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REVIEW

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The biological, social and clinical bases of drug addiction: commentary and debate

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Abstract This article summarizes the main discussions at a meeting on the biological, social and clinical bases of drug addiction focused on contemporary topics in drug dependence. Four main domains are surveyed, reflecting the structure of the meeting: psychological and pharmacological factors; neurobiological substrates; risk factors (including a consideration of vulnerability from an environmental and genetic perspective); and clinical treatment. Among the topics discussed were tolerance, sensitization, withdrawal, craving and relapse; mechanisms of reinforcing actions of drugs at the behavioural, cognitive and neural levels; the role of subjective factors in drug dependence; approaches to the behavioural and molecular genetics of drug dependence; the use of functional neuroimaging; pharmaceutical and psychosocial strategies for treatment; epidemiological and sociological aspects of drug dependence. The survey takes into account the considerable disagreements and controversies arising from the discussions, but also reaches a degree of consensus in certain areas.

Key words Dependence · Addiction · Drug abuse · Craving · Relapse · Tolerance · Sensitization · Withdrawal · Opponent process theories · Subjective · Discriminative effects · Reinforcement · Habit · Neural systems · Psychomotor stimulants · Amphetamine · Cocaine · Opiates · Alcohol · Nicotine · Hallucinogens · Amygdala · Striatum · Nucleus accumbens · Dopamine · 5-HT · Cerebral cortex · Functional neuroimaging · PET · Transcription factors · Behavioural genetics · Strain-dependent effects · Quantitative trait loci · Individual differences · Risk factors · Personality and dependence · Biological markers of dependence · Co-morbidity · Schizophrenia · Depression · Pharmacological treatment for dependence · Psychosocial treatment of dependence · Sociology of dependence · Epidemiology of dependence · Animal models of dependence

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Introduction

The study of drug dependence and addiction is truly multidisciplinary, with a span from molecular and cellular biology to psychiatry and sociology. Recently there have been rapid advances at the molecular, cellular, neural and behavioural levels that have raised important conceptual issues with clinical and social implications. These new developments make a multidisciplinary discussion particularly timely, in order to facilitate future research and advance the field, especially as there is often a lack of understanding of and a failure to appreciate the achievements and limitations of work outside researchers' own domains. Progress is being held up,

certainly in the UK, because there is relatively little interaction between basic scientists on one hand and clinical and social scientists on the other, and because most workers focus on a single class of drugs and so may be failing to appreciate commonalities in the field, even within a domain.

As a step towards enhancing communication in the field, the Wellcome Centre for Medical Science organized a four-day discussion meeting, followed by a one-day open meeting, in September 1994. The aim was to foster the awareness of the powers and limitations of the various approaches to drug dependence and to discuss controversies in several different domains of this huge area of research. Forty-five leading researchers discussed key issues in interdisciplinary groups, with the emphasis on concepts rather than data presentation. The intention was not to reach a consensus but to highlight current problems, unresolved questions and areas of disagreement, future research directions and educational and funding issues. The discussion focused on the main legal drugs, alcohol and nicotine, and the controlled drugs such as the psychomotor stimulants and narcotic opiates; major prescription drugs such as barbiturates and benzodiazepines were also included.

The report that follows is based on notes taken during these discussions by four of us (A.M., G.D.P., S.G. and R.O.). It is not intended to be a comprehensive review but rather a summary of the views of the participants on various aspects of the field. Primary citations have been limited to the key theoretical and experimental work discussed in the text and to very recent publications; other references can be found in the comprehensive reviews cited. With respect to the main issues discussed, it is made clear below where there was consensus or, alternatively, broad agreement by a majority of participants, or when a minority view was expressed. The full list of participants is given in the acknowledgements but, because many of the issues discussed are contentious, not all of the views reported below are necessarily endorsed by all of the participants.

1 What is drug addiction?

1.1 Definitions

Even the terms 'drug use' and 'abuse', 'dependence' and 'addiction' gave problems, particularly as 'addiction' and 'dependence' are used interchangeably by many researchers and clinicians. The position that received most support is that 'addiction' is an unofficial term used by the courts and governmental agencies to describe a relatively extreme, pathological state in which obtaining, taking and recovering from a drug represents a loss of behavioural control over drug taking which occurs at the expense of most other activities and despite adverse consequences. This state is included in the broader term 'dependence' in the official psychiatric manuals, the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (American Psychiatric Association, 1994; DSM-IV) and the World Health Organization's *International Classification of Diseases, version 10* (WHO 1992; ICD-10). In DSM-IV, 'dependence' is used to describe individuals who have a maladaptive pattern of substance use leading to clinically significant impairment or distress, associated with difficulty in controlling substance-taking behaviour, withdrawal symptoms in the absence of the drug and tolerance to its effects; the definition in ICD-10 is similar, and both manuals stress that the drug user's life is not necessarily governed by the drug. In psychiatry, 'dependence' is not restricted to psychoactive drugs, in distinction to its rather different application in other branches of medicine (e.g. insulin-dependent diabetes).

The problem of definitions is further compounded in two ways. First, dependence is not an all-or-none condition but a continuum of intensity related to many factors: to the amounts of drug used, frequency of use and route of use; to the persistence of drug taking in the face of physical damage and disruption to social life, and to the development of tolerance and withdrawal syndromes (see Sects. 2 and 3). Individuals therefore have to be defined by their *degree* of dependence and not in all-or-none terms. Second, psychoactive drugs do not all produce the same symptoms, which can affect how taking a particular compound leads to dependence. For example, at low doses nicotine is reported to have mildly beneficial effects on some aspects of cognitive performance (e.g. Sahakian et al. 1989), whereas alcohol almost invariably impairs cognition (e.g. Koelega 1995), but abuse of either drug may lead to dependence (U.S. Department of Health and Human Services 1988, 1989).

It is clear that users of many drugs never become dependent or addicts. Drugs can be used intermittently in recreational contexts without dependence developing, as with social alcohol drinking or 'chipping', the American street parlance for occasional heroin smoking (Powell 1973). Personal and social circumstances and whether a drug is legal or illegal all play a part in how particular instances of drug taking are defined. The term 'abuse' is often applied to any non-prescribed use or, for legal substances, any use disapproved by society (including use of alcohol and nicotine by minors). DSM-IV, on the other hand, defines drug abusers as those who are not dependent but have a recurrent, maladaptive pattern of use leading to clinically significant impairment or disease arising from social, vocational, legal or family problems, or use in dangerous situations.

Definition of terms used in this report

Given these confusions, we have adopted the following definitions in what follows, although the terms are often employed differently elsewhere in the literature [for a thorough discussion of terminological problems see US Congress, Office of Technology Assessment (1994); Grant (1989) compares the DSM-IIIR, the previous edition of DSM, and ICD-10 categories specifically for alcohol dependence]:

Addiction is restricted to the extreme or psychopathological state where control over drug use is lost.

Dependence refers to the state of needing a drug or drugs to function within normal limits; it is often associated with tolerance and withdrawal, and with addiction as defined above.

Abuse indicates use of a drug or drugs leading to problems for the individual (e.g. loss of effectiveness in society; behavioural psychopathology, perhaps leading to criminal acts).

Use is applied to taking or consuming any psychoactive drugs for non-medical purposes. Note that neither the terms 'abuse' nor 'use', as employed here, imply anything about the physiological or psychological state of the user.

Tolerance, *sensitization*, *withdrawal* and *craving* are phenomena that may accompany dependence. They are defined and discussed in detail in Sects. 2 and 3.

1.2 Development of dependence and addiction in humans and animals

The path through dependence to addiction in humans has been characterized as occurring in several key epochs or stages, although progress from one to the next is not inevitable. The first stage is initiation or acquisition, which may lead to heavy, habitual use, dependence and sometimes loss of control. At any point in this sequence, the user may stop taking the drug but often relapses to drug taking after a period of abstinence. Thus even in one individual, drug-taking status may change from time to time; both DSM-IV and ICD-10 provide for this change by categorizing the current state of the disorder as well as its history.

Different neurobiological and psychological mechanisms may underlie the various epochs, so it is important to determine which stage is being investigated and exactly what is being modelled in animal experiments. Some delegates at the meeting thought it was not clear that the equivalent of addiction, as defined above, can be discerned in animal experiments and considered that not all animal models of drug-taking behaviour are models of dependence. If animals are given only restricted and/or limited access to the drug, then dependence may not develop. Distinction also must be made between the acute, short-term effects of a drug, which may be directly related to its specific initial molecular actions at the neuronal level, and the chronic effects, which can include further diverse neuronal adaptations, associated with behavioural adaptations and habit formation. These considerations point to a further problem: not only are terms defined differently in the different disciplines investigating drug dependence and addiction, but there may well be fundamental differences in their application at the molecular, neural, psychological, behavioural and sociological levels.

It is important to recognize that the criteria set out in manuals like DSM-IV and ICD-10 are practical checklists for diagnosis, treatment and clinical research; they are not pointers to fundamental processes or necessarily to basic research. Until such fundamental processes are identified through research, it is obvious that terms such as 'dependence' and 'addiction' are little more than operational definitions. Nevertheless, such diagnostic categories are essential for clinical research and they do provide a good starting point for neurobiological and psychopharmacological investigations because animal models ultimately must be evaluated against the human condition. The evaluation is a two-way process: diagnostic categories and criteria also have to be continuously evaluated, changed and allowed to evolve in parallel with the evolution of sociological, psychological and neurobiological knowledge. It therefore seems appropriate here to outline aspects of the 'natural history' of drug-taking that were discussed at the meeting.

1.3 Demographic and social dimensions of drug use

Drug-taking in humans is a complex behaviour, in which basic biological mechanisms interact with social, cultural and political pressures. The history of drug use in the United States reveals a succession of changes in public and official attitudes to various drugs, particularly morphine and heroin, cocaine and alcohol (Musto 1991; Walker 1994), as well as, more recently, nicotine. For many drugs there has been a period of acceptance and easy availability, succeeded by alarm then tight controls, including punishment for using or dealing in the drug. As use of a drug becomes less common, controls are eased and for a time the 'problem' disappears. With changing political and economic pressures, the cycle seems to be repeating itself (Musto 1991). Some delegates at the meeting felt that seeing current trends in drug use and abuse in terms of a longer-term pattern provided a useful perspective.

Sociological and epidemiological research has revealed: high risk among adolescents, particularly when there is drug use within their families; association of drug use with pre-existing psychiatric conditions; patterns of use specific to particular drugs; the influence of variables such as availability; and a high rate of spontaneous remission. Changes in the law can produce large changes in drug use; altering access to drugs may affect the state of the prospective user, e.g., by inducing anxiety about the consequences of use. All of these factors complicate how effectively laboratory-based models can isolate the main factors contributing to drug dependence.

Who will start to use and become dependent on drugs can sometimes be successfully predicted, e.g. adolescent or young adult males with family and peer involvement with drugs and a history of antisocial behaviour are very vulnerable. Acquisition usually starts with use of one class of drug but later there is often expansion to include other classes. The greater the involvement with any one drug, the more likely the individual is to use multiple drugs. The progression generally begins with tobacco,

alcohol or inhalants, followed by marijuana, then either hypnotic sedatives or stimulants, and finally opiates (see Yamaguchi and Kandel 1984). The order is not immutable and varies with availability, price and changes in the level of social disapproval. Personality factors also play a part in choice of drug (see Sect. 4). It appears that people may add new drugs to the set they abuse rather than switch from one to another (see below). Delegates at the meeting considered that insufficient attention has been directed to identifying the predictors of regression and cessation of drug involvement, where demographic factors and early social circumstances are not strong predictors. The exception is cigarette smoking, where cessation is strongly related to age, social class and partner's smoking status (US Department of Health and Human Services 1990).

Which drugs people choose appears to depend chiefly on availability and fashion. In the US before the Vietnam war, amphetamines were more popular than opiates, with opiate use occurring almost exclusively among those who had used amphetamines. The pattern reversed for servicemen in Vietnam, where opiates were readily available: use of amphetamine became less common than of opiates and occurred almost exclusively among those using opiates. The earlier pattern reappeared after the soldiers returned to the US (Robins et al. 1974).

Patterns of drug consumption by individuals do not, however, always relate to drug availability. For example, most use of cocaine and other stimulants, and of alcohol in some individuals, occurs in binge patterns. Animals also show irregular binge patterns of cocaine use. Nicotine use is the most regular; opiates tend to be consumed regularly when supplies are available but here use patterns are often dictated by the difficulty of securing stable supplies.

Most addicts seeking treatment have a preference for one drug but many will consume a great variety. Poly-drug abuse, where two or more drugs are used at the same time or within a short timespan, is now frequently seen (Clayton 1986). For alcohol and nicotine it is now well established that the use of one is associated with an increased likelihood of use of the other. A US national survey found that 50% of non-smokers had used alcohol in the last 30 days but for smokers the figure was 76% (US Department of Health and Human Services 1988).

The causes of simultaneous use of drugs in two or more categories are not well understood, although there is a positive relationship between frequency of drug use and number of drugs used together (Clayton 1986). Reasons often given include enhancing or stabilizing a high, e.g. speedballs (cocaine and heroin); modifying side effects; extending the effects of a drug, or diversifying effects ('novelty seeking'). Interactions between drugs may also form new active compounds, such as cocaethylene from cocaine and ethanol (Hearn et al. 1991). Substitution for a preferred drug that is temporarily unavailable is one explanation for sequential use.

Experimenting with different drugs is characteristic of early-onset poly-drug users (see Clayton 1986 for a review), who often display high novelty-seeking traits (see Sect. 4) and may seek out new drugs. In late-onset poly-drug users, use of multiple drugs may be associated with anxiety reduction. Long-term abusers of cocaine often abuse alcohol and benzodiazepines, perhaps to counteract the side effects of cocaine such as anxiety, depression and sleep disturbances. Clinical experience shows that drug of preference also tends to change with time, especially among stimulant users: after some years; amphetamine and cocaine users either give up or move to more sedative drugs such as opiates or alcohol.

1.4 Overview of topics discussed at the meeting

Sections 2–5 reflect the division of the delegates into four groups representing the main disciplines of research in the drug addiction field: psychopharmacology, neurobiology, psychology and sociology, and clinical. The topics dealt with in these groups were also discussed in interdisciplinary groups. Each section represents the within-discipline discussion, modified and extended in the light of the relevant interdisciplinary conversations. Each group first discussed matters specific to its own domain, but the main brief given to all groups was to examine the contributions to drug dependence of tolerance, sensitization, withdrawal and craving from the perspective of their domain. Most of this latter discussion is included in Sects. 2 (psychopharmacology) and 3 (neurobiological mechanisms).

The contributions of inheritance and environment to the individual's susceptibility to becoming dependent on drugs are summarized in Sect. 4, while Sect. 5 reports the discussions on current approaches to therapy and the problems of designing clinical trials. Towards the end of the meeting and at the subsequent open meeting, the discussion turned to future needs, such as more appropriate animal models, and to general developments, such as education. Section 6 reflects some of the conclusions reached, although, in the present state of the field and given the structure of the meeting, these must not be taken as definitive; rather, growth points for the future are indicated.

2 Psychological and pharmacological determinants of dependence and addiction

Pharmacological factors cannot easily be separated from behavioural ones in the study of addiction, as can be seen from the discussion of four major determinants: tolerance, sensitization, withdrawal and craving. While none of these factors appears to be sufficient (or possibly even necessary) for the development of dependence and addiction, they each appear to make important contributions, the extent of which are difficult to gauge in exact terms. As the recent prominence of the craving construct has shown, it is important to consider subjective, as well as behavioural, concomitants of dependence and addic-

tion, and part of the discussion concentrated on the utility of subjective measures. Another main theme was the dissection of reinforcement mechanisms according to their component processes.

2.1 Conditioning mechanisms in drug-addictive behaviour

Drugs as reinforcers

Drugs that are commonly abused by humans have been demonstrated to serve as reinforcers in a variety of animal species under a wide range of experimental conditions (Schuster and Johanson 1981) (see Box 2A for definitions of terms). Most drugs that are self-administered in humans have been shown to act as reinforcers in operant paradigms with animal subjects, except for the hallucinogen LSD and delta-9-tetrahydrocannabinol (THC). A great deal of work using Pavlovian (classical) conditioning paradigms shows that a large variety of drug effects [acting as unconditioned stimuli (US) or Pavlovian reinforcers] can be conditioned. Adopting the reinforcer or US as an organizational principle for understanding the effects of drugs has brought the enormous advantage of capitalizing on the considerable accumulation of data and theory about conditioning of effects of non-drug reinforcers, such as food. Boxes 2B-2D summarize some of the main behavioural methods used to investigate drug self-administration behaviour using this approach.

There are several possible modes of action through which a drug may reinforce (i.e. increase the probability of) the behaviour upon which it is contingent. Negative reinforcement (i.e. increased probability of responding that results in the termination or postponement of an aversive event such as withdrawal) and positive reinforcement (increased probability of responding contingent upon e.g. an appetitive event) are two major modes. However, even under these headings, it is becoming increasingly clear that a drug may exert reinforcing effects via a number of distinct actions. The fact that a drug can sustain drug seeking only indicates that it is a reinforcer (or incentive); it says nothing about *how* it does so.

In the case where a drug acts as a reinforcer for instrumental (i.e. goal-directed) behaviour there are several distinct possibilities: (1) The drug may reinforce stimulus-response habits which are modulated by general motivational states. (2) Provision of the drug may be the goal of an instrumental action based upon knowledge of the action-drug outcome contingency and motivated by specific affective states, which could also have subjective (e.g. 'rewarding') correlates. (3) The drug may acquire a reinforcing action by modulation of the effects of other reinforcers (e.g. by enhancing effects of social or sexual reinforcers or positive conditioned reinforcers, or alternatively by reducing effects of aversive reinforcers or negative conditioned reinforcers). (4) The drug may gain its reinforcing effects indirectly via other functional effects, e.g. enhancing attentional function or memory, or through novel perceptual effects (hallucinogens).

As Box 2E describes, (1) and (2) represent distinct mechanisms in which the drug has a direct role as a reinforcer mediated via a hypothetical reinforcement system. For mechanisms (3) and (4) the drug acquires its reinforcing effects indirectly; both may involve the subject's regulation of internal state or, more colloquially, 'self-medication'. This requires the drug user to be able to discriminate and evaluate his or her internal state and to have had previous experience of drug-induced changes in such states, leading to beneficial effects which he or she seeks to reproduce. Drugs which apparently do not have consistent reinforcing effects in animals, such as delta-9-THC and LSD, may function in this way to induce intoxication or 'state change'. On the other hand, careful account should be taken of pharmacokinetic and schedule factors which, if suitably adjusted, might yet reveal robust reinforcing effects of such drugs in animals.

Delegates considered that it may be instructive to re-examine the reinforcing properties of drugs in the context of their other behavioural and pharmacological effects, as well as the methodologies used to assess them (Boxes 2B–D). For example, alcohol is intoxicating and clearly impairs cognitive function when taken to excess, whereas nicotine has some attentional enhancing properties (in non-smokers, as well as smokers; Sahakian et al. 1989), which may help to counteract other possible deleterious consequences of taking the drug. Nicotine has been suggested anecdotally to have a 'calming' or mild anxiolytic effect in cigarette smokers; however, objective data indicating such an action are lacking. Psychomotor stimulants such as amphetamine, pipradrol and analogues of cocaine have been shown to enhance the effects of conditioned reinforcers (i.e. previously neutral stimuli that gain their reinforcing properties by association with other forms of reinforcer such as food or water; Robbins et al. 1983). It is possible that the reinforcing effects of these drugs depend on such motivational effects mediated via actions on neural systems of reward or reinforcement (see Sect. 3). Alternatively, the reinforcing effects could simply mimic the effects of natural reinforcers such as food, which hypothetically act through similar neural pathways (see Carroll 1996 for a review).

At higher doses psychomotor stimulant drugs produce repetitive forms of behaviour (stereotypy) that may be models for compulsive forms of drug-seeking behaviour, especially as such stereotypy can come under environmental control and involve quite complex sequences of behaviour, even in the rat (see Robbins et al. 1990). It is possible that such stereotypy reflects the dysfunctioning of neural mechanisms within the striatum that contribute to the development of compulsive forms of behaviour (Fig. 1). In human studies, some delegates noted that there appear to be many more conditioning effects in cocaine addicts than in opiate or ethanol addicts (see O'Brien et al. 1992, p. 165); an interpretation of this observation might be that conditioning processes are more relevant to cocaine addiction than to other addictions.

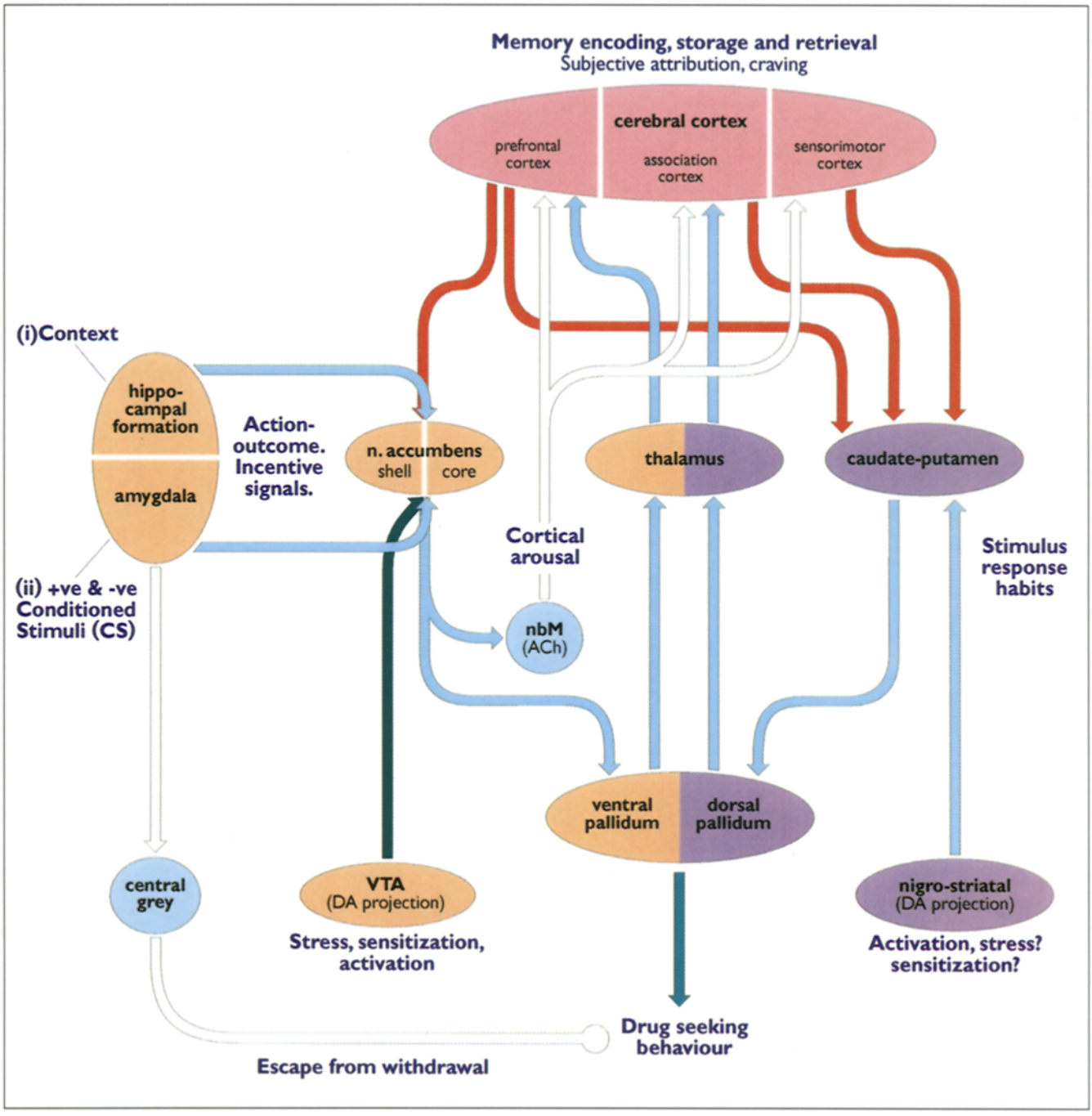

Fig. 1 Schematic diagram of the main neural systems involved in drug dependence and addiction and a brief indication of their possible contributions to the behavioural and cognitive processes implicated. Complex processing at a cognitive level, such as memory processes, subjective attribution and craving, are assumed to depend on neocortical mechanisms, although detailed evidence is lacking on these points in the context of drug dependence. The hippocampus and amygdala are shown as processing conditioned aspects of the environment, such as contextual or specific cues associated with drug taking. These limbic structures interface via their anatomical connections with dopamine-dependent processes of the ventral striatum (nucleus accumbens, core and shell compartments) to effect the control of instrumental actions and their outcomes. Also shown are the anatomical connections of the dorsal striatum (caudate-putamen), which may be implicated in the formation of habits (see Box 2A and text for explanation). The mesolimbic dopamine projection is shown from the ventral tegmental area (*VTA*) to the ventral striatum, as well as the nigro-striatal dopamine pathway to the dorsal striatum. These dopamine systems are implicated in different aspects of behavioural activation, but also in stress and sensitization. The involvement of the nigro-striatal pathway in sensitization and stress is controversial. The other main pathways shown are the descending connections via the central grey which may mediate aversive aspects of drug dependence and compete with the outputs of the striatum via the globus pallidus (dorsal and ventral striatum) to the brainstem, which are assumed to control drug-seeking behaviour. Striatal signals also go via the pallido-thalamic 'loops' to the executive regions of the neocortex such as the frontal cortex. A further possible output from the nucleus accumbens is to the cholinergic neurons of the basal forebrain (nucleus basalis of Meynert, *nbM*, in humans; nucleus basalis magnocellularis in rats, see Fig. 3), which have an important role in modulating cortical arousal, and may contribute to the mnemonic and subjective sequelae of drug reinforcement. The colour coding of the schematic anatomical connections is for the purpose of clarity and generally is of no theoretical significance. However, the special significance of the mesolimbic dopamine pathway is represented by its *heavy shading*

However, other participants argued that there was little or no empirical support for these assertions and noted that direct comparisons of the number and magnitude of conditioned effects as a function of drug class have not been conducted. It was, for example, possible that the anecdotal observation arose from a greater number of pairings of conditioned stimuli (CS) with drug during a cocaine 'binge' than seen with opiates.

Drugs may produce reinforcing effects via a number of distinct mechanisms; for example, drugs such as alcohol can lead to dependence indirectly because of the general disruption to the addict's life produced by intoxicating effects, leading e.g. to drunkenness, and resultant stress, from which he or she seeks escape by taking more drug. Whilst this instrumental behaviour also represents a 'vicious circle' maintained by negative reinforcement, the nature of the negative reinforcing event is distinct from physical withdrawal symptoms. The instrumental behaviour also presumably requires some form of cognitive mediation: drug users may have to appraise their own behavioural and cognitive capabilities. Benzodiazepine abuse may arise from at least two distinct actions of such drugs: (1) 'self-medication' to induce anxiety relief, which may derive from a pre-existing state of anxiety, or be caused in other ways, for example, to combat anxiogenic effects of a methadone maintenance regime for opiate abuse (see Farrell et al. 1994) and (2) direct positive reinforcing effects, as with intravenous (i.v.) use of temazepam (Strang et al. 1992). Preference for d-amphetamine versus triazolam depended on whether subjects were performing a vigilance task or relaxation activity, respectively (Silverman et al. 1994a). Furthermore, the reinforcing effects of caffeine can also be enhanced in humans by behavioural requirements following its ingestion (Silverman et al. 1994b). Thus, the reinforcing effects of drugs are not absolute, but depend critically upon behavioural context. These considerations lead to the prospect of refining the classification of addictive drugs in terms of their qualitatively different effects as reinforcers, which may possibly correlate with the reasons people provide to explain their drug-taking behaviour.

Drugs may also be punishers, their aversive properties decreasing the behaviours upon which they are contingent. As with reinforcers, punishers may have different modes of action. A drug may act directly as a punisher when it induces nausea (e.g. nicotine), and indirectly when it either reduces an otherwise 'satisfying' state of affairs or modifies the actions of other reinforcers. Such aversive effects may also help to limit drug intake.

General questions were raised as to whether there were any ways in which drugs differed *fundamentally* from one another as reinforcers (implying different behavioural and neural mechanisms). It may well be that differences in precise modulation of a common reinforcement mechanism depend on the specific pharmacological effects of drugs (see Sect. 3.3). And do drugs differ from other classes of reinforcer? It may be that drug taking is simply one example of the harmful behavioural excesses of positive reinforcers, of which there are many non-pharmacological examples. However, drugs differ from reinforcers such as food and water in that they are generally unnecessary for vital processes and their use can be totally discontinued. Some of their profound effects on behaviour, including compulsive aspects, may arise from their capacity to usurp mechanisms of natural reinforcers, preventing them from exerting their normal control over behaviour.

Importantly, drugs of abuse can be both reinforcing and aversive in different assays at the same dose, e.g. the same dose of a drug that is self-administered may also induce conditioned taste aversion (Goudie 1987). Thus the reinforcing action of a drug is not an immutable property of the pharmacological agent, but depends upon a complex dynamic interaction between the drug and the overall behavioural context. There are even data (Spealman 1979) that can be interpreted to demonstrate that cocaine can concurrently have both positive and negative reinforcing actions in monkeys in a self-administration setting. Monkeys would respond on one lever under one schedule reinforced by the delivery of i.v. cocaine, but in different stimulus conditions would respond on a separate lever under another schedule to postpone the schedule of cocaine reinforcement in operation on the first lever. Spealman's results can be interpreted as demonstrating a complex hierarchy for the motivational processes underlying the reinforcing effects of cocaine; the argument is that the monkey may choose to avoid stimuli which nevertheless compel its drug-taking habit. Analogous complexities have been shown for food intake: rats may choose sucrose over casein when close access is allowed to both nutrients, but casein when the nutrients are presented at the far end of a maze (Young and Chaplin 1945).

The potential for abuse is an overall function of the drug's reinforcing and aversive properties. The Spealman study shows that a drug's reinforcing properties cannot be considered independent of context, which is particularly important when considering relapse. The apparently permanent propensity to relapse to drug use in the presence of certain cues (e.g. cigarette smoke) but not in their absence also illustrates when the same reinforcer can control behaviour, and when it cannot.

The theoretical analysis of the different effects of positive reinforcement was much discussed in the context of dependence. Several theoretical positions were taken, some of which are outlined below.

Theoretical analysis of drug-taking behaviour

I. Actions versus habits. For self-administration behaviour, animals have initially to learn about the response-outcome contingency, the action probably gradually becoming a habit with practice (see Box 2E). A possible problem with the concept of reinforcement is that it confounds the two separate associative processes by which action-outcome and stimulus-response habits are learned (Dickinson 1994).

