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The pharmacology of post-trial memory processing in septum

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Abstract

The septum is recognized as important in learning and memory, but relatively little is known about the role of specific neurotransmitter receptors in memory processing in the septum. We evaluated the role of the classical neurotransmitters in mice that were prepared for intraseptal microinfusion of drug solution after footshock avoidance training in T-maze. Retention for the footshock training was determined 1 week after training and drug administration. The results indicated that receptor agonists of dopamine, norepinephrine, glutamate and acetylcholine improved retention, while the antagonists impaired retention. Receptor agonists of serotonin, γ-amino butyric acid (GABA) and opioids impaired retention, while antagonists improved retention.

Keywords: Acetylcholine; Aversive conditioning; Dopamine; (γ-Amino butyric acid); Glutamate memory; (Mouse); Norepinephrine; Opiate; 5-HT (5-hydroxytryptamine, serotonin); Septum

1. Introduction

The importance of the septo-hippocampal pathway in learning in memory has received much attention over the last decade. Hippocampal theta, which has a long association with learning and memory (Stewart and Fox, 1990), depends on the integrity of the septum (Smythe et al., 1992). Septal administration of the muscarinic receptor antagonist, scopolamine, blocked hippocampal theta and impaired performance on T-maze alternation task (Givens and Olton, 1990). Septal lesions permanently block theta in the hippocampus and impair performance on a variety of tasks (Buzsaki et al., 1983; Miyamoto et al., 1987; Wilson, 1978). Low frequency stimulation of the medial septal nucleus increased hippocampally recorded theta and improved memory retention (Wetzel et al., 1977).

Two major neurotransmitter systems, γ-amino butyric acid (GABA) and acetylcholine, regulate neural activity in the medial septum (Costa et al., 1983; Leranth and Frotscher, 1989). Most of the cholinergic innervation of the hippocampus arises from neuronal cell bodies located in the medial septum (Swanson et al., 1987). The cholinergic projection from the septum to the hippocampus reduces inhibition of pyramidal and granular cells allowing response to cortical input (Alger and Nicoll, 1982; Ben-Ari et al., 1981; Benardo and Prince, 1982). The cholinergic neurons in the medial septum which project to the hippocampus are under inhibitory control of GABAergic neurons (Costa et al., 1983; Bilkey and Goddard, 1985). When muscimol or GABA were injected into medial septum, hippocampal theta, acetylcholine turnover and high affinity choline uptake were reduced (Allen and Crawford, 1984; Brioni et al., 1990; Costa et al., 1983) and muscimol impaired retention (Chrobak et al., 1989). GABA neurons in the septum may in turn be inhibited by activation of serotonin, dopamine and norepinephrine receptors as the application of the neurotransmitters to neurons in the septum inhibit cell firing (Segal, 1974, 1976).

Aside from the importance of acetylcholine and GABA in the septum, relatively little is known about the effect other neurotransmitter systems may have on post-training memory processing or consolidation. This initial study seeks to better define the role of classical neurotransmitters in post-training memory processing by determining the effect of receptor agonists and antagonists on post-training memory processing for norepinephrine, dopamine, serotonin 5-hydroxytryptamine, (5-HT), GABA, glutamate, acetylcholine and opiates in the septum of mice trained on footshock avoidance task in a T-maze.

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2. Materials and methods

2.1. Subjects

Experimentally naive male CD-1 mice, 8–10 weeks of age (Charles River Breeding Laboratories, Wilmington, MA.) served as subjects. They were housed in rooms with a 12:12 light–dark cycle (lights on at 0600) with the room temperature varying between 20 and 22°C. Water and food (Richmond Laboratory Rodent Diet 5001, formerly Purina Rodent Chow 5001) were available ad libitum. All mice were adapted to the laboratory environment for at least 2 weeks before testing began.

