-RELATED STIMULI ELICIT CRAVING AND AROUSAL IN OPIATE AND COCAINE ABUSERS

R. Ehrman, A.R. Childress, S.J. Robbins, A.T. McLellan, and C.P. O'Brien

Stimuli repeatedly signalling human drug self-administration (eg., drug-related paraphernalia, locations, people, even certain mood states) seem to act as classically conditioned stimuli, capable of eliciting responses which could prompt drug-seeking behavior. Some of the responses to drug-related stimuli seem specific to drug-use history: sniffing, tearing, yawning and other withdrawal-like symptoms occur in response to opiate-related stimuli in opiate users, but not in cocaine users viewing either opiate or cocaine-related stimuli. Other responses are common to both groups: opiate users viewing opiate stimuli and cocaine users viewing cocaine stimuli both exhibit signs of autonomic arousal (decreased peripheral skin temperature and galvanic skin resistance). In both groups of user the most prevalent subjective response to drug-related stimuli is craving, reported up to five times as often as subjective high or withdrawal responses. We are currently evaluating the ability of putative anti-craving agents for cocaine (eg., amantadine) to attenuate the craving and arousal elicited by cocaine-related stimuli.

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SUBSTITUTION OF THE ISOMERS OF MDA AND MDMA IN RATS TRAINED TO DETECT THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE

M. W. Emmett-Oglesby, C. L. Pickering and S. L. Abdel-Malek

Human users describe the effects of methylenedioxymethamphetamine (MDMA) as having components that are somewhat like amphetamines and somewhat like hallucinogens. This experiment tested the hypothesis that the amphetamine-like effect might be confined to one of the optical isomers. In addition, MDMA is metabolized to methylenedioxyamphetamine (MDA); thus, we also tested whether the amphetamine-like effect might be associated with one of the optical isomers of MDA. Rats were trained to detect the discriminative stimulus effects of cocaine, 10 mg/kg, using a two-lever choice task with food reinforcement. Cocaine was given i.p., 15 min prior to training. Following training, cumulative dosing procedures were used to test substitution of cocaine, (+)-MDA, (-)-MDA, (+)-MDMA and (-)-MDMA for the cocaine training dose. The isomers of MDA and MDMA were given 15 min pre-test, but orderly dose-effect data for cocaine could only be obtained when the dosing interval in the cumulative tests was reduced to 10 min pre-session. Cocaine substituted for the training stimulus, but full substitution only occurred at 20 mg/kg, perhaps reflecting the rapid metabolism of this drug that may have occurred with earlier doses in the cumulative procedure. (+)-MDA and (-)-MDMA substituted for cocaine at doses of 3.5 mg/kg. (-)-MDA and (+)-MDMA did not substitute for cocaine. These results agree with a previous report of the substitution of MDA and MDMA in rats trained to detect cocaine, and they suggest that the isomers may mediate different aspects of the spectrum of effects caused by these drugs.

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DRUG DISCRIMINATION USED TO STUDY WITHDRAWAL

M. W. Emmett-Oglesby and G. A. Rowan

Withdrawal from long-term use of psychoactive drugs produces a variety of readily discernible subjective phenomena in humans. This review considers evidence that drug discrimination methodology can be used to study animal analogues of withdrawal. Two approaches for establishing such models have been reported. One is based upon the observation that withdrawal frequently contains a component of anxiety. Thus, if it were possible to train a subject to detect the stimulus properties of an anxiogenic drug, such a discrimination might have utility in detecting withdrawal from a variety of different drugs of dependence. The discrimination of pentylenetetrazole (PTZ) has been proposed to have predictive validity for identifying anxiogenic stimuli, and we review evidence that the discrimination of PTZ is useful for detecting withdrawal from a variety of drugs of dependence, particularly those of the sedative-hypnotic class. A second approach for establishing models of withdrawal has been to maintain subjects on a baseline of chronic drug administration and to train withdrawal as a controlling stimulus. To date only discriminations based on precipitated withdrawal (opioids and benzodiazepines) have been reported using this method. We will review evidence showing that the stimulus controlling behavior in these experiments is difficult to specify. Because the subject is maintained on a baseline of chronic drug, the discrimination may be based, at least in part, upon the direct effects of the drug of dependence. To avoid this problem, we propose that a traditional discrimination based upon a simple two manipulanda choice procedure must be expanded to a three choice procedure that includes training the drug of dependence, the drug producing withdrawal and saline as the three elements of the choice procedure.

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DISCRIMINATIVE STIMULUS PROPERTIES OF HALLUCINOGENS AND RELATED DESIGNER DRUGS. R.A. Glennon.

Classical hallucinogens can be broadly divided into two categories: indolealkylamines (tryptamines, β-carbolines, and ergoline analogs), and phenylalkylamines (e.g. phenethylamines such as mescaline, and phenylisopropylamines such as DOM and DOB). Examples of most of these types of agents have been used as training drugs in drug discrimination studies; however, the two agents that have been the most widely used are DOM and the ergoline LSD. Particularly with DOM as the training drug, it has been possible to (a) classify which agents produce a DOM-like effect, (b) study the action of metabolites, (c) formulate in vivo structure-activity relationships (SARs), (d) demonstrate a correlation between stimulus-generalization potencies and human hallucinogenic potencies, and (e) investigate mechanisms of action. Indeed, there is a significant correlation between generalization potencies and 5-HT2 receptor affinities leading to the hypothesis that hallucinogens act as (at least partial, though not necessarily as selective) 5-HT2 agonists.

The phenylisopropylamine amphetamine (AMPH) does not produce DOM-like stimulus effects. Using groups of rats trained to either (±) AMPH or (±) DOM, it has been possible to classify various phenylisopropylamine designer drugs and related agents as being (a) DOM-like (e.g. α-desmethyl DOB), (b) AMPH-like (e.g. all four isomers of 4-methylaminorex or "U4Euh"), (c) similar to both (e.g. MDA), (d) neither (e.g. both optical isomers of N,N-dimethyl amphetamine), or (e) perhaps distinct from either DOM or AMPH (e.g. MDE or "Eve"; N-OH MDA). [Supported, in part, by PHS grant DA 01642.]

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DISCRIMINATIVE PROPERTIES OF AMPHETAMINE, CATHINONE AND RELATED AGENTS

A.J. Goudie

This paper will review recent findings from animal studies on the discriminative properties of amphetamine, cathinone and related agents. Studies with cocaine will not be considered because the discriminative properties of cocaine, although similar to those of amphetamine, may not be identical. The assumption that general conclusions can be drawn about the nature of "stimulant" cues may consequently be invalid.

Much evidence indicates that the amphetamine cue is mediated by central (possibly accumbens) DA systems. Studies with selective D1 and D2 agents suggest that, although both D1 and D2 antagonists typically block the amphetamine cue, only D2 (and generally not D1) agonists generalise to the amphetamine cue. Amphetamine can generalise partially to the D2 cue, but it does not generalise to the D1 cue. Collectively, these data suggest that D2 receptors are probably of greatest importance in mediating the amphetamine cue, although D1 systems are clearly also involved in some way. Further work is required to clarify the role of D1/D2 receptor interactions in the mediation of the amphetamine cue. Other issues to be briefly reviewed which require attention in the future in this research area include: (i) The potential role of noradrenergic systems in the mediation of amphetamine/cathinone cues; (ii) The significance of individual differences in responses to such cues; and (iii) The extent to which it is valid to use these cues as preclinical indicators of potential abuse liability (and lack of abuse liability) for drugs such as antidepressants, histamine antagonists and anorectics.