In the context of human studies, Tiffany (1990) has explicitly argued that most drug taking or drug seeking is probably habitual and relapse is often caused by simple re-exposure to the eliciting cues. The theoretical approach outlined in Box 2A provides an interesting way to achieve further precision in the experimental analysis of drug-seeking behaviour and may have considerable implications for our attempts to identify the neural systems involved in these processes. Although the habit hypothesis was advanced mainly to explain addictive behaviour rather than as a suggestion for treatment, some unsuccessful attempts at treatment (Sect. 5) can be explained in terms of the behaviour having gained habitual properties and 'devaluation' procedures (see Box 2E) consequently being unsuccessful. For example, it was maintained that disulfiram treatment is not always effective in alcoholics even though it devalues alcohol (but see Sect. 5.2). If the effects of punishment represent some form of reinforcer devaluation, it is relevant that punishment may only transiently suppress drug intake, suggesting the establishment of a strong habitual tendency that is impervious to devaluation of the drug reinforcer.

The contribution of different types of conditioning mechanisms to drug dependence raised the issue of their mediation via separable neural systems. White (1989) for example, has suggested that the ventral striatum, together with the amygdala, subserves stimulus-reward (incentive) learning and that the dorsal striatum is involved in stimulus-response (S-R) (i.e. habit) learning (Fig. 1). A further elaboration of this scheme is that the amygdala–ventral striatum system is particularly important for mediating how conditioned reinforcers gain control over instrumental responding (Cador et al. 1989). Thus, the amygdala–ventral striatum system may be an important interface at which incentive learning is transformed into instrumental behaviour, comprising action-outcome associations (Box 2E). Both the dorsal and ventral striatal systems are innervated by neurotransmitter systems, including, but not limited to, dopamine (see Sect. 3), that are implicated in mediating the effects of reinforcers on learning processes. Addictive drugs may act at these synapses in the neural systems via which naturally occurring reinforcers promote changes in behaviour. According to this scheme, certain drugs may first influence behaviour by action-outcome associations mediated by an amygdala–ventral striatum system (Cador et al. 1989; White and Hiroi 1993). Repeated experience of this association would lead to acquisition of a drug-reinforced habit, mediated by the dorsal striatum. Both of these learned forms of behaviour would co-exist in parallel in the brain of the addicted individual, thus complicating treatment considerations (White 1996).

Differences in neurochemical actions of abused drugs may contribute to subtle differences in the ways in which these fundamental psychological processes are modulated (White 1996). For example, in the case of psychomotor stimulants the drug reinforcer may lose part of its controlling influence over behaviour, as a goal per se, but may be amplifying the strength of S-R habits via its effects on dopaminergic mechanisms. According to Robinson and Berridge's (1993) hypothesis (see also Sect. 2.5) a sensitization of mesolimbic dopamine transmission might produce compulsive drug-seeking behaviour, which would be classified as analogous to S-R habits according to the account given above. Their hypothesis postulates a dissociation between such behavioural manifestations of drug seeking ('wanting') and the subjective responses to those drugs ('liking'). This hypothesis raises the important issue of identifying the brain mechanisms which control subjective responses to drugs (see also Sect. 3.8). There was speculation that this aspect of addictive behaviour might be cortically mediated, and that certain drugs which produce distinctive subjective effects, such as LSD and delta-9-THC, may exert some of their reinforcing effects in humans at a cortical level.

II. Behavioural economics and the matching law. As many of the criteria for the clinical definitions of drug dependence and addiction include some reference to the disruptive effects on non-drug-related activities, perspectives are relevant which take into account choice behaviour among different types of concurrently available reinforces, including other drugs. One such perspective is that of behavioural economics, which considers the applicability of concepts such as goods or commodities, consumption, price, elasticity and demand to operant behaviour (see Box 2F). Bickel et al. (1995) review the results of 16 studies of self-administration of different drugs which also made available concurrent reinforcers such as other drugs, sucrose or water. These studies showed that relationships among concurrently available reinforcers were reliable, that the contingencies for concurrent reinforcers can affect operant behaviour asymmetrically, and that the 'price' (i.e. response requirement) for reinforcers (Box 2F) can affect the outcome. As the 'price' for one reinforcer was increased in several studies, consumption of a second (generally non-identical) reinforcer with a constant 'price' increased. Examples of this were the relationships in rats between ethanol and sucrose consumption (Samson et al. 1982) and consumption of the opiate etonitazene and water (Carroll and Meisch 1979) when the drug 'price' was varied in each case in rats. However, in the case of morphine and food consumption, no such relationship was observed when the 'price' of morphine was manipulated (Dworkin et al. 1984). Finally, in some instances, concomitant reductions in consumption of *both* reinforcers were observed when the price of one of the reinforcers was increased for heroin and cigarettes in humans (Mello et al. 1987) or for heroin and food in monkeys (Griffiths et al. 1981). These relationships were not necessarily symmetrical; in the latter study, increasing the number of food pellets had no effect on heroin consumption. These findings show that drug reinforcers can function as substitutes for, complements of, or be independent from, the price of one another and can be interpreted in economic terms (see Box 2F). Such analyses have implications for the understanding of factors affecting 'loss of control'

and poly-drug abuse (Clayton 1986; see Sect. 1.3), as well as for the development of therapies, for example, those based on drug substitution (see Sect. 5) or on the provision of alternative activities for drug abusers. The data also have implications for economic and legal controls over drug taking.

An alternative perspective is that provided by Herrnstein's matching law (e.g. Herrnstein and Prelec 1992; Box 2F). According to this principle, relative operant response rates for two concurrently available reinforcers match relative reinforcement rates. It is not the case that this behavioural principle necessarily makes the same predictions as an economic analysis. The latter embodies a 'maximization' principle, according to which resources are allocated in an optimal fashion for a defined period; by contrast, Heyman (1996) elaborates on the application of a more local strategy (termed 'melioration') to problems of drug addiction, which depends on momentary choices between competing alternatives (Box 2F). This hypothesis is potentially capable of accounting for some of the paradoxes of addiction, such as apparent 'lack of control' over drug-taking behaviour and the fact that an activity such as drug taking can reduce the value of competing reinforcers and increase in rate, even as its own value decreases.

2.2 Subjective effects of drugs in humans: the problem of introspection

The subjective effects of drugs pose obvious problems of measurement and interpretation, making it difficult to gauge the true significance of such experience in addiction. In general, it is useful to consider subjective effects as responses (e.g. verbal ones) in much the same way as overt behaviour or even autonomic responses. The relationship between subjective, reinforcing, discriminative and physiological effects of drugs is generally purely correlational, and so it is particularly difficult to assess possible causal relations among them and thus to decide which, if any, is primary in controlling behaviour.

Many delegates thought it tempting to discount subjective responses as epiphenomena that arise as consequences of behaviour, rather than being the main driving force of the behaviour. Thus, these responses could reflect unconscious neural effects rationalized at the conscious/behavioural level. More problematic still, they could represent deliberate attempts by an addict to mislead the observer. This may not always be with bad intentions, as in the case of an addict trying to please his or her therapist/physician by reporting reduced craving, but in fact failing to curb his or her drug-taking behaviour. However, the possibility of ill-intentioned use of subjective data is exacerbated by the personality disorders characteristic of many addicts (see Sect. 4).

Box 2A Glossary of commonly used definitions in behavioural analyses of drug dependence and addiction

Contingency. A predictable relationship between two (or more) events that reduces the uncertainty of the subsequent event, e.g. between particular stimuli and particular responses.
Positive reinforcer. An event which increases the probability of a response upon which it is contingent, e.g. i.v. drug infusions maintaining lever pressing, alcohol ingestion maintaining licking.
Negative reinforcer. An event, the omission or termination of which increases the probability of the response upon which it is contingent, e.g. withdrawal symptoms precipitated by scheduled adminstration of naloxone in morphine-dependent animals avoided by lever pressing which postpones the naloxone infusion.
Punisher. An event presented contingent upon a response leading to the reduced probability of that same response, e.g. contingent electric shock suppressing responding maintained by a schedule of cocaine presentation.
Operant. A response upon which the presentation of a reinforcer is contingent, e.g. lever pressing. In the language of learning theory, such behaviour is often termed instrumental [i.e. obtaining a goal (or outcome or reinforcer) or as an example of voluntary action]. The learning of such behaviour is termed instrumental conditioning.
Pavlovian (or classical) conditioning. The process by which a conditioned stimulus (CS) elicits conditioned responses (CR) that are normally elicited by an unconditioned stimulus (US) after a number of pairings. Such CRs are normally considered to be involuntary reflexes. The pairings require the onset of the CS to precede that of the US (temporal contiguity) and for there to be a positive temporal correlation (i.e. predictive contingency) between the two events, e.g. tolerance to a drug effect conditioned to a particular environmental CS.
Schedule of reinforcement. A rule relating the presentation of reinforcers to the occurrence of operant behaviour; e.g. in fixed interval (FI) x seconds responding is reinforced for the first response after x seconds, and in fixed ratio (FRn), responding is reinforced for the first response after a fixed number, n, of responses is completed. Responding may also be maintained by variable interval (VI) or variable ratio (VR) schedules where the respective requirements are averages of a range of values. For two more complex examples, see also Box 2B.
Discriminative stimulus. A stimulus (or SD) in the presence of which responding is reinforced according to some schedule of reinforcement, e.g. drug cues can act as discriminative stimuli for responding maintained by food reinforcement.
Conditioned reinforcer. A stimulus which acquires its reinforcing properties (positive or negative) by pairings with other (generally primary) reinforcers such as food, drugs or electric shock. Also termed secondary reinforcers. A stimulus can function as a conditioned reinforcer or discriminative stimulus in the same situation.
Incentive. A stimulus that elicits approach behaviour (positive incentive) or withdrawal behaviour (negative incentive). A conditioned incentive acquires such properties via Pavlovian conditioning. Incentives and conditioned incentives may also function as reinforcers and conditioned reinforcers respectively, depending on environmental contingencies.
Conditioned suppression. The reduction of behaviour (usually measured on an operant baseline) caused by a Pavlovian CS. The usual example is of an aversive CS which produces freezing behaviour.

Box 2B Schedules of reinforcement of drug injection

The precise schedule of reinforcement has long been known to be a potent determinant of the reinforcing efficacy of self-administered drugs (generally, but not exclusively, intravenously) (see Young and Herling 1986, for a review). Here, we describe the use of two types of such schedules of some theoretical importance.

Second-order schedules of drug injection

Second-order schedules can be defined as when responding under one schedule of reinforcement maintained by one event [usually a brief stimulus (S) such as a light change, probably functioning as a conditioned reinforcer] also contributes to responding under a second schedule maintained by a second event (usually a drug infusion or infusions, food or sexual reinforcers). The two schedules can be different, e.g. schedule 1 could be FR n and schedule 2, FI x. The entire schedule could then be designated as FI *x* (FRn:S), according to the nomenclature of Kelleher (1966). The first schedule (in this case FR n) is often termed the 'unit schedule'. Such schedules can be used to maintain self-administration behaviour that consists of extended periods of responding between each scheduled injection. Their utility is that: (1) they can be used to model extended sequences of drug-seeking behaviour that occur when the drug is not immediately available; (2) if the terminal drug infusion or infusions are scheduled to occur only at the end of the session, then the pharmacological effects of the drug on operant behaviour itself are avoided, and the maintained behaviour is jointly dependent on the *reinforcing* effects of the brief stimulus and the drug. These separate actions can be dissociated in two main ways: (1) The effects of removing either the brief stimulus or the drug on responding can be measured (but for the drug only on subsequent sessions). (2) The temporal *patterning* of responding (e.g. FI 'scallop', FR post-reinforcement pause), presumably under independent control by each of the two reinforcers presented under distinct schedules (e.g. FR and FI), can be quantified. The overall rate of responding is somewhat, though not totally, independent of these measures. Because of the isolation of the reinforcing effect of the terminal event, the effects of different reinforcers such as food or drug infusion can readily be compared.

The main disadvantage of the second-order schedule is that it has rarely been implemented effectively in the rat, for which relatively few data exist, and the training procedure is necessarily more extended than for many other schedules. For examples of performance maintained under second-order schedules and further details, see Katz and Goldberg (1987).

Progressive ratio schedules of drug injection

Introduced by Hodos (1961), the progressive ratio (PR) schedule arranges that the ratio parameter relating maintained responding to the presentation of the reinforcer (e.g. drug infusion) increments according to a particular series of completed ratios. For example, the ratio requirement may double after each completed ratio within a session or after a sequence of ratios completed in the last session. The parameter is increased until a value is reached when responding abruptly ceases, a ratio value termed the *breaking point.*

The utility of the PR schedule is that it provides an alternative index of the reinforcing value of an event, being largely independent of response rate. There is a direct relationship between drug dose per infusion and breaking point for a number of stimulant and opioid drugs (see Young and Herling 1986). Cocaine appears to maintain some of the highest breaking points for a variety of species, doses and PR schedule parameters.

One of the main problems of interpretation for PR schedules is that the drug itself may exert pharmacological effects on responding that confound the measure not only of rate of responding, but also of breaking point itself, particularly for agents that increase responding in extinction.

Despite these misgivings, some participants were not ready to dismiss the utility of subjective responses entirely as necessarily dishonest or unreliable. They considered that we need to use all the information we can obtain; self-report data are one such source and we need to listen to what drug users tell us to help us understand both the correlations and the dissociations between self-report and behaviour. Nevertheless, as noted in a commentary on the role of the alcohol withdrawal syndrome in alcohol consumption (Stolerman 1990), we are not obliged to accept uncritically and at face value everything that drug users say. It is reasonable to question their insights into the motives for their own behaviour, as is done for patients with a wide variety of other psychiatric disorders (see also Schuster et al. 1981).

Many of the subjective responses to drugs, including euphoria and craving, have an emotional component which may make a consideration of theories of emotion highly relevant to the field of drug dependence. For example, Schachter's theory identified two crucial, interactive factors in the generation of emotion: *cognitive appraisal* (or interpretation) and *visceral arousal.* A classic experiment (Schachter and Singer 1962) manipulated the conditions under which volunteers experienced the effects of adrenaline infusions to produce different levels and qualities of emotional experience. Although the effects of contextual factors on the magnitude of the emotional response have better stood the test of time than the differentiation of such responses (Reisenzein 1983), Schachter's results have clear relevance for the measurement of subjective effects of drugs. They also suggest that differences in the cognitive appraisal or 'labelling' of drug-induced states are an important factor determining individual differences in response to the otherwise identical pharmacological effects of drugs. For example, peripheral symptoms such as stomach rumbling produced by opiate taking are generally reported as pleasant. It has long been appreciated that *social context* is important for the

Box 2C Reinforcement via oral drug self-administration

This class of techniques is obviously particularly important in the study of alcohol self-administration. Intake of the drug should be demonstrated to maintain characteristic patterns of intermittently reinforced behaviour (e.g. via intermittently reinforced licking); rates of drug- maintained behaviour should exceed rates of control vehicle-maintained behaviour; and orderly dose (or concentration) response curves should be demonstrated. It is desirable to quantify blood alcohol levels (BALs) following self-administration sessions. In general, the possibility that the animal is drinking for calories has to be considered especially when the animals are food-deprived, although most workers now believe that this explanation cannot account for all alcohol drinking.

Prandial drinking method

1. Substitution for water. A 3-h food ration is given to food-deprived monkeys to induce reliable drinking of water.
2. Low, gradually increasing drug concentrations are substituted for water.
3. The feeding period is shifted from before to after the drinking period.
4. If drinking behaviour is maintained, the three criteria stated above are employed: see Meisch and Carroll (1987) for representative data for ethanol.

This technique is often more effective in monkeys than rats.

Schedule-induced polydipsia

This method capitalizes on the well-known phenomenon of over-drinking following the periodic presentation of food pellets to (quite severely) deprived animals (Falk 1961; see Meisch and Carroll 1987 for a review). The main problems are individual variability and the need for deprivation.

A further problem for these methods has been that the voluntary consumption of solutions of ethanol of higher concentration, leading more readily to dependence, has been limited by the aversive taste of alcohol. One way of producing long-lasting preference for high concentrations of alcohol is to present such solutions in a choice with water only periodically. The alcohol can also be presented with a palatable taste (e.g. sucrose), although the caloric contribution has to be controlled. It remains the case that most alcohol drinking in humans is of flavoured beverages (e.g. cocktails).

Sucrose conditioning and fading procedure

Grant and Samson (1985) used a procedure in which rats were never food deprived when consuming ethanol. They induced rats to lick at a drinking tube containing 5% ethanol to obtain access to a dipper containing 20% sucrose to overcome the initial aversive reaction to the taste of ethanol; about 20 sucrose conditioning trials were employed. The rats were then trained to press a lever (eventually under an FR8 schedule) to gain access to 40% (v/v) ethanol, resulting in BALs of over 0.5 g/kg in 30 min, or water, as a control.

Another strategy for inducing or augmenting consumption of high concentrations of ethanol is to use rat strains which exhibit greater propensities for drinking alcohol. For example, freely feeding Wistar rats drink significantly more alcohol than rats from the Sprague-Dawley strain (see Linseman 1987 and also Sect. 4).

Some authors question the need to demonstrate dependence and intoxication resulting from consumption of high concentrations of ethanol in animal models of alcohol self-administration (Amit et al. 1986). Ultimately the validity of the animal model will have to be assessed in the light of the similarity of effects of behavioural and pharmacological treatments to those in humans.

'highs' produced by cannabis intoxication. Recent evidence has supported this view for alcohol (Doty and de Wit 1995).

For these reasons, increasing attention is being paid to such contextual determinants over subjective responses, using modern methodologies. It is also important, though difficult, to avoid providing convenient but imprecise verbal labels for the subject's experience. Another form of controllable variance is the subject's *personality*, e.g. whether they are 'sensitizers' or 'repressors' when it comes to reporting drug effects, although whether these are in fact relevant variables requires detailed research (see also Uhlenhuth et al. 1981 and Sect. 4). Such variability might be assessed by screening the subjects with personality inventories prior to assessing subjective effects of drugs. Finally, it is reasonable to assume that subjective effects are probably influenced by such factors as conditioning history and training. They may well represent a special form of learning often called 'perceptual learning', although it is unclear at present whether this is governed by the same fundamental principles of associative conditioning as other forms of learning. One possible analogue for such behaviour is the drug discrimination paradigm (see below).

As well as the conscious cognitive influences on subjective responses to drugs, it is becoming increasingly recognized that there are important covert (or unconscious) processes which can determine overt behaviour. These processes (often termed 'implicit') have been recognized at the level of spared forms of memory, perceptual capacities (e.g. 'blindsight' following brain damage), and by the demonstration of such implicit processes in normal perception and memory, e.g. 'unconscious' semantic priming, subliminal preferences for familiarity, lack of perception of the contingencies controlling behaviour under schedules of reinforcement (see Hirst 1995). In each of these cases, there is evidence that the individual lacks awareness of the factors controlling his

Box 2D Conditioned place preference

A procedure in which one distinctive environment is paired with a drug, and the other with a control injection on a number of (generally alternating) conditioning trials (i.e. sessions lasting, for example, 15 min). On the test day, the animal (rat or mouse) is given a free choice between the two sides in the untreated state, the main variable being the relative time spent between on each side in a single test session. *Conditioned place preference*(CPP) refers to a relatively greater time spent in the drug-paired than in the control compartment, and *conditioned place aversion* to significantly less time spent in the drug-paired setting.

The utility of the CPP procedure is that it measures the appetitive value of stimuli with which a drug is associated in a rate-free, choice procedure. The relatively small number of conditioning trials required means that effects of treatments on both the acquisition and expression of place preference conditioning can be determined. There are several controls that have to be performed to ensure the validity of the procedure. The first is to use a random pairing procedure, so that the drug is not consistently associated across subjects with the initially less (or more) preferred side. Unconditioned shifts in preference resulting, for example, from habituation, would in the latter case potentially confound the choice measure. This procedure usually entails the requirement that the sides are more or less equally preferred across a group of rats prior to conditioning ('balanced procedure'), rather than when consistent baseline differences in preference are present ('unbalanced procedure'). A second control is to ensure that the CPP expressed on the test day is not secondary to 'state-dependent' effects. For example, the undrugged state is more similar to that of control injection, and so the drug-paired side will be relatively more novel; potentially it thus has greater incentive value and is preferred as a result. A test with drug rather than the untreated state controls for this possibility (see Van Der Kooy 1986 for a detailed consideration of other points).

The disadvantages of the CPP procedure are that it is difficult, if not impossible, to use subjects as their own controls. This makes the construction of dose-effect curves laborious; in fact, it is often difficult to obtain consistent dose-effect curves, because frequently there is a ceiling for the maximal place preference expressed. Furthermore, CPP is theoretically difficult to interpret. The stimuli controlling the preference are not well defined and probably do not include merely spatial or place cues. Moreover, the nature of the responses which generate the preference are unclear. Theoretically, they could be Pavlovian or instrumental in nature: although the conditioning procedures involved in the acquisition of CPP are Pavlovian in nature, the expression of the preference may include an instrumental (operant) component. A final problem of interpretation is whether the conditioned cues gain their incentive or reinforcing properties because they are associated with (and therefore predict) the drug state, or whether the incentive value of the cues themselves is enhanced by the drug state.

The CPP procedure is conceptually linked to other paradigms in which the conditioned reinforcing properties of stimuli paired with drugs is measured (Davis and Smith 1987), or where the effects of drugs on conditioned reinforcers established by pairing with types of reinforcer (e.g. food or sex) are measured (e.g. Robbins et al. 1983). However, the precise contingencies for stimuli and responses that obtain in these paradigms are in general more explicitly defined.

or her behaviour. These implicit processes are especially compatible with the view that drug-taking behaviour is a form of stimulus-response habit and may provide important targets for therapy. A further corollary is that verbal or subjective reports may not always reflect the reinforcing effects of a drug because people are often incapable of verbalizing accurately what is controlling their behaviour.

The use of several somewhat independent measures of behaviour, including the verbal report of subjective experience, heightens the chances of detecting significant dissociations among these measures that may have important theoretical and therapeutic implications. Excellent examples are (1) the experiments by Lamb et al. (1991) on morphine self-administration in addicts under second-order schedules, where subjective responses were also monitored, and (2) the studies by Fischman and colleagues on the effects of potential therapeutic agents for cocaine dependence [desmethylimipramine (Fischman et al. 1990) and buprenorphine (Foltin and Fischman 1994)] which included measures of both drug intake and craving. Such dissociations between verbal behaviour describing craving and other features of dependence such as drug use indicate that these behaviours are controlled by processes only loosely associated at the psychological level, implying also a separation at the level of the controlling neural systems. There was some caution expressed that many of the demonstrations of implicit processes were in highly unusual circumstances and may not apply so easily to normal behaviour. The experiments by Lamb et al. (1991), though illuminating, were also based on rather small numbers of subjects for such experiments and may require replication.

The challenge for research in this area is the development of comprehensive models that can describe the conditions under which verbal behaviour and drug self-administration will and will not co-vary and a judgement on which, if either, is the more important variable to monitor. The importance of considering this issue of covert as well as overt responses in drug dependence is that it may be necessary to treat subjective responses as well as overt behaviour in a successful therapeutic programme.

Discriminative effects of drugs in animals

This generally refers to the capacity of animals to use drug (or placebo) states as discriminative cues to control responding maintained by food reinforcement. It is a commonly used model for investigating 'subjective' effects of drugs that may be relevant to dependence. The assumption that discriminative stimulus effects, i.e. properties of drugs that can act as cues directing behaviour, are objective indices of subjective phenomena is not mandatory. For example, drug discrimination learning could represent the development of S-R habits (Box 2E), i.e. 'if stimulus/drug state A, then perform response B'.

The lines of evidence for relating the discriminative stimulus effects of drugs to subjective experience are

Box 2E Instrumental behaviour

Drug procurement and self-administration are examples of *instrumental* behaviour because these activities are instrumental in gaining access to the drug. The drug as the outcome of the instrumental behaviour is identified as a reinforcer because it is the event responsible for reinforcing or strengthening the behaviour. Contemporary analyses of conditioning indicate that instrumental reinforcement can be mediated by two different psychological processes.

The first is the classic stimulus-response (S-R) process according to which the instrumental outcome, i.e. the drug, acts by reinforcing an association between the contextual and discriminative stimuli present at the time when the drug is procured and administered and the responses involved in these activities. Thus, instrumental behaviour controlled by this process is composed of simple, habitual responses that are elicited automatically by these stimuli, independent of knowledge of the relation between the behaviour and the drug. The involvement of a S-R habit process can be identified by the resistance of the instrumental behaviour to changing the value of the outcome. For example, the value of a food reinforcer can be reduced by conditioning an aversion to the food following instrumental training. This reinforcer devaluation often has little or no impact on the subsequent performance of the instrumental response, indicating that the behaviour is autonomous of the current value of the reinforcer. Such behavioural autonomy is typically observed after two types of training. The first is after training with a relatively weak relation between the response and the reinforcer, such as that engendered by an interval schedule where a drug is only periodically presented following a response. Under FI schedules, response rate is not so directly related to reinforcement rate as it is for FR schedules. Secondly, instrumental performance is often impervious to reinforcer devaluation following extended training, suggesting that steady-state behaviour on simple schedules is typically mediated by the S-R process.

By contrast, the initial acquisition of instrumental behaviour is controlled by a second learning process. After more limited training with a strong instrumental relation (e.g. low ratio schedules, where only a few responses are required for each reinforcer to be delivered), devaluation of the reinforcer or outcome produces an immediate reduction in the performance of the instrumental action. This devaluation effect demonstrates that performance is goal directed in the sense that it is mediated by an association between representations of the instrumental action and its outcome (A-O).

Thus, both the S-R and A-O processes may make a contribution to the performance of instrumental activities, such as those involved in drug procurement and administration. Moreover, the associative structures underlying habitual responses and goal-directed actions work in concert with different motivational processes. In the case of goal-directed actions a motivational state, which may be experienced as drug 'craving', can act by controlling the incentive value assigned to the outcome, i.e. the drug, which in turn can regulate performance through the A-O representation. In the absence of this representation, however, such incentive processes cannot control S-R habits. Therefore, the performance of S-R habits can only be affected by general activational or drive-related factors, which may be either unconditioned or mediated by Pavlovian conditioning to contextual and discriminative stimuli.

General reference

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twofold. First, there is the impressive correlation between patterns of cross-generalization in animal drug-discrimination experiments and similarities in subjective effects in human subjects. There are also very many experimental instances in which measured subjective effects of drugs in humans correlate with discriminative responses by the same subjects. Much of this literature has been reviewed by Preston and Bigelow (1991). While they report certain dissociations, the overall degree of correlation was impressive. Second, a case has been made that the correlation reflects an homology of underlying mechanism; in humans, self-reports of subjective drug effects are evident through behaviour (be it verbal or in the form of questionnaire, visual analogue scale or check-list data). Schuster et al. (1981) argued that this self-reporting behaviour is the result of a history of conditioning that resembles the history imposed upon subjects in drug discrimination experiments. This leads to the question "What is a subjective report or experience?" Probably researchers know much more about the nature of discriminative drug effects than about the nature of subjective reports. In drug discrimination experiments, we know about relevant antecedent conditions and about the stimuli that control the current behaviour. Whenever we discuss the subjective report data from untrained human subjects, we need to recognize that we have no control over relevant factors in their history. Taken together, the preceding points led some delegates to conclude that we would be unwise to regard data on human subjective experiences as the 'gold standard' for validating results of either human or animal experiments.

Relevance of drug discrimination to drug dependence

There are two perspectives from which the discriminative stimulus effects of drugs can be seen as relevant to the understanding of drug dependence. The first relates to the proposed relationship between discriminative and subjective effects. It is widely believed that some of the subjective effects of drugs contribute to the extent to which they are abused, although mixed feelings on this were expressed at the meeting. Subjective effects may not simply be a factor which maintains drug taking. If this were the case, discriminative effects would necessarily be identical with reinforcing effects but there is evidence, both formal and mechanistic, that this is not so (see e.g. Goudie 1991). The proposal has therefore been made (Meyer and Mirin 1979; Stolerman 1992), based on priming (reinstatement) phenomena (Shaham et al. 1994), that discriminative stimulus effects of drugs contribute to the initiation of bouts of drug-taking in intermittent users and to the relapse process in former drug abusers. It should be possible to test this hypothesis by studying how discriminative and reinforcing stimulus effects interact to determine drug intake; the experiment by Ator and Griffiths (1993) is one of few that have attempted to address the issue directly. These authors found that a history of self-administration of the benzo-

Box 2F Behavioural economics in models of drug addiction

Demand for a drug can be quantified by presenting the drug at different *prices* (i.e. different FR schedule values) and plotting consumption (mg/day) as a function of *unit price* (responses/mg). When plotted on log-log coordinates, the result is usually a positively decelerating function with demand decreasing faster as the price increases. If the slope of this function is >1, demand is said to be *elastic;* for example, as price increases there is a relatively rapid decline in consumption. In general, this appears to be the case for the average consumer of alcohol (US DHHS 1989), but it may not hold for heavy drinkers. Alternatively, if the slope of the function is <1, demand is *inelastic.* This means that there is little change in demand with increasing price, a characteristic generally shared by essential commodities such as food and water, rather than desirable but inessential items. Substitution of reinforcers can be defined in economic terms by demonstrating inverse relationships between the demands for reinforcers as the price of one increases and the other remains fixed (see text for examples).

Income can be defined as the amount of resources [e.g. money for humans, tokens, elapsing time (i.e. delays for experimental animals) or opportunities to work] that are available for purchasing a drug or other reinforcer. Different levels of income alter the preferences of consumers for different commodities, such as brands of cigarettes in humans (DeGrandpre et al. 1993) or food over heroin in baboons (Elsmore et al. 1980).

The matching law

This provides a quantitative principle for the measurement of choice behaviour in which the relative response rates (or time allocation) maintained by different reinforcers matches their relative rates of presentation (see Herrnstein and Prelac 1992), i.e. B1/(B1+B2)=Rf1/(Rf1+Rf2) where Bm is the behavioural measure for each response, m, and Rfn the rate of reinforcement for each alternative n. This equation has been shown to hold for several species, types of reinforcer and response measure. Matching is not necessarily always the most 'economically rational' or 'optimal' choice principle in all situations. *Melioration,* or preference for the higher local reinforcement rate, predicts a suboptimal outcome for any situation in which the consumption of a particular commodity reduces not only its own future value (e.g. through tolerance to subjective effects of drugs), but also the value of competing forms of behaviour, as occurs in addiction to drugs (Heyman 1996; see text for further details).