2.2. Drugs

Arecoline hydrobromide (muscarinic receptor agonist, 5–100 pg), AP5 (D(−)-2-amino-5-phosphono-pentanoic acid, NMDA receptor antagonist, 5–40 pg), L-glutamate (endogenous, 0.1–10 ng) was obtained from Sigma, St. Louis, MO. Bicuculline methiodide (GABA receptor antagonist, 0.1–2.0 pg) was obtained from ICN Pharmaceuticals, Plainview, NY. Imidazoline (ST587, α_2-adrenoceptor agonist, 0.1–5.0 μg) was a gift of Boehringer Ingelheim, Elmsford, NY. Baclofen hydrochloride ($R(+)$-β-(aminomethyl)-4-chlorobenzenepropranoic acid, $GABA_B$ receptor agonist, 5–40 ng), buspirone hydrochloride (8-[4-[4-(2-pyrimidinyl)-1-peperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione, 5-HT_1 receptor agonist, 1–30 μg), DOI ($R(-)$-2,5-dimethoxy-4-iodoamphetamine hydrochloride, 5-HT_2 receptor agonist, 1, 10 and 100 ng), ketanserin tartrate (3-[2-[4-fluorobenzoyl)-1-peperdinyl]ethyl]-2,4(1*H*,3*H*)-quinazolinedione, 5-HT_2 receptor antagonist 0.5–15 ng), methiothepin mesylate (1-[10,11-dihydro-8-(methylthio)dibenzo[*b*,*f*]thiepin-10-yl]-4-methylpiperazine, 5-HT_1 receptor antagonist, 1–20 ng), muscimol hydrobromide (3-hydroxy-5-aminomethylisoxazole, $GABA_A$ receptor agonist, 3–50 ng), 2-hydroxysaclofen (OH-saclofen, (±)-3-amino-2-(4-chlorophenyl)-2-hydroxy-propylsulfonic acid, $GABA_B$ receptor antagonist, 0.5–10 ng), scopolamine hydrobromide (muscarinic receptor antagonist, 0.1 to 20 μg), SCH23390 hydrochloride ($R(+)$-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine, dopamine D_2 receptor antagonist, 1–50 ng), SKF38393 hydrochloride ($R(+)$-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol, dopamine D_2 receptor agonist, 10–500 ng) and yohimbine hydrochloride (17-hydroxyyohimban-16-carboxylic acid methyl ester, α_2-adrenoreceptor antagonist, 1, 10, 100 ng) were obtained from Research Biochemicals International, Natick, MA. β-Endorphin (endogenous opioid, 10, 50 and 100 pg) was purchased from Peninsula Laboratories. Naloxone hydrochloride ([(5-α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-ylidene] hydrazide, opioid receptor antagonist, 0.001–10 ng) was a gift from Du Pont, Wilmington, Delaware. All drugs were dissolved in saline. The total amount of drug injected into the brain is given. Drug solutions were coded to prevent experimenter bias.

2.3. Training

The T-maze footshock avoidance apparatus, training and testing procedures have been previously described (Flood and Morley, 1993). The maze consisted of a black plastic start alley with a start box at one end and two goal boxes at the other. A stainless steel rod floor ran throughout the maze. The start box was separated from the start alley by a plastic guillotine door that prevented the mouse from moving down the alley until the training started.

A training trial began when a mouse was placed into the start box. The guillotine door was raised, the buzzer sounded simultaneously and after 5 s, footshock was applied. The goal box the mouse first entered on the first trial was designated as 'incorrect'. Footshock was continued until the mouse entered the other goal box, which on all subsequent trials was designated 'correct' for the particular mouse. At the end of each trial, the mouse was removed from the goal box and returned to its home cage. A new trial began by placing the mouse in the start box, sounding the buzzer and raising the guillotine door. Footshock was applied 5 s later if the mouse did not leave the start box or failed to enter the correct goal box. Retention for either training condition was tested 1 week later by continuing the training until each mouse made 5 avoidances in 6 consecutive training trials.

Two training conditions were used to test separately drug-induced improvement and impairment of retention test performance. The 'weak' training condition used an intertrial interval of 35 s, a door-bell type buzzer at 55 dB as the conditioned stimulus warning of onset of foot shock at 0.35 mA (Coulbourn Instruments scrambled grid floor shocker model E13-08). The parameters for this training condition were set so that the control groups would have poor retention (mean trials to criterion between 9 and 10) so that we could detect drug-induced improvement of retention. The 'strong' training condition used 45 s intertrial interval with the conditioned stimulus at 65 dB and footshock set at 0.40 mA. The control groups under this training condition show good retention (mean trails to criterion between 6 and 7) permitting us to detect impaired retention due to drug administration.

