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Adrenoreceptor Antagonist Treatment Influences Recovery of Learning Following Medial Septal Lesions and Hippocampal Sympathetic Ingrowth

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HARRELL, L. E., A. PEAGLER AND D. S. PARSONS. *Adrenoreceptor antagonist treatment influences recovery of learning following medial septal lesions and hippocampal sympathetic ingrowth.* PHARMACOL BIOCHEM BEHAV **35**(1) 21–28, 1990.—Previous studies have demonstrated that in male rats hippocampal sympathetic ingrowth (HSI), which is induced by medial septal lesions (MS), is detrimental to recovery of spatial learning. The present study was performed in an attempt to determine if this effect was mediated through adrenergic receptor activity. Adult male Sprague-Dawley rats underwent training on a modified version (i.e., 4 arms baited) of a radial-8-arm maze task. Following attainment of learning criterion animals underwent one of three surgical procedures: CON (sham surgeries); MSGx (MS + superior cervical ganglionectomy—to prevent HSI); MS (MS + sham ganglionectomy). Reacquisition trials were performed in the same manner as initial acquisition except animals were treated with vehicle, propranolol (20 mg/kg), or phentolamine (20 mg/kg) 30 minutes prior to testing. As expected, vehicle-treated MS animals took longer to reacquire the task than MSGx animals, who were in turn more impaired than CON animals. Propranolol (β-adrenergic antagonist) treatment impaired performance of both the MS and MSGx group, but did not alter the CON group. Phentolamine (α-adrenergic antagonist) increased the number of trials to reattain criterion in the CON group, had no effect in the MSGx group, and markedly improved performance in the MS group. The results suggest that HSI mediates its detrimental effects through α-receptors, while β-blockade, in the setting of brain injury, is detrimental to performance regardless of the presence or absence of HSI.

Learning Memory Phentolamine Propranolol Medial septal lesions Hippocampal sympathetic ingrowth Adrenoreceptors Autonomic nervous system

PERIPHERAL sympathetic adrenergic fibers originating in the superior cervical ganglia (SCG) can be induced to grow into the hippocampal formation following cholinergic denervation of the hippocampus by electrolytic lesions of the medial septum (MS) (6). Several lines of evidence suggest that these fibers are functional and can potentially modify hippocampal activity as: 1) norepinephrine levels are found to rise and parallel the number of newly formed noradrenergic nerve terminals (40), 2) hippocampal glucose metabolism can be modified by electrical stimulation of the preganglionic sympathetic trunk after sympathetic ingrowth (26), and 3) abnormal spontaneous electrical activity in the dentate gyrus returns to normal paralleling sympathetic ingrowth (2).

Behaviorally, early studies suggested that hippocampal sympathetic ingrowth (HSI) mediated no functional effects (36,37). In these investigations, ingrowth was induced by anterior hippocampal lesions. Since the behavioral tasks employed were sensitive to hippocampal dysfunction, it was possible that the effects of HSI were masked due to damage of the hippocampus. Later studies employing MS lesions were more suggestive of a functional role, as changes in activity levels and tactile reactivity were correlated to HSI (5).

More recently, the radial-8-arm maze task, which is sensitive to both cholinergic (11,62) and hippocampal dysfunction (48), has been utilized to assess HSI. Employing this task in combination with MS lesions, Crutcher *et al.* (7) and Harrell *et al.* (24) observed that once recovery processes were complete, removal of the SCG did not alter task performance. However, Harrell *et al.* (24) found that preventing HSI enhanced recovery of performance in male rats, suggesting that HSI was detrimental to relearning of a spatial/memory task. Since that time HSI has been found to be: 1) protective for regulatory behaviors (28), 2) have no effect on either passive (29) or active (unpublished observations) avoidance learning and 3) to be gender dependent (27). As ganglionectomy alone produces no effect on learned behavior (23), the effects of

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sympathetic ingrowth were concluded to be due to some interaction within the hippocampus.

In an attempt to further define the neurochemical systems through which HSI may mediate its effects, we investigated, in animals with and without HSI, the effect of administering adrenergic antagonists on recovery of a spatial learning task.

METHOD

Subjects and Experimental Groups

Male Charles-River-Sprague-Dawley rats with an initial weight of 180–200 g were housed individually in a temperature- and light-(12-hr L/D) controlled colony room with water continuously available. Prior to habituation training, animals were randomly divided into two major groups, i.e., those destined to undergo phentolamine (n = 63) or propranolol (n = 61) treatment. Animals within each major group were subsequently assigned to one of six potential groups: ConV (sham surgical procedures and vehicle treatment), ConD (sham surgical procedures and drug treatment), MS+V (medial septal lesion + V), MS+D; MSGx+V (medial septal lesions, ganglionectomy + V treatment), MSGx+D. Following randomization, all animals were deprived to 85% of the ad lib body weight. Food restriction was designed to allow 5 g body weight gain per week.