In practical terms, the matching law is generally investigated with the aid of concurrent VI schedules see Box 2A which operate independently of one another. Different relative rates of responding can be established with a number of pairs of VI parameters which thus vary relative reinforcement rate. Although the use of a relative rate measure provides a useful choice index, the procedure has not been much used in studies of self-administration behaviour. However, Iglauer and Woods (1974) did use such a schedule to show that monkeys prefer high doses of cocaine to low doses, based on relative response rates.

diazepine, midazolam, in baboons shifted the dose-response curve to the left for the generalization gradient to the drug, whereas a similar, response-independent history of midazolam resulted in a shift to the right.

Other behavioural correlates of affective states

It may be possible to gain some insight into the nature of drug-induced states by testing their ability to cross-generalize and substitute for stimuli from other well-defined situations. Examples in studies using rats include resident-intruder aggression and the discrimination of the 'anxiogenic' pentylenetetrazol (PTZ) cue (Vellucci et al. 1988), brain stimulation reward (ICSS) and cocaine, footshock stress and heroin in studies of relapse (Shaham et al. 1994), but the difficulties of equating the subjective states were pointed out. Any cross-generalization may reflect general factors such as arousal, which affect behaviour in non-selective ways.

2.3 Tolerance

Definition and types

Tolerance can be defined operationally as a shift to the right in a dose-effect function so that higher doses are required to produce the same effect. It represents an adaptation to an effect of a drug: in some cases this homeostatic-like process functions to ameliorate long-term toxic effects of drugs, although tolerance is seen to opiates, for example, when long-term toxicity is not observed. Over the years, it has gradually been realized that there are multiple forms of tolerance; for example, receptor regulation occurring with high, continuously administered doses of drugs probably depends on different mechanisms than tolerance to lower, intermittently administered doses, where behavioural factors often intervene. This should not, however, be taken to imply that such behavioural adaptations do not also involve adaptations at the neuronal level. There are also important distinctions concerning acute (i.e. short-term) versus chronic (i.e. long-term) tolerance. However, there are likely to be exceptions to any attempt to derive general principles about tolerance. For example, intermittent dosing of nicotine produces greater changes in receptor regulation than continuous administration (Sanderson et al. 1993). For both high and low doses, a number of adaptations probably occur in parallel, ranging from the molecular (see Sect. 3) to the behavioural levels, and including pharmacokinetic and pharmacodynamic forms, which involve changes in the disposition or metabolism of the drug (see Russell 1990).

Under the heading of *behavioural tolerance*, a number of distinct mechanisms operate, including both associative mechanisms (Pavlovian conditioning of opponent processes and instrumental behaviour) and non-associative mechanisms (such as habituation, the waning of a

response to a repeated stimulus). The work of Siegel (e.g. 1979) and others has extensively documented Pavlovian forms of tolerance within an opponent-processing framework, where there is an anticipatory reaction that functionally compensates for the drug effect. Instrumental tolerance includes those cases where behaviourally disruptive effects of drugs, e.g. leading to a loss of reinforcement, are ameliorated by appropriate changes in behaviour, including practice. There may be dynamic interactions between different forms of tolerance (Schuster et al. 1966). For example, pharmacokinetic and behavioural tolerance could lead to increased drug intake which produces further adaptations, e.g. via regulation of receptor mechanisms.

The area of behavioural tolerance has been well reviewed (Goudie and Emmett-Oglesby 1989; Stewart and Badiani 1993), but major puzzles remain. Why for example, does tolerance develop to some effects of a drug but not to others, which may even develop 'inverse' (i.e. opposite of) tolerance, i.e. sensitization (see Sect. 2.5)? One important experimental factor relates to the exact nature of the schedule under which the animal receives the drug. The factors determining habituation and sensitization to naturally occurring stimulus events depend on such parameters as inter-stimulus interval and intensity (Groves and Thompson 1970), as do those determining tolerance (e.g. Kalant et al. 1971).

Tolerance by drug class

One of the most dramatic forms of tolerance is to the subjective effects of LSD; there is reportedly little or no effect by the 4th consecutive day of exposure (see Isbell et al. 1956; Bridger 1978). Tolerance has been shown to occur for many effects of benzodiazepines but is more rapid for some (e.g. sedation) than others (e.g. anxiolytic) (see Woods et al. 1992). Further understanding of why some effects show tolerance and others do not will depend on determining the mechanisms that operate within particular neural systems and perhaps the involvement of different receptor types in some of the drug effects.

Nicotine has clear initially depressant effects on locomotor activity in rodents, but becomes stimulatory on repeated treatment (see review by Swedberg et al. 1990). The disruptive effects on operant behaviour show tolerance but they are contingency independent, i.e. tolerance may occur if the animal receives chronic treatment with nicotine outside the operant setting. For conditioned place preference, preliminary data indicate no tolerance but, more probably, a sensitizing effect of repeated nicotine injections. Investigating intracranial self-stimulation (ICSS), Herberg et al. (1993) have reported both tolerance and sensitization to nicotine, within narrowly defined limits of dosage and regimen. There is some tolerance to the cardiovascular and emetic effects of nicotine in humans (for review see Russell 1990). Smokers develop rapid acute tolerance over minutes to certain effects of nicotine, a somewhat reversible phenomenon (Benowitz et al. 1989; Russell et al. 1990). Results were reported showing that low levels of nicotine infusion in humans lead to increased nicotine smoking. It is possible that such results relate to the more general development of tolerance to aversive effects of drugs, which allows higher rates of drug self-administration. However, there are relatively few well-documented examples of experimentally induced tolerance to aversive effects in humans or other animals. One possible example is that drug preexposure ameliorates the effects of conditioned taste aversions to such drugs in rats (see Goudie 1987).

For opiates, whilst there is tolerance to most of the depressant effects in humans and other animals, there is equivocal evidence of tolerance to the positive reinforcing effects in rats. Thus, Nazzarro et al. (1981) demonstrated tolerance to the facilitatory effects of morphine on ICSS with electrodes in the mesolimbic system and to the suppressant effect of the drug on ICSS when the electrodes were aimed at the substantia nigra. Bozarth and Wise (1984) allowed rats to self-administer heroin 24 h a day, but after the initial few days, rates of self-administration stabilized and maximal tolerance was achieved. Nevertheless, there appears to be an initial tolerance to self-administered opiates in primates, with larger dose-effect shifts than those seen with stimulants. One example was given of monkeys with etorphine minipumps who showed a shift to the right of the dose-response function for morphine under a second-order schedule (J. Bergman, communicated at the meeting).

There is some evidence of acute and chronic tolerance to several of the effects of alcohol, including its sedative, subjective, ataxic and hypothermic effects (see reviews by Melchior and Tabakoff 1985; Portans et al. 1989; Harris and Buck 1990; Le 1990; Tabakoff and Hoffman 1992; Radlow 1994).

Apparent tolerance to the reinforcing effects of cocaine in rats has been reported following extended, daily self-administration sessions maintained by the drug under a fixed ratio schedule, as manifested by an increase in rate of infusions over the descending limb of the dose-response function (Emmett-Oglesby et al. 1993). Moreover, while the rate of self-administration increased over the first few days, the apparent tolerance dissipates over a few abstinent days, following which self-administration rates are lower (Emmett-Oglesby et al. 1993). In a follow-up study, Li et al. (1994) used a progressive ratio (PR; see Box 2B) schedule of cocaine self-administration. Seven days of chronic treatment with cocaine significantly decreased breaking-point values across the entire dose-effect curve in four of seven rats. Anecdotal evidence from researchers using non-human primates indicates that there is little change in the reinforcing effects of stimulant drugs. Yanagita (1973) found little change in breaking point under a PR schedule following a month of chronic treatment with cocaine, although there was a reduction in response rate. There is no tolerance to reinforcing effects of cocaine in humans under conditions in which tolerance to subjective or cardiovascular effects

are seen (often at the same time), although addicts do often report a long-term diminution in the subjective magnitude of 'highs' following cocaine (see Fischman and Foltin 1992).

Implications for dependence and addiction

A wide variety of views was expressed on the overall significance of tolerance, reflecting in part the reduced emphasis that clinicians seem to place on tolerance (see DSM-IV). Many aspects of tolerance were thought not to be crucial for addiction but nevertheless probably play important modulatory roles. While pharmacokinetic tolerance does not in general appear to play a major part, it is sometimes relevant when several drugs are used simultaneously. Regular drug exposure might well lead to tolerance regardless of whether dependence occurs. Tolerance may thus determine behavioural patterns of addiction such as the binge/crash cycle for psychomotor stimulants (though not opiates) and the overdosing that can occur with a change of context for drug use. Russell (1990) has outlined how repeated acute tolerance to nicotine could theoretically contribute to a withdrawal state in heavy smokers that motivates further smoking. The precise contribution of tolerance to the overall process of drug dependence for virtually all drugs of abuse, however, remains to be established.

Overall, in contrast to sensitization (see Sect. 2.5), it was felt that tolerance mechanisms were relevant to all stages of dependence development, and it was argued that conditioned tolerance may be especially important early in the career of the drug user. In general, tolerance to both positive reinforcing and aversive effects of drugs would lead to increased drug intake. Tolerance to their reinforcing effects and not to their toxic effects could also lead the user to self-administer toxic doses. It was argued that increased tolerance to the reinforcing effects of a drug would lead the individual to spend more time involved with drug acquisition, which may involve an increased level of criminal and/or antisocial behaviour. However, evidence for such tolerance is quite weak.

There was, however, disagreement about when tolerance had the greatest impact on the development of dependence. One view was that the tolerance reflected by a gradual increase in drug intake may be more a late-stage complication than the primary drive creating dependence. On the other hand, at an early stage of the drug user's career the growth of tolerance to the aversive effects of a drug may be critical. Schuckit's studies in humans indicated that lower sensitivity to the aversive effects of ethanol leads to increased chances of becoming an alcoholic (see Sect. 4.1). This demonstration of decreased responsivity to the aversive effects of ethanol cannot be attributed to pharmacokinetic factors (Schuckit 1984, 1985).

Conditioning may also play a crucial part early on by mediating the development of tolerance, where the dose and the inter-dose interval would be insufficient for the development of non-associative tolerance. Recent parametric research with morphine (Tiffany et al. 1992) indicates that the development of associative tolerance is most pronounced when drug doses are paired with distinctive environments at long inter-dose intervals. In contrast, high doses delivered at short inter-dose intervals promote the development of non-associative tolerance and disrupt the acquisition of associative tolerance. Ehrman et al. (1992b) have reported conditioned tolerance to physiological effects of morphine in human opiate abusers. Although the role of associative factors in the production of tolerance was hence not in dispute, there was considerable doubt among delegates about exactly which psychological mechanisms underlie such effects, opponent process and memorial processing accounts both having been proposed. Conditioned opponent processes have been elusive, as many factors may influence the form and direction of the conditioned response, and some have argued previously that where morphine is concerned the effects of stress (e.g. 'stress-induced analgesia') may mimic or mask conditioned tolerance effects.

Tolerance can be seen as leading to withdrawal, but it can also be found without physical dependence. Theorists such as Goudie (communication at the meeting) argue that the extent to which tolerance and dependence covary depends critically upon the mechanism by which tolerance is induced in any specific assay. Thus tolerance induced by pharmacokinetic adaptations and operant learning would not necessarily be associated with dependence. However, it could be hypothesized that tolerance which involves neuroadaptations via specific cellular and intracellular mechanisms might be associated with dependence but would not necessarily be responsible for the overall behavioural manifestation of tolerance. Generally, a good framework for conceptualizing the relationship between tolerance and dependence is whether tolerance involves a progressive reduction in the strength of a drug signal/stimulus, or whether it involves a counteradaptation to oppose the strength of a constant drug stimulus (see Young and Goudie 1995). The only tolerance mechanisms that will be associated with dependence are those that involve counteradaptations to oppose the strength of a constant drug stimulus, as it is the counteradaptations that appear as symptoms during drug withdrawal.

2.4 Withdrawal

Definition

A withdrawal syndrome is defined in terms of the clusters of signs and symptoms that result from forced or voluntary abstinence or from pharmacological precipitation (e.g. opiate antagonists in morphine-dependent animals). The syndrome may include physical features such as somatic (e.g. autonomic) and behavioural components, as well as subjective (e.g. dysphoric) components, which vary considerably across drug classes. It should be

made clear that there was no wish at the meeting to perpetuate a 'dualism' between 'physical' and 'psychological' aspects of withdrawal. It is argued that both aspects are 'physical' in the sense that they depend upon brain mechanisms; however, the 'physical' withdrawal syndrome may consist of observable somatic signs, e.g. resulting from altered autonomic responses, whereas 'subjective' aspects of withdrawal might consist of verbally reported emotional responses, such as dysphoria. These responses may co-exist and to some extent be inter-dependent; for example, it is quite likely that some of the autonomic features of withdrawal lead to dysphoric verbal responses. However, these different classes of response can also occur independently, especially across different drug classes, suggesting some separation in their controlling neural mechanisms and their potential contibutions to dependence.

Formally, the occurrence of the withdrawal state can act as an aversive stimulus, which can function as an instrumental negative reinforcer (see above), and thereby increase the probability of behaviour that postpones or terminates (via self-administration of the drug) that state. It can be linked to the hypothetical incremental development of an 'opponent process' that governs the transition from drug use and abuse to drug dependence, mainly based on evidence from the opiate class (Solomon and Corbit 1974). Whether this opponent process assumes greater importance than that based on positive reinforcement, which hypothetically decrements as a result of tolerance to hedonic effects of the drug, is unclear.

In terms of the DSM-IV definition of dependence, 'physical' withdrawal is not a necessary criterion. Indeed, clinical observations confirm that dependence can be seen even without the development of tolerance or withdrawal. In experimental tests, it is now generally accepted that withdrawal does not constitute a necessary condition for drugs to act as positive reinforcers. For example, self-administration of opiates in monkeys can be maintained at doses insufficient to engender withdrawal (e.g. Woods and Schuster 1968; Schuster and Johanson 1973; Ternes et al. 1985). Robinson and Berridge (1993) summarize the other main evidence against withdrawal being a necessary component of drug dependence. Some of the evidence relying on neural manipulations is provided in Sect. 3.

Withdrawal by drug class

It would be useful to recognize any common element of withdrawal, but this is a difficult task in the case of physical or somatic signs such as autonomic responses, because physical withdrawal syndromes caused by different drugs differ in substantial ways. However, subjective symptoms including anxiety, anhedonia, dysphoria, depression and drug craving are common to withdrawal from several drugs of abuse, including sedative-hypnotics, nicotine, opiates and psychomotor stimulants (Jaffe 1990; Gawin and Kleber 1986).

Withdrawal may proceed in stages, each having different characteristics including the risk of relapse. For cocaine it has been hypothesized that this risk is initially low, increasing after 4 days (see Gawin and Kleber 1986; Gawin 1991) but for opiates the risk for relapse is high from day 1. Dysphoria is clearly a common, central symptom. Withdrawal is a very important phenomenon in nicotine use (see Solomon and Corbit 1973). Reports by smokers of mood improvement and improved working capacity when smoking apparently reflect a labelling of the alleviation of withdrawal. Depressed individuals tend to have more intense nicotine withdrawal in terms of all symptoms (except excess eating) than non-depressed individuals. It has been reported that about 80% of subjects with a history of depression exhibit depression during nicotine withdrawal, compared with only 20% of subjects with no history of depression (Glassman et al. 1990; see also the discussion on co-morbidity, Sect. 4.2).

Alcohol withdrawal can also be severe, with high risk of serious medical complications and psychiatric symptoms, especially depression and anxiety (Tabakoff and Hofmann 1992). Some addicts have a phobia of withdrawal, and as soon as they start experiencing some signs of withdrawal, they become more and more anxious and their signs and symptoms worsen (positive feedback).

For opiate withdrawal, the state is so painful (in somatic terms; H. Kleber, communication at the meeting) that the addict uses opiates to stop the pain (in addition to other aversive components of opiate withdrawal), so its relief may also be supposed to be immediately reinforcing. Withdrawal from methadone also leads to extreme discomfort. There are obvious and well-documented differences between opiate and stimulant withdrawal. Notably, a somatic state of stimulant withdrawal is not well documented. However, a dysphoric state in withdrawal has been described for stimulants and likened to that of mild clinical depression (Gawin and Kleber 1986; Gawin 1991). The propensity of a subject withdrawn from cocaine to take more drug might be expected to be weakened by this dysphoric or depressed state (cf. Gawin and Kleber 1986) (which is presumably associated with a general disposition not to initiate behaviour) unless the drug user specifically learns to discriminate and alleviate this withdrawal state by taking more drug. The latter scenario is thus another variation of the 'self-medication' hypothesis. It is interesting to note that schizophrenics on antipsychotics are prone to abuse cocaine (see LeDuc and Mittleman 1995) or alcohol. Perhaps these drugs offer some form of relief from antipsychotic-induced 'dysphoria' (cf. Wise 1982; Jonsson et al. 1977) (see also Sect. 4.2).

Implications for addiction

Opponent motivational processes. This theoretical notion has been proposed to link the development of tolerance for hedonic effects to the opposed effects of an aversive

motivational state of withdrawal. Extending this to the neuropsychological bases of drug dependence involves testing the hypotheses that: (a) the brain reinforcement systems show tolerance and withdrawal; (b) the development of tolerance and withdrawal has motivational significance and may or may not be accompanied by somatic signs of withdrawal. These negative affective states produced by drug dependence may contribute to continued drug use and even relapse. According to Wikler's theory (Wikler 1965), the high rate of relapse observed in drug addiction is due in part to conditioned responses, occurring after detoxification, to stimuli that have been paired with either the aversive effects of drug withdrawal or the positive reinforcing effects of drug taking. In addition, this negative affective state can be conceptualized to have changed the 'set point' from which positive unconditioned or conditioned reinforcing stimuli can produce their reinforcing effects and thus change the reinforcing strength of these stimuli (e.g. Koob and Bloom 1988).

The opponent process theory could be tested by observing to what extent tolerance to positive reinforcing effects and withdrawal can be dissociated. On the question of the motivational significance of the withdrawal state, it is clear for drugs such as opiates that the somatic withdrawal syndrome is not a necessary condition for reliable self-administration to occur (see above). However, withdrawal from opiates has well-documented aversive motivational properties (Goldberg et al. 1971), and the modulatory effect of withdrawal on self-administration is probably important. Old studies such as those by Wikler and Pescor (1967) have shown that morphine-dependent animals learn to self-administer the drug faster than non-dependent animals.

A further important counter to earlier studies that appeared to de-emphasize the importance of withdrawal (e.g. Bozarth and Wise 1984) is the demonstration that methylnaloxonium (an opiate receptor antagonist that does not diffuse far in the brain) infused into the nucleus accumbens of the morphine-dependent rat has aversive effects, as assessed using a conditioned place preference paradigm and the conditioned suppression of appetitive behaviour (Koob et al. 1989, 1992). However, experimental evidence for similar aversive motivational effects of withdrawal from other classes of drugs is more limited. For cocaine (Markou and Koob 1991), opiates (Schulteis et al. 1994) and ethanol (Schulteis et al. 1996), ICSS thresholds are elevated after a binge of drug self-administration behaviour. In theory, therefore, this withdrawal state could provide the impetus for further self-administration of the drug. But for self-administration to occur, a cognitive mechanism (learning that the 'depressed/anhedonic' state is specifically alleviated by the drug) is required. A further possible problem to be addressed is whether the effects on reinforcement thresholds are sufficiently long-lasting to account for relapse after a delay.

Overall, many delegates considered that if opponent processes do play an important role in human drug abuse, subjective symptoms of withdrawal such as dysphoria were more likely to play a part than the physical withdrawal symptoms. However, they also concluded that the precise ways in which dysphoria can induce the opponent motivational process require elucidation at the psychological and neural levels.

Conditioned influences on withdrawal. There was little consensus on the importance of conditioned withdrawal effects, first documented anecdotally by Wikler (see Wikler 1965) and experimentally in studies of classical conditioning of the opiate withdrawal syndrome in monkeys (Goldberg and Schuster 1967; Goldberg et al. 1969). The latter study further showed that the conditioned withdrawal state had motivational properties, as seen from the increased rates of self-administration of morphine (which also demonstrate the operation of a negative reinforcement contingency). The presumed absence of suitable conditioned cues for withdrawal in veterans returning from Vietnam was originally assumed to account for the high spontaneous abstinence rates found by Robins et al. (1974). However, the role of conditioned withdrawal in the mediation of relapse was questioned (see Baker et al. 1986 for a critical analysis). There are a number of studies in which addicts have reported conditioned withdrawal, but many negative mood states may be sufficiently similar to withdrawal to provoke drug use through generalization. Hence such conditioned withdrawal is only one way in which aversively based motivational processes could contribute to drug use.

2.5 Sensitization

Definition

Sensitization can be operationally defined as a shift of a dose-effect curve to the left following repeated drug administration, although there are some instances in which the entire dose-effect curve appears to be shifted upwards (Ksir et al. 1987; Shoaib and Stolerman 1992). Sensitization is a progressive increase in an effect of a drug with repeated administration or a persistent hypersensitivity to an effect of the drug as a consequence of past history and exposure to drug (or stress). Sensitization may sometimes be expressed as a qualitative change in behaviour, e.g. the emergence of new responses such as stereotypy following sensitization of locomotor hyperactivity to repeated low doses of amphetamine (see Segal et al. 1981). Thus, it would appear that sensitization reflects both quantitative and qualitative changes in behaviour. However, it was argued that these apparently qualitatively different behaviours may simply reflect quantitative changes in the neurobiological threshold required before the behaviour is expressed. There is evidence for sensitization of the reinforcing effects of morphine, amphetamine and cocaine, as measured by a conditioned place preference procedure (Lett 1989; Shippenberg and Heidbreder 1995). The latter stands in contrast to appar-

ent tolerance to cocaine seen in rats for self-administration under a progressive ratio schedule (see Box 2B) (Emmett-Ogelsby et al. 1993), presumably in part a reflection of the differing methodologies and different actions of the drugs. There are also demonstrations that pre-exposure to caffeine, cocaine or amphetamine affects the acquisition of self-administration of psychomotor stimulants (Woolverton et al. 1984; Valadez and Schenk 1994; Horger et al. 1992) and that cocaine self-administration sensitizes rats to the locomotor stimulant effects of the drug (Hooks et al. 1994).

Sensitization by drug class

Sensitization has not been so widely studied by pharmacological class as tolerance but sensitization has been reported for the locomotor stimulant effects of a variety of drugs including amphetamine, cocaine, methylene-dioxymetamphetamine (MDMA; ecstasy), nicotine, opiates and ethanol (see Robinson and Berridge 1993). There is evidence of sensitization of convulsions associated with ethanol withdrawal (Becker 1994). Electrically kindling the rat (as in models of epilepsy) also results in enhanced ethanol withdrawal. This form of sensitization seems to occur even with stable alcohol consumption. Length of ethanol exposure is also a determinant of the severity of the ethanol withdrawal syndrome. These observations are of considerable interest given the progressive increases in severity of ethanol withdrawal in humans. There are some indications of sensitization to repeated morphine withdrawal in rats (Gold et al. 1994). However, tolerance to such withdrawal effects is often reported in humans (C.R. Schuster, communication at the meeting). Opiate addicts sometimes demonstrate increased anxiety following repeated opiate withdrawal but this observation may reflect the type of positive feedback that can occur in anxiety states rather than sensitization processes (see above).

Sensitization may not be seen with sedative hypnotics and benzodiazepines (Stephens et al. 1988). Very long-term sensitization changes (6 months or longer) have been observed with amphetamine and morphine, but it has proven difficult to demonstrate such persistence with cocaine.

Methodological considerations

Some of the problems in quantifying sensitization may arise because several processes, including tolerance, may develop which mask sensitization effects, and it is not easy to isolate conditioned and unconditioned mechanisms except using in vitro preparations. Although pharmacokinetic mechanisms may contribute to sensitization, there are some cases where such a contribution appears unlikely, for example where sensitization is produced by stressors or when cross-sensitization has been produced. Other discussion revolved around failures to replicate the phenomenon, probably because only certain treatment regimens are effective. A further limitation is provided by the narrow dose range producing locomotor hyperactivity in animals. Robinson and Berridge (1993) argue that measures of locomotion are often not good indicators of what is generally a robust sensitization phenomenon because amphetamine-induced locomotion does not obey a simple linear dose-effect function. Counts of rotational behaviour, or even observational rating scale measures of stereotyped behaviour in rats, are more robust because the linear dose-effect relationship is more evident in these cases.

It is generally believed that both associative and non-associative processes may contribute to the development of sensitization. Unfortunately, little systematic research has been conducted on the parameters of drug administration promoting the development of either associative or non-associative sensitization. For example, information regarding the influence of both dose and inter-dose interval on the acquisition and retention of associative and non-associative sensitization effects would be of considerable methodological, theoretical and clinical value.

Implications for dependence and addiction

The relevance of sensitization to drug dependence has been highlighted by Robinson and Berridge (1993), who suggest that drug 'wanting' (as distinct from 'liking') may be mediated by the sensitization of an incentive-motivational system that depends upon mesolimbic dopamine activity. Sensitization could potentially be relevant to the explanation of alterations in drug intake, and a generally enhanced propensity to take the drug, including relapse, reinstatement and loss of control. The possible conditioning of sensitization to environmental stimuli helps to explain the increase in drug-seeking behaviour produced by conditioned cues. However, increases in responding cannot necessarily be considered equivalent to sensitization processes, otherwise all learning processes would be subsumed under the term 'sensitization'. The apparent similarity of two phenomena (i.e. face validity) does not address the issue of homology, i.e. similarity of underlying biological mechanisms, between them (e.g. Geyer and Markou 1995). A further logical problem is how the theory can be tested, if (as is likely) in the natural setting it is the subject, not the experimenter who administers the sensitizing drug. In practical terms, in animal experiments self-administration would be confounded with more general learning. A possible way out of this dilemma is to use the self-administration of the drug to sensitize another independent action of the drug. Thus, Hooks et al. (1994) have looked at effects on locomotor activity and neurotransmitter release (see Sect. 3). Another indirect way of detecting sensitization is to relate individual differences in consumption of another reinforcer, sucrose, to subsequent responses to acute or repeated doses of amphetamine (Sills and Vaccarino 1994).

Despite these initial attempts to test the sensitization model, it was generally agreed that there is as yet little direct evidence linking sensitization processes to human drug dependence – and what is relevant is largely negative (Rothman et al. 1984). Several participants pointed out that sensitization in the form of a leftward shift in the dose-response curve for reinforcing effects would lead to *reduced* drug intake. This is of course not what is generally seen: regular drug users usually *increase* their intake and may possibly show *tolerance* to subjective effects. But caution is required when assessing this apparently clear-cut pattern for at least two reasons. First, increasing drug intake in a self-administration paradigm does not necessarily imply there is tolerance rather than sensitization to the reinforcing or rewarding properties of the drug, providing that the subjects show some regulation of intake. Logically it is possible to get tolerance to the non-reinforcing effects of the drug (e.g. anxiogenic effects) that contribute to regulation at the same time as sensitization to its reinforcing properties. To assess the relative degrees of sensitization or tolerance to the incentive/reinforcing properties of a self-administered drug, procedures could be used in which there is a choice of the drug against another non-pharmacological reinforcer. However, since the drug may affect the behaviour maintained by the latter, it might be necessary to require the subject to respond prior to the delivery of the drug (as in, for example, second-order schedules of reinforcement see Box 2B).

Second, decreased intake would not be expected if the shift in the curve following sensitization is upwards, i.e. an increase in the maximal reinforcing efficacy of a drug. This would be more consistent with a role for sensitization in dependence. In the laboratory context of self-administration in animals, there was some evidence that sensitizing regimens enhanced the acquisition of drug-taking behaviour (Horger et al. 1992; Piazza et al. 1990; Valadez and Schenk 1994) but it was rather less clear that such experience produces a shift to the left in the dose-effect curve constructed under stable conditions following acquisition.

Is there sensitization to drug effects in human addicts?

While it has been suggested that there is sensitization to stimulant-induced psychosis, a review of the literature indicates that repeated stimulant administration is not required for psychosis to develop, as a single high-dose injection of a stimulant can induce psychosis in humans (see Segal et al. 1981). The stimulant-induced psychosis may be facilitated because tolerance develops to the aversive effects of the stimulants, thus allowing the individual to self-administer doses sufficiently high to produce psychosis. In any case, the phenomenon of stimulant-induced psychosis might not be relevant to drug dependence.

It might be of interest to look for evidence of sensitization to stimulants in humans in other ways: one clearly interesting population is children or adolescents with attention deficit disorder receiving psychomotor stimulants such as methylphenidate, who could be expected to be either sensitized or tolerant to stimulants in later life, depending on their clinical regimen of medication.

Cross-sensitization. A very important issue for vulnerability (see Sect. 4) was whether sensitization to drug effects cross-generalize to more conventional stressors, as suggested by Antelman et al. (1980) and Piazza et al. (1990). Although considerable evidence supports the point, and the same cross-generalization, i.e. either 'stress' or 'drug', can produce relapse, there was some doubt that a general construct such as 'stress' could usefully be applied across the board. The paradox that a drug such as amphetamine could act both as a stressor and as a reinforcer was raised: what did this imply about either concept? As cross-sensitization appears to have been demonstrated only with experimenter-administered drugs, it remains possible that the effects result merely from the cross-generalization of effects of different stressors. Finally, published data on cross-sensitization imply that we should all be maximally sensitized by exposure to non-prohibited drugs; a typical lifetime's exposure to stressors might be similarly effective.

Overall, it was generally agreed that sensitization to drug dependence is probably most relevant in acquisition processes in animals. Some delegates considered a role for sensitization in relapse to be plausible, although supporting data are required.

2.6 Craving and relapse

Definitions

Craving and relapse to drug-use are inter-related, although it is by no means sure that the former is necessary for the latter (Marlatt and Gordon 1980). Relapse can be defined operationally as a resumption of drug seeking and self-administration behaviour following a period of abstinence. It can be measured experimentally in animals in 'reinstatement' procedures (for a summary of such experiments see Box 2G).

By comparison, there are no obvious operational definitions of craving, and there was considerable disagreement as to a definition, even at a clinical level (see also Baker et al. 1986; Pickens and Johanson 1992). The diversity of opinions voiced led some to the conclusion that we are not dealing with a unitary construct. Samples of definitions proposed and viewpoints are:

Craving may be "a sign that the addict has a problem to solve, e.g., that drug is not available. It may well be a cognitive marker indicating a real battle going on in the addict". Tiffany (1990) hypothesizes that the processes controlling drug use may operate independently of those mediating craving. In his view, craving represents the activation of effortful cognitive processing devoted to impeding or abetting the execution of automatic drug-use

behaviour. An alternative view was that craving may represent a subjective experience of "a strong or intense desire" to experience the mood-altering properties of a drug. It is unclear whether this intense desire should be interpreted as psychopathological, though much craving for non-drug stimuli is usually only mildly disruptive and seldom more than harmless, or along a continuum of strength of desire.