2.4. Surgery and drug administration

The surgical procedures used to prepare mice for 0.5 μl injection into the septum were previously described (Flood et al., 1990). The injection coordinates were +0.5 mm with respect to Bregma, 0.5 mm right of the central suture and 3 mm deep with the needle angled at 6° and pointing toward the midline. In brief, mice were anesthetized with methoxyflurane, placed in a stereotaxic instrument and a hole was drilled through the skull over the injection site

after deflecting the scalp. Mice were trained 48 h after surgery. Immediately after training mice were again placed in the stereotaxic under enflurane anesthesia. Within 3 min after training, a 0.5 μl of saline or drug solution was injected into the septum over 60 s through a 30 gauge blunt stainless steel hypodermic tubing (Small Parts, Miami, FL) attached to a 10 μl syringe with PE-10 tubing and driven by a Sage Syringe Pump (Model 341A). This method of injection resulted in reliable administration into the septum by technicians with several years experience. Only the operated-vehicle injected control group was used in these studies, as previous work has shown that operated-vehicle injected, operated-sham injected, operated not injected and control mice with no operation and receiving no injection did not have means which were significantly different from each other on the retention test (Flood et al., 1995a). The reliability of the injections was determined by locating the tip of the injection tubing in frozen brain sections (Fig. 1). The site of the injection was confirmed histologically using a mouse brain stereotaxic atlas (Slotnick and Leonard, 1975).

2.5. Statistics

Results are expressed as means and the standard error of the means. The retention test scores (mean trials to make 5 avoidances in 6 consecutive trials) for each drug was analyzed separately using one-way analysis of variance (ANOVA). Statistical differences of treatment means from the control group were determined using Dunnett's *t*-test (Keppel and Zedeck, 1989). All groups had 15 mice.