Apparatus

Animals were tested on a standard wooden, 8-arm maze (the center platform was octagonal in shape, 30 cm in diameter) with arms (75 cm long and 7 cm wide) spaced equidistant around the center platform. The entire apparatus was elevated 100 cm from the floor and was placed in a room with numerous visual cues.

Procedure

All animals received four days of habituation to the maze, during which time all arms were baited (¼ of a Kellogg's Froot Loop cereal). Following this time period, acquisition trials were begun. During these trials, 4 of the arms were baited, while 4 remained unbaited. The location of the food was determined by the use of random number tables and remained constant throughout the experiment for a given rat. A trial (one/day) continued until all 4 baited arms were visited and the food consumed, or until 5 minutes elapsed. Acquisition trials continued until a preset criterion was achieved (see below). At this point, the animal underwent whatever surgical procedure it had been randomized to initially. Three days after surgery, reacquisition trials were begun. These were performed in a similar manner to the initial acquisition trials with the exception that 30–45 minutes prior to testing, animals underwent vehicle or drug administration (as determined in initial randomization). Trials continued in this manner until criterion was reachieved. Criterion of learning, in both the acquisition and reacquisition trials, was defined as four correct responses (visiting baited arms) in the first 5 choices during a block of 5 consecutive trials. Errors were defined as either visiting unbaited arms or reentering previously visited baited arms.

Surgery

All surgery was carried out under ketamaine (87 mg/kg) and xylazine (13 mg/kg) anesthesia. Medial septal lesions (AP +0.8, LAT 0, DV −5.7) were made by passing DC current (3 mA × 15 sec) through a teflon-coated stainless steel electrode. Control animals were treated in a similar fashion except that no current was passed.

Superior cervical ganglionectomy was performed by making a midline neck incision and exposing the carotid arteries bilaterally. The ganglia were visualized and removed. Postoperatively removal was assessed by examining the animal for a Horner's Syndrome (ptosis and miosis). Sham-operated animals were treated in a similar manner except the ganglia were left in situ.

Pharmacology Treatments

Phentolamine (20 mg/kg) and propranolol (20 mg/kg) were made fresh daily in sterile water and administered intraperitoneally in a volume of 1 ml/kg. Vehicle injections were made with sterile water in a similar volume.

Histology

At completion of the experiment the animals were decapitated and the brain removed and frozen in cold 2-methylbutane (−60°C). Coronal sections (20 μm) were taken in duplicate through the septal region (every 100 μm) and triplicate throughout the hippocampus (every 200 μm). Sections from the septum were stained with cresyl violet for Nissl substance and acetylcholinesterase [(46); AChE], while those from the hippocampus were processed for Nissl substance, AChE and catecholamine histofluorescence (9).

Data Analysis

A repeated measures analysis of variance (ANOVA) was used to assess group (i.e., surgical effects), drug and trial effects and their interactions on total arm selections, total errors, and errors to baited and unbaited arms. A one-way ANOVA followed by Duncan's multiple range test was used to examine the effect of surgical and drug treatments on number of trials to pre- and postsurgical learning criterion.

RESULTS

Anatomical

Due to either surgical death (n = 7 phentolamine; n = 8 propranolol) or incorrect lesion placement (n = 21 phentolamine; n = 16 propranolol) 28 rats from the phentolamine group and 24 from the propranolol group were deleted from data analysis. Examination of the septal region in all lesioned animals (Fig. 1A) revealed complete destruction of the medial septal area throughout its anterior-posterior extent. In addition, some animals had damage to the vertical limb of the diagonal band of Broca, but no injury was observed within the lateral septal region, fornix or overlying cortical regions. In control animals, there was limited gliosis along the electrode track, but no obvious injury to the medial septum.

A normal pattern of acetylcholinesterase staining in the hippocampal formation was observed in all control animals. In lesioned groups, there was total loss of staining in the dorsal (septal) hippocampus with variable loss in the ventral (temporal) hippocampus (Fig. 1B).