A further definition focused on the uncontrollability of the urge to use drugs, because loss of control is a core aspect of recent ICD-10 or DSM-IV descriptions of dependence. These descriptions are essentially motivational hypotheses of craving, and a few discussants related them directly to motivational theories in animal behaviour. Although universally accepted animal models of craving do not exist (see Markou et al. 1993), this motivational perspective provides perhaps the best opportunity for pursuing relevant animal studies, particularly those directed at elucidating the neural systems that underlie this state. Motivational states, which represent the desire of 'wanting to take the drug', can be conditioned to extrinsic environmental stimuli; such associative learning can explain the general experience that craving can be elicited by environmental cues associated with the drugs.

A major problem for a simple motivational hypothesis is that measures of craving based on self-report may not be well correlated with behavioural measures of craving based on drug use or relapse. The failure of self-ratings of craving to correlate with autonomic indices such as heart rate also requires explanation (see Baker et al. 1986 for a critical review). Another, theoretical, issue to be addressed by the motivational theory is whether craving may reflect not only the desire to approach an appetitive stimulus but also the desire to avoid the negative aspects of withdrawal; it has been reported that behavioural indices of craving can be induced in animals either by a priming injection of the drug or by a withdrawal experience.

Craving by drug class

Craving may also depend on drug class and probably also depends on basic personality and inherited characteristics. The clinicians at the meeting considered that most of the major drug classes do elicit craving-like phenomena, though to different degrees. Clinical reports suggested that craving had been observed most strongly for opiates, stimulants, alcohol and nicotine; findings in the laboratory setting have been reviewed according to different drug classes (Baker et al. 1986).

Methodological issues

Several methodological impediments to the investigation of drug craving were identified. Craving is often, but not always, accompanied by physiological signs (i.e., changes in skin conductance, blood pressure and heart rate), but these are often selected more for their ease of measurement than to quantify the subjective nature of craving. Much of the research on subjective aspects of craving has been conducted using psychometrically inadequate, single-item instruments for the assessment of self-reported craving. Recently, multi-item measures of drug craving have been developed (Tiffany et al. 1993) which may provide more reliable and sensitive indices of the possible multidimensional features that cravers report. A direct comparison of the single-item methods and the multi-item approach of Tiffany has been provided by Schuster et al. (1995). Craving research has also been impeded by the relatively little systematic evaluation and programmatic development of effective manipulations for the production of craving under controlled laboratory conditions. Developments using the cue-reactivity paradigm to study drug craving are promising in this regard. This paradigm involves monitoring addicts' verbal, physiological and drug-use responses following presentations of drug-relevant stimuli (see Drummond et al. 1995 for a review). Finally, craving research and theory has not adequately accounted for the common finding that craving can occur without drug use and drug use can occur without craving.

Implications for dependence and addiction

There was an initial divergence of views between clinicians, who found the term 'craving' clinically useful and relevant, and some of the psychopharmacologists, who considered craving to be a correlate of behaviour essentially devoid of explanatory value. If subjective motivational states are considered simply as epiphenomena in this way, the concept of craving is not useful; alternatively, if these subjective motivational states are considered as determining behavioural actions (as the clinicians seem to believe), then they are useful explanatory constructs for behaviour. The data of Foltin and Fischman (1990, 1994), which indicate double dissociation in human addicts between expressed craving for drug and preparedness to work to gain access to it, depending on which drug is administered, was sufficient for some delegates to rule out craving as a major factor.

On the other hand, some participants argued that evidence for craving not acting as a causal factor for drug self-administration challenged certain conceptualizations that assigned craving a primary motivational role in addictive drug use. They proposed that such findings provide insufficient justification for eradicating craving from addiction research. Some suggested that any model that could explain drug self-administration but not craving would not furnish a comprehensive account of addictive disorders. It was also argued that even if craving is an epiphenomenon that arises as a conscious monitoring of behaviour, it is nevertheless an interesting reflection of cognitive processes, which is affected by many factors. Both drug-like and drug-opposite states reliably induce craving in any particular individual and such reliability further enhances the validity of the construct.

Box 2G The experimental study of relapse

The main behavioural paradigm used in the study of relapse in animals is the *reinstatement* procedure. A rat is initially trained to press a lever for the self-administered drug for several weeks. Following the stabilization of drug-taking behaviour, lever pressing for drug infusions is extinguished by substituting saline for the drug for several daily sessions. Following extinction, a non-contingent administration of the training drug (or other drugs, or non-drug events) is given prior to a daily session, and its ability to reinstate lever pressing examined. This procedure has several features that make it suitable for the study of factors involved in relapse to drug use. First, testing for reinstatement is conducted with drug-free animals that are experienced in drug-taking behaviour; they are not engaged in drug-seeking behaviour, but are free to do so (Stewart and de Wit 1987). Second, a second 'control' lever is used to assess non-specific activity, so the number of responses on the previously functional lever provides a measure of the directedness of the behaviour in the tests of reinstatement of drug seeking. Finally, the reinstatement procedure appears to have good predictive validity (Markou et al. 1993). Re-exposure to drug or drug-related cues has been shown to increase reports of craving for drugs in human addicts in a drug-free state (Childress et al. 1992; de Wit and Chutuape 1993). These same conditions have been shown to reinstate drug-seeking behaviour in the reinstatement procedure in animals (see Markou et al. 1993; Stewart and de Wit 1987). Bouton and Swatzentruber (1991) have provided a useful analysis of relapse from a learning theory perspective in which the drug-associated context assumes a critical role.

Recent studies have shown that brief exposure to a stressor can cause relapse to drug-taking in animals. A version of the reinstatement procedure was used to study the effects of stress and priming injections of heroin on relapse following long-term extinction and drug-free periods (Shaham and Stewart 1995). Brief exposure to foot-shock stress or priming injections of heroin reinstated heroin-seeking behaviour in drug-free rats after many sessions of extinction and up to 6 weeks after the last exposure to heroin. In reinstating the behaviour, the foot shock mimicked the effect of a non-contingent priming infusion of heroin. These data suggest that exposure to a stressful event can reinstate previously extinguished heroin self-administration behaviour in the heroin-free animal. The persistence of the effect after numerous extinction sessions, and after a 4- to 6-week drug-free period, shows that exposure to stress can be a sufficient stimulus for relapse.

However, there are still formidable problems for research into the craving concept to overcome. Clinicians' conceptualizations of the relationship of drug craving to drug use are probably biased because they are based on drug addicts who come to the clinic seeking help and trying to avoid drug taking. Researchers seldom see or study those drug users who are coping *successfully* with their dependence and their lives. In general, it was agreed that craving merited further careful consideration and research.

3 Neurobiology of drug addiction

3.1 Levels of analysis

There are several levels of analysis of the neural mechanisms underlying the reinforcing and other effects of drugs of abuse, as well as the psychological processes underlying dependence and compulsive drug-seeking behaviour. At a molecular and cellular level, the pharmacological actions of drugs can be defined, together with the adaptations in such cellular processes that accompany repetitive and chronic drug use; these adaptations may be important for understanding phenomena such as sensitization, tolerance, withdrawal and the progression towards drug dependence. But understanding these processes is only a first step in determining the neural substrates of dependence. The specific neuronal populations that are the primary targets of drugs of abuse form one node in a complex neural system. It is important, therefore, to identify the system, or systems, with which such drugs interact and to explore their functions and the ways in which they might be changed by persistent drug self-administration. For example, it was suggested at the meeting that the psychological processes of reinforcement and conditioning, actions and habits, as well as cognitive processes, might best be investigated at a neural systems level in order to determine the mechanisms through which drugs of abuse have their impact; in these psychological and neurobiological processes lies the basis of compulsive drug-seeking behaviour.

Many new and powerful techniques have recently been developed that allow the monitoring and manipulation of neural events. Some of the newer techniques that have provided much of the neurobiological data summarized below are described in some detail in Boxes 3A–E. It is important to emphasize that different, sometimes contradictory, results may be obtained in experiments employing very different methodologies. For example, (1) in vivo neurochemical experiments in which extracellular neurotransmitter levels are measured using either chronoamperometry, voltammetry or microdialysis together with high-performance liquid chromatography (Box 3B) have often yielded patterns of results that are difficult to reconcile with each other and with (2) cellular studies employing electrophysiological recording (Box 3B) or receptor-mediated events assessed at a biochemical or molecular level (Box 3B). It is tempting to dismiss the discrepant results arising from such different approaches because they confuse the picture. However, understanding where the discrepancies originate will inevitably lead to a better understanding of the neural processes underlying drug dependence and addiction. For example, it is possible that discrepancies arise because some techniques assess the tonic activity of neurons while others assess their phasic activity. In addition, invasive techniques such as in vivo dialysis may interact with the system under study.

The mesolimbic dopamine system has so far been the focus of attention in many studies on the neural basis of

Box 3A In vitro methods

Although in vivo methods (e.g. neurochemical and neuroanatomical, see Boxes 3B, C) provide very useful insights into the consequences of drug action (acute or chronic) at the cell/system level, the intervening steps between drug binding at its receptor and its effects are difficult to determine. In vitro assays offer an appropriate means of dissecting these processes, or testing molecular/cellular hypotheses derived from in vivo work. Similarly, in vitro experimentation must draw on the body of in vivo, behavioural and clinical data. In addition to intellectual quests, it is important to identify these molecular/cellular mechanisms in order to develop therapy and prevention strategies, as well as clinically useful medications that are devoid of dependence liability.

Because it is difficult to interpret cellular and molecular changes in heterogeneous populations of cells, studies of cultured neural cell lines can be used to identify molecular targets of drugs and, in particular, to identify long-term changes in protein synthesis and the underlying mechanisms. Electrophysiological studies using brain slices or acutely dissociated neurons prepared after chronic drug treatment in vivo have the advantage that direct correlations can be made between alterations in cell function and the behavioural effects of drugs; for example, changes in dopamine transmission after chronic psychomotor stimulant self-administration or the synaptic changes related to ethanol withdrawal hyperexcitability. Nevertheless, in vivo studies are crucial in clarifying which of the candidate drug targets identified in vitro are most relevant to the process(es) underlying addiction.

addiction (dating from early studies; Roberts et al. 1977). There was, however, general agreement at the meeting that there is an urgent need for extensive study of other neurotransmitter systems, since they may behave differently or be important during different phases of the addiction process, making it both difficult and unwise to generalize from one system to another.

3.2 Molecular and cellular sites of action of drugs of abuse

The reinforcing properties of drugs are generally believed to be most relevant to their abuse (see Sect. 2). Identifying the primary molecular and cellular sites of the initial or acute action of drugs of abuse is an important starting point for exploring the cascade of events that underlies such reinforcing effects and also leads to neuroadaptations with chronic drug use. These neuroadaptations are likely to be critical determinants of the processes culminating in addiction. There was general consensus at the meeting concerning the primary receptor sites that mediate the acute effects of drugs. However, it should be emphasized that an experimental strategy that focuses solely on the primary site of drug action might result in a failure to identify adaptive changes occurring at other neural loci, within or outside the neural system initially targeted by the drug, which may be of even greater importance to the development of dependence and addiction. For example, it is well recognized that there is a neural dissociation of the sites mediating the physical withdrawal (pontine locus coeruleus) and analgesic (midbrain periaqueductal grey) effects of opiates.

A major point of agreement that emerged during discussions at this meeting was that it is crucial to differentiate clearly the various stages of the drug addiction process, namely the initiation and maintenance of drug self-administration, dependence, withdrawal, craving and relapse, and to identify the neuroadaptations occurring at each of these stages. Many apparently conflicting findings in the literature may be attributed to the use of different behavioural paradigms reflecting different psychological and neurobiological processes that may not be relevant to all stages of the addiction process.

In terms of the major classes of drugs of abuse, the following general conclusions concerning primary sites of action were widely agreed:

Opiate drugs, such as heroin and morphine, have positive reinforcing effects that are revealed by acute self-administration; they also alleviate the aversive consequences of opiate withdrawal in dependent individuals, thereby demonstrating their negative reinforcing effects. There are three major opiate receptor sub-types in the brain, μ, ∂ and kappa. It was generally agreed that the μ receptor is important for the positive reinforcing effects of heroin and morphine (Di Chiara and North 1992). There is some evidence for a minor role for δ receptors, but none that indicates a role for kappa receptors. In morphine-dependent rats, the signs and symptoms of opiate withdrawal are also thought mainly to involve the μ receptor, indicating an important role in negative reinforcing effects, with minor roles for both δ and kappa receptors (Koob et al. 1992). The neuroanatomical locations of the μ receptors include those on the cell bodies of dopamine neurons in the ventral tegmental area (VTA; cell group A10, the origin of the mesolimbic dopamine system; see Fig. 3) and also on neurons in the basal forebrain, notably in the nucleus accumbens and associated areas of the ventral striatum (Di Chiara and North 1992; Koob 1992). Although the nucleus accumbens is a major innervation target of the mesolimbic dopamine system, the reinforcing effects of opiates here appear to be independent of alterations in dopamine transmission (Koob 1992). The amygdala has also been implicated in the reinforcing effects of opiates.

In contrast to these largely μ opiate receptor-mediated effects of morphine and heroin, other studies have indicated a role for ∂ receptors in the effects of opiates to potentiate the control over behaviour by conditioned reinforcers (e.g. G.D. Phillips et al. 1994a). Stimulation of kappa receptors, on the other hand, may produce aversive effects that could be associated with some of the consequences of opiate withdrawal. Only one type of μ receptor has been identified at the molecular level and cloned (Wang et al. 1994).

Psychomotor stimulants such as cocaine and amphetamine have primary reinforcing effects through their ac-

Box 3B In vivo neurochemistry and electrophysiology

Perhaps some of the most exciting techniques to impinge directly on the exploration of neural mechanisms underlying drug dependence are those that enable the measurement of extracellular neurotransmitter levels in freely moving animals that are self-administering drugs. These methods include: (1) In vivo microdialysis coupled with high-performance liquid chromatography (HPLC) and some form of assay system, usually electrochemical detection for monoamine transmitters and their acid metabolites or radioimmunoassay or ELISA for neuropeptides. (2) In vivo neurochemical methods utilize electrodes implanted directly in the brain to measure the oxidation potentials, and hence amounts, of specific reactive chemical species. Two related, but different, techniques are currently in use, voltammetry and chronoamperometry, and are most often employed to measure monoamines and their metabolites in the striatum.

The advantage of the *microdialysis method* is that the HPLC step enables precise identification of the compound being measured (Di Chiara 1990). The time resolution of the technique depends on the sensitivity of the detection procedure, and until recently this has been about 10–15 min, which effectively precludes tight correlations between the self-administration of a single infusion of drug and its neurochemical consequences. However, the use of microbore column technology (Church and Justice 1989) or laser fluorescence and capillary electrophoresis (Hernandez et al. 1993), has enabled much faster sampling, as low as 1 min and less. However, the active removal of transmitter by dialysis may skew the estimate of the time course of elevated dopamine during a bout of drug self-administration. Further, the absence of amino acids, peptides and other putative neuromodulators in the dialysate may modify the extracellular milieu, thereby influencing the levels of monoamine neurotransmitters. Finally, the dimensions of the dialysis probes commonly used and the drainage that occurs during active dialysis indicate that a relatively large area of tissue is contributing to the neurochemical signal, unless very slow flow rates are used. Although slow flow rates minimize drainage, they tend to affect time resolution due to the limitations of HPLC and electrochemical analysis.

On the other hand, in vivo *voltammetry* and *chronoamperometry* monitor changes in brain monoamine concentrations with high time resolution. Chronoamperometry has evoked the most debate as a novel method and involves applying a repeated voltage pulse at intervals of 1 min or less which increases the probability of observing rapid changes in dopamine concentration following drug delivery or exposure to stimuli predictive of the drug (see Sect. 2.1 on conditioned reinforcers). Time resolution is limited by the availability of working electrodes that retain selectivity for the monoamine being measured during chronic implantation. Generally, the techniques are used at present to monitor only dopamine in the striatum. The use of reverse dialysis to deliver electroactive species such as dopamine, DOPAC, noradrenaline or 5-HT enables the selectivity of electrochemical probes implanted in the same vicinity to be validated in vivo. These procedures have been employed with stearate-modified carbon paste electrodes, which have been used to monitor changes in extracellular concentrations of dopamine during cocaine and *d*-amphetamine self-administration. Chronoamperometry can be used chronically over many days, permitting the use of more powerful within-subject designs (Phillips et al. 1991).

There are three controversial issues concerning chronoamperometry: (1) Can basal neurotransmitter levels be measured using this technique and, if so, how accurately? This question relates directly to the different estimates in basal dopamine levels obtained by microdialysis and by electrochemistry. Neither technique can measure dopamine levels in the synaptic cleft and therefore they provide only estimates of overflow into the extracellular compartment. It has recently been shown that the extracellular concentration of dopamine resulting from a single pulse of medial forebrain stimulation is 0.25 mM. The concentration of dopamine within the synaptic cleft is estimated to be of the order of 1.6 mM and, depending on the temporal and spatial domain of a measurement, extracellular dopamine concentrations in the nucleus accumbens can vary over 6 orders of magnitude. Microdialysis studies estimate extracellular concentration of dopamine to be in the low (i.e. 5–30) nM range. The latest estimates using in vivo calibration with the stearate-modified carbon paste electrode are in the 60–80 nM range (limit of detection is about 20 nM). (2) Can chronoamperometry assess decreases in neurotransmitter levels below baseline? It is now clear the answer is yes, using either stearate-coated or naphion-coated electrodes. With the stearate electrode, the signal is reduced significantly by tetrodotoxin or by dialysis adjacent to the electrode. (3) How large must changes in neurotransmitter levels be for them to be detected chronoamperometrically? The change in dopamine produced by a single intravenous infusion of 1.0 mg cocaine, but not 0.25 mg cocaine, in rats has been detected. Given that decreases below baseline can be detected, it seems reasonable to conclude that small changes in neurotransmitter levels can be detected reliably. Still, a potential drawback of this technique is that the endogenous substance is not separated from other electroactive substances or from substances that, although not electroactive, can either increase or decrease, eventually in a time-related fashion, the sensitivity of the electrode to the molecular species being monitored.

In vivo *electrophysiological recordings* from awake behaving animals are rapidly providing important insights into the relationships between neuronal activity and behaviour (Chang et al. 1994; Wolf et al. 1994). By recording the activity of single neurons in different nuclei of the mesocorticolimbic dopamine system during behavioural tasks, including self-administration, researchers are providing precise correlations between both conditioned and reinforcing stimuli, behavioural activity, and responsiveness of neuronal sub-populations. Such findings will complement those of in vivo recordings from identified neurons of anaesthetized animals, as well as in vitro current, voltage and patch clamp recording analyses of drug effects on membrane voltage and identified conductances.

tions on dopamine neurons, especially those comprising the mesolimbic dopamine system. Cocaine binds to the dopamine, noradrenaline and serotonin transporters, which are members of the 12-transmembrane domain neurotransmitter-transporter gene family (Kuhar 1992). However, cocaine binding to the dopamine transporter, which blocks the re-uptake of dopamine into dopaminergic nerve terminals, especially in the nucleus accumbens, is generally believed to be the most important action mediating its positive reinforcing and psychomotor stimulant effects (Negus et al. 1993; Di Chiara 1995). Amphetamine, on the other hand, primarily enhances monoamine release, but again it was generally agreed that enhancing the release of dopamine in the nucleus accumbens is of major importance in mediating its reinforcing and psychomotor stimulant effects (Di Chiara and Imperato 1988).

The primary molecular site of action of *nicotine* is at the nicotinic acetylcholine receptor, a heteropentameric

Box 3C Quantitative neuroanatomy

Quantitative or semi-quantitative methods can now readily provide neuroanatomically precise information on changes in various neurotransmitters, neuropeptides, receptors, transporters and other drug targets or mediators of drug action, as well as information on their transcription at the gene level, by monitoring mRNAs. *Quantitative in situ hybridization* allows determination of the expression of various genes implicated in the actions of drugs of abuse both regionally and at a cellular level of resolution. At the sub-cellular level, localization is complicated by the expression of mRNAs in the cell body, which may be distant from the sites of drug action at nerve terminals. For example, cocaine acts at dopamine transporters in the ventral striatum, the mRNAs of which are transcribed in the midbrain ventral tegmental area. Several studies have reported alterations in the expression of neuropeptide mRNAs, the dopamine transporter mRNA and also mRNAs for immediate-early genes (e.g. c-*fos* and c-*jun*) in striatal neurons or in dopamine neurons of the ventral tegmental area. *Immunocytochemical procedures* allow visualization and precise subcellular localization of the protein products of such genes, and of metabolic enzymes involved in neurotransmitter synthesis and degradation, for example. *Quantitative receptor autoradiography* has been used for studying the impact of drugs of abuse for many years.

One particular advantage of these procedures, despite their labour-intensive nature, is that they enable investigation not only of the primary targets of drugs of abuse, but also possible adaptations in the responses of these targets to repeated exposure to the drug. Moreover, in neuroanatomically heterogeneous and complex structures, such as the striatum, the possibility of compartmentally specific effects of self-administered drugs can be investigated. Thus, differential effects of amphetamine and cocaine on the patch and matrix compartments of the striatum have been reported that may be important for understanding their different behavioural effects. Such neuroanatomically precise information cannot be obtained using other contemporary neurobiological techniques. Finally, responses to drugs may be studied at a systems level using, for example, the transynaptic induction of immediate-early genes. This technique has been successfully employed to map the consequences of drug action at discrete, but interconnected, sites in the forebrain. However, the difficulties in quantifying such changes should not be minimized, even with the advent of fully or semi-automated quantitative image analysis.

Box 3D Molecular neurobiology

Gene cloning has contributed enormously to our understanding of the molecular targets of addictive drugs. Identification of a cDNA sequence provides new insights into mechanisms of action and regulation of the target molecule and commonalities with other proteins. Gene cloning has revealed remarkable heterogeneity of proteins on the one hand (e.g. numerous versions of nicotinic and GABA-A receptor subunits and adenylyl cyclase isoforms, having different patterns of expression in the brain) and, on the other hand, the occurrence of 'superfamilies' that share a common protein structure (e.g. nicotinic and GABA-A receptors are ligand-gated ion channels, each composed of five subunits having the same topology) (see Schofield et al. 1990). In addition to differences at the gene level, heterogeneity of gene products may also be introduced by alternative splicing and mRNA editing, e.g. a splice variant of the GABA-A receptor g2 subunit is implicated in sensitivity to ethanol (Wafford et al. 1991). Identification and cloning of a particular gene or its expression then allows manipulation of the gene or its expression, using transgenic, knockout or antisense technologies.

Thus, *knockout* mice that do not express dopamine D1 or dopamine D2 receptors are currently being studied in psychomotor stimulant self-administration, locomotor stimulation and electrophysiological experiments and have already yielded interesting and challenging results (Xu et al. 1994a, b). This new approach will be of great importance in understanding the importance of these and other transmitter receptors in the acute effects of psychomotor stimulants and other drugs of abuse, especially opiates, and it will not be long before *transgenic* mice that over-express specific receptors, transporters etc., or with a wide variety of gene knockouts, will be available for studies of this type. It should be borne in mind, however, that in both knockout and transgenic animals, the induced changes are not restricted to particular brain regions, or even to the brain alone, and they are present throughout development, as well as in adulthood when functional studies are made. This presents several problems of interpretation. Inducible gene knockouts in adult animals may prove to be an important further development of this technology, since such genetic manipulations may be focused on specific neural regions in adult animals.

Although still in its formative stage, *antisense technology* shows much promise in providing the ability to limit or halt gene expression selectively within discrete brain regions (see Wahlestedt 1994). Short stretches of oligonucleotides, complementary to the target mRNA, are introduced into cells where they bind to endogenous mRNA and thereby prevent its translation into protein. An advantage of this technique is that changes can be produced in a normal adult animal (in contrast to the transgenic approach, where the change is introduced into the embryo and compensatory mechanisms may occur during development). Changes are transient and can readily be reversed upon cessation of antisense administration. On the other hand, the technique is less amenable to long-term suppression of translation, which might be advantageous for analysing long-term phenomena like tolerance or sensitization. Antisense oligonucleotides can be administered intra-cerebroventricularly or to discrete brain nuclei, so targeting specific neuronal populations. This offers a major advantage over the transgenic approach, where a gene is usually knocked out or enhanced in all cells that express it, and limiting expression of the transgene to the CNS is often difficult.However, it is apparent that in many studies to date, infusing antisense oligonucleotides often has generally toxic consequences which may be associated with gross neural damage. These difficulties have yet to be overcome by novel approaches to the design of the probes. Moreover, the precise molecular mechanisms by which antisense oligonucleotides reduce expression of the target gene require further elucidation.

ligand-gated ion channel that is usually opened by acetylcholine. Clearly, as a psychomotor stimulant, nicotine shares some of the behavioural properties of cocaine and amphetamine, and it seems generally agreed that these stimulant effects of nicotine are also mediated in large part by increasing dopamine release from the terminals of the ascending mesolimbic dopamine pathways (Di Chiara and Imperato 1988). Consistent with this view are the following observations: (1) Nicotinic receptors are located on dopaminergic cell bodies in the VTA and substantia nigra, and on dopaminergic terminals in the nucleus accumbens and elsewhere in the striatum. (2) Nicotine increases the firing of nigrostriatal neurons and increases the release of dopamine in the nucleus accumbens and dorsal striatum, effects which have been demonstrated by both in vivo microdialysis and in vitro studies (see Box 3B). Studies using in vivo microdialysis indicate that dopaminergic terminals in the nucleus accum-

bens are more sensitive to nicotine than those in the dorsal striatum in terms of increasing dopamine release in these areas. (3) Lesions of the mesolimbic dopamine pathway decrease the self-administration of nicotine in rats. However, there are conflicting reports concerning effects of chronic nicotine treatment on dopamine release; different studies using in vivo microdialysis have reported increased release, no change or even a decrease (see Stolerman and Jarvis 1995 for review).

Ethanol differs from many other drugs of abuse in that it appears to have multiple specific primary targets that include, for example, ligand-gated ion channels and one type of adenosine transporter (Nagy et al. 1990). Delegates considered that the great diversity in the effects of ethanol may be due to actions mediated by specific sites on different target proteins that bind ethanol, or to its interaction with microdomains of lipids in the membrane, which alters the activity of specific proteins that interact with these domains.

At low concentrations of acutely administered ethanol, effects have been reported on receptor-mediated cAMP production, adenosine transport, dopamine release and on a variety of ligand-gated ion channels, including those associated with GABA/benzodiazepine, NMDA, 5-HT3 and opiate receptors (Tabakoff and Hoffman 1992). Different forms of neuroadaptations have been shown to occur at many of these sites and also at others not obviously involved in the acute actions of ethanol. After chronic ethanol exposure, changes in adenosine transporter sensitivity, decreased cAMP production, increased voltage-dependent calcium channel activity, changes in GABA receptor-mediated function, increased NMDA receptor-mediated activity and increased expression of signal-transducing G-proteins, protein kinase C, opiate receptors and pre-pro-enkephalin mRNA have all been reported (Tabakoff and Hoffman 1992). The many specific effects of ethanol on neuronal membranes may indicate that it produces its reinforcing effects by altering the activity of multiple neurotransmitter systems at diverse neuroanatomical sites (see below).

Benzodiazepines act through high-affinity binding sites on the benzodiazepine/GABA receptor ionophore to increase the effect of GABA on chloride conductance. Their effects at this site are blocked by antagonists such as flumazenil. Other sites, such as those on calcium-dependent potassium channels, have also been described but their importance is uncertain (Carlen et al. 1993). It has been shown using, for example, intravenous self-administration (Szostak et al. 1987) and conditioned place preference procedures (Spyraki and Fibiger 1988), that benzodiazepines have positive reinforcing effects but the neural loci important for mediating these effects are much less clear than for opiates or psychomotor stimulants. A possible role for dopamine in mediating the reinforcing effects of benzodiazepines is indicated by the observation that the acquisition of a conditioned place preference (see Box 2D) is impaired by pre-treatment with haloperidol or following 6-hydroxydopamine-induced lesions of the dopaminergic innervation of the nucleus accumbens (Spyraki and Fibiger 1988). Furthermore, increased firing of dopaminergic neurons in the ventral tegmental area has been reported to follow the acute administration of benzodiazepines. However, the acute administration of benzodiazepines is associated with decreases in extracellular dopamine levels in the nucleus accumbens, as measured by in vivo microdialysis (Finlay et al. 1992).

3.3 Potential common molecular mechanisms mediating neuroadaptations to drugs of abuse

Despite their different primary sites of action, there may be some common molecular mechanisms mediating the effects of the different classes of abused drugs. It was agreed at the meeting that, generally, the primary molecular sites of action are not regulated in a major way with acute or chronic drug use. For example, in animal studies the expression of the dopamine transporter or the μ opiate receptor mRNAs both appear to be relatively unchanged following exposure to cocaine or heroin, respectively. However, nicotinic receptor sites are upregulated in response to chronic nicotine treatment (Sanderson et al. 1993). Daily injection or continuous infusion of nicotine in rats results in an increase of about 40% in the number of receptors, appearing after about 3 days and reaching a maximum at around 7 days. The brains of human smokers examined post mortem also show an increase in nicotinic receptors when compared with non-smokers. This paradoxical upregulation (agonists generally *down*regulate their receptors) is considered to be a consequence of receptor desensitization and arises from a decrease in the rate of receptor degradation, rather than an increase in gene transcription. The limited data available suggest that receptor upregulation is paralleled by a corresponding *decrease* in receptor function (Sanderson et al. 1993).

