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Modulation of Memory Processing in the Cingulate Cortex of Mice

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FARR, S. A., K. UEZU, T. A. CREONTE, J. F. FLOOD AND J. E. MORLEY. *Modulation of memory processing in the cingulate cortex of mice.* PHARMACOL BIOCHEM BEHAV **65**(3) 363–368, 2000.—To evaluate the possible role of the cingulate cortex in memory processing for training using a noxious stimulus, we trained mice on foot shock avoidance in a T-maze. Cholinergic, GABAergic, serotonergic, and glutamatergic agonists and antagonists were administered into the cingulate cortex immediately after training. Retention for the foot shock avoidance training was tested 1 week later. The results indicate that muscarinic and nicotinic agonists improved retention, while antagonists impaired it. GABA and serotonin agonists impaired retention, while antagonists improved it. Drugs acting on $GABA_A$ and $GABA_B$ receptors had similar effects on retention, as did drugs acting on serotonin 1 and 2 receptor subtypes. Glutamate improved retention, and AP5, an antagonist of the excitatory amino acid site of the NMDA receptor, impaired retention. The cingulate cortex, like other parts of the limbic system, is involved in memory processing that occurs shortly after training. © 2000 Elsevier Science Inc.

Cingulate cortex Foot shock Memory processing

STUDIES using different approaches, including lesions, electrical stimulation, and electrophysiology, have implicated the cingulate cortex in numerous functions such as emotion, pain, maternal and feeding behaviors, attention, and learning. Overall, the cingulate cortex "may be viewed of as both an amplifier and filter, interconnecting the emotional and cognitive components of the mind" (4). The anterior cingulate cortex has been found to be involved in both emotional and behavioral responses to noxious stimuli (4). The cingulate cortex was further characterized as being important in response selection associated with presentation of conditioned stimuli, expression of nonautonomic behavioral sequences, and coactivation of visceromotor and skeletomotor areas of the anterior cingulate cortex.

The cingulate cortex receives projections from the thalamus (39,40), which may be the source of information concerning noxious stimuli (16,23,29). The thalamic projection from the medial dorsal thalamus to the cingulate cortex is excitatory using glutamate as a neurotransmitter, with $GABA_A$ and $GABA_B$ regulating the response of cingulate cortex neurons to thalamic stimulation (18). The cingulate cortex receives GABA containing fibers projecting from the septum and diagonal bands of Broca to the cingulate cortex (3,14,15). The anterior cingulate cortex is richly innervated by serotonergic fibers coming from the dorsal and medial Raphe nuclei, which mostly terminate in the deep layers of the cingulate cortex (35). The anterior cingulate cortex of the rodent receives direct limbic input from the CA1 region of the hippocampus and the basolateral nucleus of the amygdala (30).

Receptor binding studies and electrical recordings indicate that the cingulate cortex has receptors for acetylcholine, GABA, glutamate, and serotonin, as well as many neuropeptides (2,22,32). Because the cingulate cortex is involved with recognition of noxious stimuli and making the appropriate response to such stimuli, we decided to determine if the cingulate cortex was part of the memory processing system involved in retention of foot shock avoidance conditioning. Mice were trained on foot shock avoidance conditioning in a T-maze. Immediately following training mice received injections of agonist or antagonist of cholinergic, glutamatergic,

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GABAergic, or serotonergic drugs. These classes of drug were selected because they have been found to effect neurotransmitters that control normal daily activity within the cingulate cortex (2). Retention was tested 1 week after training and drug administration.

In these studies, injections were given after training so that the drugs would not effect acquisition; a paradigm originally developed by McGaugh (28). Pretraining administration of a drug may have their primary effects on learning, and only a secondary effect on memory processing. A drug given prior to training could improve acquisition by altering sensorimotor abilities. When a drug is administered after training, it cannot directly effect acquisition. Because we used a 1-week retention period, and the drugs are 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).

METHOD

Subjects

Experimentally naive male CD-1 mice, 8–10 weeks of age (Charles River Breeding Laboratories, Wilmington, MA) served as subjects. Mice were housed in rooms with a 12 L:12 D cycle (lights on at 0600 h) with the room temperature varying between 20 and 22°C. Water and food (Richmond Laboratory Rodent Diet 5001) were available ad lib. All mice were adapted to the laboratory environment for at least 2 weeks before testing began. These studies received institutional approval as stated in the principles of laboratory care as outlined in the NIH guide for the use of laboratory animals.