Examination of the hippocampal formation for catecholamine histofluorescence in lesioned animals without ganglionectomy revealed typical peripheral sympathetic fibers (6). Large, thick, "knobby" appearing noradrenergic fibers were observed coursing through the molecular layer (not shown) of the dentate gyrus to eventually surround the dentate granule cells (Fig. 1C). Peripheral fibers were also observed surrounding the pyramidal cells of the CA_3 region (not shown). As expected, peripheral noradrenergic fibers were also observed around blood vessels, choroid plexus, and the pineal gland. In the MSGx animals, no peripheral

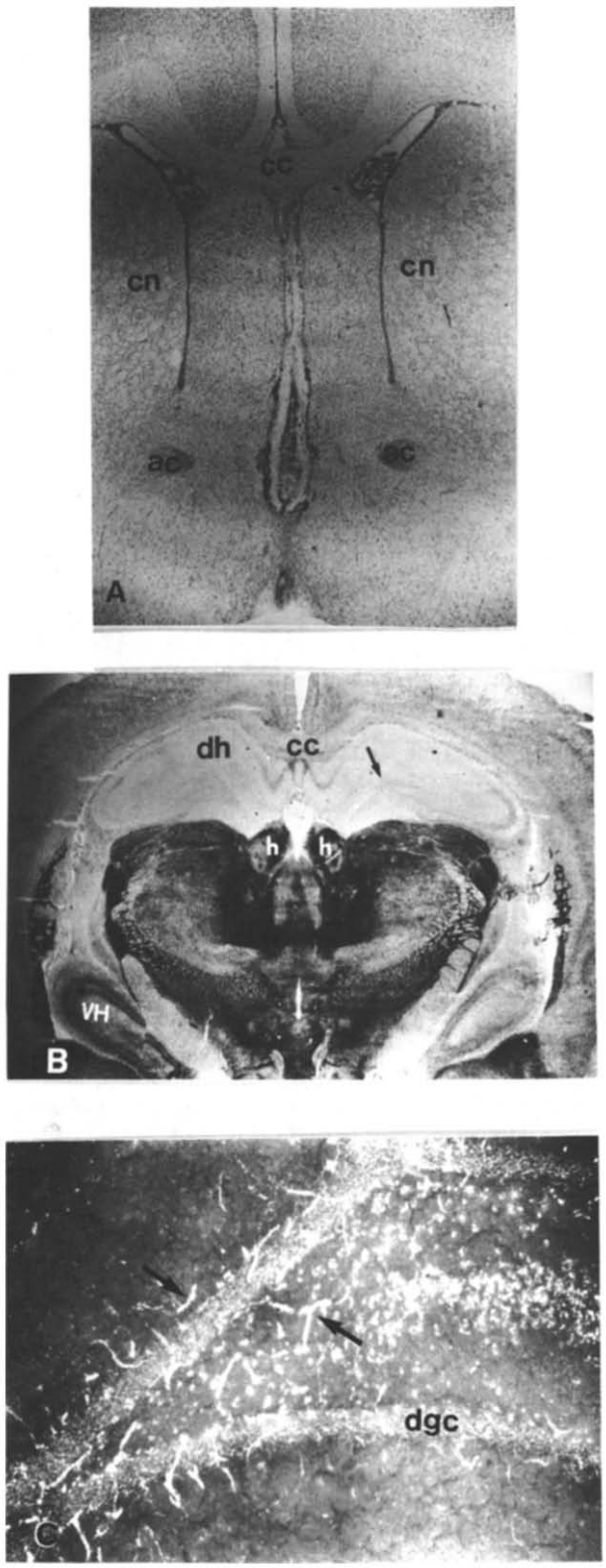

FIG. 1. Photomicrographs of representative medial septal lesion (Panel A; cresyl violet; ×3.44), dorsal hippocampal AChE depletion (Panel B; AChE stain; ×1.72), and hippocampal sympathetic ingrowth (Panel C; NE histofluorescence; ×34.4). The black arrow on Panel B defines where the photomicrograph was obtained for Panel C. Arrows on Panel C indicate HSI. ac = anterior commissure; cc = corpus callosum; cn = caudate nucleus; dgc = dentate granule cells; dh = dorsal hippocampus; h = habenula; vh = ventral hippocampus.