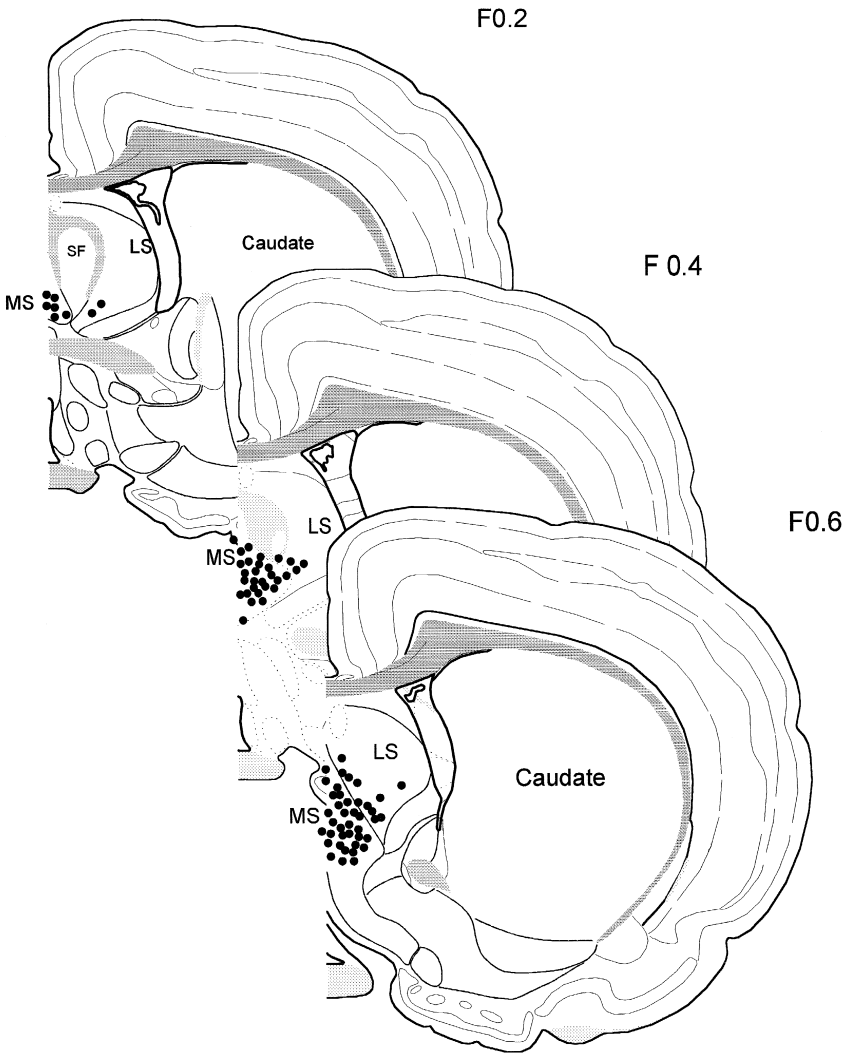

Fig. 1. A random sample of brain sections show the location of tip of the injection needle in frozen brain sections after retention was tested. All injections were given within the septum most in the lateral and medial areas. These plates represent coronal sections 0.6, 0.4 and 0.2 from a stereotaxic atlas of the mouse brain (Slotnick and Leonard, 1975). The figures are based on brain maps by Swanson (1992).

3. Results

3.1. GABA

As GABA regulates cholinergic neuronal activity projecting to the hippocampus (Costa et al., 1983; Swanson et al., 1987), we determined the effect of $GABA_A$ receptor antagonist (bicuculline) and agonist (muscimol) on post-training memory processing. Administration of a $GABA_A$ receptor antagonist should reduce inhibition of cholinergic transmission to the hippocampus and improve retention, while an agonist should impair retention. Bicuculline administration after weak training had a significant effect on retention test performance, $F(5,84) = 7.22$, $P < 0.001$, generating a U-shaped dose–response curve (Fig. 2) with 0.25 and 2.0 pg having means significantly lower than that of the control group (0 pg). Muscimol administered after the stronger training condition had a significant effect on retention test scores, $F(4,70) = 12.23$, $P < 0.001$, with groups receiving 10 to 50 ng having means significantly greater than that of the control group (Fig. 2).

To determine if modulation in $GABA_B$ receptor activity had similar effect on post-training memory processing, we tested OH-saclofen, $GABA_B$ receptor antagonist, and baclophen, a $GABA_B$ receptor agonist. OH-Saclofen administered after weak training had a significant effect on retention, $F(5,84) = 6.80$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 2) with groups receiving 0.5 to 5.0 ng having significantly lower means than that of the control group (0 pg). Baclofen given after the stronger training had a significant effect on retention test performance, $F(4,70) = 20.31$ $P < 0.001$, with 10 to 40 ng having means significantly higher than that of the control group (Fig. 2).

