Stria terminalis lesions attenuate the effects of posttraining oxotremorine and atropine on retention

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In these experiments, we examined the effects of posttraining administration of the cholinergic agonist oxotremorine and the cholinergic antagonist atropine on retention in rats with lesions of the stria terminalis (ST). Male Sprague-Dawley rats, with either sham or bilateral ST lesions, were trained in a one-trial step-through inhibitory-avoidance task and a Y-maze discrimination task. Immediately after training on each task, they received i.p. injections of saline, oxotremorine (50.0 $\mu\text{g/kg}$), or atropine (3.0 mg/kg). Retention of each task was tested 1 week following training. Lesions of the ST did not affect retention of either task in otherwise untreated animals, but blocked both the memory-enhancing effect of oxotremorine and the memory-impairing effect of atropine. These findings suggest that activation of pathways within the ST is involved in cholinergic influences on memory, and are consistent with the view that the amygdaloid complex is involved in integrating neuromodulatory influences on memory storage.

The findings of numerous studies have implicated central muscarinic-cholinergic mechanisms in memory storage (Bartus, Dean, Goss, & Lippa, 1980; Bartus, Dean, Pontecorvo, & Flicker, 1985; Davies, 1985; Karczmar & Dun, 1978; Russell, 1982; Stratton & Petrinovich, 1963). In general, cholinomimetic agents facilitate memory (Dunnett, 1985; Flood, Smith, & Cherkin, 1983, 1984, 1985; Haroutunian, Kanof, & Davis, 1985; Introini & Baratti, 1984; Introini-Collison & McGaugh, 1988; Murray & Fibiger, 1985), whereas muscarinic receptor antagonists induce amnesia (Drachman, 1977; Drachman & Leavitt, 1974; Flood, Landry, & Jarvik, 1981; Introini & Baratti, 1984; Introini-Collison & McGaugh, 1988). These effects have been observed in a wide variety of tasks, including an appetitively motivated task (Stratton & Petrinovich, 1963), active avoidance (Flood et al., 1981), inhibitory avoidance (Gower, 1987; Introini-Collison & McGaugh, 1988), and aversively motivated discrimination learning (Introini-Collison & McGaugh, 1988). These findings suggest that acetylcholine released during or immediately after training is involved in the modulation of memory storage (McGaugh, 1989).

Recent evidence suggests that opioid peptidergic systems interact with the cholinergic system during memory storage. Posttraining administration of oxotremorine and naloxone, in doses that are subeffective by themselves, significantly facilitate retention when given together immediately posttraining (Baratti, Introini, & Huygens, 1984). Furthermore, atropine blocks the memory-facilitating effects of naloxone, whereas oxotremorine an-

tagonizes the amnestic effects of both morphine and β -endorphin (Baratti et al., 1984; Introini & Baratti, 1984). These findings are in agreement with extensive neurochemical evidence indicating that opioid agonists inhibit acetylcholine release and that the inhibition is reversed by opioid antagonists (Jhamandas, Hron, & Sutak, 1975; Jhamandas & Sutak, 1974, 1983).

There is also extensive evidence indicating that the cholinergic system interacts with the adrenergic system in influencing memory storage. We recently found that atropine blocks the memory-enhancing effect of low doses of epinephrine, whereas the amnesia induced by high doses of epinephrine is completely blocked by oxotremorine and is partially attenuated by physostigmine (Introini-Collison & McGaugh, 1988).

The stria terminalis (ST) is a main afferent-efferent pathway of the amygdala (Cowan, Raisman, & Powell, 1965; De Olmos, Ahleid, & Beltramiro, 1985; De Olmos & Ingram, 1972). The findings of previous studies indicate that lesions of the ST block the memory-enhancing effects of posttraining epinephrine (Liang & McGaugh, 1983b) and naloxone, as well as β -endorphin-induced amnesia (McGaugh, Introini-Collison, Juler, & Izquierdo, 1986). In view of the evidence that both epinephrine and opioid peptides interact with the cholinergic system in modulating memory storage, the present experiments were undertaken to determine whether the effects of cholinergic drugs on memory storage also involve the ST.