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ACUTE TOLERANCE IN ETOH NAIVE AND ETOH PRE-TREATED RATS

A.J. Hiltunen and T.U.C. Järbe

The studies presented were designed to investigate a reduction in response to ethanol (ETOH) during the descending phase of drug action (acute tolerance) as a function of previous ETOH exposure. In rats trained to discriminate the stimulus properties of ETOH, then tested with doses lower than and equal to the training dose, a positive correlation was found between the discriminative stimulus properties of ETOH and the concentrations of ETOH in rebreathed air during both the ascending and descending phases of ETOH intoxication (Hiltunen et al., Alcohol, 6: 39-43, 1989). Thus, these initial results indicated that acute tolerance did not occur in ETOH pre-treated rats. In the first study, the development of acute tolerance as a function of acute ETOH dose and previous ETOH exposure was examined. For the ETOH-experienced condition, rats were trained to discriminate ETOH from saline, then tested with doses of ETOH higher and lower than the training dose. For the ETOH-naive condition, rats were tested after ETOH administration for spontaneous behaviours in an open-field. Acute tolerance was induced in both drug-naive and drug-experienced animals; however, for drug-experienced animals acute tolerance occurred only when doses of ETOH that were higher than those previously experienced were administered. In the second study, a one-lever FR-10 bar-pressing procedure was used to evaluate the generality of the above results. Four groups of rats were used. Two of the groups were exposed to ETOH and the other two to saline, after the daily bar-pressing training sessions during 20 days before the tests for assessing tolerance and acute tolerance. The results indicated that i) the ETOH pre-exposed groups had significantly higher response rates than the saline pre-exposed groups, and that ii) acute tolerance (increase in response rates during the descending phase of drug action) was only observed for saline pre-treated rats. Thus, the development of tolerance to a given dose seems to diminish the acute ETOH tolerance to that dose, but not to higher doses of ETOH.

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DISCRIMINATIVE STIMULUS FUNCTIONS OF CANNABINOIDS CANNABIMIMETICS

T.U.C. Järbe

Drug discrimination learning (DDL) techniques have been increasingly used as an in vivo bioassay in psychopharmacology research. DDL procedures are based on the ability of animals and humans to detect the presence and absence of certain effects induced by a training drug stimulus. Differential responding is the dependent variable. The discriminative stimulus functions of tetrahydrocannabinols (THC) and related agents is the focus of this overview. Research to date has indicated that the cue produced by THC is pharmacologically specific. Across species only cannabimimetics generally have been found to substitute for the THC cue, including hashish-smoke. Tests with combinations of naturally occurring cannabinoids (THC, CBN, and CBD) indicate interaction effects that may, however, be species specific. For the THC metabolites tested, 11-OH-THC is more potent than the parent substance. Other metabolites have been found to be much less active than THC itself. The activity of (+)-THC is much less than that of the natural (-)-enantiomer, indicating stereoselectivity. Absolute stereospecificity was evident in tests with the enantiomers of the dimethylheptyl homologs of 11-OH-delta-8-THC. The (+)-isomer did not produce response generalization even at doses a thousand times higher than those of the ED50 of the (-)-enantiomer, the (-)-enantiomer being at least seventy times more active than (-)-delta-9-THC. Additional stereochemical aspects of the THC stimulus will be discussed.

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Discriminative Stimulus Properties of Diazepam in Humans

C. E. Johanson

The discriminative stimulus effects of diazepam (DZ) and other anxiolytics have been studied in experimental animals. While the DZ discrimination appears to be sensitive and specific, barbiturates also substitute for DZ and new types of anxiolytics, such as buspirone, do not. To train a discrimination based upon anxiety-reduction, it may be more realistic to use human subjects. However, it is first necessary to determine whether humans can be taught a DZ discrimination within the limitations of human research protocols. In the present study, 19 human volunteers participated and the training drugs were 10 mg DZ and placebo. On each session, participants filled out mood questionnaires, ingested a capsule, and then were free to leave, i.e., they returned to their daily activities. One, 3 and 6 hrs later, subjects filled out additional questionnaires. During phase 1 (4 sessions), 10 mg DZ and placebo were identified prior to ingestion using letter codes. During phase 2, subjects were not told which capsule they received and were asked to telephone 6 hrs after ingestion to report their discrimination using the letter codes. If they were correct, they received bonus money. If a subject correctly identified the capsules on 5 of the 7 sessions, they participated in a third phase of 12 sessions. Six of these sessions were additional training sessions. Randomly intermixed with training were 6 test sessions when subjects received 2 mg DZ, 5 mg DZ, 1 mg lorazepam, 2 mg lorazepam, 50 mg pentobarbital, or 10 mg d-amphetamine. Subjects were not aware that a test session was scheduled until they telephoned and they received bonus money regardless of their response (i.e., there was no correct answer by definition). Sixteen of the 19 subjects learned the discrimination with overall accuracy of 90% during phase 2 which was maintained at a level of 85% during phase 3. When 2 and 5 mg DZ were administered drug-appropriate responding was 7% and 64%, respectively. Drug-appropriate responding increased from 29% at 1 mg lorazepam to 86% at 2 mg. Sixty-four percent of the subjects called 50 mg pentobarbital drug whereas only 21% discriminated amphetamine as DZ. The subjective effects of DZ were typical of benzodiazepines. These results indicate that it is possible to train humans to discriminate DZ and this discrimination is sensitive to differences in dose and appears specific to sedative-like drugs. Further studies will be designed to determine whether the discrimination can be based exclusively on alternations in levels of anxiety.

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EFFECTS OF PHENCYCLIDINE, KETAMINE AND MK-801 IN RATS DISCRIMINATING FENTANYL FROM SALINE: CHARACTERISTICS OF PARTIAL GENERALIZATION

Wouter Koek and Francis C. Colpaert

In rats trained to discriminate 0.04 mg/kg of fentanyl from saline, phencyclidine (PCP) and the PCP-type drugs, ketamine and MK-801, produced effects typically referred to as partial generalization, i.e., a maximum level of drug-appropriate responding intermediate between those produced by the training conditions. The PCP-type drugs produced maximum levels of drug-appropriate responding ranging from 36 (ketamine) to 58% (PCP), and their curves relating dose to drug-appropriate responding had slopes similar to that of fentanyl. Furthermore, they decreased drug-appropriate responding produced by the training dose of fentanyl with an amount ranging from 14 (MK-801) to 25% (PCP), but did not exert less antagonist effects in animals in which they had any agonist activity than in those in which they did not. Naltrexone antagonized drug-appropriate responding produced by fentanyl, but not that produced by PCP-type drugs. The PCP-type drugs produced intermediate levels of drug-appropriate responding at doses that 1) reduced the rate of responding, 2) increased the lever selection latency, and 3) increased responding on the nonselected lever, both before and after lever selection occurred. This behavioral profile, which was not produced by doses of fentanyl and haloperidol that decreased the rate of responding to the same extent as the PCP-type drugs, resembled that shown by animals in which the training conditions did not exert reliable DS control. Thus, the PCP-type drugs produced drug-appropriate responding through mechanisms unlikely to involve low intrinsic activity at opiate receptors. State-dependency constitutes a conceivable mechanism whereby PCP-type drugs produce drug-appropriate responding without inducing stimulus generalization with fentanyl.