One reason why the primary molecular targets of some drugs are apparently not modified may be related to differences in their transduction mechanisms, and it is at the latter level that neural adaptations may preferentially occur, sometimes over remarkably variable time courses ranging from milliseconds to minutes or hours, days, months and perhaps years (Nestler 1992; Nestler et al. 1993). The special importance of these changes in transduction mechanisms is that they place emphasis on receptor function and not receptor number. More specifically, abused drugs interact acutely with specific proteins

Fig. 2 PET scans showing the rates of cerebral glucose utilization in human volunteers with histories of polydrug abuse. Rates of glucose metabolism, determined using the [^{18}F]-deoxyglucose method, are indicated on the colour bars (highest, red and orange). The scans show sections through the hemispheres parallel to a plane joining the bottom of the orbit and the external auditory meatus. Rostral is at the top of each picture. The scans *above* were taken after administration of placebo, those *below* from the same subjects under the influence of active drug (40 mg cocaine i.v. or 30 mg morphine i.m.). Both cocaine and morphine reduced cerebral glucose metabolism, as clearly seen in the section shown here. (Courtesy of E.D. London, National Institute on Drug Abuse, USA)

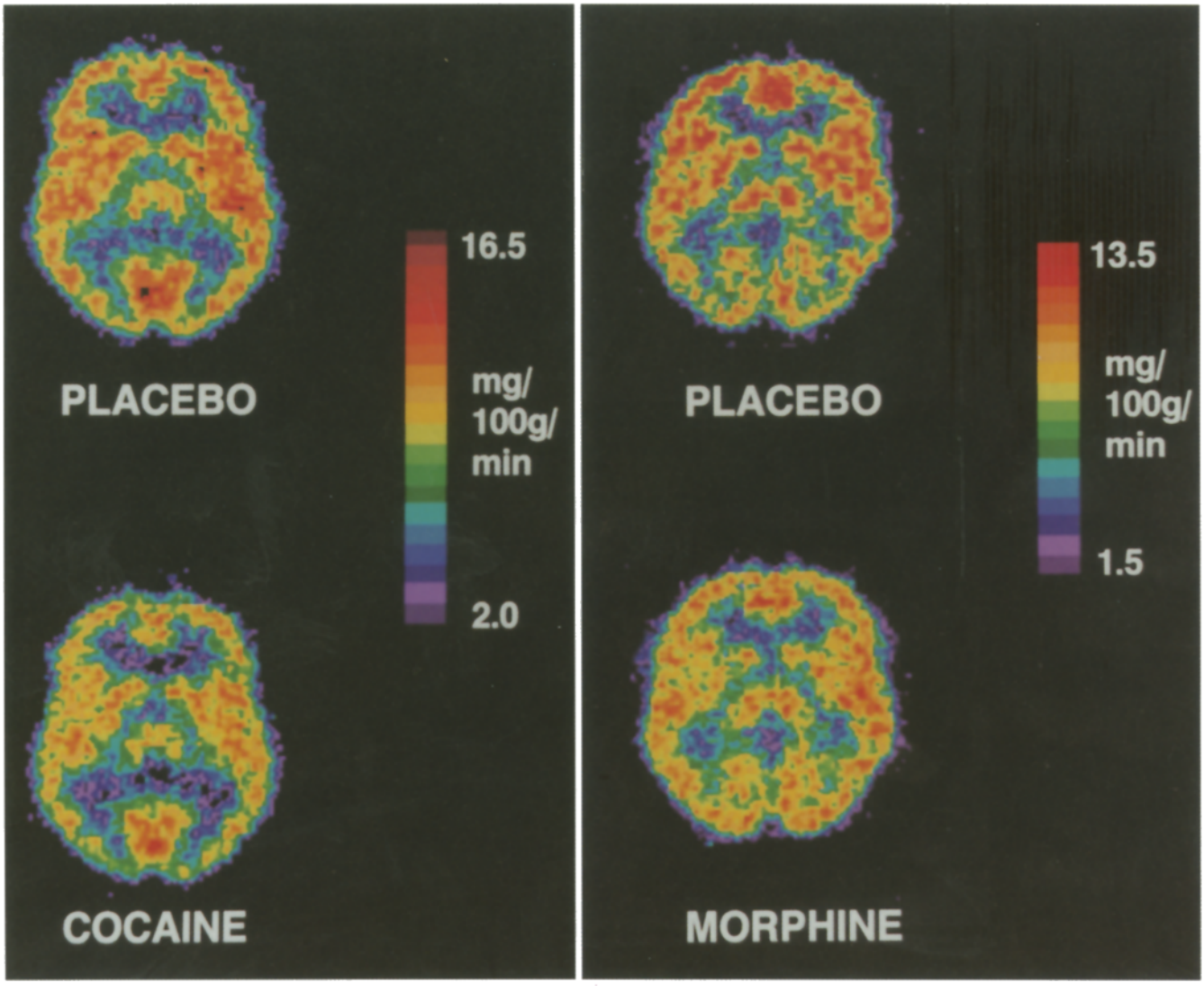
Box 3E Functional brain imaging

A variety of cerebral functional imaging techniques can be applied to questions related to drug abuse. They include electrophysiological approaches as well as assessments of brain chemistry. Mapping of electrical activity in the brain and measurements of event-related potentials allow exquisite time resolution, but localization of the source of activity within discrete neural structures is limited and subcortical sites that contribute to the cortical signals are not identified. Based upon the paramagnetic properties of haemoglobin, *functional magnetic resonance imaging* can yield maps of cerebral blood flow (CBF) in control and activated states, a methodology under active development in many laboratories.

The best developed techniques for functional imaging involve *positron emission tomography* (PET), a nuclear medicine approach that has been used to measure regional CBF (rCBF) and glucose metabolism. Assays of glucose metabolism have limited time resolution (uptake of the radiotracer, [^{18}F] deoxyglucose, generally proceeds for 30–45 min before the measurement of radioactivity in the brain). PET assays of rCBF, which afford greater time resolution, do not distinguish between the effects of drugs on brain function (neuronal activity) and effects on the cerebral vasculature. None of these functional assays are neurotransmitter specific.

PET can also be used to assay neurotransmitter function using radioactive (positron-emitting) tracers that can be displaced by endogenous neurotransmitters. Similar assessments can be made with *single photon emission computed tomography* (SPECT), although the radioisotopes of iodine and ^{99m}Tc, which are used to label tracers for SPECT, do not provide the radiochemical flexibility afforded by the ^{11}C and ^{18}F radiochemistry used in PET.

The acute effects of drugs of abuse on brain function have been studied using PET with [^{18}F] deoxyglucose as tracer. In polydrug abusers, acute, euphorigenic doses of morphine and cocaine globally reduced cerebral glucose metabolism (see Fig. 2). When corrected for the effects of drugs on respiration, statistically significant effects of morphine were limited to telencephalic areas. The reduction of cerebral glucose metabolism, especially in cortical areas, has generally been observed when drugs such as morphine, cocaine, alcohol, a barbiturate, benzodiazepines and amphetamine, but not delta-9-THC, were given to human subjects (London et al. 1990; London 1993). Despite the global nature of these metabolic effects, correlations with subjective effects of morphine and cocaine are restricted to a few brain regions, primarily in the temporal lobe, e.g. the amygdala.



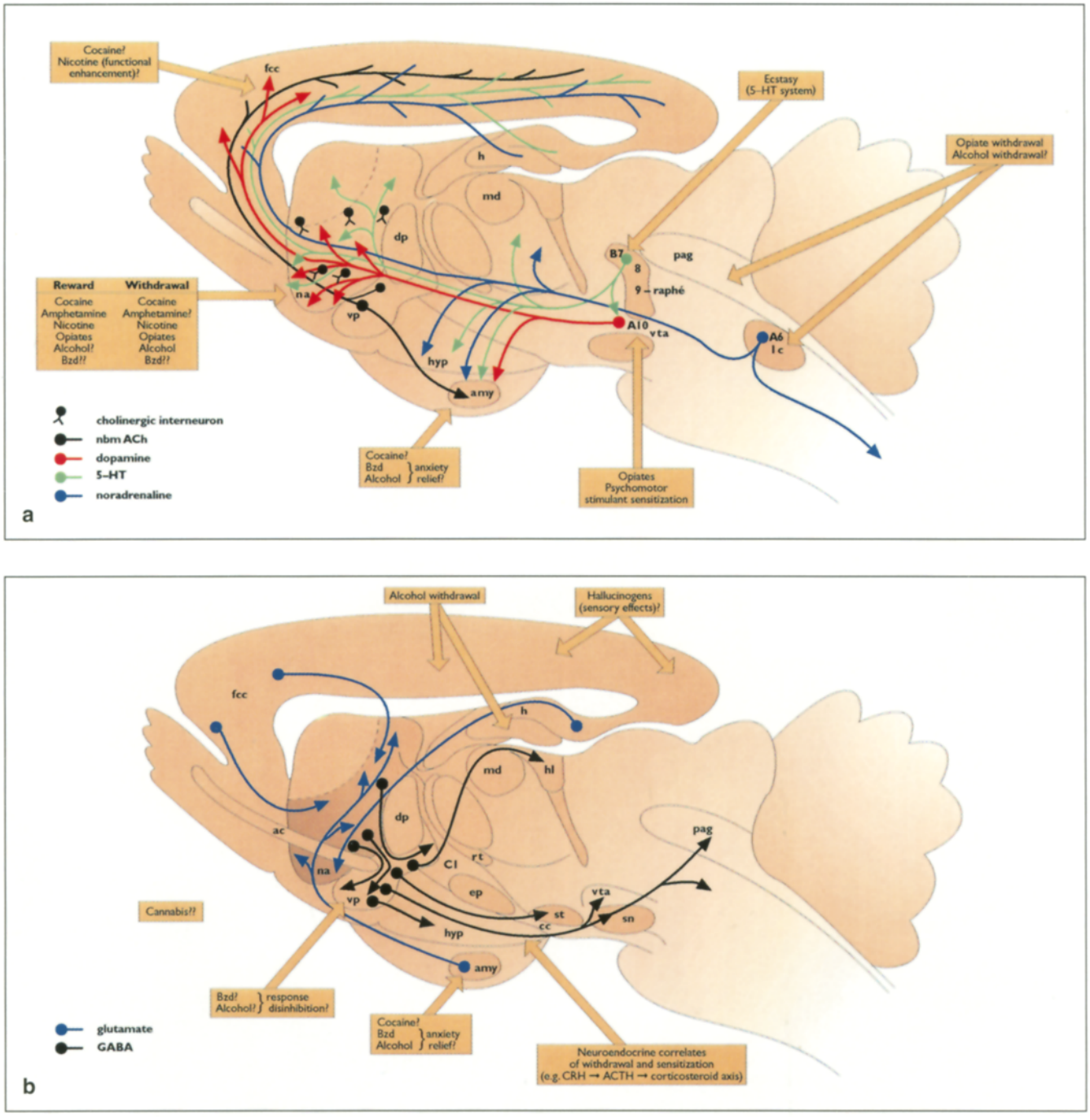


Fig. 3a, b Schematic diagrams of sagittal sections of the rat brain to show: **a** projections of the diffuse, chemically defined neural systems of the reticular core and the possible sites of action of several classes of drugs of abuse; **b** the limbic cortical-ventral striato-pallidal system that is the target of several elements of the neurochemical systems illustrated in **a** and within which the nucleus accumbens forms a focal point for the actions of many drugs of abuse. In both diagrams, *boxes* list drugs and some of their putative actions in the context of the neural site(s) where those actions have been shown, or are suspected, to occur. After a drug or process indicates conflicting data around this issue; ?? indicates little or no information, but considerable speculation concerning the particular drug/site/process. Further discussion of these issues is to be found in the text. Abbreviations: *fcc* frontal/prefrontal cortex, *na* nucleus accumbens, *vp* ventral pallidum, *dp* dorsal pallidum, *hyp* hypothalamus, *amy* amygdala, *md* medial dorsal thalamus, *h* hippocampus, *B7, 8, 9* 5-HT-containing nuclei of the midbrain raphé, *A10* mesolimbic dopamine neuron cell bodies, *vta* ventral tegmental area, *pag* midbrain periaqueductal grey, *A6* noradrenergic neurons of the locus coeruleus (lc), *ac* anterior commissure, *CI* internal capsule, *rt* reticular thalamus, *ep* entopeduncular nucleus, *cc* cerebral peduncle, *st* subthalamic nucleus, *hl* habenula, *sn* substantia nigra (pars reticulata)

(drug targets) that include ligand-gated ion channels, (e.g., nicotine, phencyclidine (PCP), and probably ethanol), G-protein-linked receptors (e.g. opiates, delta-9-THC) and neurotransmitter transporters (cocaine, amphetamine and probably ethanol). Drug occupancy of these proteins can yield very rapid alterations in such processes as ion channel conductance. For example, opiate agonists acting at μ opiate receptors desensitize the metabotropic receptor by uncoupling the G protein; the downstream effectors (G protein adenylyl cyclase) become upregulated. Changes in intracellular second messenger cascades may, over rapid time courses, also alter receptor and transporter phosphorylation states. Changes in second-messenger concentrations, alterations in cytosolic Ca^{2+} content via ligand-gated ion channels and release from cellular stores can each alter the expression of transcription factors, which in turn change expression of downstream genes encoding structural and functional neuronal proteins (see Nestler et al. 1993).

These biochemical alterations can be accompanied by differences in the compartmentalization of proteins through altered turnover, intracellular sequestration and other means. Thus, candidate biochemical mechanisms to explain acute tolerance include rapidly acting adaptive processes such as altered ion-channel receptor and transporter phosphorylation and/or internalization. Adaptive processes in long-term tolerance could include alterations in the expression of G-proteins, influencing the effects of drug occupancy at G-protein-linked receptors, and alterations in active protein half-life. Longer-term behavioural processes could be accompanied by the changed expression of genes such as those encoding structural proteins, with consequent alterations in features such as dendritic spine density. Changes in the expression of functional genes represent a plausible candidate mechanism that may mediate the 'memory-like' (i.e. long-term) consequences of chronic drug taking (see below).

While there is general agreement about the occurrence of these molecular and cellular events, important questions remain as to how these mechanisms bring about the specific effects observed after chronic drug self-administration. Future research should focus on identifying which of these candidate molecular mechanisms are relevant to the process(es) of drug dependence in both animals and humans. To address this question, it will no doubt be critical to study these molecular processes in vivo, for example, using gene knockout and transgenic strategies, differential display or other methods based on subtractive hybridization, as well as molecular interventions exploiting the effects of specific antisense oligonucleotides to prevent the expression of candidate genes (see Box 3D). Such approaches will allow connections to be made between the different levels of analysis, but it is important that these studies are made under conditions where the drugs are self-administered, rather than being given non-contingently (see Sect. 2).

3.4 Neural systems and sites of action of drugs of abuse

Whereas the molecular and cellular approaches emphasize differences in the primary sites of action of drugs of abuse, the neural systems approach has tended to explore the possible commonalities of the actions of such drugs (Koob and Goeders 1989). Stated simply, it may be that the self-administration of many different classes of drugs of abuse is the result of convergence of their actions onto a neural system that underlies reinforcement or incentive motivational processes. What might such a neural system be?

The major focus of experimental investigation has been the mesolimbic dopamine system that originates in the VTA dopaminergic neurons and projects richly to the ventral striatum, which includes the nucleus accumbens, and to other limbic sites such as the amygdala and septal nuclei (see Fig. 3). A mesocortical dopamine system that also originates in the VTA and projects mainly to the prefrontal and cingulate cortices is sometimes viewed as a separate system but is often grouped with that innervating the ventral striatum and collectively called the mesocorticolimbic dopamine system.

It has long been accepted that the psychomotor stimulants increase dopamine transmission and that such drug-induced changes in the activity of the mesolimbic dopamine system are of special importance in the initiation and maintenance of amphetamine and cocaine self-administration. A contemporary debate, however, concerns the degree to which all drugs of abuse increase dopamine transmission in the nucleus accumbens region. In this context, in vivo neurochemical methods have had a major impact in recent years, since they have enabled changes in extracellular dopamine to be measured in animals self-administering or receiving a variety of drugs of abuse (see Box 3B). Generally, delegates agreed that the action of many such drugs is correlated with increased extracellular dopamine in the nucleus accumbens in the following rank order of effectiveness: stimulants > nicotine>opiates>ethanol>caffeine>benzodiazepines/barbiturates (Di Chiara and Imperato 1988; Pettit and Justice 1989; Di Chiara 1995; Wise 1993). There was a lack of consensus as to whether benzodiazepines and barbiturates do indeed alter dopamine levels in the nucleus accumbens (or elsewhere in the striatum), as there have been reports showing no effect. Drugs such as delta-9-THC, PCP and hallucinogens, such as LSD, were generally viewed as not having primary or major effects on dopamine levels in the striatum.

A number of critical issues arose from this discussion. First, it remains unclear to what degree the ability to increase dopamine levels in the nucleus accumbens is a critical determinant of the self-administration of a drug or is merely a correlate of its action. The ability of many drugs to increase dopamine in the ventral striatum can be related to the increase in dopamine seen in animals in the presence of food, sexual partners, aggressive opponents, ICSS and stimuli predictive of their occurrence (Phillips et al. 1989, 1991; Tidey and Miczek 1994). However, it was pointed out that opiates, nicotine and caffeine may

not release dopamine in the nucleus accumbens to the same extent as amphetamine or cocaine, but may do so in a more physiological pattern. Thus, effectiveness in the context of alterations in dopamine transmission cannot be judged according to the quantity of induced dopamine release alone.

Second, psychopharmacological data challenge the view that changes in ventral striatal dopamine are necessary and sufficient for the self-administration of all drugs. For example, systemic or intra-accumbens blockade of μ opiate receptors has been shown to impair heroin self-administration, whereas treatment with dopamine receptor antagonists or dopamine depletion from the nucleus accumbens did not (Pettit et al. 1984). These findings suggest a dopamine-independent component of the reinforcing effects of self-administered opiates. Similar findings were reported for ethanol, where there is experimental evidence for dopamine-dependent and -independent self-administration in animals (Koob 1992). Dopamine antagonist treatments or dopamine lesions do, however, block cocaine, amphetamine and nicotine self-administration, which has been taken as strong evidence in support of a key role for the mesolimbic dopamine system in stimulant self-administration. However, there are several clinical reports that treatment with haloperidol, a dopamine receptor antagonist, fails to alter stimulant self-administration. For example, schizophrenics on neuroleptics continue to use cocaine and to smoke cigarettes; haloperidol has no effect on cigarette smoking; and similarly the D2 dopamine receptor agonist, bromocriptine, has no effect on ethanol intake in humans (see LeDuc and Mittleman 1995).

Third, it was uniformly agreed that the almost exclusive focus on dopamine, which in part results from the relative ease with which it can be manipulated and measured in the ventral striatum, may have diverted attention away from other important neurochemical mechanisms. Even in the case of cocaine and amphetamine, it is clear that their primary effects on noradrenaline and serotonin transmission are poorly understood in terms of abuse liability. These neurochemical systems have not been studied extensively, although lesions of forebrain 5-hydroxytryptamine (5-HT) neurons have been reported to facilitate cocaine self-administration (Roberts et al. 1994); possibly, elevated 5-HIAA levels in the nucleus accumbens and elsewhere following amphetamine and cocaine could modulate and even limit the reinforcing actions of these drugs. Moreover, low 5-HT in the cerebrospinal fluid in humans is associated with impulsivity and risk-taking behaviour (see Sect. 4.1), suggesting that 5-HT could be involved in the propensity for drug abuse.

Fourth, it has become increasingly apparent recently that a variety of aversive stimuli, or stressors, are also associated with increased dopamine release in the nucleus accumbens. Thus social stressors, such as post-weaning isolation; acute stressors, such as electric foot shock; and conditioned stimuli predictive of aversive events all increase extracellular dopamine in the nucleus accumbens. Such data emphasize that it is too simplistic to equate changes in mesolimbic dopamine release with positive reinforcement alone; this system may be more generally involved in the responses to both appetitive and aversive unconditioned and conditioned stimuli and in the processes by which the conditioned stimuli gain motivational salience and thereby control over behaviour (Robbins et al. 1989; Everitt and Robbins 1992).

Fifth, a key issue to explore and understand is the degree to which conditioned stimuli, i.e. stimuli associated with the effects of a drug or of its absence, can induce changes in the activity of dopamine neurons or alter dopamine release. Several studies have demonstrated that stimuli paired with ingestive, sexual or drug rewards increase the firing of populations of VTA dopamine neurons or increase extracellular dopamine concentrations in the nucleus accumbens (Phillips et al. 1991; Schultz 1992). Aversive CSs (i.e. stimuli paired with foot shock) have a similar effect (see Robbins and Everitt 1992). The impact of such conditioned changes in mesolimbic dopamine activity are not well understood; indeed, there is no uniform agreement that they occur. But these conditioned neurochemical responses may prove to be extremely important in the drug-seeking or 'craving' that can be elicited by a variety of conditioned environmental cues in cocaine, opiate and alcohol addicts (Childress et al. 1992; see Robinson and Berridge 1993 for review).

Lastly, it is no longer adequate to consider the mesolimbic dopamine system in isolation when exploring the neural basis of addictive drug action. There are clearly important afferent systems that regulate the firing frequency and pattern of VTA dopamine neurons. Moreover, these dopamine neurons are likely to exhibit plasticity in response to such afferents. Indeed, whereas dopamine neurons are initially excited by positive reinforcers, they habituate to such stimuli while simultaneously developing sensitivity to other previously neutral stimuli that are paired in a predictive manner with the reinforcer (Schultz 1992). Experimental investigations should therefore be focused on the nature of the interactions between dopamine neurons, other afferents to the ventral striatum and the intrinsic neurons of the ventral striatum that receive these afferents and form the origin of ventral striatal efferents. To understand the functions of dopamine in the ventral striatum in the context of a particular behaviour, it is necessary to elucidate the 'neural context' in which dopaminergic activity is expressed. A significant contribution in this context is the pattern of glutamatergic transmission in the limbic cortical innervation of the nucleus accumbens, which in large part converges on the same striatal neurons as the dopaminergic afferents (see Everitt and Robbins 1992; Robbins and Everitt 1992; Burns et al. 1993).

3.5 The ventral striatopallidal system

It is now well established in the rat that there are rich connections between 'limbic' forebrain structures and the ventral striatum (illustrated in Fig. 3). Briefly, the basolateral amygdala, the hippocampal formation (espe-

cially the ventral subiculum) and specific regions of the medial pre-frontal cortex all project richly onto the nucleus accumbens and ventromedial caudate-putamen, collectively known as the ventral striatum. The ventral striatum projects in large part to the ventral pallidum, which in turn projects via the medial dorsal nucleus of the thalamus to the prefrontal cortex, so providing the key element of re-entrant cortico-striatal circuitry (see Groenewegen et al. 1990). In addition, the ventral pallidum projects directly to brainstem motor areas, especially to the subthalamic nucleus, substantia nigra pars reticulata and mesencephalic locomotor region (the region of the pedunculo-pontine nucleus), as well as to midbrain dopamine neurons and the cholinergic neurons of the nucleus basalis magnocellularis, which project diffusely to the neocortex. Thus, the limbic cortex, via its projections through the ventral striatum, has access to motor output domains of the brainstem, specific (via the thalamus) projections to the prefrontal cortex and access to a major diffuse cholinergic cortical arousal system.

Recent descriptions of anatomically, and perhaps functionally, distinct domains of the nucleus accumbens has indicated further complexity in this basic circuitry. The 'core' and 'shell' regions of the nucleus accumbens (Zahm and Brog 1992; Heimer et al. 1995) each receive distinctive patterns of cortical afferents and have distinctive projections to medial and lateral pallidal sites, impinging to some extent on structures regarded to be part of the extended amygdala (Alheid and Heimer 1988).

Mogenson was the first to draw attention to the possible functional importance of this so-called limbic-motor interface and his laboratory provided experimental evidence showing interactions between limbic afferents and striatal or pallidal neuronal activity that could be modulated by dopamine. For example, electrical stimulation of the amygdala or hippocampus elicited alterations in the firing of ventral striatal and ventral pallidal neurons that were subject to modulation by direct manipulations of dopamine within the nucleus accumbens. Locomotor activity, the main dependent variable in Mogenson's behavioural experiments, elicited either by excitatory amino acid infusions into temporal lobe limbic structures or by exposure to a novel environment, was also modified by coincident manipulations of dopamine in the nucleus accumbens, or of GABA within the ventral pallidum or the mesencephalic locomotor region (see Mogenson and Yang 1991).

In the context of the effects of abused drugs, there is a growing body of data indicating interactions between drug effects on dopamine transmission in the nucleus accumbens and the activity of limbic cortical afferents (Cador et al. 1989; Robbins et al. 1989). It is clear that glutamatergic agonists and antagonists can affect dopamine release and also modify the effects of indirect (i.e. presynaptic) dopamine agonists. Moreover, lesions of some limbic sites, most notably the ventral subiculum, significantly attenuate the locomotor stimulant effects of intra-accumbens amphetamine, as well as the potentiation of the control over behaviour by a conditioned reinforcer (Burns et al. 1993).

Several recent studies have also shown that lesions of ventral pallidal and/or sublenticular extended amygdala sites in the basal forebrain greatly modify both cocaine and opiate self-administration or place preferences conditioned by exposure to opiates, psychomotor stimulants, food or sexual interaction (Everitt et al. 1991; McAlonan et al. 1993; Robledo and Koob 1993). Such studies are at an early stage but they may in time reveal the neural systems underlying discrete processes affected by self-administered drugs, e.g. locomotor stimulation versus reinforcement. The involvement of limbic structures such as the basal and lateral amygdala in mediating the formation of stimulus-reward associations and the impact of these associations on the reinforcing effects of psychomotor stimulants and opiates are also beginning to reveal the neural basis of conditioned influences on addiction (see Sect. 3.10).

Another important, but as yet relatively unexplored, aspect of the functions of the ventral striatopallidal system concerns the actions of drugs with relatively small, or even no, measurable effect on dopamine transmission in the nucleus accumbens. Such drugs might affect processing within the ventral striatopallidal system independent of changes in dopamine, by influencing downstream events via, for example, the medium spiny GABA neurons of the striatum, the GABA neurons of the pallidum or any of the other nodes in this circuitry. Such downstream effects may explain the dopamine-independent effects of opiates within the nucleus accumbens. Whether such considerations apply to ethanol or, perhaps most interestingly, to benzodiazepines is not clear at present.

3.6 Neurobiology of tolerance

At the meeting, it was discussed whether tolerance and dependence could be conceptualized within the framework of tolerance involving a progressive reduction in the effects of a drug. Alternatively, tolerance could represent a counter-adaptation to oppose the effects of a drug. The tolerance mechanisms which will be associated with dependence, if any, may be those that particularly involve counter-adaptations to oppose the strength of a constant drug stimulus, such as the counter-adaptations that are expressed as withdrawal signs in the absence of the drug (see Young and Goudie 1994).

Accordingly, it was suggested that tolerance and withdrawal, at least in some cases, may be distinct phenomena at the cellular level. For example, acute ethanol treatment increases cAMP levels in cultured neurons. If such neurons are exposed chronically to ethanol, they show a decrease in cAMP levels and subsequent acute exposure to ethanol fails to increase cAMP levels. However, if the ethanol is rapidly removed and the cells are acutely rechallenged with ethanol, cAMP levels return to those seen in control cells. Thus, these data suggest a form of cellular withdrawal: cAMP levels in chronically alcohol-exposed cells are decreased in the absence of ethanol, causing altered cellular responses, and they resemble

control cells only in the presence of ethanol. There seems to be no tolerance in this biochemical process since acute ethanol exposure causes the same increase in cAMP levels in control cells and in cells chronically exposed to ethanol. In contrast, tolerance to the effects of acute ethanol does develop if adenosine transport is measured. In control cells, ethanol inhibits adenosine uptake, but after chronic exposure to ethanol and its rapid removal, adenosine uptake is no longer inhibited by ethanol, i.e. transport has become tolerant to ethanol. Therefore, in a single cell type, one biochemical process (cAMP production) is changed by withdrawal of ethanol and another (adenosine transport) develops tolerance, indicating that distinct molecular mechanisms are responsible for tolerance and withdrawal in some cases.

Increases in the activity of dihydropyridine-sensitive calcium channels are also seen with chronic ethanol treatment, although there is little acute effect on these channels. Preventing this upregulation by concurrent chronic administration of dihydropyridines prevents the development of tolerance to ethanol and the expression of withdrawal signs. Consequently, chronic dihydropyridine treatment can reverse the behavioural effects of ethanol and also prevents the adaptations to chronic ethanol (Whittington et al. 1991).

Delegates generally agreed that the molecular and cellular basis of the tolerance to opiates is far from clear. For example, tolerance to morphine is not necessarily, or even usually, accompanied by μ or δ opiate receptor downregulation. Tolerance to cocaine has not reliably been associated with downregulation of specific dopamine receptors, although the availability of specific D3 and D4 dopamine receptor ligands, together with the D1 and D2 ligands already available, will facilitate further exploration of this issue. At a molecular level, chronic cocaine exposure reduces the ability of a subsequent acute exposure to the drug to induce the immediate-early gene c-*fos*, while at the same time being paradoxically associated with a marked induction of AP-1 DNA binding activity (AP-1 is the sequence of DNA to which FOS, the protein product of c-*fos*, and related proteins bind to alter downstream gene expression). It has been suggested these data indicate that acute and chronic cocaine may induce different types of FOS-like proteins, and, indeed, novel FOS-related antigens (FRAs) have been identified by blot immunolabelling studies. They may be intracellular adaptations to chronic cocaine associated with the development of tolerance to some of its effects (Nestler 1992).

Tolerance to nicotine could arise from the chronic desensitization of nicotinic receptors in the brain, manifested in their upregulation (see Sect. 3.3), and thus may represent an adaptive response, albeit inadequate or incomplete, that compensates for loss of function (see Wonnacott 1990; Marks et al. 1992; Peng et al. 1994). This phenomenon might explain why the first cigarette of the day is credited with having the maximum impact, because receptor desensitization is diminished by overnight clearance of the drug.

3.7 Neurobiology of withdrawal

As withdrawal from psychomotor stimulants, opiates, ethanol and nicotine results in withdrawal syndromes that are characteristic for each drug (see Sect. 3.2), a variety of cellular and molecular changes are likely to be associated with withdrawal from each of them. There was some discussion at the meeting concerning the conceptual framework within which to consider these changes. One conceptualization that gained some support was 'within- and between-systems' adaptations (Koob and Bloom 1988), which, although relative, may provide a framework for studying neuroadaptations at a particular level of analysis. For example, adaptations in the mesolimbic dopamine system and its associated receptors in the nucleus accumbens, or the 5-HT innervation of the nucleus accumbens by the midbrain raphé, may be viewed as 'within system' for psychomotor stimulant withdrawal, because the same system is implicated in the acute, reinforcing effects of these drugs. However, such adaptations within the ramifications of the ventral striatopallidal system might also be opposed by those occurring elsewhere in systems not directly implicated in the acute reinforcing effects of psychomotor stimulants – i.e. 'between systems' – for example in the noradrenergic neurons of the locus coeruleus or in the midbrain periaqueductal grey (Bozarth and Wise 1984; Koob and Bloom 1988; Koob et al. 1992).