METHOD

Subjects

Male Sprague-Dawley rats (180 g, 60 days old; Charles River Laboratories) were individually housed upon arrival and maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.) with food and water available ad lib.

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Surgery

Approximately 1 week after arrival, stereotaxic surgery was performed under ketamine anesthesia (100 mg/kg i.p.) on rats pretreated with atropine (0.5 mg/kg i.p.) and xylazine (5 mg/kg i.p.): approximately half of the animals received bilateral ST lesions and half received sham lesions. The ST lesions were produced by radio-frequency current (1.5 V, 20 sec; Grass Instruments Model LM-3) administered through bipolar electrodes (twisted, paired stainless steel wires with tips 0.5 mm apart, insulated except for the 0.5 mm at the tip) at brain coordinates AP -0.5 mm from bregma, ML $\pm$ 2.5 mm, DV -4.1 mm from the dura, nose bar elevated 0.5 mm (McGaugh et al., 1986). Sham lesions followed the same procedure except that the electrodes were lowered to DV -3.5 mm below the dura and no current was passed. Skull bones were sealed with wax and Gelfoam.

Inhibitory-Avoidance Training

One week after surgery, the rats were trained on a trough-shaped inhibitory-avoidance (IA) apparatus (McGaugh et al., 1986) consisting of two compartments separated by a sliding door that opened by retracting into the floor. The starting compartment was illuminated by a tensor lamp, which provided the only illumination in the testing room. On the training trial, each rat was placed in the lighted compartment, facing the closed door. When the rat turned around, the door leading to the dark compartment was opened. In previous research, we have determined that these procedures reduce the variability in response latencies. When the rat stepped through the door into the dark compartment, the door was closed, a footshock (0.35 mA, 60 Hz) was delivered, and the response latency was recorded. A footshock duration of 0.7 sec was used in the experiment examining the memory-enhancing effect of oxotremorine, whereas a footshock duration of 2.0 sec was used to assess the memory-impairing effects of atropine. These procedures were used to avoid possible floor and ceiling effects in assessing the effects of the drugs on retention performance. Following the training trial, the rat was immediately removed from the apparatus and injected as described below. On the retention test 1 week later, the rat was placed in the lighted compartment as on the training session and the step-through latency (maximum of 600 sec) was recorded (McGaugh et al., 1986).

Y-Maze Discrimination Training

One week later, the rats were assigned to new treatment groups and trained on a Y-maze discrimination (YMD) task. The left alley of the Y-maze was illuminated, and the rat was trained to enter the left alley to escape from a footshock as described below. On the first trial, the rat was placed in the start alley and the sliding door of this alley was opened while the door leading to the right alley remained closed. Following a 10-sec delay, a footshock was delivered and remained on until the rat entered the left arm. The rat was then replaced in the start compartment after an intertrial interval of 40 sec. On the second trial, the door to the left alley was closed so that the rat was forced to enter the right (dark) alley, where it received a footshock. Immediately after entering the dark alley, the sliding door was closed and the rat was removed and placed in the start compartment. On subsequent trials (20-sec intertrial intervals), the rat was allowed to choose between the alleys, and each trial was terminated when the rat entered the left alley. If a rat failed to enter the left alley within 60 sec, it was placed in the left alley and retained there for 20 sec. Training was continued until the rat chose the lighted arm on three consecutive trials. The rat was then removed and immediately injected as described below. The nominal footshock intensity (i.e., read from meter) was 0.85 mA. The shock source used in the study investigating the effects of oxotremorine was replaced by a new one prior to the study of the effects

of atropine. Although the nominal footshock intensity was the same in the two studies, it was clear from the animals' responses to the shock (as well as the retention scores of control animals) that the new shock source produced a higher effective footshock level.

Retention was assessed 1 week later. The procedures used for the retention test were similar to those in the original training, except that the position of the safe alley was reversed—that is, the animal could escape from the shock only by entering the right (dark) alley. Each rat was given six trials (20-sec intertrial interval) with both alleys open. The number of errors made on the reversal-training trials was used as the measure of retention. The use of this procedure to assess retention was based on the assumption that retention of the original task impairs acquisition of the reversed discrimination. Furthermore, in previous work using this task, we have found that if the discrimination is not reversed—that is, if the animals are simply retrained on the original discrimination—the animals make very few errors and, consequently, the task is insensitive to memory-enhancing treatments (McGaugh et al., 1986).