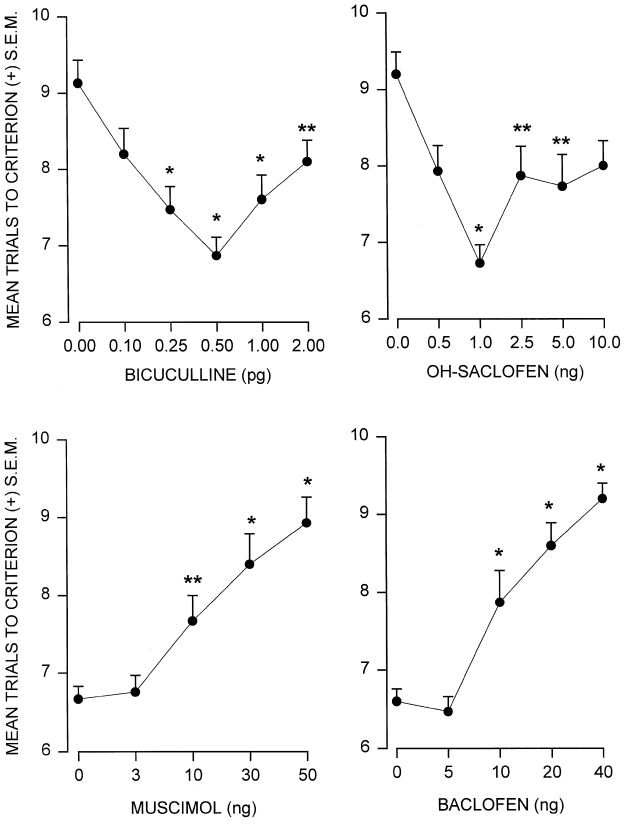

Fig. 2. Effect of $GABA_A$ receptor antagonist, bicuculline, agonist, muscimol, and $GABA_B$ receptor antagonist, OH-saclofen, agonist baclofen on retention. Bicuculline and OH-saclofen show U-shaped dose–response curves typical of a memory enhancing compound, while muscimol and baclofen show dose–response curve typical of drugs that impair memory process. The $*$ indicates that the value differs for the control (0) at $P < 0.01$ or $**$ at $P < 0.05$.

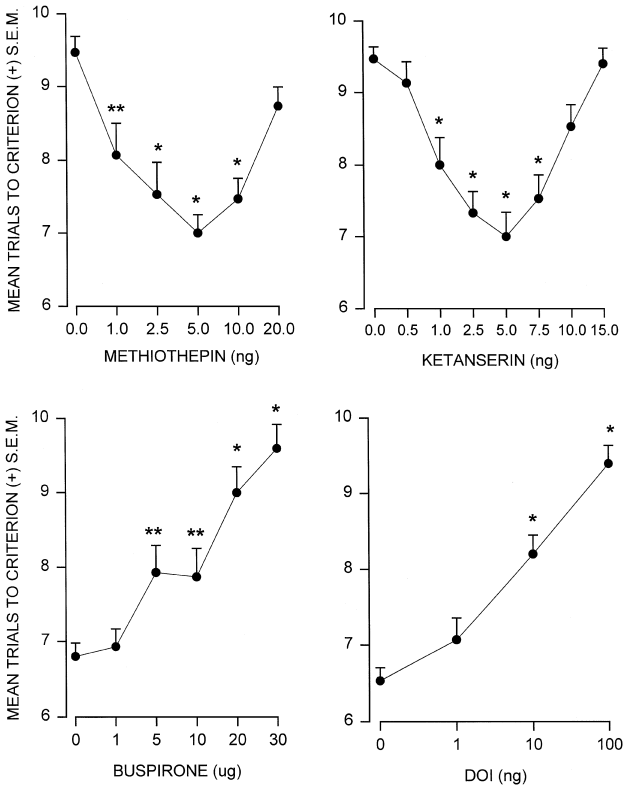

Fig. 3. Effect of 5-HT_1 receptor antagonist, methiothepin, agonist, buspirone and 5-HT_2 receptor antagonist, ketanserin, and agonist, DOI, on retention. Methiothepin and ketanserin enhanced retention, while buspirone and DOI impaired it. The $*$ indicates that the value differs for the control (0) at $P < 0.01$ or $**$ at $P < 0.05$.

3.2. Serotonin

Serotonin is believed to regulate the GABA neurons that modulate cholinergic projects to the hippocampus (Ben-Ari et al., 1981; Benardo and Prince, 1982). Methiothepin, 5-HT_1 receptor antagonist, and buspirone, a 5-HT_1 receptor agonist were tested to determine their effects on post-training memory processing. Methiothepin given after weak training had a significant effect on retention test performance, $F(5,84) = 8.43$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 3) with groups receiving

1 to 10 ng having means significantly lower than that of the control group. Buspirone administered after the stronger training had a significant effect on retention, $F(5,84) = 13.66$ $P < 0.001$, with dose groups 5 to 30 μg having means significantly higher than that of the control group (Fig. 3).

We also determined if 5-HT_2 receptor antagonist, ketanserin, and receptor agonist, DOI, had similar effect on retention test performance. Ketanserin given after weak training had a significant effect on retention test performance, $F(7,112) = 11.36$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 3) with groups receiving 1 to 7.5 ng having means significantly lower than that of the control group. DOI administered after stronger training had a significant effect on retention, $F(3,56) = 29.17$ $P < 0.001$, with 10 and 100 ng resulting in means significantly higher than that of the control group (Fig. 3).