Withdrawal from psychostimulants, morphine and ethanol in dependent rats has been reported by most laboratories to be associated with a reduction in basal extracellular concentrations of dopamine in the ventral striatum and in the caudate-putamen, as estimated by brain microdialysis (Acquas and Di Chiara 1992; Diana et al. 1993; see Di Chiara 1995 for review). Thus, withdrawal from various drugs of abuse is associated with a reduction in dopamine transmission in the ventral striatum, an effect that is opposite to the common property of drugs of abuse to stimulate dopamine transmission (Di Chiara and Imperato 1988). This reduction in dopamine transmission following cocaine and ethanol withdrawal is probably related to the dramatic reduction in the basal activity of VTA dopamine neurons seen under these circumstances. The transient decrease in dopamine transmission in the nucleus accumbens seen during abstinence or following 'binge' self-administration has been suggested to contribute to the negative affective state of dysphoria (or anhedonia) measured, for example, by increases in ICSS thresholds (Markou and Koob 1991). Withdrawal-induced anhedonia, in turn, has been proposed to contribute to cocaine self-administration through a negative reinforcement process (Koob 1992). However, it remains to be established whether withdrawal anhedonia, which is known to blunt the impact of non-drug and drug reinforcers, as well as ICSS, can result in increased responding for intravenous drug self-administration (see Di Chiara 1995 for discussion) In the case of the cocaine 'crash' (Gawin and Kleber 1986), withdrawal anhedonia is often associated with a reduction in craving (see Di Chiara 1995 and below, Sect. 3.9).

In addition to reductions in striatal dopamine concentrations, decreases in 5-HT levels and enhanced dopamine-5-HT interactions in the nucleus accumbens have been reported during cocaine withdrawal (Dworkin et al 1995b; Parsons et al. 1995). Marked changes in striatal 5-HT levels are also seen during ethanol withdrawal (Smith et al. 1994).

It has been accepted for some time that the physical signs of opiate withdrawal are mediated in part by neuroadaptations within the midbrain periaqueductal grey (e.g. Koob et al. 1992) and the noradrenergic neurons of the locus coeruleus; the latter is consistent with the use of clonidine to treat these withdrawal signs (Esposito et al. 1987; Rasmussen et al. 1990). Such data have often been cited as good examples of between-systems adaptations in withdrawal. Other data show that place aversions in opiate-dependent rats can be conditioned following injections of an opiate antagonist into the nucleus accumbens, in the absence of physical withdrawal signs (Koob et al. 1992). Taken together, these data indicate that a complex set of within- and between- systems adaptations occurs following opiate withdrawal that might underlie the motivational and somatic aspects of the full withdrawal syndrome (Koob et al. 1992).

However, a recent report (Harris and Aston-Jones 1994) indicated that adaptive changes in the nucleus accumbens dopamine system are of major importance in the withdrawal syndrome following withdrawal from opiates. Thus, administration of a dopamine D2 receptor agonist either systemically or directly into the shell of the nucleus accumbens in morphine-dependent rats greatly reduced the severity of somatic withdrawal signs following naloxone-precipitated withdrawal. These findings indicate that somatic withdrawal signs are dependent on adaptations in dopamine transmission in the nucleus accumbens, rather than solely on the well-known changes occurring in brainstem sites. Indeed, injection of dopamine D2 receptor antagonists directly within the shell of the nucleus accumbens could by itself elicit somatic withdrawal signs. These data place a markedly different emphasis on the genesis of neuroadaptations underlying opiate withdrawal from the view prevailing hitherto.

An exceptionally diverse pattern of changes is seen following ethanol withdrawal, perhaps consistent with its multiple potential sites of action within the CNS (see Sect. 3.2; Tabakoff and Hoffman 1992): (1) In the hippocampus, GABA-A receptor coupling to chloride channels decreases; NMDA receptor sensitivity increases; glutamate release increases; noradrenaline beta-receptor density increases; and noradrenaline release increases. (2) In the hypothalamus, a pattern of changes similar to those in the hippocampus is seen, together with an increase in corticotropin-releasing hormone (CRH) levels. (3) In the pituitary, both ACTH and β-endorphin levels increase, and there is also increased secretion of glucocorticoids from the adrenal cortex. (4) The adrenal medulla increases its secretion of both adrenaline and noradrenaline. (5) In the nucleus accumbens, alcohol withdrawal is associated with marked reductions in extracellular dopamine levels (Rosetti et al. 1992a, b). Repeated withdrawal from alcohol may also have neurotoxic consequences due to increased excitatory amino acid transmission; accordingly, hippocampal damage has been seen in rats following alcohol withdrawal.

There is some evidence for decreases in GABA-A transmission during ethanol withdrawal, but this effect may not be as important as previously thought. Some investigators have demonstrated a clear absence of such changes; e.g. no decreases were seen in GABA-A-mediated IPSPs in isolated hippocampal slices prepared after a chronic ethanol schedule in vivo, despite hyperexcitability in field potential recordings and behavioural changes (Whittington et al. 1992). Conversely, chronic ethanol administration has been shown to result in changes in the function of the GABA-A receptor Cl^- channel complex and the NMDA receptor channel complex that together might be expected to enhance the activity of the NMDA receptor-coupled channels and promote ethanol withdrawal seizures (see Tabakoff and Hoffman 1992). GABA-A receptor agonists can suppress ethanol withdrawal seizures, supporting the hypothesis that subsensitivity of the GABA-A receptor Cl^- channel complex in some areas of the CNS may occur as an adaptive response to chronic stimulation by ethanol, and thereby contributing to ethanol withdrawal seizures. In fact, a single injection of the GABA-A receptor antagonist, flumazenil, 14 h before withdrawal of mice from chronic ethanol ingestion reduced the severity of ethanol withdrawal seizures (Buck et al. 1991; see Tabakoff and Hoffman 1992).

More consistent reports have been obtained from receptor binding and electrophysiological studies, which have demonstrated increases in NMDA receptor-mediated responses and in the activity of the L-subtype of calcium channel during withdrawal from chronic ethanol administration. Increases were found both in NMDA receptor-mediated slow EPSPs and in the fast, AMPA/kainate receptor-mediated EPSPs (Little 1991).

Ethanol withdrawal hyperexcitability in rodents is blocked by dihydropyridine-sensitive calcium channel antagonists and by NMDA antagonists at doses which do not affect the behavioural actions of bicuculline, a GABA-A receptor antagonist (Whittington et al. 1991). Although benzodiazepines are used to decrease ethanol withdrawal signs, these compounds decrease the actions of many convulsant drugs, such as NMDA and strychnine, so their effectiveness does not necessarily provide evidence for underlying changes in GABA-A transmission. Recording convulsion thresholds to a range of convulsant drugs in separate groups of mice at 4-h intervals for 24 h after withdrawal from chronic ethanol treatment did not reveal decreases in the thresholds to bicuculline, even though there were increases in handling-induced behaviour, increases in convulsions in response to audiogenic stimuli and decreases in convulsion threshold to NMDA.

While there was general agreement about many of the molecular and cellular mechanisms of tolerance and

withdrawal, it was less clear whether they are of relevance to clinical observations or have application to behavioural tolerance (see Sects. 2.3 and 2.4).

3.8 Neurobiology of sensitization

In terms of neurobiological mechanisms underlying sensitization (see Sect. 2.5), there were several areas of general agreement (see also reviews by Sorg and Kalivas 1993; Robinson and Berridge 1993). (1) The neural sites of drug action necessary for the induction of long-term changes in the dopamine system are different from those important in the expression of dopamine sensitization. Thus, drugs such as amphetamine acting in the somatodendritic region of dopamine neurons, particularly in the VTA, are required for the induction of sensitization, whereas the actions of the drug in dopamine neuron terminal regions, in particular in the nucleus accumbens, are necessary and sufficient for the expression of the sensitized response to a subsequent drug challenge. (2) Sensitization occurs in neural systems thought to be important in mediating the incentive-motivational and positive reinforcing effects of drugs, namely in the mesolimbic dopamine neurons. (3) Different neuroadaptations may mediate sensitized behavioural outcomes at different times, or for different drugs. There appears to be a time-dependent 'cascade' of neuroadaptations, some of which may be transient (in the VTA) but necessary for the development of subsequent alterations, which come to control the expression of sensitized behaviour. (4) It is becoming clear that sensitization is similar to other forms of synaptic plasticity, for example certain forms of long-term potentiation (LTP). Like these other models of 'learning', sensitization and certain of its neuronal correlates are prevented by treatment with NMDA receptor antagonists, e.g. MK801 (Karler et al. 1989; Wolf et al. 1994). Such excitatory amino acid receptor-dependent sensitization processes seem primarily to involve interactions within the VTA, presumably on the dopamine neurons themselves. (5) Cross-sensitization between stressors and psychomotor stimulants may indicate interactions with the hypothalamo-pituitary-adrenal cortical axis; both glucocorticoids and CRH influence the development and/or expression of sensitization to amphetamine, using either an amphetamine or a stress sensitization protocol (Piazza et al. 1993).

Two major neural correlates of amphetamine sensitization are enhanced dopamine release in the nucleus accumbens following subsequent psychomotor stimulant challenge and the increased sensitivity of dopamine D1 receptor-mediated responses (Kalivas and Duffy 1993). It has also generally been assumed that the expression of opiate sensitization is related to an increased effect of opiates to stimulate dopamine release. For example, in vivo microdialysis experiments have demonstrated a sensitized nucleus accumbens dopamine response to morphine challenge both at 3 and 30 days after the sensitization pre-treatment (see Di Chiara 1995 for review). In addition, Nestler (1992) has reported adaptations in a variety of intracellular signal transduction mechanisms following opiate-induced sensitization which are also similar to those seen after sensitization to cocaine.

These changes in function of the mesolimbic dopamine system might not only contribute to drug-seeking behaviour, but might also facilitate the control over such behaviour by environmental stimuli associated with the reinforcing and other effects of the drug (see Sect. 2.1). In this way, drug-associated stimuli might become progressively more powerful in controlling drug seeking or craving. An important issue where the experimental data are not consistent is whether drug-associated conditioned stimuli, or conditioned reinforcers, themselves increase dopamine release and receptor-mediated responses in the nucleus accumbens and whether such effects also sensitize [as postulated in the incentive sensitization theory of addiction (Robinson and Berridge 1993)]. Particularly for in vivo voltammetric studies, clear increases in extracellular concentrations of dopamine in the nucleus accumbens have been measured following exposure to conditioned cues associated with drugs and ingestive and sexual rewards (DiCiano et al. 1995a; Phillips et al. 1991). However, for in vivo dialysis studies, such changes in extracellular dopamine have been very small or unmeasurable (Fibiger 1993). This remains an important area of study.

3.9 Neurobiology of craving

There has been little or no direct investigation of the neural basis of craving, largely because there is relatively little consensus concerning animal paradigms that provide operational measures of craving (see Markou et al. 1993 for review). Second-order schedules of drug reinforcement might be valid constructs as models of craving, especially because they distinguish between drug-seeking and drug-driven behaviour. In typical second-order schedules of drug self-administration (see Box 2B), animals respond for CSs previously paired with the i.v. infusion of cocaine or heroin for extended periods before administering the drug itself. Lesions of the basolateral amygdala impair the acquisition of responding for cocaine under such a schedule but do not impair responding for cocaine per se (Whitelaw et al. 1996). This finding may indicate that drug seeking, or craving, elicited by conditioned stimuli may be mediated by limbic structures, such as the amygdala, that may influence dopamine release in the nucleus accumbens (see Fig. 3).

Some delegates suggested that there might be so-called 'drug-specific profiles' of craving. For example, opiate anticipation is associated with both craving and opiate withdrawal signs; cocaine anticipation, by contrast, is associated with euphoria, perhaps as a result of conditioned dopamine release. The situation with alcohol and nicotine is less clear cut: in type 2 alcoholics (see Sect. 4.1) who are drug-free, treatment with the 5-HT-2 receptor agonist, mCPP, results in strong craving for alcohol that is indistinguishable from that induced by alco-

hol itself (M. Linnoila, communicated at the meeting). Preliminary PET studies (Box 3E) in which cocaine addicts focused on mental images associated with drug taking revealed increased rCBF in temporal lobe structures, including the region of the amygdala (O'Brien and Childress, communicated at the meeting). This kind of functional approach in humans shows great promise for revealing areas activated during episodes of drug-craving, in addition to those activated in response to the drug itself.

3.10 Neural basis of conditioning processes in addiction

Relatively few studies have investigated the neural basis of conditioning processes that lead to the association of drug effects with environmental stimuli. If such conditioning processes are critical in the processes underlying drug dependence, then studies of the neurobiological adaptations associated with drug dependence must be undertaken with animals receiving the drug in a self-administration paradigm rather than in non-contingent, experimenter-administered procedures. Indeed, studies from laboratories using different methodologies (behavioural or in vivo and ex vivo neurochemistry) and two stimulant drugs (amphetamine and cocaine) indicate that rats self-administering stimulants show greater dopamine efflux in the nucleus accumbens than yoked animals receiving the drug non-contingently (e.g. DiCiano et al. 1995b). These results indicate that stimulants have quantitatively different neurochemical effects when administered in these different ways. Moreover, it has been reported that non-contingent cocaine administration in rats is associated with significantly increased mortality compared with rats receiving the same treatment contingently (Dworkin et al. 1995).

One obvious neural focus for conditioning factors in addiction is the limbic cortical innervation of the ventral striatum (Fig. 3). The amygdala has long been implicated in the formation of stimulus-reward associations; interactions between the amygdala and the ventral striatum might form part of the neural systems underlying the control over instrumental behaviour by conditioned reinforcers (Everitt and Robbins 1992). Lesions of the basolateral amygdala impair the acquisition of a new response with conditioned reinforcement, thereby diminishing the impact of psychomotor stimulants on the control over such behaviour (Cador et al. 1989; Burns et al. 1993). In most studies of this kind, the previously neutral CS gained its conditioned reinforcing properties by association with natural rewards such as water or sucrose. But in more recent, preliminary studies, CSs associated with self-administered i.v. cocaine supported the acquisition of a new response with conditioned reinforcement, but non-contingently administered i.v. cocaine did not. Such acquisition was not observed in self-administering animals with lesions of the basolateral amygdala (Everitt, communicated at the meeting). Taken together with the effects of lesions of the basolateral amygdala on the acquisition of cocaine self-administration under a second-order schedule (see above), it was proposed at the meeting that the amygdala-ventral striatal interface and its interactions with the mesolimbic dopamine system might be intimately associated with some conditioned drug effects.

In some cases, effective clinical treatment regimes may require close account to be taken of the impact of cues associated with drug taking or withdrawal on relapse to the drug-taking habit. Understanding the neural basis of these conditioning processes and of extinction of conditioned drug effects may be useful in the development of such treatment programmes in the clinic and in the community.

4 Risk factors

Given the powerful interaction between neurobiological mechanisms and drug exposure, a question that came up repeatedly during the meeting was why we do not all become addicts. The answer seems to lie in a number of risk factors that make some individuals more vulnerable than others. These range from personality type and temperament, which have their roots (at least in part) in a variety of genetic and early environmental factors, to age, stress and co-existing psychiatric conditions. An individual may become dependent on drugs because of a single factor or, more likely, several interacting factors. This matrix of factors is in turn influenced by social constraints and drug availability, which may play a crucial role in determining who becomes addicted. In general, much of the evidence provided is correlational in nature, with all of the attendant problems of interpretation; the most valuable data allow some assessment of the likely causal significance of the factors (i.e. particular characteristics are shown not only to result from drug abuse, or not to be mere correlates of a more important factor).

4.1 Individual vulnerability

Personality variables

It was difficult to find a consensus concerning these factors, largely because of a paucity of relevant data. One way of understanding personality is as an interaction between temperament and character, each of which have several component variables. Presumably, the adult personality results from interactions between these components during development. Cloninger's (1994) hypothesis is that the components of temperament are emotion-based habit patterns, about 50% heritable, and are stable from childhood to adult. In contrast, character refers to the self-aware goals and values that influence our voluntary intentions and attitudes; it is weakly heritable, moderately influenced by sociocultural learning and matures from infancy to late adulthood.

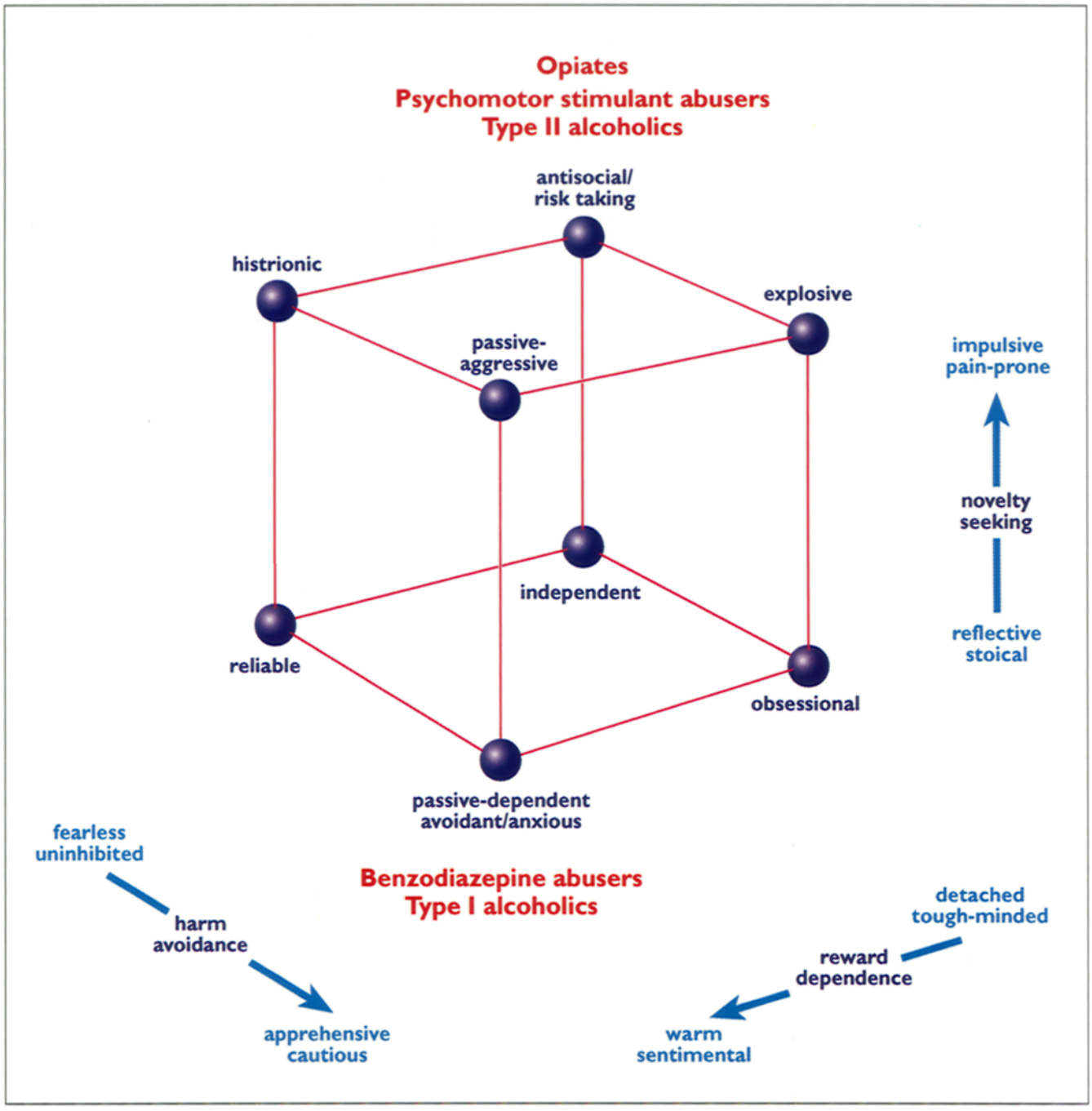


Fig. 4 Possible scheme of the relationship of personality type to drug preference. The personality types are depicted as a cube with the extremes at the corners. The antisocial, risk-taking type, who is high in novelty seeking, needs extraordinary stimulation to feel happy and thus tends to seek euphoriant drugs such as stimulants. Type 2 alcoholics also belong to this group. In contrast, the passive-dependent and anxious type, who is high in harm avoidance and low in novelty seeking, tends to chose antianxiety drugs or to be a so-called type 1 alcoholic. (Reproduced with permission of C.R. Cloninger; copyright 1995, Washington University Center for Psychobiology of Personality)

According to this concept, the interactions between the four components of temperament and the three character traits can be depicted as a cube, with the most extreme personality types forming the eight corners (Fig. 4). Psychopathologies lie at the extremes, that is they can be seen as an imbalance between the components of temperament and character (Cloninger 1994). Some of these types seem particularly at risk for drug dependence. For example, shy and aggressive children, who are high in harm avoidance and in novelty seeking, have personalities lying on the line between passive-aggressive and explosive. Longitudinal studies show that these traits, to some extent together with low dependence on reward, predispose such children to behavioural disinhibition, leading to antisocial personality in adulthood (Cloninger 1994). Children of this type were reported to show increased persistence and are low in self-directed, self-transcendent and co-operativity measures. They are very likely to start using drugs young and have two-to-three times the average rate of becoming drug abusers,

possibly because of failed socialization at school. In contrast, those who are simply shy seem to be protected (Kellam et al. 1983).

In broad terms, Cloninger sees a distinction between those who are high in novelty seeking and low in harm avoidance, the adventurous and antisocial personalities, and those who are high in harm avoidance and low in novelty seeking, the passive-dependent and anxiety-prone personalities. The former are hypothesized to require extraordinary stimulation to feel happy, prefer stimulants and avoid sedatives, as they have a low sedation threshold (Cowley et al. 1993). In contrast, the latter are hypothesized to prefer anti-anxiety drugs and avoid stimulants. According to Cloninger's view, individuals high in both harm avoidance and novelty seeking tend to be poly-drug users, liking both stimulants and sedatives. They are also most likely to be neurotic and personality disordered. However, drug abuse is often irrational and people may experiment with a variety of drugs in a way that does not correspond to their ratings of what makes them feel good.

Beyond Cloninger's own research, relatively little work has been done on the influence of personality variables on drug taking in a laboratory setting. One way of doing this is to relate drug choice to personality variables in normal volunteers. For example, McNair et al. (1970) found that persons with low levels of acquiescence responded more favourably to benzodiazepines than placebo. On the other hand, Uhlenhuth et al. (1981) showed no such relationship for volunteers choosing d-amphetamine over placebo, and also found that the dimension introversion-extraversion failed to predict preference for the drug, against Eysenck's (1963) hypothesis.

There is a high correlation between antisocial personality disorder (ASPD) and type 2 alcohol abuse, which is characterized by early onset, aggression and an inability to abstain from drinking but a low probability of becoming psychologically dependent on alcohol. In contrast, type 1 alcohol abusers start drinking later, drink sporadically but easily lose control and suffer guilt and fear about alcohol dependence. These 'binge drinkers' tend to be passive-dependent or anxious personalities (Fig. 4) and suffer from depression (Cloninger 1987).

These personality traits also seem to underlie dependence on other drugs (Fig. 4). ASPD is now associated with failure in methadone maintenance programmes: delegates estimated that about 50% of those failing in methadone maintenance, a treatment for opiate addiction (see Sect. 5), have ASPD. However, precise estimates for success among those with ASPD do not seem to be available (H. Kleber, communicated at the meeting). People with high scores for neuroticism, i.e. anxiety proneness (harm avoidance) and immaturity (low self-directedness), are frequently dependent on nicotine and benzodiazepines, possibly because they have increased stress reactivity. Personality status is an important influence on the potential to develop dependence on benzodiazepines. When subjects ceased to take benzodiazepines, withdrawal symptoms were found predominantly in those with 'dependent' personalities (Murphy and Tyrer 1991), which may be due to rebound anxiety.

Evidence that personality disorders might have a neurochemical basis is beginning to emerge. There is some evidence for ASPD. Monkeys bred for low levels of the 5-HT metabolite 5-HIAA in cerebrospinal fluid (CSF) and raised by their own mothers or foster mothers show greater vulnerability to acquire alcohol drinking at excessive levels. The risk is amplified when the monkeys are raised by mothers who are also low in CSF 5-HIAA and themselves exhibit several behavioural problems, an indication of the important interactions between environmental and genetic factors. The low-CSF 5-HIAA monkeys have poor impulse control (see also Sect. 3.4), show increased perseveration and are highly aggressive (which also correlates with high testosterone levels). Their lower thresholds for initiating a particular form of behaviour and their higher degree of perseveration in it may contribute to their increased propensity to drink alcohol until they become unconscious (J.D. Higley, S. Suomi, M. Linnoila, unpublished observations 1995).

Recent human data support the idea of a serotoninergic abnormality: responses to the 5-HT-2 receptor agonist, mCPP, discriminate between type 2 and type 1 alcoholics (Benkelfat et al. 1991). There is also some evidence of reduced central 5-HT function in alcohol-abusing patients with other psychiatric diagnoses (Virkkunen et al. 1995) (see also Sect. 3.4).

Biological markers of vulnerability

Delegates reviewed several physiological and biochemical markers that have been reported to be associated with alcoholism and abuse of other drugs. For example, decreased amplitude and, to a lesser degree, increased latency of visual evoked potentials (P300) has repeatedly been shown in type 2 alcoholics and also in first-degree relatives of alcoholics, i.e. it is a trait marker but is also associated with state (Begleiter et al. 1984; see Schuckit 1987 for a review). These changes in P300 may reflect an underlying reduction in attentional processes and altered impulse control. Changes in P300 have not been studied in abusers of other drugs.

Low voltage/monomorphic alpha rhythms in alcoholics are not such a well-established trait marker as P300. However, this pattern of alpha rhythm may not be specific to alcoholics: it is found in 5–10% of normal relaxed individuals but occurs at 4 times this frequency in alcoholics and 7–8 times more frequently in those with anxiety states (Enoch et al. 1995). These observations also need to be extended to other drug addictions.

The galvanic skin response (GSR) and other autonomic responses to alcohol cues tend to be increased in alcoholics and are related to the level of alcohol dependence (overall correlation with a composite measure of cue reactivity including GSR, finger volume, cardiac inter-beat interval, and subjective measures; r=0.55, n=35) (Glautier and Drummond 1994). The increase is a non-specific reflection of autonomic reactivity that may be normalized by alcohol (Drummond and Glautier 1994). In smokers, heart rate responses, but not GSR to cues as-

sociated with smoking correlated significantly (r=-0.27, n=40) with the outcome of treatment for smoking as measured by behaviourally rated coping skills (Abrams et al. 1988), and increased resting systolic blood pressure predicts poorer outcome in nicotine abstinence trials. Cocaine addicts have an elevated heart rate and GSR when presented with drug-associated cues. The larger this conditioned response, the worse the prospects of the addict maintaining abstinence for 6 months (O'Brien et al. 1992; Ehrman et al. 1992a, b).

Monoamine oxidase B (MAOB) activity is low in platelets and other tissues of alcoholics and is suggested to be a marker for increased risk of alcoholism in general, with higher risk for type 2 than for type 1 alcoholics. However, because families of alcoholics tend to have higher levels of psychiatric illness than the general population, it appears that MAOB activity is a marker for an underlying pathophysiological process that leads to alcoholism and other psychiatric illness (Devor et al. 1994).

Levels of adenylyl cyclase activity in platelets varies from family to family but no correlation with alcoholism has been detected (Devor et al. 1991). Even so, prospective studies in children of alcoholics are in progress, but it was pointed out that ethanol inhibition of adenylyl cyclase (see Sect. 3) may persist after years of abstinence (Nagy et al. 1988), which would make it hard to know whether to regard adenylyl cyclase as a marker for state or trait. Furthermore, studies of platelets may not accurately reflect central neural processes.

An apparent innate resistance to alcohol is found in first-degree relatives of alcoholics and may be an important predictor of future dependence. Among a group of college students (n=227) who were moderate drinkers, those with an alcoholic parent showed about 25% reduction in subjective responses to the drug about 1 h after being given alcohol to drink in laboratory experiments, compared with controls, and a similarly significant degree of reduction of alcohol-induced body sway (Schuckit 1985, 1994). A low-level response to alcohol at age 20 was associated with a fourfold greater likelihood of future alcoholism than in controls (Schuckit 1994). The situation has become more complicated with the work of Cowley et al. (1992), who gave benzodiazepines to a similar high-risk group and found an unexpected increase in pleasurable effects compared with controls. As both alcohol and benzodiazepines act at the GABA-A receptor, this response could again indicate a vulnerability to alcohol. Some delegates speculated that drunkenness cues, and their sequelae, especially hangover, may be more important in limiting intake in low-risk individuals, who have to learn to overcome these unpleasant effects.

Relationship to different stages of drug dependence

At the meeting it was considered useful to relate risk factors such as personality variables to different stages of drug dependence, such as initiation of compulsive drug use, recovery and relapse.

Initiation. There are variations in vulnerability with age, with adolescence being the most likely time to start using drugs. Controlling for years of exposure, the earlier the age of onset of drug use/abuse, the more likely the risk of dependence in later life and the poorer the prognosis, at least for nicotine (Taioli and Wynder 1991) and possibly for cocaine. Early antisocial behaviour is also a good predictor of later drug dependence. These factors hold for different ethnic groups and time periods. The converse does not, however, hold: not all addicts have a history of antisocial behaviour and early onset (see Hawkins et al. 1992).

There are no distinguishing personality patterns diagnostic of those who at least try drugs, and for most drugs only a small proportion of those who experiment progress to dependence. Nicotine is the exception, where a high proportion of users quickly become dependent (Stolerman and Jarvis 1995). In general, delegates considered that the progression from use to dependence is better predicted by the number of risk factors present than by the 'strength' of any one factor.

Recovery and relapse. It is difficult to predict which factors govern recovery from dependence or addiction. Perhaps recovery relates to a variety of factors such as social support, 'ego strength' and significant employment. A retrospective study of heroin addicts found three groups: (1) normal, (2) deviant and (3) those who suffered childhood trauma. A positive outcome of treatment, as judged by reductions in drug use, criminality and psychopathology, was greatest in group 1, followed by group 2, with group 3 doing least well (Rounsaville et al. 1982). With nicotine addicts, the earlier in the day the first cigarette is smoked, the poorer the prognosis. The time of the first cigarette is an even stronger predictor of failure to quit than the number of cigarettes smoked (Nides et al. 1995).

Delegates considered that recovery may also relate to taking on an adult rather than an adolescent role, that is, being in control of one's life and acknowledging responsibilities. This fact may well explain the greater motivation of addicted doctors, who often begin to take drugs later in life, to engage in treatment. In individuals with ASPD, drug habits tend to resolve as the personality matures, when the subjects are in their 40s. Marital status, social class, education and occupation are other factors that influence the likelihood of recovery.

Relapse to drug abuse after abstinence is more likely when the drug is easily available. The relapse rate for Vietnam veterans in the Philadelphia area was significantly higher than the rate for the national sample reported in Robins' 1974 survey (O'Brien et al. 1980). Relapse seems most likely in those who have depressive tendencies, as seen in nicotine studies, or who suffer from stress.