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STATE-DEPENDENT LEARNING EFFECTS WITH SOCIAL DRUGS.

G. Lowe

The interactions between alcohol and social stimulants (e.g. caffeine and nicotine) are generally regarded as complex, with antagonistic, synergistic and mixed effects being reported. These social drugs are frequently ingested in close temporal proximity, yet relatively little is known about the state-dependent learning effects of such drug combinations. Several experiments are reported in which moderate doses of alcohol, caffeine and nicotine were administered to groups of human subjects in a 2x2 SDL design. The results demonstrate the dissociative effects of alcohol-caffeine and alcohol-nicotine combinations on learning and recall. Thus, a significant proportion of everyday forgetting could be due to state-dependent learning effects, particularly since drug combinations offer an increased range of dissociation possibilities.

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DISCRIMINATION OF AN AMPHETAMINE-PENTOBARBITONE MIXTURE IN RATS. E.A. Mariathasan, H.S. Garcha, I.P. Stolerman.

Rats readily acquire discriminations based on compound interoceptive stimuli (mixtures of drugs). In previous studies with mixtures of nicotine and midazolam it appeared that components of a compound drug-produced stimulus were perceived separately rather than as a homogeneous entity. The present study extends this concept to mixtures of (+)-amphetamine and pentobarbitone. Two-bar procedures and tandem schedules of food reinforcement were used.

The role of training dose was tested by keeping the dose of amphetamine constant at 0.4 mg/kg (SC) and increasing that of pentobarbitone from 5 mg/kg to 20 mg/kg (SC). Initially stimulus control was attributable to amphetamine, but as the pentobarbitone dose increased, stimulus control switched to pentobarbitone; responses to components of the compound stimulus were systematically related to doses of drugs used for training. A strong stimulus produced by pentobarbitone appeared to overshadow the stimulus produced by amphetamine.

Different rats were trained to discriminate amphetamine (0.5 mg/kg) plus pentobarbitone (12 mg/kg), or either drug separately, from saline. After 40 sessions, accuracy reached 88%, 92% and 87% in rats trained with mixture, amphetamine and pentobarbitone, respectively. Rats trained with mixture generalized to the component drugs. Rats trained with amphetamine did not generalize to pentobarbitone, but pentobarbitone attenuated the response to amphetamine. Rats trained with pentobarbitone showed minimal generalization to amphetamine, and amphetamine did not influence the response to pentobarbitone. The results confirmed that components of a compound stimulus can be perceived separately. Drugs from more pharmacological groups must be examined to determine if this is a general characteristic of discriminations based on drug mixtures (research supported by NIDA grant DA-05543).

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REBOUND FROM A SINGLE LARGE-DOSE OF MIDAZOLAM SUBSTITUTES FOR PENTYLENETETRAZOLE BY RATS TRAINED ON A THREE-LEVER TASK

D.A. Mathis and M.W. Emmett-Oglesby

In previous studies, rats trained to discriminate between the anxiogenic compound, pentylenetetrazole (PTZ), and saline, substitute withdrawal from chronic diazepam treatment for the PTZ stimulus (Emmett-Oglesby et al., J. Pharmacol. Exp. Ther, 244:892, 1988). In addition, rats trained to discriminate between chlordiazepoxide (CDP) and PTZ, then injected with a large dose of CDP, detect a PTZ-like stimulus at 12 to 18 h after CDP administration (Michaelis et al., Psychopharmacology, 96:15, 1988). In the present study, the time-course of PTZ substitution and return to baseline after a single administration of midazolam (MDZ; 4 mg/kg) was assessed. Rats were trained to discriminate between MDZ (0.5 mg/kg), PTZ (16 mg/kg) and saline on a three-lever operant task under an FR10 schedule of food reinforcement. The discrimination was acquired after approximately 40 sessions for each training condition. Substitution was tested at 1, 3, 6, 12, 18 and 24 h post MDZ injection. At 1 h post injection, rats primarily selected the MDZ lever; by 12 h post, rats primarily selected the PTZ lever. Saline-lever selection was obtained 24 h post MDZ administration. Thus, these data support the hypothesis that rebound withdrawal after MDZ administration produces a stimulus that is similar to the stimulus produced by the anxiogenic drug PTZ, and that a discrimination between a benzodiazepine, PTZ and saline is useful for assessing onset and recovery from benzodiazepine withdrawal.
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THE DISCRIMINATIVE STIMULUS PROPERTIES OF LSD: SEROTONERGIC AND CATECHOLAMINERGIC INTERACTIONS.

T.F.Meert, P.L.A.J. De Haes and P.C.M. Vermote.

The discriminative stimulus properties of LSD were assessed in rats trained to discriminate 0.16 mg/kg LSD (IP, T-15 min) from saline in a two lever food reinforced drug discrimination test procedure in rats. The test compounds included LSD, DOM, 8-OHDPAT, buspirone, isapirone, TFMPP, Ru-24969, ritanserin, risperidone, R 79 598, haloperidol and prazosin. All compounds were given at 60 min before testing.

In terms of stimulus generalization with 0.16 mg/kg LSD, a complete substitution was observed with LSD (ED_{50}: 0.26 mg/kg), 8-OHDPAT (0.13 mg/kg) and DOM (0.13 mg/kg). Partial generalization was present with buspirone and TFMPP, while all other compounds were inactive. In terms of an antagonism of the discriminative stimulus properties of 0.16 mg/kg LSD, a complete antagonism was observed with ritanserin (ED_{50}: 11.60 mg/kg) and risperidone (0.028 mg/kg); R 79 598 was partially active (up to 60 %). Although haloperidol and prazosin were without any effect on LSD, both compounds potentiated the LSD antagonist properties of ritanserin. The combined treatment of 0.01 and 0.04 mg/kg haloperidol with ritanserin reduced the ED_{50} of ritanserin to 0.39 and 0.22 mg/kg, respectively. Also with 0.01 and 0.04 mg/kg prazosin, a decrease in the ED_{50} of ritanserin to 2.71 and 0.13 mg/kg was obtained.

These results indicate that i) different 5-HT agonists are able to produce a stimulus generalization to LSD and ii) for a potent LSD antagonism, both a $5\text{-}HT_2$ and catecholamine antagonism is needed.

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A DRUG DISCRIMINATIVE ANALYSIS OF LORECLEZOLE, A NEW ANTILEPTIC AGENT.

T.F.Meert, P.L.A.J. De Haes and P.C.M. Vermote.

Loreclezole (R 72 063), a new anticonvulsant with a broad-spectrum activity (Wauquier et al., Drug. Dev. Res., 1990, in press), was compared with chlordiazepoxide, clobazam and carbamazepine in two groups of rats trained to discriminate either 5 mg/kg chlordiazepoxide (IP, T-15 min) or 20 mg/kg metrazol (IP, T-15 min) from saline in a two lever food reinforced drug discrimination test procedure in rats. All test compounds were given orally at 60 min before the beginning of the experiment.

In the chlordiazepoxide trained animals, a complete stimulus generalization was observed with chlordiazepoxide, loreclezole and clobazam; the relative order of potency was chlordiazepoxide > loreclezole > clobazam. At doses up to 40 mg/kg, carbamazepine was inactive.