Drugs

Arecoline hydrobromide (muscarinic receptor agonist, 1–75 pg), AP5 (D(−)-2amino-5-phosphono-pentanoic acid, NMDA receptor antagonist, 10–250 pg), DMPP (1,1-dimethyl-4-phenylpiperazinium iodide, nicotinic receptor agonist, 0.01–5 μg), scopolamine hydrobromide (1–10 μg), and L-glutamate (5–50 ng) were obtained from Sigma Chemical Co., St. Louis, MO. Bicuculline methiodide ($GABA_A$ receptor antagonist, 0.1–1.0 pg) was obtained from ICN Pharmaceuticals, Plainview, NY. Baclofen hyrobromide (R(+)-β-(aminomethyl)-4-chlorobenzenepropranoic acid, $GABA_B$ receptor agonist, 5–40 ng), Buspirone hydrochloride (8-[4-[4-(2-pyrimidinyl)-1-peperaziny]butyl]-8-azaspiro[4,5]decane-7,9-dione, 5-HT_1 receptor agonist, 5–40 μg), DOI (R(−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride, 5-HT_2 receptor agonist, 5–150 ng), Ketanserin tartrate (3-[2-[4-flurobenoyl)-1-peperdinyl]ethyl]-2,4(1H,3H)-quinazolinedione, 5-HT_2 receptor antagonist, 1–20 ng), mecamylamine hydrochloride (cholinergic nicotine receptor antagonist, 1–10 μg), methiothepin (1-[10,11-dihydro-8-(methylthio)dibenzo [b,f]thiepin-10-yl]-4-methylpeperazine, 5-HT_1 receptor antagonist, 1–20 ng), muscimol hydrobromide (3-hydroxy-5-amino-methylisoxazole, $GABA_A$ receptor agonist, 10–75 ng), and 2-hydroxysaclofen (OH-saclofen, (±)-3-amino-2-(4-chlorophenyl)-2-hydroxy-propylsulfonic acid, $GABA_B$ receptor antagonist, 0.25–5 ng) were obtained from Research Biochemicals International, Natick, MA. All drugs were dissolved in saline, which was the vehicle for the control groups. Drug solutions were coded to prevent experimenter bias.

Training

The T-maze foot shock avoidance apparatus, training, and testing procedures have been previously described (7). 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, foot shock was applied. The goal box the mouse first entered on the first trial was designated as "incorrect." Foot shock 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. Foot shock 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 five avoidances in six consecutive training trials.

Two training conditions were used to test separately drug-induced improvement and impairment of retention test performance. The weaker training condition used an intertrial interval of 35 s, a doorbell-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 stronger training condition used a 45-s intertrial interval with the conditioned stimulus at 65 dB and foot shock set at 0.40 mA. The control groups under this training condition show good retention (mean trails to criterion between 6 and 7), which permits us to detect impaired retention due to drug administration.

Surgery and Drug Administration

Saline or drug solution was injected unilaterally into the right cingulate cortex at a volume of 0.25 μl. The injection coordinates were +0.5 mm with respect to bregma, 0.5 mm right of the central suture, and 1.8 mm deep with the needle angled at 4 degrees, 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, 0.25 μl of saline or drug solution was injected into the cingulate cortex over 90 s through a 30-gauge blunt stainless steel hypodermic tubing (Small Parts, Inc., 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 cingulate cortex by technicians with several years experience. The reliability of the injections was determined by locating the tip of the injection tubing in frozen brain sections. The site of the injection was confirmed histologically using a mouse brain stereotaxic atlas (33). Figure 1 shows a random sample of injection sites. Based on studies in this and other laboratories, infusion of 0.5 μl of drug would remain within the hippocampus (1,5,6).