Animal models of vulnerability

Piazza et al. (1989 1990) reported that in rats both acute and chronic stress increased the response to both the psychomotor and the reinforcing effects of amphetamine. Rats with higher locomotor responses to novel environments also showed increased psychomotor effects and were more likely to acquire self-administration of amphetamine than those with low locomotor responses to novelty. These results are thus relevant to 'sensitization' theories of drug addiction (see Sects. 2.5, 3.8). These authors have also reported that rats with an enhanced corticosterone response in novel environments are more sensitive to the effects of amphetamine, leading to the hypothesis that exposure to stress and responsivity to novelty may be vulnerability factors for drug dependence (Piazza et al. 1993).

Whilst there appear to be some discrepancies for this hypothesis to resolve [e.g. the predictive power of locomotor activity does not extend to the strength of place preference conditioning following amphetamine (Erb and Parker 1994)], the delegates agreed that the original predictive relationship is replicable under specific circumstances. However, the implication that high activity and amphetamine susceptibility are co-determined genetic traits was queried. The initial tests that were used to select high and low responders could have had an entirely non-genetic influence on the propensity to self-administer amphetamine; the presence of individual differences is relevant to genetic factors, but is not of course solely the result of them. The correlation between initial activity in an open field and drug self-administration, corticosterone release and other signs of stress has not been examined in rats. In mice, however there is little relationship between initial open field activity, initial stimulant response to alcohol and sensitization with repeated alcohol (Phillips et al. 1995; see also Cunningham 1995).

Studies in young monkeys reared under stressful conditions have shown that alcohol consumption increases markedly (Higley et al. 1991). There has been little experimental testing with stressors in human volunteers in studies of drug choice or preference. However, it is interesting to note that there is an association between low arousal levels and a preference for amphetamine over placebo (Uhlenhuth et al. 1981), consistent with the notion that subjects may take amphetamine to optimize arousal levels. This observation seems at variance with the hypothesis advanced by Piazza et al. (1993), which is based on data showing that the more active and exploratory rats are most susceptible to the acquisition of self-administration of d-amphetamine. On the other hand, Piazza et al. (1993) suggest that these rats are models of 'sensation-seeking' traits in humans susceptible to drug abuse. There appears, however, to be a problem in determining the antecedents of 'sensation-seeking' (or 'stress-seeking', Piazza et al. 1993) behaviour. Prior exposure to stress increases novelty-seeking, amphetamine sensitization and the initiation of amphetamine self-administration (see Piazza et al. 1990). However, it is unclear why this antecedent state of 'stress' should elicit further 'stress-seeking' behaviour (Piazza et al. 1993) or, more particularly, how this state might be related to the hypo-aroused state which appears to promote preference for the drug in humans (Uhlenhuth et al. 1981). The parallels between the human situation and animal model are intriguing, but need to be analysed further.

4.2 Co-morbidity

Co-morbidity in drug addiction refers to the presence of a diagnosable psychiatric disorder in an addict but says nothing about the direction of cause and effect. The associations between co-morbid psychiatric illnesses and drug abuse are higher in the clinical population than in the general population, where the correlations between psychiatric conditions and drug abuse may be no greater than between any other pairs of psychiatric conditions. The stronger associations in clinical samples may be caused by the symptoms of other disorders bringing the patients into treatment. Severity of the psychiatric disorder has the highest negative correlation with the likelihood of recovering from addiction.

The relationship between affective disorders and drug abuse is complex. Some information comes from smoking, where depression predicts earlier onset (A.H. Glassman and L.S. Covey, unpublished data) and may make quitting less likely, especially in males (Glassman 1993). Co-morbidity of smoking and depression seems to be more prevalent for females (Kendler et al. 1993), which is not surprising since depression is more common in females than in males. In addition, minor psychiatric disorders are strongly associated with cigarette smoking in population studies.

The cause-and-effect relationship between drug dependence and other psychiatric disorders was the subject of some debate. Meyer (1986) proposed that there are at least five possible relationships:

1. Substance abuse may lead to psychological problems, e.g., panic disorder, bipolar affective disorder.
2. Psychiatric illnesses, such as attention deficit disorder, may lead to substance abuse. Schizophrenics may abuse drugs to treat negative symptoms (LeDuc and Mittleman 1995), although their positive symptoms may then get worse, and people with bipolar affective disorder may take cocaine to alleviate the depressive phase, that is, they are using the drug for self-medication (see Sect. 2).
3. Psychiatric problems can be secondary (i.e. due to non-pharmacological factors) to the lifestyle of a substance abuser.
4. The association may merely be correlative.
5. There may be no relationship.

The view was expressed that the first hypothesis is the most common and that drug abuse is perpetuated as self-medication after the psychiatric disorder develops. But it can be difficult to determine whether the disorder or the drug abuse occurs first, especially when drug use starts

early in life, before the psychiatric disorder manifests itself. It was argued that nicotine may not be effective as self-medication because stress levels are reduced, not increased, after quitting (Cohen and Lichtenstein 1990).

4.3 Genetics

The interaction between environment and genes has been little investigated in drug dependence, although illness-promoting and protective factors exist at both genetic and environmental levels. Estimates of the genetic contribution to drug dependence provided by discussants varied between 50% and 70%. Genetic risk factors may turn out to be those involved in general behavioural control mechanisms and in co-morbid disorders. Possible genetic variations could lead to considerable variability in sensitivity to drug effects. So far no unequivocal candidate genes directly related to drug abuse have been found. The claims for the dopamine D2 receptor gene polymorphisms relating to alcohol and drug abuse (Blum et al. 1990) remain controversial, as several laboratories have been unable to confirm the original finding (see Goldman et al. 1992).

In humans, estimates for the contribution of genetic factors to alcohol dependence vary considerably, with figures from twin and adoption studies ranging from 10% to 77% in males. The association in females is much weaker (McGuffin et al. 1994). Twin studies indicate that the inheritability of both smoking and depression is about 50–60%. Common environment accounts for 27% of the variability and liability to smoking, but seems not to contribute to major depression (Kendler et al. 1993). These data suggest that the relationship between smoking and major depression could be mediated through genes that influence the liability to both conditions.

Much attention has been paid to aldehyde dehydrogenase (ALDH) in alcoholism, as about 50% of orientals have an inactive form of mitochondrial ALDH. The enzyme is responsible for most acetaldehyde oxidation, so the inactive enzyme results in higher blood acetaldehyde levels on drinking (the same effect produced by Ant-abuse and Abstem treatment; see Sect. 5.2 and Hodgkinson et al. 1991). The low incidence of alcoholism in orientals could be due to this enzyme deficiency, but the protective action of the gene is limited, as about 5% of Japanese alcoholics have the mutation; they continue drinking despite the adverse effects of alcohol.

Potential applications of genetics research include the following projects: the identification of those at risk; the control of variability in behavioural studies; the use of dizygotic twins to reduce variation in subject populations by 25%; and improving our understanding of mechanisms of dependence in terms of the spectrum of genetically controlled systems relevant to dependence. When studying patterns of inheritance it is important to stratify by sex and ethnic origin, as different allelic frequencies can be expected in the different groups.

Box 4A Behavioural genetics

There are several strategies for analysing genetic contributions to drug effects, using *inbred strains, selectively-bred lines*, and *recombinant inbred strains* (Crabbe and Belknap 1992). All members of an inbred strain are genetically identical, and a particular allele has been fixed homozygous at each gene. The particular alleles fixed in a given inbred strain are the result of chance. More than 100 inbred strains of mice and rats are commercially available. An important use of inbred strains is to establish the existence of genetic correlation. For example, examination of the patterns of correlation among inbred strains for a number of ethanol-related traits has revealed a pattern of genetic co-determination of sensitivity to some traits (e.g. ataxia and depression of locomotor activity), and a fair degree of genetic independence of different groups of responses.

The use of artificial selection for drug-response traits of relevance represents the major historic thrust of research with genetic animal models. In much the same way that animals have been bred for desired agricultural or aesthetic characteristics, lines of mice and rats have been systematically mated to respond characteristically to alcohol and drugs. Selected lines serve as a powerful test system for studying the presence of genetic correlation. In well-constructed selected lines, any other difference between a pair of selected lines is presumed to be due to the common influence, or pleiotropism, of the genes determining the selected response. It is this use of selected lines that has been very powerful for studies of neurobiological mechanisms.

Recombinant inbred (RI) strains are derived from two inbred strains by inbreeding from their F_2 (genetically heterogeneous) cross. Each RI strain thus represents a random sample of the genetic variability available in the two parent strains. When a battery of RIs are tested for a drug response trait, the distribution of strain means may then be compared with the allelic distribution for marker genes mapped in the RI battery. For the existing RI strains, this is a considerable number, with many representative markers on each chromosome; there are more than 1300 marker genes mapped in virtually all of the 24 RI strains derived from the cross of C57BL/6J and DBA/2J inbred progenitor strains. In this way, quantitative trait loci (QTLs) affecting the drug response of interest can rapidly be located on mouse chromosomes (Plomin et al. 1991). Since the markers on mouse and human chromosomes are highly conserved, the human homologues of drug-related loci identified in mice can be rapidly ascertained.

Clarification of genotype may assist in predicting risk of dependence and chance of recovery. However, risk assessment must not be perceived as the primary or even a likely goal, as risk may not be specific to drug dependence; the statistical assessment of risk is the best that can be hoped for. Moreover, programmes designed to identify those with a high-risk genotype or phenotype raise the spectre of stigmatizing people and so may be hard to implement, even though they could focus interventions directed at prevention. For example, genetic influences increase risk for type 2 alcoholism significantly, but only 1 in 5 of those at risk develop alcoholism. Although those at risk can be identified pre-school, and even though early prevention is the best approach, intervention would mean labelling individuals and creating other social problems and self-fulfilling situations.

Animal genetic models

Genetic models are likely to provide a powerful method for assessing the potential influence of non-genetic risk and protective factors. They also seem well suited for studying the interaction of specific environmental interventions with particular genetic risk or protection profiles. The breeding strategies for analysing genetic contributions to drug taking, all of which use mice and rats, are summarized in Box 4A.

Models based on strain comparisons and/or selective breeding strategies have been employed for many classes of drugs, including ethanol (by far the most common), opiates, benzodiazepines, nicotine, cocaine, amphetamines and neuroleptics. One well-characterized mouse model of this type has been developed for differential genetic susceptibility to severity of withdrawal from ethanol (Crabbe and Phillips 1993). The susceptibility extends to chronic intoxication with diazepam, phenobarbital and nitrous oxide, suggesting that some genes predispose to severe withdrawal responses to various addictive drugs. Other studies with this model have helped to illuminate several neurochemical features of the neuroadaptive responses accompanying ethanol dependence and withdrawal, including increases in the number of dihydropyridine-sensitive calcium channel binding sites in whole brain homogenates, reduced zinc content in dorsal hippocampal mossy fibres and several differences in GABA-A receptor subunits (Crabbe and Phillips 1993; see also Sect. 3).

Genetic analyses with long-sleep and short-sleep lines of mice and with inbred strains have made a major contribution to clarifying the importance of the GABA-benzodiazepine receptor complex for mediating several effects of ethanol (summarized in Buck and Harris 1991). Some acute and chronic physiological and behavioural effects of nicotine, including the development of tolerance, are correlated with differences in the binding of various nicotinic ligands across different strains of inbred mice (Marks et al. 1989a, b). These differences could be a basis for variations in vulnerability but the studies do not seem to have been extended to dependent variables clearly related to addiction, such as nicotine self-administration and the nicotine withdrawal syndrome.

Animal genetic studies of drug taking per se are largely limited to oral self-administration, such as several rat lines developed for preferring to drink 10% ethanol or water. Preferring (P) and non-preferring (NP) rats are the best characterized (Crabbe and Li 1995). P rats will voluntarily drink 10–30% ethanol solutions and develop tolerance and physical withdrawal signs with chronic drinking. NP rats can be induced to drink ethanol only with difficulty and clearly differ from P rats in their avidity for ethanol. P rats are more sensitive to stimulation by low doses of ethanol, develop tolerance to the ataxia-inducing properties of ethanol more quickly and remain tolerant for a longer period than NP rats (Li et al. 1993). Several pieces of evidence suggest that P and NP rats differ in 5-HT function in some brain regions, although other limbic forebrain transmitters are also implicated in the differences between these lines.

As described in Box 4A, recombinant inbred (RI) strains are valuable for mapping drug-related loci on mouse chromosomes. This area of research is currently causing excitement because the location on human chromosomes of drug-response genes identified in mice can often be directly inferred. One set of specialized mouse lines, the BXD Recombinant Inbred (BXD RI), has been employed to identify quantitative trait loci (QTLs; see Box 4A). QTL mapping has been employed to study approximately 20 alcohol response traits, ranging from locomotor sensitivity (Phillips et al. 1995) to withdrawal and drinking (T.J. Phillips et al. 1994), and conditioned place preference (Cunningham 1995) as well as multiple responses to morphine, cocaine, nitrous oxide and pentobarbital (Crabbe et al. 1994). QTLs for two alcohol withdrawal sensitivity loci on chromosome 2 have been verified; candidate loci in this area include the glutamic acid decarboxylase gene, which codes for the rate-limiting enzyme in GABA synthesis. Using multiple QTL analyses, candidate genes including the dopamine D2, 5-HT-1B and δ opioid receptors and the dopamine transporter have been identified as possibly determining several drug responses.

Genetic contributions to individual differences in sensitivity to the various effects of a single drug, or to the responses to multiple drugs, can be surprisingly discrete. For example, a multidimensional scaling analysis in inbred strains of mice examined the co-ordinate genetic control of temperature disruption and locomotor stimulation in response to four concentrations of each of four drugs. A certain degree of similarity in control of responses to morphine was found: strains that responded strongly to one dose also tended to respond strongly to other doses, for both behaviours. However, for ethanol, there was little genetic similarity among responsiveness to different doses, nor was there similarity across behavioural responses (Crabbe et al. 1994).

4.4 Environmental factors

Human studies

Although genetic variation clearly causes some of the variance in the risk of developing drug dependence, the effects of macrosocial processes (such as attitudes) in determining prevalence of drug use and availability are massive. Short-term, large-scale changes in drug use in the population, such as the sixfold variation in alcohol consumption and the changes in cocaine consumption in the USA over the last 100 years (Musto 1991; Courtwright et al. 1989) and massive reductions in Dutch alcohol consumption between 1890 and 1930, cannot be due to genetic factors. Changes in social attitudes and public policy may have unintended effects on the growth and recession of drug problems. For example, between epidemics of drug abuse, information available about drug

problems becomes less available, which may contribute to the escalation in use at the start of a new epidemic.

Microsocial factors such as parenting practices, peer groups and interactions with the school system also play a considerable part in determining whether individuals at risk become addicts (for review see Hawkins et al. 1992). For example, only 1 in 5 of those genetically at risk actually become alcoholics. The fact that many army veterans became dependent on heroin while in Vietnam illustrates the importance of the current situation or context on the likelihood of becoming dependent. Many were able to stop using heroin on return to the USA, while those who continued to use heroin often did not become dependent or did so only briefly (Robins et al. 1974). In Vietnam, the soldiers had easy access to inexpensive, pure opiates and no family members or significant others around to disapprove. They considered the 1-year assignment in Vietnam as a period disjunctive with the rest of their lives. On return, they still had access to opiates but these both had weaker effects and were more expensive. These individuals faced disapproval from those they cared about and they needed to obtain and succeed in jobs; such pressures are incompatible with heavy drug use. However, as noted above, relapse was found to be higher in Philadelphia, where drugs were readily available (O'Brien et al. 1980).

Animal studies

If drugs of abuse act on the systems through which non-pharmacological, more 'natural' reinforcers (such as food) work (see Sect. 3.4), then other environmental determinants may also alter the way in which drugs affect these systems. Such determinants are being studied in animal models and are focusing both on exposure to specific contingencies and on more general environmental manipulations, such as variations in early experience. For example, as mentioned in Sect. 3.10, rats yoked to partners that are self-administering drugs showed lower dopamine levels in the nucleus accumbens than their partners, although both received the same amount of cocaine or amphetamine (DiCiano et al. 1995b). The yoked rats did not learn to self-administer cocaine when given the opportunity later (Dworkin et al. 1992). The question remains whether yoked animals will learn to avoid administration of the drug.

Further evidence for more general interactions of environment with the mesolimbic dopamine system comes from rearing rat pups in isolation after weaning (G.D. Phillips et al. 1994c,d). Compared with their group-raised siblings, these animals were slower to learn to self-administer high doses of cocaine and d-amphetamine but learned faster with low doses (Howes et al. 1995). In parallel with these behavioural data, the isolated rats exhibited an elevation in stimulant-induced release of dopamine in the striatum, as assessed using microdialysis, and an apparent dysfunctioning of D2 dopamine receptors in the nucleus accumbens (Wilkinson et al. 1994; G.D. Phillips et al. 1994d). These data may indicate a general 'shift to the left' in the dose-response curve for the isolated animals, consistent with an enhanced susceptibility to psychomotor stimulants. This simple interpretation is, however, contradicted by strong evidence for a *rightwards* shift in dose-response after learning to administer high doses (G.D. Phillips et al. 1994c, d) and by data suggesting impaired place preference conditioning to such drugs (Schenk et al. 1986). Isolated animals are known to have a reduced response to opiates (Schenk et al. 1983) as a consequence of the effects of early experience on the expression of opiate receptors in the CNS. In fact, it is likely that isolation rearing affects responses to various drugs of abuse in different, sometimes opposite, ways. Overall, it is clear that, although this experimental paradigm may have some use as a heuristic model, the mechanisms underlying modification of drug taking by variations in social experience (including conditions sometimes considered as 'stressful', i.e. away from the animal's normal range of experience) are complex, and probably incompatible with contemporary models that depend on simple unidimensional factors.

5 Treatment of drug addiction

5.1 General considerations

There are two components of the treatment of addiction: getting addicts off their drug (withdrawal or detoxification) and maintaining well-being (on or off maintenance drug). Delegates agreed that drug addiction has to be seen as a chronic relapsing condition, so the aim should not necessarily be to cure (which implies an ability to go back to controlled use of the substance) but to enable the addict to live a more stable, productive life. Many treatment efforts therefore now highlight the need for improvement in the way an individual uses drugs to reduce complications to themself and/or to society, rather than total abstinence.

A prevalent misconception in both the medical profession and the general public is that the treatment of drug addiction is a uniform failure. This is wrong. The treatment of withdrawal for most drugs is effective and safe, although there is scope for improvement (cf. McLellan et al. 1992). Reduction of withdrawal syndromes associated with nicotine, e.g. with a nicotine patch, assists in achieving abstinence. The treatment of withdrawal from alcohol is essential, as severe ethanol withdrawal is a very toxic state that can result in neurotoxic events within the brain and even death if not treated. Long-term abstinence maintenance therapy is also effective when offered by centres of excellence. Comparisons of the effectiveness of treatments in the addictions with those in other chronic diseases, such as diabetes, hypertension and asthma, show essentially similar success rates, with 30–60% good outcomes (quoted by C. O'Brien at the Wellcome Trust Open Meeting, London

1994, see also McLellan et al. 1992). Indeed the main reason for treatment failure is the same in all these conditions: non-compliance.

These data prove that nihilism about therapy is an inappropriate attitude that must be challenged and changed if the achievements of the best treatment programmes are to made more generally available. To improve outcome requires not just the development of more effective pharmaceuticals but also much wider application of well-informed, integrated treatment programmes. Addicts are not a homogeneous population, and every one has a different set of problems. Treatment needs to be targeted to particular patient groups. At best each patient should have a flexible, individually tailored treatment programme. For instance, nicotine replacement therapy is of most benefit to more severely dependent patients, and naltrexone works best in opiate addicts with good social functioning. To date not much emphasis has been put on finding pharmacotherapies for patient subtypes, which may be a more realistic and practical approach. The most notable exception is the large MATCH study in the USA; which is evaluating interventions in alcoholics tailored to biopsychological variables. Its findings will be reported soon.

A wide range of therapies is used in addiction, which makes full assessment of their efficacy difficult. Despite the claims of some therapists, it seems unlikely that comparing pharmacological with cognitive and behavioural therapies will be particularly fruitful; it is already clear that the best treatment is a combination of pharmaco- and psychosocial therapy, with optimized dosing of both (McLellan et al. 1993). The treatment approach should be systematic, with a policy of moving on if there is no response to the initial treatment, and different strategies may need to be employed with the same patient at various stages of treatment. The proper design and application of such treatment requires specialist skills, which has wide-reaching implications for the training of doctors, psychologists and social workers. Its provision requires integrated drug treatment facilities, ideally with provisions for in-house research.

Compliance with treatment is not only a major problem but also an important predictive factor. Self-reporting of illicit drug use is unreliable (see Sect. 2.2), and independent measures are required to assess progress (see Sect. 5.5). Motivational factors and the stages of change in motivation need to be better studied. Techniques such as motivational interviewing, which encourages and fans the flames of the patients' nascent desires to control their addiction, need to be more fully explored.

As co-morbidity of drug abuse with psychiatric disorders is common (see Sect. 4.2), it is essential to treat the accompanying psychiatric disorder in order to improve the prognosis for the drug addiction. For example, people with history of depression and nicotine abuse respond well to treatment with tricyclic antidepressants in the context of a comprehensive behavioural smoking cessation programme that includes nicotine replacement. A significant minority of young male alcoholics and drug abusers have social phobia and find it easier to control their drug use if the anxiety is appropriately treated. Here early detection and intervention are important to prevent the secondary consequences of drug and alcohol use with their negative effects on outcome.

5.2 Pharmacotherapy

Pharmacotherapeutic strategies for the treatment of addiction, excluding withdrawal, fall into four types:

1. Replacement or substitution, e.g. methadone for heroin and nicotine patches or gum for cigarettes.
2. Drug antagonists, such as naltrexone, which blocks the reinforcing euphoric effects of opiates and can diminish those of alcohol.
3. Aversion/avoidance, e.g. emetine/electric shocks or disulfiram for alcoholics.
4. Appetite/craving-suppressing agents, which act, for example, on 5-HT neurotransmission

(see also Fulco et al. 1994, 1995).

Replacement/substitution therapies

These treatments use a drug that produces similar effects to the illicit drug to establish addicts in treatment with the aim of improving personal and social functioning and, in the case of methadone substitution for heroin, the reduction of intravenous drug use. Methadone is the prototypical and best-established substitution therapy and has been shown to reduce illicit drug use, crime and the spread of HIV and other infections (Farrell et al. 1994).

Pharmacokinetic variables are critical in replacement treatment. The ideal substitute drug has a slow onset of action to diminish acute euphoriant effects, so reducing the likelihood of the drug being sold and producing addiction in others (also known as diversion). Long-lasting action is required so that dosing can be once a day or less, which reduces health-provision costs if clinic attendance is required for dispensing, as with methadone. Moreover, the less frequently the drug has to be taken, the easier it is for addicts to return to normal life.

Substitution should provide effective relief of symptoms of craving and withdrawal to prevent addicts topping up prescribed drug with illicit ones. It should also block the actions of these, reducing their reinforcing value, leading to extinction of drug-taking behaviour, reduced injecting and so to harm avoidance. Methadone has been shown to do all of these and may well improve intellectual performance relative to street opiates. Moreover, the unborn foetus fares better when the mother is in a methadone programme than when she is using street opiates, as medical and obstetric needs are much better controlled.

One drawback to methadone is that it requires daily dosing, usually under supervision, which is costly to provide, as well as limiting to the patients. Giving addicts several days' supply brings the risk of diversion and

overdose. An alternative strategy is to use a longer-acting agonist such as LAAM (*L*-alpha-acetoxy-methadol). This has an effective half-life of about 2 days so needs to be given every 2–3 days. Because it is a pro-drug and has to be metabolized to more active compounds, its reinforcing potential is even less when used intravenously and so the risk of diversion is reduced. LAAM has recently become available for use in the USA and can now be evaluated in other countries that have problems with opiate addiction.

Dosage is also an issue: delegates emphasized that failure of replacement therapy is often due to giving an insufficient dose, causing the addict to 'top up' with the drug of abuse. Higher doses of methadone have been shown to improve maintenance in treatment programmes. A key element in substitution therapy is that it engages addicts in regular contact with health-care professionals and so enables them to receive additional forms of intervention.

The duration of therapy has to be individually tailored and may need to be very long term. It is compatible with a successful career and there are examples of high-achieving professionals who are long-term methadone users. A graduated programme of psychosocial intervention has been shown to be helpful in rehabilitating methadone-maintained patients and getting them to stop using other illicit drugs, especially cocaine. Stopping methadone use must be done cautiously, as cases of extreme relapse with secondary psychiatric disorder and even suicide have been recorded. Prior training in behavioural and cognitive coping techniques may help to reduce this risk.

Substitution therapy has three major problems: diversion, continuation of the addict 'self image' and overdose by the addict or by others, especially children. One way of reducing the first and last of these is to use partial agonists. These are agonists that have lower efficacy than full agonists, i.e. their effects are in the same direction as full agonists but with a lower maximum. For example, the partial opiate agonist buprenorphine causes much less respiratory depression than heroin, making it much safer in overdose. Yet it has sufficient agonist action to be reinforcing and so keeps addicts in treatment. Partial agonists also act as antagonists when taken in combination with full agonists and thus block the actions of illicitly used opiates, again reducing 'top-up' use of street drugs.

Substitution therapy for stimulant users is more controversial (Myles and Weinstein 1996). However stimulants such as methylphenidate or d-amphetamine may be useful in addicts with attention deficit disorder where illicit stimulants are being used as self-medication. As with methadone this approach reduces crime and increases social functioning. In those dependent on other stimulants, such drugs can make matters worse, and authorities argue that the risks of chronic amphetamine use, such as the possible development of psychosis, make this approach unethical. More outcome studies are required to evaluate its benefits and risks. The use of alternative, less reinforcing stimulants such as pemoline should also be considered. Directly acting dopamine agonists such as bromocriptine have been tried with limited success due to high drop-out rates. Amantidine appears to be useful only in the first few weeks after cocaine is stopped. Delegates suggested that the use of indirectly acting dopamine agonists such as selegiline (deprenyl) should be considered.

Nicotine substitution therapy is well established in the form of nicotine gum and patches. These have demonstrable efficacy in helping people quit smoking but their place in relapse prevention is less clear, although they may help smokers stay in other forms of therapy. Underdosing appears to be common, perhaps because they are expensive and not routinely reimbursed by governments or health insurers. Studies of nicotine replacement therapy in pregnancy have not been conducted. Some heavily dependent smokers find the onset of effects too slow, and it has been suggested that giving nicotine by a nasal spray could be better in this population. It produces a plasma nicotine profile very similar to that of smoking and so acts as a cigarette substitute, although there is concern about its potential abuse liability.

In parts of the UK where i.v. temazepam abuse ('hotlining') is rife, some therapists are prescribing long-acting benzodiazepines, such as chlordiazepoxide, to reduce i.v. use. The discovery of partial agonists at the benzodiazepine receptor has implications for the treatment of benzodiazepine abusers, although no trials have yet been undertaken. Several members of this class of benzodiazepine agent have now been tried in anxiety disorders, and their safety in humans is proven (Potokar and Nutt 1994). Those that are no longer in development as anxiolytics, e.g. bretazenil, appear ripe for trials in benzodiazepine abuse. They might also be useful in alcoholism, where substitution therapy with chlormethiazole (a GABAergic agent) was tried in the 1970s but found to be of limited utility. At the meeting, it was argued that dependence on benzodiazepines would be preferable to alcoholism, especially in terms of physical health. In most cases, however, alcoholics tend to drink on top of benzodiazepines, and abstinence is the preferred goal of most alcohol treatment programmes.

Antagonist therapies

Antagonists bind to a receptor, have no direct action themselves but block the effects of agonists. The best example is naltrexone, used to treat heroin abuse. When addicts are stabilized on naltrexone, street opiates no longer produce a high, use stops and extinction of drug-taking behaviour and craving can follow. Although sound in theory, in practice antagonist treatment with naltrexone has not been very successful because of problems with compliance. Establishing addicts on naltrexone can be difficult because the transition has to be slow in order to avoid the precipitation of withdrawal, which is very aversive. During this period the risk of relapse is correspondingly high. Long-term naltrexone use can produce a low-grade dysphoria but this is rarely severe enough to cause

drop-out from treatment. Naltrexone has a relatively short half-life, which means that addicts can skip a dose, usually over the weekend when they are not supervised, and get back a proportion of their drug high; to counter this, increased doses are usually given on Fridays. Long-acting alternatives (see below) or a depot preparation may give better results. Despite these limitations, naltrexone has a place in the treatment of opiate addiction in well-motivated individuals, e.g. doctors who will lose their jobs if they relapse and patients on probation who lose their liberty if they fail to comply.

Antagonist therapy for other drugs of abuse is in its infancy. Naltrexone, in conjunction with coping-skills therapy, has been used successfully to treat alcoholism (O'Malley et al. 1992; Volpicelli et al. 1992). It is presumed that endogenous opiates contribute to alcohol craving and reward and are blocked by the antagonist.

An antagonist for nicotine, mecamylamine, blocks many of the central effects of cigarette smoking in humans. However this leads to an increase in various measures of intake, which suggests it is blocking the reinforcing actions of nicotine and smokers are attempting to overcome this (Stolerman et al. 1973). Nevertheless, mecamylamine could have a role in preventing relapse once abstinence has been established, and this needs to be studied.

Dopamine receptor antagonists, such as the neuroleptic haloperidol, have been tried in cocaine addicts without a great deal of success, so new avenues are being explored. One is the development of drugs that bind to the dopamine transporter and prevent the binding of cocaine without interfering with dopamine uptake. Novel dopamine uptake blockers such as GBR12909 have already been shown to reduce the neurochemical actions of cocaine (Rothman et al. 1991), although they too may also show some liability to cause dependence. An even more innovative approach is the use of immunization. It has proved possible to induce anti-cocaine antibodies that bind to and deactivate cocaine and heroin in animals. Although passive immunization would only last a few weeks, if an active form of immunization such as that recently reported in rats (Carrera et al. 1995) could be developed for humans, in theory this could give lifelong resistance to the drug.

Antagonists at benzodiazepine and delta-9-THC receptors now exist and could be considered as treatments for the abuse of these drugs, pharmacokinetic parameters permitting. Many drugs have been claimed to be alcohol antagonists (Lister and Nutt 1987). Most has been published on agents such as TRH and Ro 15–4513, which offset some of the acute intoxicating actions of alcohol. Although these effects are reproducible they are unlikely to be of therapeutic relevance. Acamprosate (calcium homotaurate) is an excitatory amino acid antagonist that reduces the intake of alcohol in experimental animals and alcoholics (Lhuintre et al. 1990). Two recent major placebo-controlled studies have confirmed this finding in much larger samples: acamprosate, either alone or with disulfiram (see below), reduced relapse and increased the period of sobriety in alcoholics (Littlejohn 1995; Paille et al. 1995). Whether acamprosate should be classified as an alcohol antagonist is uncertain at present but its clinical profile looks very promising.