In the metrazol trained rats, there was no stimulus generalization at all. The relative order of potency to antagonize the discriminative stimulus properties of metrazol was chlordiazepoxide > loreclezole > clobazam > carbamazepine (inactive).

Additional experiments, using animal models of anxiety, indicated loreclezole to possess behavioural disinhibitory properties similar to the benzodiazepines. However, as opposed to the benzodiazepines, loreclezole induced less sedative side-effects.

These results are discussed in terms of the use of loreclezole as an antiepileptic agent.

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APPLICATION OF DRUG DISCRIMINATION TO DEVELOP NEW THERAPEUTIC AGENTS

T.F. Meert and F. Awouters

In the study of new therapeutic agents, the drug discrimination test procedure provides additional information to basic screening tests, especially when training drugs with a complex pharmacological profile are used. Sometimes, drug discrimination tests greatly elucidate interactions of a new compound with various neurotransmitter systems. In the present study R 79 598, a new neuroleptic known to act on central D2 and 5-HT2 receptors, was compared to haloperidol (mainly D2), ritanserin (5-HT2) and risperidone (5-HT2, D2) in four groups of rats trained to discriminate 0.63 mg/kg DOM, 0.16 mg/kg LSD, 10 mg/kg cocaine or 1.25 mg/kg d-amphetamine from saline. In terms of antagonism of the DOM cue, the relative order of potency of the tested drugs was R 79 598 > risperidone > ritanserin > haloperidol (inactive). For antagonism of the d-amphetamine cue, the relative order was R 79 598 > haloperidol > risperidone > ritanserin (inactive). The potency of the tested compounds to antagonize the DOM cue corresponds to the antagonism of tryptamine-induced bilateral convulsions; the antagonism of the d-amphetamine cue resembles the antagonism of apomorphine-induced agitation and stereotyped behaviour. With respect to the LSD cue, the relative order was risperidone > ritanserin > R 79 598 (partial) > haloperidol (inactive). For cocaine antagonism it was R 79 598 > haloperidol = risperidone > ritanserin (inactive). For both the antagonism of LSD and cocaine, no simple relationship with 5-HT2 or D2 antagonism was found. The differences between behavioural and cueing actions of training drugs with a complex pharmacological profile are discussed especially in relation to the central activity of R 79 598.

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TOLERANCE TO THE ANALGESIC, BUT NOT THE "CUE" PROPERTIES OF MORPHINE AFTER BRIEF SOCIAL STRESS

K. A. Miczek

One of the most prominent consequences of the distinctive experience of defeat in a social confrontation is the long-lasting tolerance to the analgesic effects of opiates. The present experiment examined (1) what kind of social experiences lead to morphine tolerance, (2) whether or not the morphine tolerance in defeat-experienced rats extends to the discriminative stimulus and behaviorally suppressive effects of morphine, and (3) how long morphine tolerance lasts after a defeat experience. Male Long-Evans rats were trained in a two-lever task on a Fixed Ratio 10 schedule of milk reinforcement so that responding on one lever was reinforced when the animal was injected i.p. 30 min earlier with 2.5 mg/kg morphine, and reinforcement on the other lever was available in alternate 10-min sessions after administration of saline. Under these conditions, the ED_{50} for the morphine "cue" was 1.5 mg/kg. Additional determinations with higher morphine doses revealed the ED_{50} for the analgesic effects of morphine to be 8.9 mg/kg in the tail-flick assay. Housing the animals singly, pair-housing the males with a female or male partner, each for 3 weeks, did not significantly alter the ED_{50}'s for the morphine cue or analgesia. However, when the animals were exposed to the attacks and threats by a resident rat in 5 5-min encounters, the dose-effect curve for morphine analgesia showed a twofold shift to the right, whereas 3 out of 9 rats responded to the morphine "cue" at lower doses than before. In a separate group of rats, the tolerance to morphine's analgesic effects after defeat in a social confrontation was detected 3 months after this behavioral intervention, whereas no changes in morphine effects on response suppression or "cue" properties were found. These findings provide evidence for development of tolerance and sensitization within the same individual to separate opiate effects, possibly suggesting the involvement of different opiate receptor populations.

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DRUG DISCRIMINATION: A HISTORICAL PERSPECTIVE. Donald A. Overton

In pharmacology, the drug discrimination (DD) procedure has become a useful assay instrument even though its psychological properties are not yet well understood. However, in psychology, DDs are part of the complex and extensively studied phenomenology of contextual and discriminative control of behavior. Although understanding of the SDL (state dependent learning) and DD phenomena has advanced substantially during the 150 years since SDL was first described, major technical and scientific issues still need to be addressed including the following. (1) The degree of overlap between cues produced by "dissimilar" drugs needs to be elucidated since it hardly seems plausible that all types of dissimilar drug cues are equally dissimilar to one another. Instead of categorical reports of dissimilarity, methods are needed that will provide quantitative measures of degree of similarity/dissimilarity between cues produced by dissimilar drugs. Multidimensional Scaling might provide a method for determining the degree of overlap. (2) A more detailed knowledge of the relevance of DD results to abuse liability is needed that will indicate which drug cues are relevant to drug abuse, and which are not. (3) An experimental design is needed for the study of SDL which is superior to the 2x2 design; perhaps multiple regression will provide a method for estimating the relative strength of several drug effects which are concurrently produced. (4) Training and test procedures that provide quantitative instead of qualitative results are needed, as is a method for quantitatively comparing the strength of cues produced by drugs in different pharmacological classes.

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ELECTRICAL BRAIN-STIMULATION AS A DISCRIMINATIVE AND REWARDING STIMULUS
A.G. Phillips and J.P. Druhan

Electrical brain-stimulation (EBS) shares several properties in common with certain psychoactive drugs, including the ability to serve as a discriminative or conditional stimulus ("cue" properties) and as a rewarding stimulus. These shared properties of both EBS and drugs raise two reciprocal questions: 1) Do the rewarding properties give rise to the "cue" properties? 2) Can the "cue" properties be defined in terms of natural sensory processes? If so, can this information be used to describe and explain the rewarding properties of EBS and drugs?

Studies employing EBS will be reviewed in light of these questions and the following conclusions will be discussed. 1) The "cue" properties of EBS in different brain regions are not mediated by a single neuroanatomical or functional system. 2) Brain-stimulation reward is not subserved by a single system. 3) Despite the heterogeneous nature of these two phenomena, recent evidence supports functional and neuroanatomical links between the "cue" and rewarding properties of EBS involving the mesotelencephalic dopamine system. 4) This dopamine system may also mediate both the sensory and rewarding properties of psychomotor stimulant drugs. In support of the last two hypotheses, data will be presented to demonstrate that "amphetamine-like" stimulus properties can be produced by EBS of reward sites in the ventral tegmental area.

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THREE WAY DISCRIMINATION OF PENTYLENE-TETRAZOLE, MIDAZOLAM AND SALINE IN RATS. S.L. Pugh and M.W. Emmett-Oglesby.