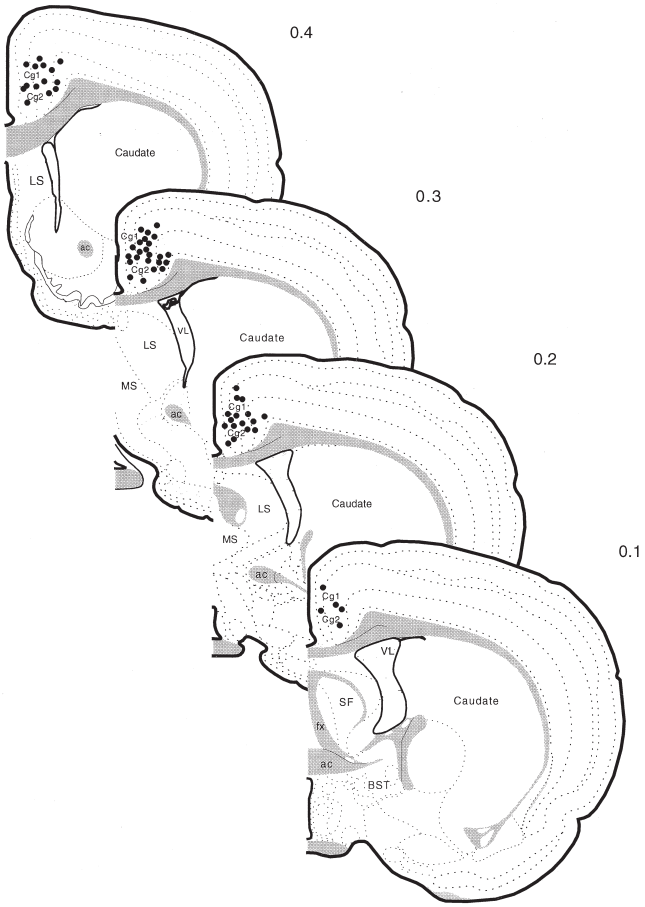

FIG. 1. A random sample of brain sections shows the location of the tip of the injection needle in frozen brain sections after retention was tested. All injections were given within the Gg1/Gg2 cingulate cortex. These plates represent coronal sections 0.1–0.4 from a stereotaxic atlas of the mouse brain (33). The location of Cg1 and Cg2 was obtained from a mouse brain atlas by Franklin and Paxinos (13). The figures are based on brain maps by Swanson (34).

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 mice with no operation had mean retention test scores that were not significantly different from each other (8).

Statistics

Results are expressed as means and the standard error of the means. The retention test scores (mean trials to make five avoidance responses in six consecutive trials) for each drug were analyzed separately using one-way analysis of variance (ANOVA). Statistical differences between treatment and control group means were determined using Dunnett's *t*-test (24).

RESULTS

Acetylcholine

Arecoline, a muscarinic receptor agonist, and scopolamine, a muscarinic receptor antagonist, were tested. Arecoline, given after weak training, had a significant effect on retention test performance, $F(6, 98) = 9.53$, $p < 0.001$, generating a U-shaped dose–response curve (Fig. 2) with groups receiving 5–75 pg having means significantly lower than that of the control group. When scopolamine was administered after the stronger training, it significantly effected retention test performance, $F(4, 70) = 10.72$, $p < 0.001$, with dose groups 2.5–10 μg having means significantly higher than that of the control group (Fig. 2).

The nicotinic receptor agonist, DMPP, and antagonist, mecamylamine, were also tested. DMPP given after weak training had a significant effect on retention test performance, $F(6, 98) = 10.35$, $p < 0.001$, with groups receiving 0.05–1 μg having means significantly lower than that of the control group (Fig. 2). When mecamylamine was administered after the stronger training, it significantly effected retention test performance, $F(3,56) = 13.16$, $p < 0.001$, with dose groups 5 and 10 μg having means significantly higher than that of the control group (Fig. 2).

GABA

To determine if modulation in $GABA_A$ receptor activity would effect retention, the $GABA_A$ receptor antagonist, bicuculline, and the corresponding receptor agonist, muscimol, were administered after training. Bicuculline administration after weak training had a significant effect on retention test performance, $F(5, 84) = 7.02$, $p < 0.001$, generating a U-shaped