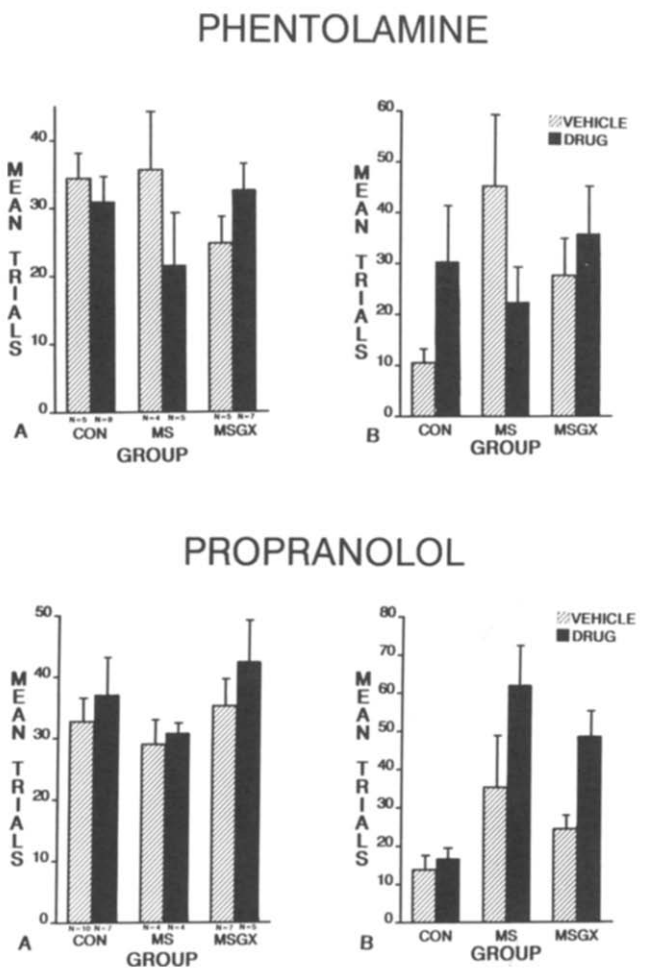

FIG. 2. Mean number of trials to achieve training criteria prior to (Panel A) and following (Panel B) surgical procedures in the phentolamine- (upper histogram) and the propranolol- (lower histogram) treated animals.

sympathetic fibers were found anywhere in the central nervous system. Central fibers were observed in the hypothalamus and hippocampus, thus validating the staining techniques in these animals. In control animals both peripheral and central fibers were observed in their appropriate anatomical territories.

Behavioral

Phentolamine treatment. The number of trials to preoperative criterion was not statistically different among the various groups of animals (Fig. 2). Following surgery, performance was found to be dependent upon group and treatment variables, $F(5,29) = 2.57$, $p<0.04$. Thus, vehicle-treated MS animals took significantly longer to reacquire performance than the MSGx group (Duncan's, $p<0.05$), who in turn were more impaired than control animals ($p<0.05$). Phentolamine treatment increased the number of trials to reattain performance criterion in control animals ($p<0.05$). This effect was not observed in the MSGx, where vehicle- and drug-treated animals performed in a similar manner. In the MS group (i.e., with HSI) phentolamine treatment reduced the number of trials to reattain performance criterion ($p<0.05$). In fact, their behavior was not statistically different from vehicle-treated *control* animals (i.e., without lesions).