3.3. Acetylcholine

Aside from the cholinergic neurons located in the medial septum which project to the hippocampus, there is also a concentration of such neurons in the lateral septum believed to regulate a local GABA neuronal population which may project to the hippocampus (Freund and Antal, 1988). Arecoline, a muscarinic receptor agonist, and scopolamine, a muscarinic receptor antagonist, were tested. Since arecoline has previously been shown to improve retention in other brain regions (Flood et al., 1996), we determined if it improved retention test performance when injected into the septum.

Arecoline given after weak training had a significant effect on retention test performance, $F(5,84) = 13.95$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 4) with groups receiving 10 to 50 pg having means significantly lower than that of the control group. When scopolamine was administered after the stronger training, it significantly affected retention test performance, $F(6,98) = 7.97$ $P < 0.001$, with dose groups 0.5 to 20 μg having means significantly higher than that of the control group (Fig. 4).

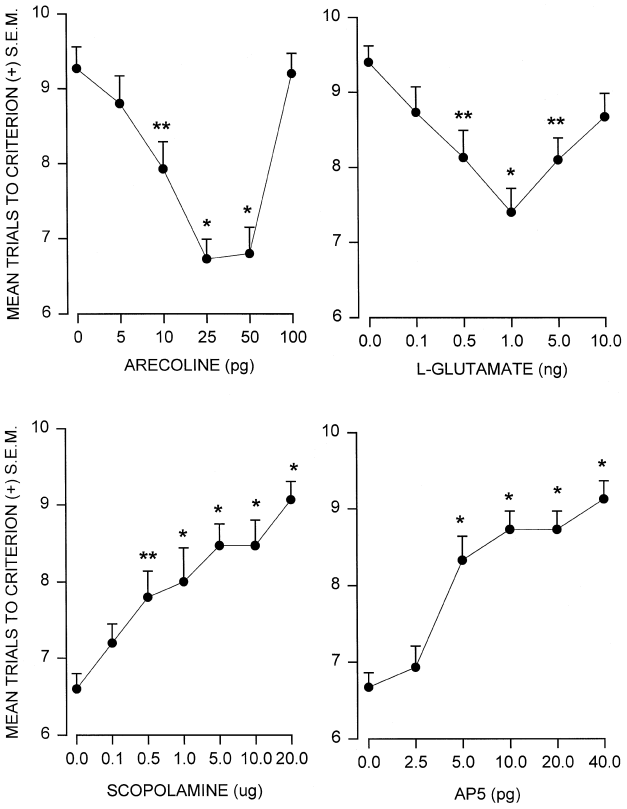

Fig. 4. Arecoline, a muscarinic receptor agonist, enhanced retention, while the cholinergic antagonist, scopolamine, impaired it. L-Glutamate enhanced retention, while a NMDA receptor antagonist, AP5 impaired retention. The $*$ indicates that the value differs for the control (0) at $P < 0.01$ or $**$ at $P < 0.05$.

3.4. Glutamate

Aside from glutamate neurons in the septum, glutamate from the hippocampus is thought to support feed back inhibition to the septum. The glutamate containing neurons in the septum may regulate the mammillary bodies (Swanson et al., 1987), which have been shown to be involved in memory processing (Flood et al., 1995b). L-Glutamate given after weak training had a significant effect on retention test performance, $F(5,84) = 5.22$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 4) with groups receiving 0.5 to 5.0 ng having means significantly lower than that of the control group. AP5, an antagonist acting at the excitatory amino acid binding cite, administered after the stronger training impaired retention, $F(5,84) = 17.74$ $P < 0.001$, with dose groups 5 to 40 pg having means significantly higher than that of the control group (Fig. 4).

3.5. Catecholamines

Little is known about the manner in which catecholamines make connections with neurons and processes in the septum. Segal (1974) reported that they usually hyperpolarized membranes in the septum. We determined the effect of dopaminergic and noradrenergic receptor agonists as well as receptor antagonists on post-trial memory processing. SKF38393, a dopamine D_2 receptor agonist, and SCH23390, the corresponding receptor antagonist, were tested to determine their effects on post-training memory processing. SKF38393 given after weak training had a significant effect on retention, $F(5,84) = 12.68$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 5) with groups receiving 5 to 25 ng having means significantly lower than that of the control group. SCH23390 administered after the stronger training had a significant effect on retention test performance, $F(3,56) = 40.16$ $P < 0.001$, with dose groups 5 to 10 ng having means significantly higher than that of the control group (Fig. 5).