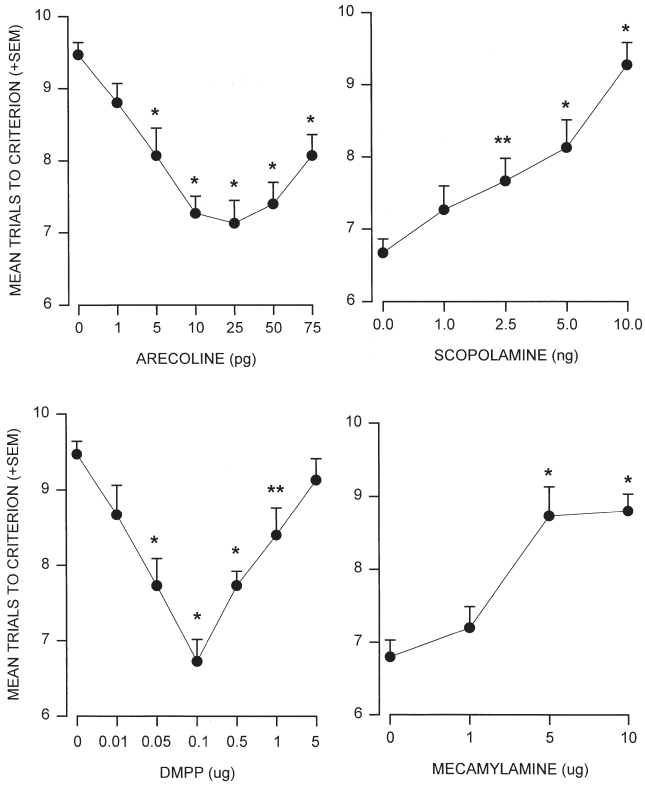

FIG. 2. Effect of cholinergic muscarinic and nicotinic receptor agonists and antagonists on memory processing. The muscarinic agonist, arecoline improved retention, while the muscarinic antagonist, scopolamine, impaired retention. The nicotinic agonist, DMPP, improved retention and its antagonist, mecamylamine, impaired retention. The * indicates that the value differed from the control (0) mean at $p < 0.01$ or ** at $p < 0.05$.

dose–response curve (Fig. 3) with 0.25 and 1.0 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, $F(4, 70) = 17.87$, $p < 0.001$, with groups receiving 25–75 ng having means significantly higher than the control group mean (Fig. 3).

To determine if modulation in $GABA_B$ receptor activity had similar effect on posttraining memory processing, we tested OH-saclofen, a $GABA_B$ receptor antagonist, and baclofen, a $GABA_B$ receptor agonist. OH-Saclofen administered after weak training had a significant effect on retention, $F(5, 84) = 18.76$, $p < 0.001$, generating a U-shaped dose–response curve (Fig. 3) with groups receiving 0.25–5 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, $F(4, 70) = 23.41$, $p < 0.001$, with 10–40 ng having means significantly higher than the control group mean (Fig. 3).

Serotonin

Methiothepin, a 5-HT_1 receptor antagonist, and buspirone, a 5-HT_1 receptor agonist, were tested to determine their effects on posttraining memory processing. Methiothepin given after weak training had a significant effect on retention test performance, $F(4, 70) = 8.51$, $p < 0.001$, generating a U-shaped dose–response curve (Fig. 4) with groups receiving 5–20 ng, having means significantly lower than that of the control group. Buspirone, administered after the stronger training, had a significant effect on retention, $F(5, 84) = 29.47$, $p < 0.001$, with dose groups 10–40 g having means significantly higher than that of the control group (Fig. 4).