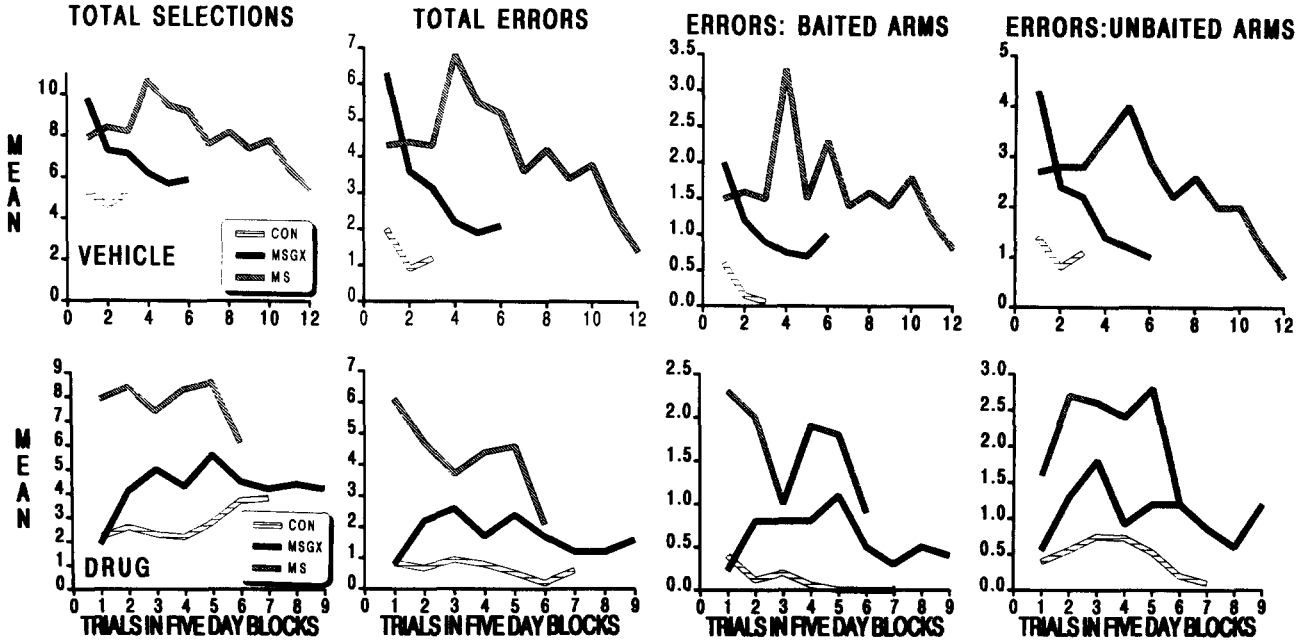

FIG. 3. Mean (±SEM) number of total arm selections, total errors, errors to baited and unbaited arms following surgical procedures for vehicle- (top panels) and phentolamine- (bottom panels) treated groups. Note that total number of trials to criterion was different between the vehicle- and drug-treated groups resulting in differences in total trials displayed on the X-axis.

To evaluate overall postoperative learning, a repeated designed ANOVA, assessing groups, drug, trials and their interaction on total arm selections, total errors, errors to both baited and unbaited arms was performed (Fig. 3). This analysis revealed a significant group and drug effect on total arm selections, $F(2,68)=11.51$, $p<0.0001$; $F(1,68)=8.55$, $p<0.004$, and errors to baited arms, $F(2,68)=9.82$, $p<0.0001$; $F(1,68)=4.03$, $p<0.004$, while only a group effect was observed on total errors, $F(2,68)=10.03$, $p<0.0001$, and errors to baited arms, $F(2,68)=8.98$, $p<0.0002$. No overall trial or interaction effects were observed on any aspect of learning. Further post hoc analysis revealed that overall on all measures of learning (i.e., total arm selections and errors, errors to baited and unbaited arms) the MS group was more impaired than the MSGx group which was more impaired than the control group (Duncan's $p<0.05$).

Since the main interest of this study was to assess the effect of drug therapy on learning after HSI, it seemed reasonable to further explore this issue by examining each group individually. Drug treatment of control animals was found to produce a decrease in total arm selections, $F(1,9)=19.11$, $p<0.0001$, which was reflected in a decrease of total errors, $F(1,9)=4.09$, $p<0.04$. Analysis of errors revealed no alterations in those toward baited arms, but a decrease in those to unbaited arms, $F(1,9)=5.05$, $p<0.02$. In the MSGx group, drug treatment was found to reduce total number of arms selected, $F(1,17)=14.1$, $p<0.0004$. Total errors were also reduced, $F(1,17)=6.24$, $p<0.01$, with this occurring in a nonspecific manner, i.e., errors to both baited, $F(1,17)=4.52$, $p<0.03$, and nonbaited arms, $F(1,17)=4.22$, $p<0.04$. Phentolamine treatment in the MS group was found to have no effect on any aspect of learning, but yet was found to reduce the total number of trials to achieve criterion (Table 1).

Propranolol treatment. Number of trials to achieve initial learning criterion (Fig. 2, Table 1) were similar among animals assigned to the various treatment groups. Following surgery, however, the number of trials to reacquire criterion was influenced by MS lesions, the presence or absence of ingrowth and drug treatment, $F(5,31)=17.3$, $p<0.001$. As expected, vehicle-treated animals with MS lesions and HSI took significantly longer to reacquire the task than the MSGx group (Duncan's, $p<0.05$), who in turn took longer than control animals ($p<0.05$). Propranolol treatment did not alter the number of trials to reacquire the task in control animals. However, in animals with lesions, drug treatment markedly impaired performance ($p<0.05$). Animals in both lesioned groups required on an average 25 extra trials to reacquire performance criterion when compared to their vehicle-treated controls ($p<0.05$). This treatment did not alter the detrimental effects of HSI as the propranolol-treated MS group took significantly longer to regain performance criterion than the MSGx group ($p<0.05$).