Rats were trained to discriminate pentylenetetrazole (PTZ), midazolam (MDZ), and saline in a three-lever operant procedure where food reinformcement was only delivered following 10 responses on the correct lever (FR 10). Initially, doses of 15 mg/kg PTZ and 0.5 mg/kg MDZ were trained. After 81 sessions, PTZ and MDZ doses were increased to 20 and 1 mg/kg, respectively. After an additional 56 sessions the discrimination was acquired to a criterion of 9 out of 10 sessions with correct lever selection at the beginning of the session. In stimulus subsitution test, PTZ (5 mg/kg - 20 mg/kg) and MDZ (0.125 mg/kg - 1 mg/kg) substituted for their respective training doses in a dose-related manner. Substitution of diazepam (DZP) was obtained for MDZ; however, DZP substituted only partially for MDZ, with the highest percentage of MDZ selection being 67% at 2.5 mg/kg. In addition, the dose-effect curves for MDZ and DZP covered a much broader range of doses than the PTZ dose-effect curve. The dose-dependent substitution of DZP and MDZ across a wide dose regimen suggests that this training dose of MDZ is a weak controlling stimulus. The length of time to train the discrimination also suggests that this was a very difficult discrimination to acquire, which is consistent with the suggestion that MDZ served as a weak controlling stimulus. The observation that diazepam never fully substituted for the MDZ stimulus suggests that although these two drugs belong to the same class of agents, that they may differ in their profile of subjective effects.

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LACK OF AMPHETAMINE-LIKE EFFECTS OF THE NOOTROPIC DRUGS, OXIRACETAM AND PIRACETAM. C. Reavill, A.J. Hunter and R.G. Hill

Behaviourial tests in man and animals have provided evidence that nootropic drugs possess cognition- and memory-enhancing qualities. The mechanisms by which these compounds exert their effects are still uncertain, although some studies have indicated that central cholinergic or catecholaminergic systems may be involved. Also, a minority of patients have shown psychotic episodes when treated with high doses of nootropics. For this reason we have examined the possibility that oxiracetam and piracetam may have amphetamine-like effects by using the amphetamine-discriminative stimulus paradigm as a behaviourial assay. Male hooded Lister rats (200-250g at the beginning of the experiment) were trained to press one of two bars under a tandem variable interval 60 sec, fixed ratio 10 schedule of food reward. Amphetamine (0.5mg/kg sc) or saline (1ml/kg sc) were injected 15 min prior to 15 min training sessions. For each rat the same bar was always paired with amphetamine and the other bar was paired with the saline vehicle. Once stimulus control had been established (28 daily training sessions) the rats were tested for responding in 5 min extinction sessions 1 hour after administration of a range of doses of nootropic drug (32-320 mg/kg ip) or vehicle (1ml/kg ip). Baseline responding was tested 15 min after saline (1ml/kg sc) or amphetamine (0.5mg/kg sc). Saline produces less than 10% responding on the drug-paired bar, and this was reliably increased to above 90% after amphetamine. After administration of oxiracetam or piracetam, drug-bar responding remained below 10%, and was not significantly different from responding after saline or vehicle. Although compared with saline, amphetamine produced response rate suppression as measured by total responses on both bars, no dose of oxiracetam or piracetam reduced responding compared to that recorded after saline or vehicle. It is concluded that at the doses tested neither oxiracetam nor piracetam possess subjective effects similar to amphetamine.

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EXTINCTION AND REACQUISITION OF DIFFERENTIAL RESPONDING FOR RATS TRAINED TO DISCRIMINATE CHLORDIAZEPOXIDE FROM SALINE
H.J.Rijnders, T.U.C.Järbe and J.L.Slangen

Rats were trained to discriminate between either 6.0 mg/kg p.o. CDP and saline (N=12), or between 30.0 mg/kg p.o. CDP and saline (N=13) using a food reinforced (FR10-VI40) operant procedure. Dose generalization tests were run in both groups. Sessions thereafter were executed without reinforcements while the drug (D) and the saline (S) administrations were continued (extinction phase). After a maximum of 30 extinction sessions, or after the rats did not emit 10 responses on either lever 3 times in a row (extinction criterion) reinforcements were reinstated (reacquisition phase). Finally, additional dose generalization tests were run. The major findings were: 1) The high dose group reached the extinction criterion sooner than the low dose group. Also, the response-rate reduction occurred more rapidly for the D condition than for the S condition in the high dose group. 2) While the response rate decreased over extinction sessions, reinforcement omission did hardly affect the discriminative control of the D and S administrations. 3) Once the reinforcements were reinstated, the response rates increased very rapidly yielding no differences between groups and D and S conditions. 4) Generalization tests executed before the extinction phase and after 10 reacquisition sessions yielded similar results and were in agreement with earlier findings. To conclude, the higher dose of the training drug seemed to be more salient, providing the rats with more information about the change in reinforcement contingency. Further, the degree of stimulus control exerted by the D and S administrations was not affected by prolonged reinforcement omission.

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NICOTINIC AND MUSCARINIC AGONISTS AND ANTAGONISTS AS DISCRIMINATIVE STIMULI

J.A. Rosecrans and H.F. Villaneueva

This overview will discuss the discriminative stimulus (DS) effects of the nicotinic cholinergic (N-Ch) agonist, nicotine (Nic), muscarinic cholinergic (M-Ch) agonists such as arecoline (Are) and oxotremorine (Oxo), and the M-Ch antagonist scopolamine (Scop). Besides the ability of these agonists to induce very specific stimulus effects, these agents also appear to exhibit a differential generalization to a central increase in endogenous brain acetylcholine (ACh) levels elicited via the administration of cholinesterase (ChE) inhibitor, physostigmine (Phy). M-Ch agonists generalized to Phy while the DS elicited by Sco was also antagonized by this cholinesterase inhibitor suggesting a central role for ACh in the mechanism of stimulus control by these cholinergic drugs. In addition mecamylamine, a centrally acting N-Ch antagonist, was unable to alter the DS elicited by Phy, and the nicotine DS failed to generalize to the Phy-induced increase of endogenous ACh levels. The overall results of these studies indicate that M-Ch agonist DS effects, but not that of the N-Ch agonist, nicotine, were mediated via an effect on endogenously released ACh. An explanation of these findings is based on the theory that the N-Ch receptors may be readily desensitized by ACh or Nic.

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DRUG DISCRIMINATION DATA AND THE UNITED STATES CONTROLLED SUBSTANCES ACT F.L. Sapienza

Stimulants, depressants, hallucinogens and narcotics with abuse potential may be placed under the U.S. Controlled Substances Act (CSA). The lengthy process made it difficult to keep pace with "designer drug" chemists. Recent amendments have addressed this by allowing (1) the temporary control of a substance on an emergency basis; and (2) treatment of controlled substance analogues as Schedule I substances. Control actions are based on scientifically accurate and legally defensible data. Scheduling requires findings of abuse potential, accepted medical use and safety or lack thereof and dependence liability. Findings are made only after consideration of a substance's abuse liability including its pharmacology, chemistry and toxicology, actual abuse including its history, pattern, scope, duration and significance of abuse, public health risk and dependence liability. International control requires similar considerations.
A controlled substance analogue is defined as a substance which (1) has a chemical structure or (2) produces or is represented to produce a stimulant, depressant or hallucinogenic effect, substantially similar to that of a controlled substance. 4-phenylpiperidines, 4-anilinopiperidines, phenethylamines, phenylisopropylamines, oxazolines, and arylcycloalkylamines have been found in the illicit drug traffick recently and emergency controlled or treated as controlled substance analogues. Drug discrimination data played a key role in characterizing the substances and in expeditiously determining whether or not they should be placed under the CSA.