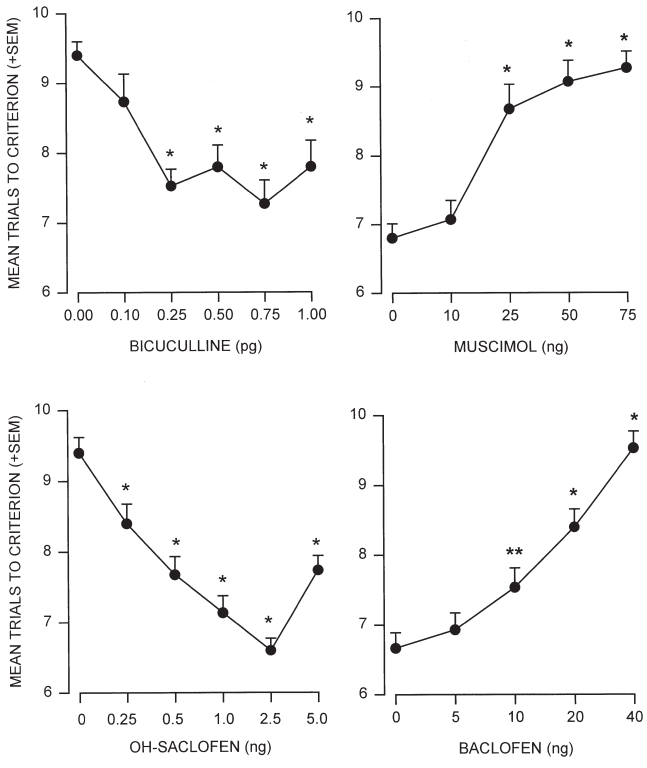

FIG. 3. Effect of $GABA_A$ and $GABA_B$ agonists and antagonists on retention. $GABA_A$, bicuculline, and $GABA_B$, 2-hydroxysaclofen, antagonists improved retention. $GABA_A$ and $GABA_B$ agonists, muscimol and baclofen, impaired retention. The * indicates that the value differed from the control (0) mean at $p < 0.01$ or ** at $p < 0.05$.

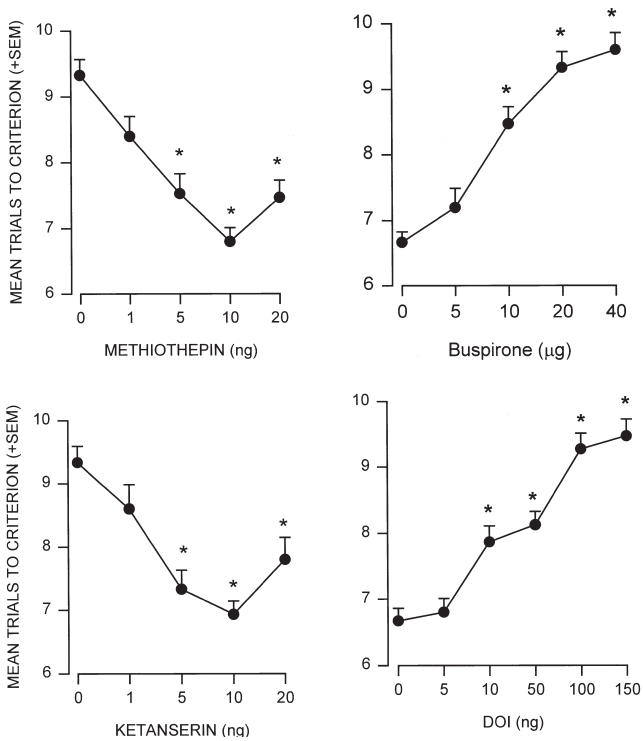

FIG. 4. Effect of serotonin agonists and antagonists on retention. 5-HT_1 and 5-HT_2, methiothepin and ketanserin, antagonists improved retention. 5-HT_1 and 5-HT_2, agonists, buspirone and DOI, impaired retention. The * indicates that the value differed from the control (0) mean at $p < 0.01$.

We also determined if 5-HT_2 receptor antagonist, ketanserin, and receptor agonist, DOI, had similar effect of retention test performance. Ketanserin given after weak training had a significant effect on retention test performance, $F(4, 70) = 10.78$, $p < 0.001$, generating a U-shaped dose– response curve (Fig. 4) with groups receiving 5–20 ng having means significantly lower than that of the control group. DOI administered after stronger training had a significant effect on retention, $F(5, 84) = 29.47$, $p < 0.001$, with 10 and 150 ng resulting in means significantly higher than that of the control group (Fig. 4).

Glutamate

L-Glutamate, given after weak training, had a significant effect on retention test performance, $F(4, 70) = 10.82$, $p < 0.001$ (Fig. 5) with groups receiving 10–50 ng having means significantly lower than that of the control group. AP5, an antagonist acting at the excitatory amino acid binding site, administered after the stronger training impaired retention, $F(5, 84) = 14.63$, $p < 0.001$, with dose groups 25–250 pg having means significantly higher than that of the control group (Fig. 5).

DISCUSSION

Overall, the studies show that acetylcholine, GABA, serotonin, and NMDA receptors in the cingulate cortex are in-

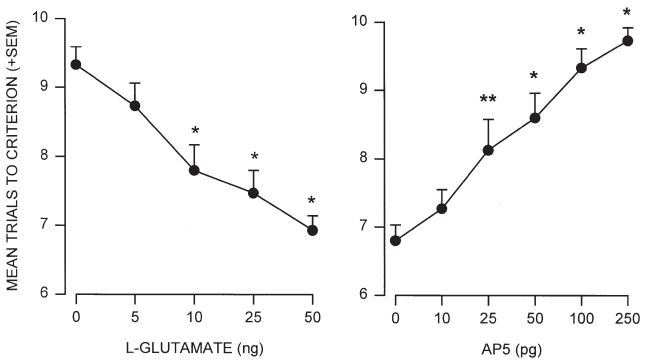

FIG. 5. Glutamate improved retention, while AP5, an antagonist of the excitatory amino acid site of the NMDA receptor, impaired retention. The * indicates that the value differed from the control (0) mean at $p < 0.01$ or ** at $p < 0.05$.