Analysis of postoperative learning (Fig. 4) revealed a group effect on all aspects of performance including total selections, $F(2,80)=36.55$, $p<0.0001$, total errors, $F(2,80)=34.43$, $p<0.0001$, errors to baited, $F(2,80)=26.06$, $p<0.0001$, and errors to unbaited, $F(2,80)=32.0$, $p<0.0001$, arms. As expected, the control group was found to be less impaired than either the MSGx or MS group (which did not differ from one another) (Duncan's, $p<0.05$). While a drug effect was found to occur only on errors to baited arms, $F(1,80)=9.92$, $p<0.001$, significant group × drug interactions were found on total selections, $F(2,258)=3.68$, $p<0.02$, total errors, $F(2,258)=4.05$, $p<0.01$, and errors to baited arms, $F(2,258)=4.36$, $p<0.01$. Performance was found to improve over time (trial effects) on all aspects of learning [total selections: $F(24,80)=3.01$, $p<0.0001$; total errors: $F(24,80)=3.58$, $p<0.0001$; errors to baited arms: $F(24,80)=3.87$, $p<0.0001$; errors to unbaited arms: $F(24,80)=3.31$, $p<0.0001$]. However, this was influenced by propranolol treatment [drug × trial effect; total selections: $F(17,258)=2.90$, $p<0.0002$; total errors: $F(17,258)=3.00$, $p<0.0001$; errors to baited arms: $F(17,258)=4.91$, $p<0.0001$; errors to unbaited arms: $F(17,258)=1.92$, $p<0.01$]. Finally, triple interaction effects (i.e., group ×

TABLE 1

MEAN (±SEM) NUMBER OF TRIALS TO OBTAIN LEARNING CRITERION BOTH PRIOR TO AND FOLLOWING SURGICAL PROCEDURES

	Propranolol		Phentolamine	
Groups	Presurgery	Postsurgery	Presurgery	Postsurgery
Controls:				
Vehicle	32.8 ± 3.2 (10)	13.8 ± 1.7	34.4 ± 4.0 (9)	10.5 ± 1.6
Drug	37.2 ± 5.8 (7)	16.8 ± 1.3	31.0 ± 4.3 (5)	30.4 ± 10.3
MS+Gx:				
Vehicle	35.5 ± 3.8 (7)	24.5 ± 3.3	24.8 ± 4.3 (5)	27.8 ± 6.1
Drug	42.8 ± 6.6 (5)	49.2 ± 6.9	32.7 ± 4.0 (7)	36.1 ± 9.4
Ms:				
Vehicle	29.1 ± 2.8 (4)	35.5 ± 8.5	35.7 ± 8.5 (4)	45.5 ± 14.4
Drug	31.0 ± 1.2 (4)	62.5 ± 9.5	21.6 ± 5.8 (5)	22.4 ± 6.6

No drugs were administered presurgery. Postsurgery pharmacological agents were administered 30 minutes prior to daily testing. Number in parentheses is number of animals in each group.

drug × block) were found on total selections, $F(12,258)=1.90$, $p<0.03$, and errors to baited arms, $F(12,258)=2.0$, $p<0.02$.

When drug effects were examined by group it was found that propranolol treatment did not alter learning in the control animals. Although the MSGx group was clearly impaired when compared to controls (see above), propranolol treatment did not alter any specific aspect of learning. However, in the MS group propranolol treatment was found to impair all aspects of learning including total selections, $F(1,25)=22.2$, $p<0.0001$, total errors, $F(1,25)=22.57$, $p<0.0001$, errors to baited, $F(1,25)=14.05$, $p<0.0003$, and errors to unbaited, $F(1, 25)=23.17$, $p<0.0001$, arms.

DISCUSSION

The results of these studies confirm and extend our previous findings. As expected, medial septal lesions were found to transiently disrupt performance on the radial-8-arm maze, with recovery of behavior occurring over time (24, 27, 49). Moreover, hippocampal sympathetic ingrowth was again confirmed to be