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TOLERANCE: ROLE OF CONDITIONING PROCESSES
Shepard Siegel

Results of numerous experiments have demonstrated that tolerance to the last of a series of drug administrations is more pronounced in the drug administration environment than in an alternative environment. Such findings suggest that Pavlovian conditioning processes contribute to tolerance. That is, over the course of repeated drug administrations an association develops between predrug cues and the systemic effects of the drug. This association, which may be seen by presenting the usual predrug cues but without the drug, is manifest as an anticipatory compensation for the drug effect. That is, the drug-elicited feedback processes that mediate tolerance are augmented by feedforward processes occurring in anticipation of the drug.

Considerable evidence suggests that Pavlovian conditioning importantly contributes to tolerance. This evidence comes from experiments indicating that nonpharmacological manipulations of drug-predictive cues have predictable effects on the development of tolerance. Thus, drug tolerance, like Pavlovian conditioning, is subject to extinction, partial reinforcement effects, inhibitory learning, higher-order conditioning, and compound conditioning phenomena (overshadowing and blocking).

Finally, recent research indicates that a variety of predrug cues, in addition to environmental cues, may become associated with a drug and control the display of tolerance. These include pharmacological cues, and interoceptive processes that occur prior to drug self-administration.

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SCHEDULE-INDUCED POLYDIPSIA AND DRUGS AS REINFORCERS. G. Singer

In our laboratories we have combined a self-injection technique with a food delivery schedule and developed the method of schedule-induced self injections (SISI). We have been able to classify drugs according to acquisition patterns and have shown that the stimulus complex necessary for self-injection to occur varies with the type of drug presented. The presence of a food delivery schedule, and the state of nutrition interact with the drug molecule in the acquisition and maintenance of drug intake behaviours.

The model can be used in traditional pharmacological studies to investigate specific and general blockers of drug intake. Other studies have shown the importance of intact dopaminergic neurons in the nucleus accumbens septum for the acquisition and maintenance of drug intake behaviour.

Biochemical studies of the SISI model have shown that an increase in corticosteroid levels is associated with schedule-induced behaviours.

The theoretical implications as well as implications for legislation and therapeutic programs will be discussed.

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NALOXONE AS A STIMULUS IN DRUG DISCRIMINATION LEARNING: GENERALIZATION TO AND DISCRIMINATION FROM OTHER OPIATE ANTAGONISTS

S. Smurthwaite, M. Kautz, B. Geter and A. Riley

Rats administered naloxone (1 mg/kg) 15 min prior to the pairing of saccharin with LiCl and the naloxone vehicle 15 min prior to a nonpoisoned exposure to the same saccharin solution rapidly acquired the drug discrimination, avoiding saccharin consumption when it was preceded by an injection of naloxone and consuming saccharin following the distilled water vehicle. Once the discrimination was established, both naltrexone and diprenorphine substituted for naloxone in a dose-dependent manner.

Although diprenorphine initially substituted for naloxone, when naloxone subsequently signalled a saccharin-LiCl pairing and diprenorphine signalled a saccharin-distilled water pairing, animals avoided saccharin consumption following naloxone and consumed saccharin following diprenorphine. During subsequent substitution tests, the mu antagonist naltrexone substituted for naloxone whereas the primarily kappa antagonist nalorphine substituted for diprenorphine.

That naltrexone and diprenorphine substituted for naloxone in naloxone-trained animals is consistent with the fact that opiate antagonists likely share some common activity at opiate receptors. That naloxone and diprenorphine could be discriminated with subsequent drug-drug training and the pattern of substitution was selective is consistent with the fact that although both are opiate antagonists, they are thought to act at different subtypes of the opiate receptor.

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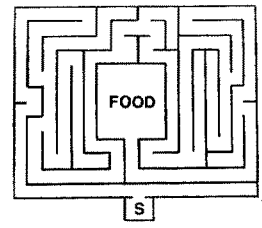
PERFORMANCE OF RATS ON A HAMPTON COURT MAZE. J. M. Stahl and T. M. Richardson

The purpose of this research was to establish a test that requires performance learned over an extended period of time for use in testing for state dependent learning. Although the Hampton Court Maze had been cited in the early literature (Kinnaman, 1902; Porter, 1904), we could find no published data. Thus we established test procedures and acquired data on running times, errors, and latencies to leave the start box. Six naive male Long-Evans hooded rats between 90-140 days of age (300-410g) served as subjects. The apparatus was a modified version of the maze which Small (1900) modeled after the famous hedge maze in the Gardens of Hampton Court Palace. Following adaptation procedures, testing began. An error was recorded if the rat turned into an incorrect alley or if it began to backtrack. There were five trials a day every other day. Mastery was defined as two or less errors on four out of five consecutive trials. Results show a great deal of individual differences on all measures. Latencies to leave the start box ranged from 3-120 seconds. The number of sessions it took subjects to learn to leave the start box varied between 3 to 17 test days with latencies decreasing over test days and remaining low for all subjects. Subjects varied between 34 seconds to 10 minutes in the time it took them to traverse the entire maze. Although latency data look like learning curves, the running time data was not at all gradual. This data is more indicative of what has been called "insight" with abrupt changes from very long to much shorter running times. The test will be discussed in terms of how it can be used in studies of state dependent learning with drugs and alcohol.



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THE DISCRIMINATION OF DRUG MIXTURES. I.P. Stolerman.

Subjects can discriminate effects of drug mixtures from undrugged states. This paper surveys (1) some theoretical background to such discriminations, partly in terms of the conceptualization of Jarbe and Swedberg, (2) data on their characteristics and (3) their applications.

Stimuli generated by single drugs may have two or more components and characteristics of the resulting compound stimulus may depend upon the ways that these component stimuli are perceived, and how they interact with each-other. The main questions include whether the stimulus complex is perceived as the sum of its components or as a qualitatively distinct entity, and whether and how psychological processes (e.g. overshadowing and blocking) influence the acquired discriminations. It is important to know if the complexity of a stimulus influences its pharmacological specificity, and to understand the effects of varying the salience of the component stimuli. Answers to these questions are needed to ensure that the power of drug discrimination methodology can be fully exploited.

Recent work in rats attacks some of these questions with mixtures such as nicotine plus midazolam, amphetamine plus pentobarbitone, pentazocine plus tripelennamine, and caffeine plus phenylpropanolamine. The present data suggest (1) mixtures are not normally perceived as new entities distinct from their component drugs, (2) training dose-ratio influences characteristics of discriminations in an orderly manner, (3) pharmacological specificity remains largely intact and (4) overshadowing of one drug by another may be an important factor determining the characteristics of cues produced by drugs. Results of studies on mixtures may be applicable to single drugs with multiple effects (e.g. at receptor subtypes), to clinically used mixtures, and to polydrug abuse (research supported by NIDA grant DA-05543).

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QUANTAL AND QUANTITATIVE DRUG DISCRIMINATIONS.
I.P.Stolerman, H.S. Garcha and F. Rasul.

It has been suggested that discriminative responses controlled by drug effects are inherently quantal (all-or-none), but other workers have maintained that such responses can be quantitative (graded). The characteristics of individual responses have therefore been examined under a range of commonly encountered conditions. Throughout the studies, rats were trained to discriminate nicotine (SC) from saline in two-bar procedures with food reinforcement.