volved in posttraining memory processing. However, just because a receptor is capable of modulating memory processing, it does not indicate that it is a receptor at which plastic changes are occurring, such as those hypothesized to support long-term memory. To effect memory processing, a drug only needs to increase activity in the pathway(s).

The findings here are similar to those found in other limbic system structures such as the hippocampus (10,19,21), septum (11,21), mammillary bodies (9), and amygdala (21). The results indicate that in the cingulate cortex muscarinic and nicotinic agonists improved retention, while antagonists impaired it. GABA and serotonin agonists impaired retention, while antagonists improved it. Drugs acting on $GABA_A$ and $GABA_B$ receptors had similar effects on retention, as did drugs acting on serotonin 1 and 2 receptor subtypes. Glutamate improved retention and AP5, an antagonist of the excitatory amino acid site of the NMDA receptor impaired retention. In our studies using foot shock avoidance in a T-maze, we have found that the dose range over which a given drug improved or impaired retention was similar across structures (10–12). DMPP, a nicotinic agonist, was almost a 1000 times more potent in the mammillary bodies than in the hippocampus, septum, or cingulate cortex (9). This is probably because the mammillary bodies are part of the hypothalamus, and the density of nicotine receptors in the hypothalamus is much higher than elsewhere in the forebrain.

Although we did not find other studies that had injected drugs into the cingulate cortex after training to determine if this area of the cortex was important for memory processing, a number of studies using lesions and drugs established its importance for normal learning. Devinsky et al. (4) published an extensive review of human and monkey literature related to functions of the anterior cingulate cortex. Because differences in paradigms between human and monkey studies vs. rodents make a direct comparison difficult, we recommend this review article for those interested in this literature. In rats, Peretz (31) found that avoidance conditioning was impaired with anterior cingulate cortex lesions using either foot shock or shaking as the aversive stimuli. Cingulate cortex-lesioned rats acquired a lever press for food reinforcement significantly faster than sham-lesioned rats; the basis of the pathological increase in acquisition is unknown. Gabriel et al. (16,17) reported that anterior cingulate cortex lesions moderately impaired acquisition of a differential tone discrimination foot shock avoidance task in rabbits, while complete cingulate cortex lesions caused severe impairment. Acquisition of a condition emotional response was impaired by anterior cingulate cortex lesions in rats (37). Kimble and Gostnell (25) reported that rats showed severe deficits in foot shock avoidance in a two-way (shuttlebox) active avoidance. Also, in cats, cingulate cortex lesions impaired acquisition of a shuttlebox, but not, a one-way foot shock avoidance task (26). Both increased and decreased emotionality have been used to explain the deficit in shuttlebox conditioning in cats and rats with cingulate cortex lesions (27). However, Kimble and Gostnell (25) found no correlation between either of two measures of emotionality in rats and performance in the shuttlebox. Freezing, a tendency for an animal to remain stationery in response to foot shock or when a conditioned stimulus is presented, may account for some of the deficit in shuttlebox acquisition of cingulate cortex subjects. This increase in nonadaptive behavior is consistent with Vogt's view that the anterior cingulate cortex is involved in "(i) specifying the affective content of noxious stimuli; (ii) motor response selection for noxious stimuli; (iii) learning associated with the prediction and avoidance of noxious stimuli)" (4). Thomas and Slotnick (36) found that increased hunger, resulting in increased activity, reduced the tendency to emotional freezing during shuttlebox conditioning in rats with cingulate cortex lesions, but without food deprivation, rats with cingulate cortex lesions made about half as many foot shock avoidance responses as control subjects. Cingulate cortex lesions in monkeys decreased pain sensitivity (4). Impaired neuronal conduction through the cingulate cortex in rats caused by an injection of lidocaine reduced their emotional response to pain (38). The cingulate cortex, like other parts of the limbic system (amygdala, hippocampus, septum, and mammillary bodies), is involved in memory processing that occurs shortly after training (9–11,20,21).

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