Drugs and Experimental Groups

Immediately after training on both the IA and the YMD tasks, the rats were injected i.p. with saline, oxotremorine sesquifumarate (Sigma; 50 μ g/kg), or atropine sulfate (Sigma; 3.0 mg/kg). The drugs were dissolved in saline to a volume of 1 ml/kg. Doses are expressed as the base.

Histology

Lesions were verified histologically. All rats with ST or sham lesions were sacrificed by an overdose of pentobarbital (100 mg/kg i.p.) and perfused with physiological saline solution (0.9%) followed by formalin (10%). The brains were removed immediately afterward, stored in (10%) formalin at least 48 h, and sliced (40 μ m). The slices were stained with cresyl violet. The tissues were examined for location of the lesions, blindly with respect to both treatment and behavioral performance. Behavioral data of rats with lesions that either missed the ST or invaded adjacent areas (e.g., the fimbria-fornix) were excluded from the final analysis. Animals were included only if the ST was substantially lesioned bilaterally in one of the coronal sections within AP 0.4 to AP -1.0. The extent of the maximum and minimum lesions of the animals included are shown in Figure 1.

Statistical Analysis

Data obtained in the IA task are expressed as median and interquartile ranges, and data obtained in the YMD task are expressed as the mean $\pm$ SEM. Statistical analysis was performed with ANOVAs, and *p* values of less than .05 were considered significant. The number of animals per group is indicated in the figure legends.

RESULTS

Figures 2 and 3 show the results obtained with animals injected with oxotremorine following training in the IA and YMD tasks, respectively. In both cases, the ANOVAs indicated significant differences among the groups [IA, $F(3,30) = 6.3$, $p < .002$; YMD, $F(3,35) = 5.4$, $p < .005$]. In both tasks, posttraining administration of oxotremorine significantly enhanced retention in the sham-operated rats ($p < .01$ in both cases). ST lesions completely blocked oxotremorine-induced memory facilitation in both tasks. As a consequence, the interactions between the lesion and drug treatments were statistically

Figure 1. Maximum (left) and minimum (right) stria terminalis lesions in successive coronal sections (From *A stereotaxic atlas of the rat brain*, by L. J. Pellegrino, A. S. Pellegrino, and A. J. Cushman, 1979, New York: Plenum. Copyright 1979 by Plenum Press. Reprinted by permission.)

significant [IA, $F = 9.2$, $p < .005$; YMD, $F = 4.4$, $p < .05$].

Figures 4 and 5 show the results obtained with animals injected with atropine following training in the IA and YMD tasks, respectively. On both cases, the ANOVAs indicated significant differences among the groups [IA, $F(3,36) = 27.4$, $p < .0001$; YMD, $F(3,36) = 12.1$, $p < .0001$]. In both tasks, posttraining administration of atropine significantly impaired retention in the sham-operated

rats ($p < .01$ in both cases). ST lesions completely blocked atropine-induced amnesia in both tasks. As a consequence, the interactions between the lesion and drug treatments were statistically significant (IA, $F = 35.5$, $p < .0001$; YMD, $F = 11.0$, $p < .005$).

DISCUSSION

The present results are consistent with extensive evidence indicating that muscarinic cholinergic agonists generally facilitate memory (Dunnett, 1985; Flood et al., 1983, 1984, 1985; Introini-Collison & McGaugh, 1988; Murray & Fibiger, 1985), whereas muscarinic blockers typically induce amnesia (Blozovski & Dumery, 1984; Elrod & Buccafusco, 1988; Introini-Collison & McGaugh, 1988; Lo Conte, Bartolini, Casamenti, Marconcini-Pepeu, & Pepeu, 1982; Wirsching, Beninger, Jhamandas, Boegman, & El-Defrawy, 1984). In both the IA and the YMD tasks, posttraining systemic administration of oxotremorine enhanced retention, whereas atropine impaired retention. Furthermore, the findings indicating that the effects of both oxotremorine and atropine require an intact ST indicate that the amygdala is involved in the action of cholinergic systems in memory modulation. These results are consistent with the findings of Blozovski and Dumery (1984) indicating that, in young rats, retention is impaired by atropine injected into the basolateral nucleus of the amygdala prior to training. It is of interest to note that for both the memory-enhancing effects of oxotremorine and the memory-impairing effects of atropine,