ST587, an α_2-adrenoceptor agonist, and yohimbine, the corresponding receptor antagonist, were tested to determine their effects on post-training memory processing. ST587 given after weak training had a significant effect on retention test performance, $F(6,98) = 7.14$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 5) with groups receiving 0.1 to 2 μg having means significantly lower than that of the control group. Yohimbine administered after the stronger training had a significant effect on retention test performance, $F(3,56) = 17.79$ $P < 0.001$, with dose groups 10 and 100 ng having means significantly higher than that of the control group (Fig. 5).

3.6. Opioid

Opioids are present in most areas of the central nervous system. Relatively little is known about their effects on memory processing. We determined the effect of naloxone, an opioid receptor antagonist, and β-endorphin, an endogenous opioid on retention test performance. Naloxone given after weak training had a significant effect on retention, $F(5,84) = 12.04$ $P < 0.001$, generating a U-shaped dose–response curve (Fig. 6) with groups receiving 0.01 to 1.0 ng having means significantly lower than that of the control group. β-Endorphin administered after the stronger training had a significant effect on retention, $F(3,56) = 29.38$ $P < 0.001$, with dose groups 50 and 100 pg having means significantly higher than that of the control group (Fig. 6).

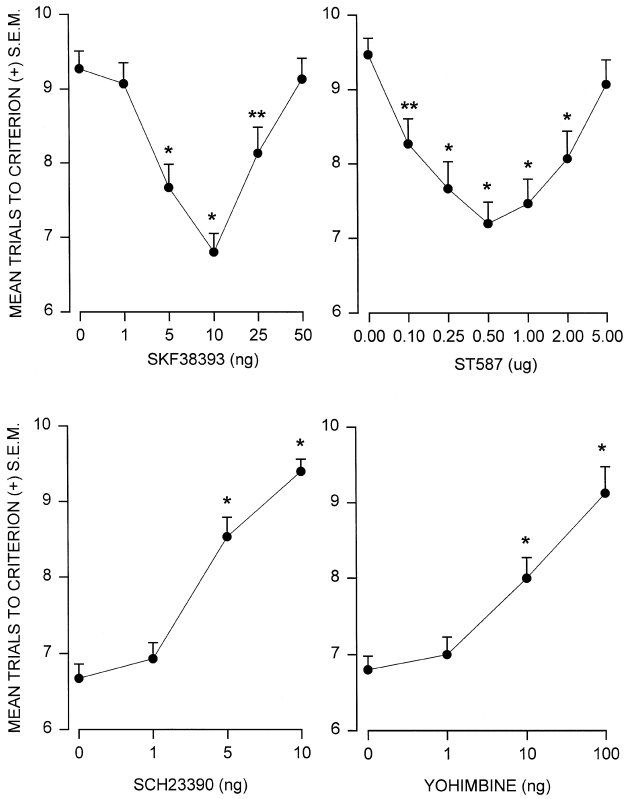

Fig. 5. Effect of dopamine D_1 and α_2-adrenoceptor agonists and antagonists on retention. SK38393, dopamine D_1 receptor agonist, enhanced retention, while the antagonist, SCH23390, impaired it. ST587, α_2-adrenoceptor agonist, enhanced retention, while yohimbine, an antagonist, impaired it. The $*$ indicates that the value differs for the control (0) at $P < 0.01$ or $**$ at $P < 0.05$.

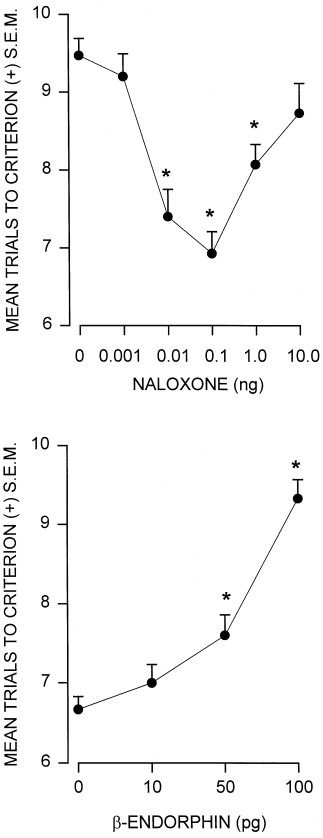

Fig. 6. Effect of opioid receptor antagonist, naloxone, and agonist, β-endorphin, on retention. Naloxone is typical of drug enhanced retention, while β-endorphin impaired it. The $*$ indicates that the value differs for the control (0) at $P < 0.01$.