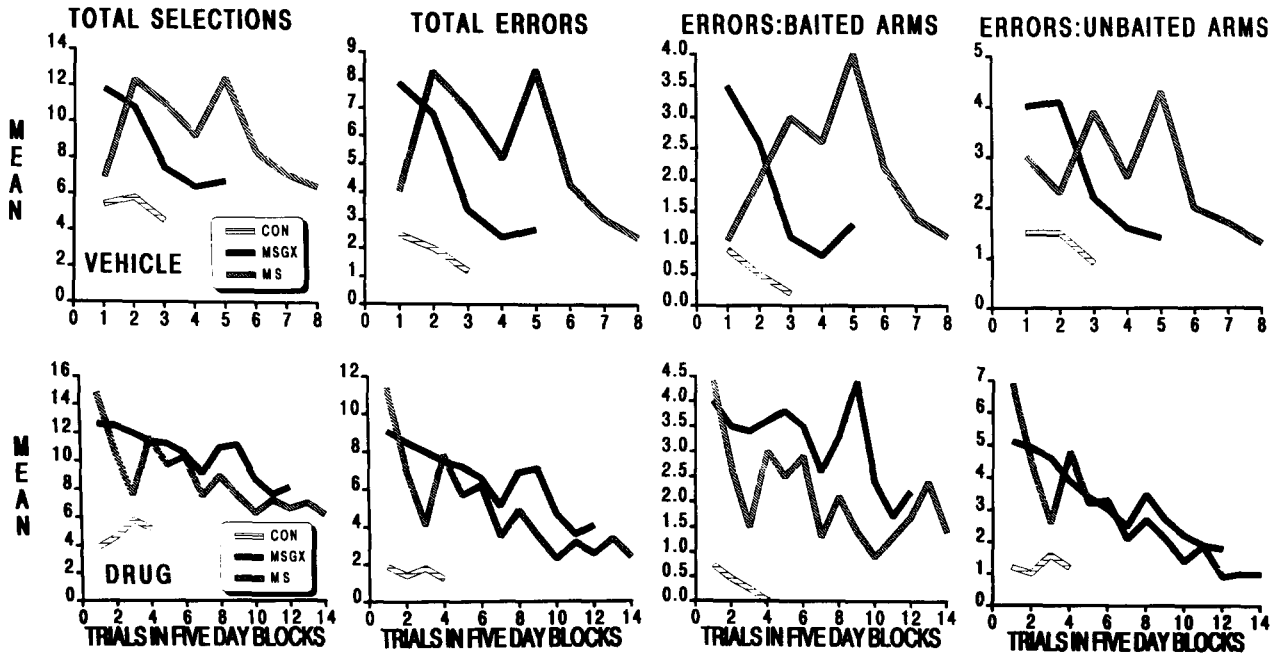

FIG. 4. Mean (±SEM) number of total arm selections, total errors, errors to baited and unbaited arms following surgical procedures for vehicle- (top panels) and propranolol- (bottom panels) treated groups. Note that total number of trials to criterion was different between the vehicle- and drug-treated groups resulting in differences in total trials displayed on the X-axis.

deleterious to this recovery, as animals with medial septal lesions and ganglionectomy recovered performance significantly faster than those with ingrowth (24,27). Finally, and most importantly, our results suggested that treatment with an adrenoreceptor antagonist could influence the rate of recovery. However, the effect of treatment was dependent upon the agent employed and the physiological state of the animal. Thus, phentolamine was found to impair overall performance (i.e., total number of trials to criterion) in normal animals, exert no effect in lesioned animals without ingrowth, and enhance performance in animals with HSI, while propranolol appeared to exert a deleterious effect only in the setting of brain injury, regardless of the presence or absence of HSI. These results suggest that HSI mediates its detrimental effects through α-adrenergic receptors and that β-receptor blockade in lesioned animals disrupts learning/memory.

The mechanisms and/or neuronal populations through which these effects were mediated are of course unknown. Moreover, recent investigations in the hippocampus have suggested that, in addition to residing on adrenergic neurons, both α and β receptors are found on other neurotransmitter systems. For example, propranolol appears to act as an antagonist at the serotonin (5-HT) 1A/1B autoreceptors and causes the release of 5-HT (12, 42, 43), while α_2 receptors are present on 5-HT nerve endings and decrease the release of 5-HT (15,20). Moreover, serotonergic axons may actually regulate/modulate the number of β-receptors (55) and α_1 agonist sites (55,61). Furthermore, 5-HT decreases the release of acetylcholine in the hippocampus (which is antagonized by propranolol) (41) and enhances the release of norepinephrine (13) which can reduce the release of acetylcholine (44,60). In addition, α_2 receptors have also been found associated with GABAergic nerves and to increase the release of GABA (50).

Thus, treatment with an adrenergic antagonist is not as straightforward as investigators once believed, making mechanistic interpretation of our behavioral findings difficult. Moreover, we choose to employ only one dose of the antagonist. Perhaps smaller doses would influence behavior in a different fashion by activating specific neurotransmitter systems, preferentially. However, the goals of this study were to determine whether or not the behavioral effects of HSI could be altered by pharmacological intervention. Regardless of the dose issue, this seems to be the case, since differential effects were seen within and between treatment groups depending on the presence or absence of HSI.