Aversive agents

The use of aversion techniques has a long and probably underrated pedigree, especially in alcoholism. Nausea-inducing agents make alcoholics feel very ill when intoxicated and develop a powerful conditioned aversion to alcohol. This approach gained notoriety when used to treat other conditions, especially homosexuality, but a recent reappraisal of its efficacy in alcoholism concluded it might have been abandoned too soon (Elkins 1991); perhaps a proper controlled trial is warranted.

Disulfiram (Antabuse) and calcium carbimide (Abstem) have a different action: they block aldehyde dehydrogenase, so producing the threat of severe reactions if alcohol is drunk. Although several small trials found these drugs efficacious, the major study in the USA was more equivocal (Fuller et al. 1989). Compliance is a major problem as alcoholics can easily omit a dose and begin to drink again. Some centres use disulfiram injections to improve compliance, although these have not been formally evaluated in a controlled trial.

Another aspect of aversion is the addition of opiate antagonists to agonist mixtures (usually analgesics) to reduce i.v. use. When used orally with pentazocine, naltrexone has little action as it is rapidly metabolized by the liver. However, when naltrexone is injected by an opiate addict, the antagonist readily penetrates the brain and blocks the action of the pentazocine, so removing the reason for its use. Moreover, if opioids are present the i.v. naltrexone precipitates withdrawal, which is very aversive, and one-trial avoidance learning usually occurs!

Agents that reduce drug appetite or craving (see also Sects. 2.6 and 3.9)

These drugs act on brain mechanisms that are not the direct substrate of the abused drug. Many animal and human studies have found that drugs which increase brain 5-HT function, especially 5-HT reuptake inhibitors, reduce alcohol consumption (see Sellars et al. 1992), although clinical trials in alcoholics as opposed to heavy drinkers have been disappointing. Buspirone, a partial agonist at 5-HT-1A receptors, has recently been shown to improve outcome in alcoholics with co-morbid anxiety disorder, probably by treating the anxiety (Kranzler et al. 1994). Tiapride, which appears to be a weak neuroleptic, has also been shown to have some efficacy, supporting a role for dopamine in alcoholism (Shaw et al. 1994).

Animal studies show that 5-HT-2 receptor antagonists fairly consistently reduce alcohol self-administration,

and clinical studies with drugs such as amperozide are now under way. The use of naltrexone in alcoholics and desipramine (a noradrenaline reuptake blocker) in cocaine users could also be considered in this category. It seems likely that such approaches may work only in subgroups of patients, and a pressing need is to identify these. For example, in alcoholics with a family history of alcoholism the intake of alcohol leads to an increase in the blood levels of β-endorphin; this may be reinforcing and would be blocked by naltrexone.

5.3 Psychosocial therapy

Behavioural/psychological support has additive and/or synergistic effects with pharmacotherapy. Unfortunately, the matching between the severity of the addiction and psychological therapy is not as good as with pharmacological dosing. Delegates thought that better 'dosing' could improve the cost-effectiveness of behavioural treatment. For example, some studies have reported that cues associated with cocaine are harder to extinguish than those associated with opiates, indicating that dosing of behavioural treatment has to be determined case by case, or at least by particular drug class (see also Sect. 2.1).

Interactions and close relationships with a significant other, such as a family member, spouse or priest, is extremely important and a good prognostic factor for treatment. Best outcomes with some pharmacotherapies where compliance is a problem, e.g. disulfiram, are achieved when a significant other supervises drug taking. Although there is growing evidence that different types of therapies have different outcomes, non-specific factors such as time spent with a psychotherapist and the personality and interests of the psychotherapist can also play a significant role. So in studies comparing various types of therapy, this therapist factor must be taken into consideration and the enthusiasm of the therapist must not be confounded with the treatment approach.

Relapse prevention is an important aspect of treating addiction (see Sect. 2.6). It is very important for the therapist to be accepting of the patient and not refuse therapy to individuals who have relapsed. Patients who relapse with other diseases, like heart disease, or psychiatric diseases such as schizophrenia, are not treated as harshly as drug addicts. Acceptance of relapses, however, has to happen in a way that does not encourage relapse.

It is now widely recognized that therapy implementation using manuals and carefully constructed protocols is a great asset. Using manuals improves the consistency of treatment, helping to reduce the noise from therapist variables. It also makes possible the calculation of 'units' of treatment, a built-in advantage of pharmacological treatments that would benefit assessment of non-pharmacological treatments.

Therapies in use or development

Cue-extinction techniques attempt to reduce or abolish the addict's conditioned responses to certain drug-related cues. These may be objects like syringes and other apparatus used in drug taking, places drugs were purchased or consumed, or people that sold or shared drugs. Detoxified addicts exposed to such cues are liable to relapse and severity of conditioning, especially that producing withdrawal reactions on exposure, predicts poor recovery. Treatments that modify conditioning have only limited efficacy for reasons that include the lack of knowledge of dose-response functions and the wide range of cues that can become drug associated. It may never be possible to get complete extinction because small changes in the environment may act as drug-related cues. Ideally extinction should be carried out in the same context as acquisition, which is usually impractical.

Extinction therapies are generally more effective when combined with other treatments, e.g. disulfiram with alcoholics and coping techniques with cocaine. A recent study of heroin users showed no difference in numbers who relapsed or time to relapse either 2 or 6 months after relapse-prevention programmes (Dawe et al. 1993) although this conflicts with similar studies from other centres (Caroll et al. 1991). Other studies have suggested that patients on methadone did better when they were also given extinction, but extinction had no advantage over traditional psychotherapy.

Several other psychological techniques are being or have been evaluated. Alternative response strategies help addicts turn away from drug use in times of stress. Problem-solving training appears better for patients with antisocial personality. Motivational therapies may encourage compliance with other treatments. Interpersonal psychotherapy can be used to deal with the consequences of drug use for the individual. Cognitive therapy has established a large following in the treatment of depression and anxiety. It is possible that conditioned urges could be elaborated as cognitions so that cognitive strategies could be used to deal with them. Aversion therapy has been tried with smokers, using rapid smoking to produce nausea and tachycardia, but its efficacy is limited and combining it with other behavioural techniques might produce a better outcome.

Self-help groups like Alcoholics Anonymous and Narcotics Anonymous have a long history in treating addictions but there have been no controlled trials; the success rate is estimated at about 20% but, because participants are self-selected, it is impossible to compare this with outcomes of other approaches.

One novel approach, successfully used in a cocaine programme consistent with a 'behavioural economics' approach which considers alternative sources of reinforcement (see Sect. 2.1 and Box 2F), has been to reward addicts with vouchers for drug-free urines (Higgins et al. 1994). Compliance was induced by increasing the value of the vouchers in parallel with the number of clean urines. Although the value of the vouchers was low

[$1–3], when used as part of a rehabilitation programme they appeared surprisingly motivational, perhaps because the total sum that could be obtained was over $1000. This population of addicts may never before have achieved any success, so earning vouchers is a major achievement that could begin a process towards normal social behaviour.

5.4 Alternative treatments

Acupuncture and transcranial electrical nerve stimulation (TENS) are two treatments of withdrawal that are in current use. Acupuncture so far seems to offer little benefit but it is too early to decide about TENS. It has been argued that by altering stimulation parameters different neurotransmitter systems (and potentially brain sites) may be influenced. TENS has been found active compared with placebo in both opiate and cocaine withdrawal (Taylor 1995) and is used in several smoking cessation programmes, although good clinical trials are lacking.

5.5 Design of trials

Many variables may need to be taken into account when designing clinical trials of treatments for drug abuse. These include gender, family history, age, pattern of drug use, physiological and psychological responses, levels of 5-HIAA in cerebrospinal fluid, genotype, co-morbidity, compliance, severity of dependence and recruitment. Drug responsiveness, i.e. subjective performance and cognitive processes, may also be important. In practice it is rarely possible to randomize or stratify for more than two variables without leading to impossibly high numbers of subjects, so the influence of many of these factors is still poorly understood.

Outcome goals should reflect several parameters, such as level of drug use, psychopathology and social function. Abstinence at a single time point may not be the best measure, as relapse and recovery within trials may occur. Matching patients to treatment may be crucial to show treatment effects; for instance, more severely dependent patients benefit most from nicotine replacement. It is inevitable that large multicentre trials will be needed and this will incorporate further variability.

Gender

More studies are needed to assess the role of gender in drug addiction. The male:female ratio varies across the addictions, with men far exceeding women except for smokers under the age of 35. The ratio is strongly influenced by ethnic background. Differences in response to treatment may be important, e.g. the outcome for women is slightly better than for men for most addictions, except for female smokers, who generally do as badly as men, or even worse if they are depressed.

Symptom profiles may vary between the sexes, e.g. more women alcoholics than men show an excess of guilt and bingeing behaviour (type 1 alcoholism). Hormonal cycles may need to be taken into account as there is evidence for changes in brain receptor number and function with the menstrual cycle.

Family history

Two problem areas in assessing family history are the accuracy of the diagnoses and the interpretation of the extent of the genetic loading. To obtain reliable data, positive and negative reports from probands need to be confirmed by direct interviews with relatives. Family size and degree of relationship have to be considered when characterizing genetic loading. Relatives with the highest coefficient of relationship, such as sibs, offspring and parents, provide the most information on genetic loading of a proband; the quality obtained declines steeply with the distance of genetic relationship.

Age and patterns of drug use

The effects on outcome of age at onset and type of drug (see Sect. 4.1) need to be assessed so that trials can be correctly evaluated. Ageing effects need to be studied in animal models to define neurochemical changes with age: for instance central levels of 5-HIAA increase, whereas central dopamine and blood testosterone levels decrease. These changes appear gradually when looking at groups but possibly occur rapidly in individuals. Ageing effects seem to be personality-subtype specific: type 1 alcoholics (late onset, binge drinkers often with comorbid anxiety) continue to drink throughout life and experience a steady social decline, whereas type 2 alcoholics (early onset, more sociopathic, continuous drinkers) generally 'burn out' around age 40 and stop drinking, although they have a higher mortality before this. Polydrug use (see Sect. 1.3) also has to be taken into account when assessing subjects in trials.

Biological markers

As mentioned in Sect. 4.1, alcoholics show several abnormal physiological responses, e.g. in P300 and monomorphic alpha rhythm, that could potentially be used as predictive variables in clinical trials. The P300 findings have been based on group means. It may be important to gather information on individuals and to stratify trials accordingly to assess the importance of this trait on treatment outcome. A possible confounding variable is volunteer bias, i.e. sensation seekers need to be accounted for. There seem to be no data on how heart rate measurement is affected by treatment strategies, but if this could be used as a gauge of outcome success or otherwise, it might provide a screen for putative therapeutic drugs. As already mentioned the strength of conditioning is negatively related to outcome with both opiate and cocaine users.

In the future, genetic variables undoubtedly will begin to be used as predictors of treatment response. A recent trial in depression using selective serotonin reuptake inhibitors found that harm avoidance, which is thought to reflect central 5-HT function, predicted the antidepressant response to a 5-HT reuptake blocker (Joyce et al. 1994).

Co-morbidity

As discussed above (Sects. 4.2, 5.1), many addicts coming into therapy have other psychiatric problems, which may affect treatment responses. For example, type 2 alcoholics with ASPD respond better than type 1 to training in coping skills, whereas interpersonal therapy works better for type 1 alcoholics, and ASPD adversely effects outcome in methadone maintenance programmes.

Personality traits and temperament should also be controlled for; for instance, high harm avoiders are less likely to initiate drug-taking behaviour but once started have more difficulty in stopping. Rating of personality and making psychiatric diagnoses should preferably be done when the subjects are drug free. Self-report gives 70% overlap with rating scales, but the use of corroborative information is important.

Compliance

This is a major predictive factor for outcome and a crucial factor in clinical trials. It is important to measure it in a placebo group, otherwise compliance rather than treatment response is being assessed; this effect has already contaminated clinical trials, such as those of lithium for alcoholism and desipramine for cocaine addiction. As self-reports cannot be relied on, various objective measures can be used. For example, riboflavin can be added to the treatment drug and detected in urine, although this can give false positives if taken only the night before measurement, instead of chronically. Tracer doses of phenobarbitone give a good indication of methadone compliance. Other methods include: the monitoring of blood levels, especially for long-lasting metabolites; taking sweat profiles with a transducer on the skin, to measure alcohol. Pill counts and microchip-containing caps on drug containers are alternative means of checking that treatment drugs have been taken in the prescribed amounts.

Although not strictly a compliance measure, hair profiling, which may register a quantifiable change in concentrations of opiates, cocaine, amphetamines or THC, can be used to estimate continued illicit use and thus the effectiveness of interventions.

Recruitment

Randomization of trials can be affected by volunteer bias and patient preferences. Factors which may encourage treatment seeking include self-perceived dependence; concomitant psychiatric disorder; social class and/or gender, e.g. women opiate addicts present earlier than men; judicial and penal factors; physical complications associated with addiction; severity of dependence, e.g. patients with severe withdrawal syndromes tend to present earlier.

Stratification of trials by each of these variables is not feasible as sufficient numbers of subjects would be too difficult to recruit. Given the lack of data on the relative importance of each variable (and others), it may be better to rate them and use post-hoc stratification to analyse combinations of variance using appropriate statistical methods.

Delegates stressed that in trials to assess the efficacy of any pharmacotherapy, psychotherapeutic factors have to be taken into account. Psychotherapy can be critical in gaining patient compliance and entry into trials, but the 'dose', type and method of administration of psychotherapy need to be measured and optimized as an inevitable feature of any trial. The degree and type of interaction between pharmacotherapy and psychotherapy is an important new dimension in drug addiction research but so far there are only a few studies across drug classes. One concern is that excessive psychotherapy can produce a ceiling effect that decreases the power of the therapeutic drug being studied.

Placebo-controlled trials are critical to establish the efficacy of any treatment. Licensing therapies without this is unethical. As placebo treatment is often a significant intervention in itself, delegates considered that 'usual care' would be a helpful secondary control group. Evaluation of therapy may also benefit from careful selection of control treatment and conditions: should a drug treatment be evaluated against a placebo condition, against population quit rates or against some other treatment?

6 Summary of future prospects

This section highlights some of the main areas of discussion at the meeting which may lead to future advances in the field. An overall summary of the major constructs considered is provided in Fig. 5.

6.1 Laboratory studies of drug dependence and addiction

Different models are needed for the various stages or epochs of drug abuse (initiation, maintenance, loss of control, withdrawal, relapse) not only at the behavioural, but also at the molecular, cellular and neural systems levels. Determining when animals become dependent would provide the basis for investigating the nature of the

Fig. 5 Overview of the main topics and constructs under discussion at the meeting. The concept of positive reinforcement was central to most discussions of drug-seeking behaviour, but the various mechanisms of reinforcement, via relief from withdrawal or anxiety, positive subjective effects or functional consequences (e.g. via cognitive enhancement) and the various neural adaptations that modulate these effects of drugs were also considered. The role of conditioning mechanisms, e.g. through Pavlovian conditioned (*CS*) stimuli or discriminative stimuli, or with the stimuli acting as conditioned reinforcers (*CR*) for instrumental or operant behaviour is discussed in the text. Hypothetically, many environmental and genetic influences can be seen to modify the effects of drugs as reinforcers. These modifications are shown schematically to impinge on the final common pathway of positive reinforcement, but may of course act on any of the modulatory constructs defined in the diagram. They include schedules of reinforcement, factors related to behavioural economics, prior behavioural history and current social context, as well as genetic factors that may be expressed in terms of trait factors or co-morbidity with other forms of psychiatric disorder. This figure is a version of a diagram constructed at the meeting with the aid of Dr I. Stolerman

mechanisms – behavioural, cognitive and neural – that underlie the progression from drug-taking behaviour to compulsive drug use and dependence. For example, several hypotheses were developed during the meeting concerning the transition from goal-directed actions to compulsive habits and their underlying neural substrates.

Many delegates thought that two crucial distinctions must be made when developing models: between acute and chronic drug administration regimens and between response contingent (i.e. active) versus non-contingent (passive) consumption. It is already apparent that these two important variables affect how the brain responds to drugs, chronic regimens involving self-administration clearly being far more relevant to human drug dependence.

The transition between stable intake and loss of control (i.e. bingeing) can be reproduced in drug self-administration paradigms to a degree (Markou and Koob 1991). For example, rats given an unlimited supply of cocaine will show apparent loss of control after 1–2 h intake of 100–200 mg/kg of drug. In contrast, rats will self-administer heroin at regular intervals for long periods without apparent loss of control; there is some early escalation in dose but this stabilizes. Alcohol consumption in rats also escalates to some extent but there are often periods of spontaneous withdrawal. Some of these phenomena appear to be at the core of the problem of addiction and deserve further study at all levels of analysis. The development of various theories of operant behaviour based on behavioural economic theory may facilitate this analysis; it may also be informative to compare the factors producing bingeing and relapse in drug addiction to similar phenomena in other forms of psychopathology, such as bulimia nervosa (cf. Carroll 1996) and gambling, as similar principles may apply.

More account must be taken of how factors such as tolerance, sensitization and withdrawal interact to generate drug dependence, as it was clear from the discussions that their explanatory power is limited when considered in isolation. While commonalities among drugs were emphasized, it was evident from the meeting that it is important to acknowledge differences among them, including their different modes of self-administration. For example, it is still difficult to replicate the complex human mode and pattern of nicotine and alcohol administration. Smoking tobacco provides frequent, small doses of nicotine, which can be exquisitely regulated to optimize delivery to the brain. Animals will not voluntarily inhale and nicotine is usually delivered by injection, usually non-contingently, although there are reports of successful i.v. self-administration (e.g. Goldberg and Spealman 1982). Similarly, few animal species readily drink alcohol voluntarily (but see Box 2C). The factors underlying such clear species differences must be explored if we are to understand why humans do, but animals generally do not, self-administer these drugs.

Two issues that raised considerable concern were craving and relapse, neither of which have been much studied in animals. There was a lack of consensus about the definition of craving, which can be attempted at both behavioural and subjective levels. Correlates of craving can be studied at the neurobiological level. The implication of the discussions was that several aspects of craving should be pursued, including animal models at the behavioural level, and that they need to be evaluated in terms of the success in predicting relapse. This multidisciplinary endeavour could act as a focus for the development of cognitive therapy and pharmacological treatment.

Some delegates considered animal experiments simplistic, as they rarely take into account the multifactorial nature of drug abuse. Certain aspects of addiction, particularly sociological factors, may be impossible to study in animals; however, the richness of environmental contingencies in the human situation can be modelled to the extent of providing animals with a choice among reinforcers (see Sect. 2, Box 2F; and review by Bickel et al. 1995). This is particularly important in quantifying the concept of 'lack of control' in drug taking. For example, using concepts from behavioural economics, previous studies have shown that in non-dependent animals food consumption is inelastic whereas cocaine consumption is elastic (Elsmore et al. 1980). Such experiments might be interesting to repeat in dependent animals. Alternative approaches to the 'behavioural economics' of addiction should also be explored (cf. Heyman 1996).

In the context of neurobiological investigations of dependence and addiction, it was generally agreed that studies at molecular, cellular and systems levels must be conducted within an appropriate behavioural setting and with clear distinctions made concerning the stage of the process under examination. Two major issues for this area are the utility of a reductionist approach that focuses upon a set of molecules (e.g. transmitter receptors; intracellular messengers and transcription factors) and the problems of applying neurobiological findings obtained from animals to drug-dependent humans. A major hypothesis that was discussed at the meeting was that there may be specific molecular processes that are regulated at different phases of the dependence process in discrete brain regions. It was conjectured that there are specific molecular targets that mediate the primary effect of each category of drug, but that this in turn initiates cascades of intracellular events that may be common to many classes of drugs and to the associated neuroadaptations underlying dependence. It was obvious from the discussions that these studies are in their infancy, especially those being conducted within an appropriate behavioural setting. Moreover, the impact of new molecular strategies, including targeted gene mutations and the use of in vivo antisense oligonucleotide treatments, has yet to be felt but they are likely to prove informative.

It was agreed by many at the meeting that a number of key psychological processes can now be studied at a neural systems level. One way of conceptualising these is as action-outcome (i.e. instrumental) associations and the transition to drug-taking (stimulus-response) habits (see Box 2E and Fig. 1), as well as the more general is-

sue of conditioning processes that imbue environmental cues with salience so as to induce craving and withdrawal. The basis for such future studies is rooted in the neuroanatomical advances that have defined the relationships between limbic structures, such as the amygdala and hippocampus, and striatal structures. Thus, areas of the brain long implicated in emotion, learning and memory – the so-called limbic system – are now seen to be intimately related to areas where addictive drugs have their primary sites of action, and these anatomical connections may mediate conditioning influences known to strengthen drug-seeking propensities (see Fig. 3).

There was little disagreement that the meso-accumbens dopamine system has at least some important role in the processes underlying addiction and dependence on a number of drugs, even for those not having a primary dopaminergic site of action (e.g. alcohol). However, there was considerably less consensus about the involvement of other neurochemical systems that may be related to behavioural aspects of addiction, such as loss of control, as well as neural adaptations during withdrawal, sensitization and tolerance. Learning mechanisms that may dictate the course of sensitization and tolerance may well implicate glutamate receptors of the NMDA subtype. In the contexts of loss of control and withdrawal, studies of the forebrain 5-HT system are assuming greater importance. Indeed, the issue of whether there are independent neural systems that mediate aversive effects of drugs in an opponent manner, e.g. the periaqueductal grey and locus ceruleus, is a major question for future research. One alternative hypothesis is that such motivational opponent processes are an emergent property of dynamic changes in regulation of the meso-accumbens dopamine system.

While these advances in identification of neural systems contributing to addiction may enhance our understanding of the effects of drugs as reinforcers in experimental animals, serious questions remain as to their applicability to the dependent human. For example, the dopamine hypothesis of drug dependence has been little tested in humans, although this may be feasible in a therapeutic context using positron-emitting dopamine receptor antagonists. Positron emission tomography (see Box 3E) may also be useful in a functional neuroimaging setting for testing hypotheses concerning the neural substrates of conditioned drug responses and for understanding the neural correlates of subjective responses such as craving.

Another major area of expansion is clearly that of predisposition (or vulnerability) to drug dependence produced by environmental and genetic factors. One of the attractions of the sensitization hypothesis is the possibility that life experiences, particularly early in development when the brain is still undergoing maturation, may alter subsequent responses to the reinforcing effects of drugs. There is a burgeoning body of data which suggests that various stressors may influence the propensity to self-administer a variety of drugs of abuse. However, an all-encompassing conclusion that stressors inevitably enhance the reinforcing effects of drugs must be tempered by more detailed analyses of the different effects of various forms of stress and by investigations into which epochs of the addiction process are most at risk. For example, the initiation of, or relapse to, drug self-administration may be affected differently from the maintenance of such behaviour.

The fact that so many stressors have comparable effects on the reinforcing effects of drugs suggests that there may be common neuroendocrine mechanisms that modulate the neurochemical modes of action of these drugs. A particularly interesting possibility is that steroids such as corticosterone may modulate central dopaminergic mechanisms and that 'stress hormones' such as corticotrophin-releasing factor (CRF) may exert comparable effects in areas of the brain concerned with aversive (i.e. opponent) processes and also with sensitization. Such neuroendocrine mechanisms may also be important in the context of gender, a factor possibly under-investigated so far in experimental studies.

Many responses relevant to drug reinforcement have been shown to have a genetic component. Genetic animal models, such as those for alcohol-drinking preference, alcohol locomotor stimulation and sensitization, could fruitfully be employed to dissect reinforcement mechanisms more completely. The increasing use of behavioural genetic strategies will hopefully ultimately marry with the more molecular approaches described above and in Sect. 3 (see Box 3D).

6.2 Sociological, epidemiological and historical studies of drug dependence and addiction

Reliable measures in humans have to be developed that are relevant to the biological and psychological constructs emerging from animal experimentation. Only through such studies in humans can animal researchers ultimately evaluate their models. When designing experiments it is important to remember that control of previous drug use in humans is difficult in experimental conditions and samples made up of treatment seekers may not therefore be representative.

Several areas where human data are required were identified: (1) Long-term studies in humans to clarify the continuum from drug use to dependence. (2) Poly-drug use is now the norm but little is known about the effects of drugs such as heroin, cocaine, cannabis, nicotine and alcohol in combination. Drug interaction studies require substantial time in order to understand the complex dose relationships but this understanding is critical to developing useful treatments. (3) The relationship between sleep and drug use is also complex. Sleep deprivation could contribute to either drug seeking or drug toxicity but more information is required to understand this relationship. (4) Research on risk factors, comparing those who have never tried drugs with those who have tried and not become dependent and with those who have become dependent/addicted. (5) The relationship between behavioural or psychiatric history and co-morbidity needs to

be examined in order to assess possible causal relations between the propensity to drug dependence and other forms of psychopathology.

Population-based epidemiological studies are essential for describing and identifying the nature and extent of drug-related problems within the general population. They provide a context within which we might better understand the complex nexus of factors that predict, albeit with less than 100% accuracy, those who will or will not use, abuse and become dependent on drugs and exhibit other forms of psychopathology. However, additional work is needed to improve the questions these studies seek to answer. Some examples discussed at the meeting follow.

Most epidemiological studies measure the nature and extent of drug use, abuse and dependence, together with their correlates and consequences, in the general population. As a result they often miss the more deviant and drug-involved segments of society: people who often have no stable residences or who maintain low visibility. To compensate for this limitation, social indicator or catchment studies examine 'high-risk' groups, e.g. clients in treatment programmes, prisoners and the homeless. In the USA at least, many studies of both population and social indicator type are focused on understanding the nature of drug consumption patterns at the 'national' level.

At some point, for both scientific and fiscal reasons, it may be possible to use the broad epidemiological studies of the general population and of selected groups as a basis for selecting smaller targeted samples that can be brought into the laboratory to test specific hypotheses. Further, the broader epidemiological studies provide a basis for identifying certain samples to be followed prospectively and longitudinally. If attrition from the sample/study can be held to a minimum, the longitudinal samples can be used to extrapolate the findings about success rates and their social and economic impact to larger populations.

Only recently have serious attempts been made to connect the national studies into a comprehensive and integrated view of drug use, abuse and dependence at local community levels, where fiscal and human capital resources are needed to deal directly with those needing various types of intervention. Although appropriate lists of social indicators that can be measured at the community level are being developed, consensus has not been reached on which data elements are essential social indicators or how they should best be measured. Much more work is needed on the development of reliable screening methods, first, to differentiate between use, abuse and dependence, and second, to measure various types of comorbidity.

A better understanding of how genetic factors interact with brain and behavioural processes and how this interaction is affected by social and environmental factors is now urgently needed. Despite reasonably strong and consistent evidence that a family history positive for alcoholism or drug abuse or a psychiatric disorder is correlated with the presence of these disorders in the offspring, the precision of predictions based on these data is not perfect. What accounts for the false positives and negatives found in every study? Some delegates suggested the answer lies in resilience: some people who are considered high risk simply defy the odds. If so, then nature and nurture are interactive, each accounting for some independent variance in outcome, with some shared variance.

Significantly more work is needed to understand better the relationship between drug involvement and social roles. Individuals with varying biological and genetic vulnerabilities are nested within various types of pro- and antisocial contexts e.g. their family of origin (parents and siblings), their family of procreation (partner, children), other intimate interpersonal relationships, work and social relationships, their peers, neighbourhood and community, including community-based organizations such as churches and, for adolescents, their schools. Each of these contexts, e.g. biological/genetic, family, psychological, social, situational, cultural, could act either independently or interactively to influence all the stages and aspects of involvement with drugs of abuse. Some evidence exists that changes in social roles, e.g. work, marriage and parenting, influence an individual's increasing or decreasing involvement with drugs.

The effects of cultural, historical and socio-legal contexts complicate the aetiology of drug use, abuse and dependence even further. We need a better understanding of how individuals are influenced by their cultural traditions, which may or may not be those of the country they reside in, and how these traditions increase the risk of, and protection from, involvement with drugs.

Historical studies on drug issues such as the social response to new drugs, styles of control, and comparison among cultures of use and attitudes have been rare. Yet there is an extensive and relevant history whose investigation should be encouraged. The two American episodes of attraction toward and later repulsion from cocaine – at an interval of almost a century – afford a useful perspective on the natural history of a drug 'epidemic'. The varying national approaches toward drugs before World War Two have rarely been studied, although cocaine appeared in large quantities in the 1880s and morphine half a century earlier. Such studies would add a dimension to biological and contemporary social analyses of drug use.

6.3 Education

Education is badly needed in four areas: among scientists working in the field and for the medical profession, policy makers and the public. Improved education of physicians, including general practitioners, would mean that screening for addictions could take place in general practice, providing a major opportunity for early, minimal intervention. Paraprofessionals or practice nurses could also be trained to detect addiction and initiate treatment.

Education remains a crucial way to prevent people from becoming addicted but it is a complex and controversial topic. In some areas, such as specific interventions by general practitioners to reduce smoking and drinking, good effects have been observed. The key here is to detect and educate early, before the drug abuse has solidified into addiction.

There was general agreement that anti-drugs education in schools is ineffective, not least because most adolescents have feelings of invulnerability and rebellion. Moreover, giving information about the pharmacology and toxicology of addictive drugs to schoolchildren, although commonly done, may increase interest, demystify and reduce fear.

A better approach seems to be total community projects, with sustained alterations in public attitude. A few successful pilot programmes point the way: projects set in a community-wide effort for education that includes the workplace and religious and social groups, with advertising that deglamorizes drug taking (Pentz et al. 1989). In those projects where some suitable alternative activity is found for children at risk, the initiation into use of tobacco, cannabis and solvent abuse has been delayed (Schuster and Kilbey 1992). Parental monitoring of children also plays an important part: a study in Baltimore (Chilcoat et al. 1995; Chilcoat and Anthony 1995) substantiated that well-monitored children had much lower drug use than those poorly monitored, while another recent study has shown that children involved in some form of 'religious' activity two or three times a week were also less likely to use drugs (Johanson et al. 1996). The historical perspective could also be informative. Extensive records exist of various forms of anti-drug education used early in this century and their consequences. These may help to illuminate contemporary quandaries regarding the best approach to informing school children.

The wide-ranging nature of these summary suggestions for further studies should emphasize the overall need to consolidate the opportunity for communication and integration across disciplines provided by this meeting. The message for psychopharmacological studies is that the analysis of how drugs affect behaviour in terms of pharmacological and behavioural factors is now sufficiently sophisticated to begin to investigate new factors and contemplate the value of evolving theoretical constructs. The eclectic nature of this multi-disciplinary field may enable the development of novel forms of pharmacological and psychological therapy for drug dependence which can rapidly be brought into clinical trials.

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