4. Discussion

We used footshock avoidance in a T-maze because it detects experimental manipulation related to drugs, strain, aging, sex and lesions. Recently, we found that lesions as small as 50% of the septum or hippocampus severely impaired acquisition and retention on this task in mice. In our studies, injections were given after training so that the drugs did not effect acquisition; a paradigm developed by McGaugh (1973). Since, we used a 1 week retention period, and the drugs are rather promptly metabolized, the drugs cannot directly affect performance on the retention test. If the drugs, by virtue of the time of the injection, cannot directly influence acquisition or retention, any improvement in performance is interpreted as being the result of altered neurotransmitter receptor activity occurring shortly after training (i.e., memory processing).

Methodologically, related studies can be divided into those giving drugs prior to training, whether they are studying effects on acquisition or working memory, and those that gave the drugs after training. Among the studies using pre-training drug administration, an injection of bicuculline into the septum impair working memory for radial arm maze (Chrobak and Napier, 1991). Intraseptal administration of muscimol impaired working memory for radial arm maze (Chrobak et al., 1989) and water maze (Brioni et al., 1990). DeSousa et al. (1994) reported muscimol and baclofen impaired working memory for maze learning. Intraseptal administration of muscimol or baclofen impaired working memory for radial arm maze training (Stackman and Walsh, 1994). Buspirone impaired passive avoidance and spatial learning when it was injected prior to testing in rats (Rowan et al., 1990). In all these reports, the drugs impaired working memory. A major problem with administrating a drug shortly before testing is that it alters working memory, which may be due to altered sensorimotor abilities or motivation. Only a few studies determined if drug administration has no effect on sensorimotor systems.

Relatively few studies have used post-training drug administration to explore the pharmacology of the septum in long term memory processing. Waltz et al. (1992) reported that glutamate receptor antagonists injected after training into the medial septal nucleus impaired retention. Picrotoxin, glutamate, oxotremorine and norepinephrine infusion into the medial septum facilitated retention for step-down passive avoidance training, while muscimol impaired it (Izquierdo et al., 1992). Substance P injected after passive avoidance training into the septum, facilitated retention is a dose dependent manner (Staubli and Huston, 1980). Intraseptal administration of muscimol after radial arm maze training, impaired performance on retention tests given 1 to 4 h after training (Chrobak et al., 1989). With such a short retention test interval, drug effects on sensorimotor systems cannot be ruled out as the cause of the poor retention test performance.

Post-training drug administration using the same drugs as in our study but in different brain structures, Castellano et al. (1989) reported that post-training administration baclofen into the amygdala after passive avoidance training impaired retention. Intra-amygdaloid administration of naloxone after active and passive footshock avoidance training improved retention in rats (Introini-Collison et al., 1989). Administration of the dopamine receptor agonist, LY171555 but not SKF38393, into the caudate after footshock-stimulus pairing, facilitated retention as determined by conditioned emotional response (White and Viaud, 1991). The doses of SKF38393 tested may have been too high, as we improved retention with 5 to 25 ng; they tested 500 to 2000 ng. Using the post-training paradigm, administration of glutamate after passive avoidance training improved retention, while muscimol impaired retention (Izquierdo et al., 1992). The effect of localized infusion of OH-saclofen, methiothepin, ketanserin, DOI, SCH23390, yohimbine and scopolamine injected after training on retention have not been previously reported in mice.

Overall, the studies show that all receptors of the classical neurotransmitters in the septum may be involved in post-training memory processing. However, just because a receptor is capable of modulating memory processing, does not indicate that it is a receptor at which plastic changes are occurring. To effect memory processing, a drug only needs to increase activity in the pathway. Further, studies are needed to determine how the various neurotransmitters present in the septum regulate the GABA and acetylcholine projections to the hippocampus.

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