Additionally, several other factors also need to be considered. Firstly, to induce HSI, direct current lesions of the medial septum were employed. This type of lesion results in damage not only to the cholinergic neurons, but also to noncholinergic neurons, and results in disruption of hippocampal NE and 5-HT systems by damaging fibers of passage from the locus coeruleus and raphe nuclei, respectively (16). The effect of this denervation, which is known to increase both 5-HT (45) and β-receptors (56) and produce variable results on α-receptors (53, 56, 59) was not considered. Secondly, the adrenergic antagonists were given on a chronic basis, a treatment recognized to alter both α and β receptor levels (57). Thirdly, the effect of adrenergic antagonists on peripheral adrenergic systems was not considered, even though these systems can alter behavior (18). Finally, even though it is recognized that 1) the hippocampus contains multiple opioid receptor types (30), which can alter the release of NE and acetylcholine (34,35) and affect behavior (17), and 2) the superior cervical ganglia contains enkephalin-like material (10), the possible effects of opioids on learning/memory were not addressed.

Despite these limitations in mechanistic interpretation, our behavioral data clearly implicate adrenergic receptors in learning/memory. Previous investigations have suggested that both α and β adrenoreceptor subtypes are involved in memory modulation (19, 31, 51, 54). However, whether they facilitate or inhibit memory processes appears dependent upon the particular behavioral paradigm. In agreement with other studies, we found that β-blockade in normal animals did not disrupt performance on the radial-8-arm maze task. Alpha-adrenergic blockade, however, was found to significantly alter task performance in control animals, a finding contradictory to those previously reported (3). These differences may have arisen secondary to differences in drug dosage and/or the behavioral paradigm (i.e., previous study baited all 8 arms). Although impairment of performance of control animals in our study was most likely due to nonspecific effects of the drug, a direct effect on learning cannot be totally excluded since the reduction in errors was directed only toward the reference memory (i.e., unbaited arm errors) portion of the task and not the working memory portion (i.e., errors to baited arms). Recent studies also suggest that α-adrenergic receptors may play a direct role in learning/memory, as 1) spontaneous forgetting may be alleviated by treatment with yohimbine, an α_2-antagonist (52), and 2) clonidine, an α_2-agonist, ameliorates the age-related decline in learning normally observed in aging primates (1).

The role of adrenergic receptors in learning/memory in the brain injured animal has received little attention. Recent studies have implicated central noradrenergic systems in the modulation of memory associated with opioid and cholinergic systems as treatment with a β-antagonist prevents the protective effect of naloxone on learning/memory (32,33) and 6-hydroxydopamine lesions enhanced the disruptive effect of scopolamine on learning/memory (8). However, few investigations have attempted to study the interaction of brain injury, subsequent neuronal reorganization and pharmacological treatments. Our study suggests that pharmacological effects are dependent not only upon the agent employed and the primary brain lesion, but also on the neuronal reorganization. Hence, β-antagonist treatment was found to impair performance, in the setting of medial septal lesions regardless of the presence or absence of ingrowth. Whether this finding could be replicated with just any brain injury or is dependent on alteration of limbic systems structures is unknown. However, it seems likely that the latter would have to occur for several reasons. First, when propranolol is administered peripherally the greatest central nervous system concentrations occur in the hippocampus (21). This may explain the observed drug effects on working memory (i.e., errors to baited arms) rather than reference memory (i.e., errors to unbaited), since the hippocampus and its cholinergic projections are thought to be intimately involved in working memory processing (25, 47, 58). Secondly, propranolol has been found to disrupt the spread of cerebral engrams following bitemporal puromicin injection (14). Thirdly, long-term potentiation, a process postulated to underlie basic learning/memory processes (39), is inhibited by β-blockade (22). Finally, direct intraamygdaloid injection of propranolol disrupts memory (38).

Unlike β-blockade, the effect of α-antagonist treatment on learning/memory was found to be dependent on the presence or absence of HSI. In the MSGx group, as in the control group, phentolamine treatment appeared to produce a nonspecific effect since responses were depressed on all aspects of learning. However, unlike the control group, phentolamine treatment did not prolong total number of trials to reattain learning criteria. Thus, it appears that in this group phentolamine therapy did not alter overall learning/memory. In the MS group, phentolamine had no effect on the number or types of errors, but yet markedly enhanced animals' ability to reacquire task performance. This clearly suggests that somehow the presence of HSI modulates the pharmacological effect of phentolamine and that HSI mediates its detrimental effect through α-adrenergic mechanisms.

In conclusion, our results have demonstrated that by the administration of an adrenoreceptor antagonist it is possible to attenuate or improve a behavioral deficit usually attributed to

deficiencies in hippocampal cholinergic activity. As treatments directed toward augmentation of cholinergic function have produced little benefit, our results provide a new direction of research. Moreover, this finding may have therapeutic implications for the treatment of Alzheimer's disease, an illness associated with memory loss, cholinergic denervation, hippocampal dysfunction and peripheral sympathetic ingrowth (4,63).

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