When the dose of nicotine used to maintain discriminations was 0.4 mg/kg, the schedule of reinforcement influenced the results. Individual rats trained under a tandem VI-1 min FR-10 schedule responded almost exclusively on one bar at doses of nicotine that produced intermediate mean results (quantal cue). In contrast, rats trained under a simple VI-1 min schedule responded on both bars at intermediate doses (quantitative cue). Repeated tests with intermediate doses confirmed that the schedule of reinforcement determined the outcome. However, after training with 0.1 mg/kg of nicotine, the schedule was unimportant; rats responded on both bars at intermediate doses under tandem VI-1 min FR-10, simple VI-1 min, and simple FR-10 schedules. Finally, after training with 0.4 mg/kg of nicotine under a tandem schedule and with presession intervals of 5 or 20 min, rats responded mainly on one bar when tested at an intermediate dose; with a presession interval of 35 min, rats responded on both bars.

The results suggest that discriminative responses controlled by drug states can be either quantal or quantitative, depending on the schedule of reinforcement, the dose of drug, and the presession interval. It is clear that this attribute of drug-produced cues is not fixed and immutable, but the result of a dynamic interaction between multiple factors (research supported by Medical Research Council).

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DISCRIMINATIVE STIMULUS PROPERTIES AND REWARD ASSOCIATED WITH LUTEINIZING HORMONE RELEASING HORMONE (LHRH).

N.E. Van de Poll and R. de Beun.

Many studies now have shown a release of LH and subsequent activation of the gonadal axis upon psychosexual stimulation in males of a diverstity of species, including man. The behavioral relevance of these hormonal changes, however, is not known. In a series of experiments on gonadectomized, testosterone implanted male rats, the psychological relevance of these acute hormonal changes was investigated.

Using a drug-discrimination paradigm, male rats were trained to discriminate intraperitoneal injections of LHRH in doses sufficient to activate the pituitary gonadal axis, from saline. Subsequent generalization tests showed a clear dose-response relation, whereas a relatively sharp injection-test interval-effect curve indicated optimal discrimination at the injection-training interval of 45 minutes. A place-preference paradigm was used to investigate affective properties of LHRH-treatment. Injections of various doses of LHRH were shown to induce preference for the hormone-associated side of the testbox in a dose-dependent manner.

On base of these results future research will be aimed at investigating the psychological relevance of psychosexually stimulated activation of the pituitary gonadal axis in the human male. Effects of LHRH-associated activation of this axis will be studied using a human drug discrimination paradigm and various tests to assess the emotional concommittants of activation of this axis.

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IS THE CONDITIONED TASTE AVERSION PROCEDURE A USEFUL TOOL IN DRUG DISCRIMINATION RESEARCH?

A.van Hest[1], J.L.Slangen[2], B.Olivier[1].

The conditioned taste aversion (CTA) paradigm has recently been described as an alternative approach to more traditionally used two-lever choice response procedures. In CTA, thirsty rats are given daily access to saccharine water. Drug injections are given prior to saccharine/LiCl pairings. Vehicle treatment precedes exposure to saccharine water alone. Alternating drug and vehicle injections are given until rats avoid saccharine consumption following drug administration. It has been argued that conditioning to the CTA paradigm occurs more rapidly, and requires less frequent exposure to drugs than other, more traditional conditioning procedures.

Different group of rats were trained to discriminate the 5-HT_{1a} agonist 8-OH-DPAT (0.4 mg/kg) or the benzodiazepine chlordiazepoxide (CDP, 20 mg/kg) from saline. Discrimination training took 40 sessions. A dose-response curve was determined for CDP. Some procedural changes were made for subjects trained to discriminate 8-OH-DPAT, but stable baseline performance was not achieved. The daily testing routine (i.e. preparing drug and/or vehicle solutions, weighing saccharine, calibrating drinking tubes, reading off drinking tubes after testing) was very laborious. The test is also very bothersome to the laboratory animal. Rats are injected twice daily, and are regularly subjected to sickening effects of LiCl treatment. Experimental subjects gained considerable less weight over the experiment than controls. In addition, separate groups of rats were needed to examine the effects of repeated drug treatment on saccharine consumption.

In summary, the method was found more time-consuming, less accurate, and more bothersome to the animal than traditional drug discrimination procedures.

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CHARACTERIZATION OF THE NICOTINIC CUE IN RATS TRAINED TO DISCRIMINATE (-)-NICOTINE OR 3-PMP.

H. F. Villanueva, E. E. Hinkle, A. M. Ismaiel, R. A. Glennon and J. A. Rosecrans

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Previous research by Chance et al (Br J Pharmac, 63: 609-616, 1978) has shown that both the (+) isomer of nicotine and the structurally related compound 3-pyridylmethyl-pyrrolidine (3-PMP) generalize to the discriminative cue produced by (-)-nicotine in the rat. Both (+)-nicotine and 3-PMP were found to be 10 times less potent than (-)-nicotine. In order to further characterize this discriminative cue, male Sprague-Dawley rats were trained on a standard two-lever operant drug-discrimination paradigm (fixed ratio 10). Six rats were trained to discriminate 3-PMP from saline, while eight rats were trained to discriminate (-)-nicotine from saline. Following training, all rats were tested with various doses of (+)-nicotine, (-)-nicotine, and 3-PMP to determine the relative potencies of these compounds. Animals trained to the (-)-nicotine failed to respond > 70% on the drug-correct lever following either (+)-nicotine or 3-PMP. Animals trained to the 3-PMP cue responded 90% on the drug-correct lever to a dose of (-)-nicotine which was 1/8th the concentration of the training doe of 3-PMP, however, no dose of (+)-nicotine produced > 50% responding among these animals, and the dose of (+)-nicotine which was equipotent to the training dose of 3-PMP completely abolished all responding. These results suggest that while the discriminative cue produced by 3-PMP is similar to that produced by (-)-nicotine, it is not similar to the cue produced by (+)-nicotine.

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DISCRIMINATIVE-STIMULUS PROFILE OF THE LOW-EFFICACY OPIOID AGONIST NALBUPHINE E.A. Walker and A.M. Young

These experiments examined the discriminative-stimulus profile of nalbuphine, a **mu** opioid agonist with low intrinsic efficacy. Twelve male Sprague-Dawley rats were trained to discriminate between 3.2 mg/kg nalbuphine and saline under a FR 15 schedule of food delivery. During tests of cumulative doses, nalbuphine doses of 0.032 to 3.2 mg/kg progressively increased responding on the drug lever; a dose of 10 mg/kg suppressed responding completely. Compounds with different receptor profiles and different levels of intrinsic efficacy were tested for nalbuphine generalization. The high efficacy **mu** agonist etorphine (0.1-3.2 ug/kg) evoked complete generalization in all subjects and suppressed response rates at a dose of 3.2 ug/kg. Morphine (0.1-3.2 mg/kg) evoked complete generalization in six rats and no drug-appropriate responding in the other six. A dose of 3.2 mg/kg morphine suppressed rates. The lower intrinsic efficacy agonists buprenorphine (0.001-0.1 mg/kg) and nalorphine (0.1-32.0 mg/kg) evoked similar generalization patterns, with approximately half of the rats responding entirely on the drug lever at one or more doses and the remaining rats responding only on the saline lever. The slope of the generalization gradient for etorphine was steep whereas the slopes for morphine, nalorphine, and buprenorphine were shallow. The **kappa** agonist U50,488H (0.32-3.2 mg/kg) evoked only saline-appropriate responding and decreased rates by a dose of 5.6 mg/kg. Ketamine (0.1-3.2 mg/kg) evoked predominantly saline-appropriate responses. The nalbuphine discriminative stimulus appears to be pharmacologically selective for **mu** opioids. In addition, high efficacy compounds such as etorphine evoke consistent generalization to the nalbuphine discriminative stimulus. Lower intrinsic efficacy compounds, such as morphine, nalorphine, and buprenorphine evoke marked inter-subject variability in generalization. These observations are consistent with the predication that a training drug with low intrinsic efficacy will produce a wide range of discriminative effects. (DA03796 and K02 DA00132)