Figure 2. Effects of posttraining oxotremorine ($50 \mu\text{g/kg}$) on step-through inhibitory-avoidance (IA) retention in sham-operated and stria terminalis-lesioned rats. One week following surgery, rats were trained on the IA task then given posttraining injections of saline or oxotremorine. They were tested for retention 1 week later. $**p < .01$ as compared with the other groups. $N = 10$ –14 rats per group.

Figure 3. Effects of posttraining oxotremorine (50 μ g/kg) on retention of a Y-maze discrimination (YMD) task in sham-operated and stria terminalis-lesioned rats. One week after completion of inhibitory-avoidance testing, rats were trained in the YMD task and given posttraining injections of saline or oxotremorine. Retention was tested 1 week later. ** $p < .01$ as compared with the other groups. $N = 10$ –12 rats per group.

Figure 4. Effects of posttraining atropine (3.0 mg/kg) on step-through inhibitory-avoidance (IA) retention in sham-operated and stria terminalis-lesioned rats. One week following surgery, rats were trained on the IA task then given posttraining injections of saline or atropine. They were tested for retention 1 week later. ** $p < .01$ as compared with the other groups. $N = 10$ –14 rats per group.

Figure 5. Effects of posttraining atropine (3.0 mg/kg) on retention of a Y-maze discrimination (YMD) task in sham-operated and stria terminalis-lesioned rats. One week after completion of inhibitory-avoidance testing, rats were trained in the YMD task and given posttraining injections of saline or atropine. Retention was tested 1 week later. ** $p < .01$ as compared with the other groups. $N = 10$ –12 rats per group.

findings comparable to those reported above were obtained even if animals with larger lesions (which invaded the fimbria-fornix) were included in the analyses. (These analyses are not reported in the Results section.)

Previous findings indicate that ST lesions also block the impairing effects of posttraining electrical stimulation of the amygdala (Liang & McGaugh, 1983a) as well as the memory-enhancing effects of systemically administered epinephrine (Liang & McGaugh, 1983b). Other findings from our laboratory suggest that the effects of epinephrine on memory involve the release of acetylcholine (Introini-Collison & McGaugh, 1988). We have also found that ST lesions block both the memory-enhancing effects of naloxone and the impairing effects of β -endorphin (McGaugh et al., 1986). Furthermore, lesions of the ST also block the memory-enhancing effects of intra-amygdala injections of norepinephrine (Liang, McGaugh, & Yao, 1989).

In the present experiments, the drugs were injected systemically. Thus, we do not know whether the site of action of the drugs involves cholinergic receptors within the amygdala (Blozovski & Dumery, 1984) or at loci in other brain regions. Lesions of the ST might attenuate the memory-modulating effects of the drugs either by blocking inputs from, or by blocking outputs to, cholinergic systems. The memory-modulating effects of the drugs may be mediated by influences on the amygdala or may simply require an intact amygdala. In view of the evidence that ST lesions block the memory-modulating influences of a variety of posttraining treatments, including brain stimulation as well as drugs affecting several neuromodulatory systems, it seems possible that the amygdala is a site of integration of neuromodulatory influences on memory storage. This view is consistent with other evidence indicating that memory storage can be modulated by posttraining intra-amygdala injections of agonists and antagonists affecting a variety of receptor systems (Brioni, Nagahara, & McGaugh, 1989; Gallagher & Kapp, 1978, 1981; Introini-Collison, Nagahara, & McGaugh, 1989; Kesner, 1981; McGaugh, Introini-Collison, & Nagahara, 1988).

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