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THE DISCRIMINATIVE STIMULUS EFFECTS OF OPIOIDS
J.H. Woods, C.P. France and S. Comer

The discriminative stimulus effects of opioids will be reviewed with special attention to three issues. First, selected results will be presented to describe the relationship between discriminative stimulus effects and other effects produced by opioids, including analgesia, dependence, reinforcement and effects on respiratory function. Second, qualitative differences in discriminative stimulus effects of opioid agonists have produced discrete classification of agonist actions (e.g., mu, kappa) that have broad generality across species and preparations. Examples will be given of two approaches of drug discrimination studies that have proven useful for differentiating among opioid receptor types: differential substitutions in animals discriminating receptor-selective opioid agonists; differential affinities of opioid antagonists in attenuating discriminative stimulus effects of agonists (e.g., pA_2 analysis). Finally, general theoretical considerations regarding efficacy will be discussed along with empirical evidence demonstrating the utility of this concept with regard to drug discrimination studies and "partial generalizations".

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A REVIEW OF THE PHARMACOLOGY OF THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE
W.L. Woolverton

Pharmacological analysis of the discriminative stimulus (DS) effects of a drug can provide information relevant to its mechanism of action in the CNS. In addition, since classification of drugs according to DS effects by animals is similar to classification of drugs according to subjective effects by humans, the drug discrimination (DD) paradigm is considered to be an animal model of subjective effects. Therefore, DD can provide an indication of the CNS actions involved in the subjective effects of a drug.

Cocaine blocks the reuptake of monoamine neurotransmitters. A substantial amount of research suggests that many of the behavioral effects of cocaine, including DS effects, are mediated by the consequent increase in the concentration of dopamine (DA) in synapses in the brain. Indirect DA agonists such as *d*-amphetamine, nomifensine, mazindol, bupropion and GBR 12909 have been reported to substitute fully for cocaine in animals. Direct DA agonists, whether of the D1 or D2 type, have usually been found to partially substitute for cocaine. DA antagonists of either type have been found to block or partially block the DS effects of cocaine, often at doses that disrupt ongoing behavior. Thus, evidence suggests that stimulation of D1 and D2 receptors is necessary but not sufficient for the expression of the DS effects of cocaine.

Other monoamine neurotransmitters appear to play neither a necessary nor sufficient role in the DS effects of cocaine. NE and 5-HT agonists, whether direct or indirect, substitute for cocaine only partially if at all. Moreover, NE and 5-HT antagonists fail to block the DS effects of cocaine. Interestingly, MAO-B inhibitors have been reported to substitute for cocaine, suggesting that endogenous ß-phenylethylamine mediates the DS effect of cocaine. Cocaine also has effects on other neuronal systems but it is unknown what role, if any, these systems might play in the DS effects of cocaine.

Taken together, this research suggests that the DS effects of cocaine are mediated primarily by indirect DA agonist effects in the CNS and that actions at both D1 and D2 receptors are necessary to the expression of this effect. Further, it is likely that DA plays a major role in the subjective effects of cocaine in humans. If side effects can be minimized, compounds that modify DA neurotransmission may be therapeutically useful for modifying the subjective effects of cocaine. The involvement of other non-DA neurotransmitter systems in the DS effects of cocaine should be assessed as modification of these effects may represent a viable approach to modifying the subjective effects of cocaine. (Supported by NIDA Grant DA-00250)

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DISCRIMINATIVE STIMULUS PROPERTIES OF THE SEROTONERGIC COMPOUND ELTOPRAZINE
C.E.Ybema, J.L.Slangen, B.Olivier' and J.Mos'

The serotonergic drug eltoprazine (DU 28853:1-(2,3dihydro-1, 4-benzodioxin-5-yl) piperazine hydrochloride) specifically reduces offensive aggressive activity in animal aggression models. Receptorbinding studies have shown that eltoprazine strongly binds to both 5-HT1a and 5-HT1b receptors and somewhat weaker to 5-HT1c and 5-HT1d receptors. Investigations with eltoprazine and related compounds, however, suggest that the anti-aggressive actions of eltoprazine may be related to its affinity for the 5-HT1b site, although a role for the 5-HT1a site cannot be excluded.

In a two-lever operant drug-discrimination task, a group of 14 rats was trained to discriminate eltoprazine (0.5 mg/kg, i.p.) from the solvent saline. After acquisition to the task, both the time- and the dose-dependency of the eltoprazine-cue were examined. Lowering the training-dose or increasing the injection-test-interval resulted in a gradual decrease in the number of animals selecting the drug-appropriate lever. In generalization-tests, both the 5-HT1a agonist 8-OH-DPAT and the 5-HT1b agonist TFMPP substituted completely and dose-dependently for eltoprazine.

In another experiment two groups of rats were trained to discriminate either 0.1 mg/kg (i.p., n=13) or 2.5 mg/kg (i.p., n=12) of 8-OH-DPAT from saline. Eltoprazine generalized completely to the 8-OH-DPAT-cue in the group trained with the high dose , but in the group trained with the low dose of 8-OH-DPAT eltoprazine caused only 33.3% drug-lever-selection.

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TOLERANCE TO DRUGS ACTING AS DISCRIMINATIVE STIMULI

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A psychoactive drug can acquire discriminative stimulus control of behavior through processes of differential reinforcement. Development of tolerance to drug stimulus control reflects a dynamic interaction of conditioning and pharmacodynamic processes. Development of tolerance requires the interplay of both repeated treatment regimens appropriate to the agent under study and behavioral conditions that limit an organism's ability to learn a new discrimination. Studies with opioids and behavioral stimulants suggest that tolerance to drug discriminative control has several important characteristics. First, the dose of a training drug required to evoke stimulus control can be increased by repeated treatment with high supplemental doses of drug. However, the development of tolerance to drug stimulus control may require that discrimination training be suspended during the period of supplemental drug treatment. Second, tolerance to drug stimulus control appears to be limited to the period of supplemental drug treatment, as stimulus control by lower doses reappears as a function of time after termination of supplemental treatment, without the re-introduction of discriminative training. Third, tolerance to drug stimulus control appears pharmacologically specific. For instance, repeated treatment with behavioral stimulants or sedative-hypnotics does not confer tolerance to stimulus control by opioids. Finally, where examined, the onset, magnitude and decay of tolerance to drug stimulus control appear to parallel those for other drug effects, suggesting common pharmacodynamic bases. (DA03796 and K02 DA00132)

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