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Nicotine Enhances the Learning and Memory of Aged Rats

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ARENDASH, G. W., P. R. SANBERG AND G. J. SENGSTOCK. *Nicotine enhances the learning and memory of aged rats.* PHARMACOL BIOCHEM BEHAV 52(3) 517–523, 1995.—The cognitive performance of young adult (2–3-month-old) and aged (22–24 month-old) rats was characterized in one of three different behavioral tasks, and the ability of daily nicotine treatment to alleviate age-related learning and memory deficits was evaluated. Aged rats received an IP injection of either nicotine (0.2 mg/kg) or saline vehicle 15 min prior to daily testing; young control rats received saline vehicle injections. Compared to young controls, aged control rats were severely impaired in the acquisition of one-way active avoidance pole jumping over 12 days of testing. Nicotine pretreatment of similar aged rats markedly improved overall learning and the rate of learning compared to aged controls. In Lashley III maze performance, aged control rats made substantially more alternation errors than young controls; however, aged rats pretreated with nicotine made significantly fewer errors over the entire 20-day test period compared to aged controls. During 30 days of 17-arm radial maze testing, aged control animals were severely impaired in general learning and reference (long-term) memory, but only mildly impaired in working (short-term) memory. Nicotine pretreatment of similar aged rats induced a substantial enhancement in overall learning and reference memory, but did not affect working memory. These results indicate that chronic nicotine administration can improve the impaired learning/memory abilities of aged rats in several tasks, and suggest that stimulation of central nicotinic receptors may be of considerable therapeutic value to treat age-related memory impairment.

Nicotine Learning and memory Aged rats Age-related memory impairment

A FUNDAMENTAL role has clearly been established for CNS cholinergic neurons in normal cognitive function and dysfunction (3,7). Given the prominent loss/atrophy of basal forebrain cholinergic neurons and associated reductions in presynaptic cholinergic markers in senile dementia of the Alzheimer's type (SDAT), as well as studies demonstrating a positive correlation between these changes and the degree of cognitive impairment/neuropathology shown by SDAT patients (2,35), numerous laboratories have been investigating the potential of improving cognitive function by enhancing cholinergic transmission (3,4). In this context, there is growing interest in treating SDAT with nicotinic agonists because: a) SDAT brains have large reductions of nicotinic receptors in both the neocortex and hippocampus (1,40), and b) chronic nicotine treatment results in an upregulation, rather than a downregulation of nicotine binding site densities in these same brain areas (30,41). In rats with cholinergic lesions of the basal forebrain (to model the cholinergic hypofunction of SDAT), nicotine treatment has been shown to attenuate or eliminate lesion-induced cognitive deficits (10,20,28,44). Consistent with these animal studies are clinical studies reporting that nicotine administration to SDAT patients enhances their attention and information processing (24,33,39,47).

Impairment of cognitive function is not exclusive for SDAT, however; rather, it occurs commonly as a normal consequence of human aging. This age-associated memory impairment (AAMI), though more modest than that associated with SDAT, can routinely interfer with daily life. Experimental animals also exhibit AAMI, as exemplified by studies showing aged rats to be impaired in the acquisition and/or memory retention of a wide variety of avoidance and spatial tasks (14,17,23,45,50). Although these studies suggest the aged rat to be an appropriate animal model for AAMI, no studies have thus far investigated the cognition-enhancing potential of nicotine or nicotinic agonists in an aged rat model. Rather, investigation of nicotine's cognitive effects in rats have universally involved young adults, in which nicotine treatment ($\leq$ 0.2 mg/kg) generally results in improved acqui-

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sition and/or memory retention [see (26) for review]. However, the relevence of these nicotine-induced cognitive improvements in young adult animals to the treatment of AAMI is uncertain.

The purpose of the present study was twofold: first, to characterize the cognitive deficits of aged rats in three different tasks and, second, to determine the ability of chronic nicotine administration to alleviate/prevent any cognitive deficits exhibited by aged rats in those tasks. We have previously found that, through 24 months of age, aged Sprague–Dawley rats are characterized by several features usually associated with normal human brain aging (9,15)—specifically, no decrease in nicotine receptor densities within the neocortex, no decrease in neocortical choline acetyltransferase (ChAT) or acetylcholinesterase (AChE) activities, and an atrophy (but no loss) of nucleus basalis (NB) neurons (8,49). These neurochemical and histological findings are consistent with an anatomically intact, albeit atrophied NB cholinergic system in 24-month-old rats. Nonetheless, several reports of age-related decreases in neocortical acetylcholine synthesis (16) and depolarization-induced acetylcholine release (32) suggest that the functionality or responsivity of rodent NB cholinergic neurons is compromised with age.

The results of the present study demonstrate that chronic nicotine administration has clear and consistent cognition-enhancing effects in aged rats for all three tasks investigated. We propose the use of these tasks as a reference for evaluating the potential of newly developed nicotinic ligands to improve the cognitive function of aged rats.

METHOD

General Protocol

Inbred male Sprague-Dawley rats, 2–3 months (young adults) and 22–24 months (aged), were behaviorally tested in one of the following tasks: one-way active avoidance, Lashley III maze, or 17-arm radial maze. For each task, all young rats and approximately half of the aged rats received an IP injection of isotonic saline vehicle solution (1 ml/kg) 15 min prior to daily behavioral testing. The remaining aged rats were given an IP injection of nicotine (0.2 mg/kg as the hydrogen tartrate salt) 15 min before daily testing. Parenthetically, this dose of nicotine was chosen because it does not affect locomotor activity, does not alter pain sensitivity, and has been shown effective in enhancing the cognitive performance of young adult rats in previous studies (26). Young and aged animals selected for Lashley III maze and 17-arm radial maze testing were weight reduced to 80% and 60%, respectively, of their initial body weights prior to initiation of testing. A greater degree of weight reduction is necessary for proper motivation of aged rats in Lashley III maze and 17-arm radial maze testing (personal observations), most likely because aged rats have a higher proportion of fatty tissues than do young adult rats. For both of the appetitive tasks, the cereal Froot Loops served as the food reward.

One-Way Active Avoidance Testing

Testing was done in a pole-jumping apparatus equipped with a shock grid floor. The conditioned stimulus (overhead light on in apparatus) was presented for 5 s followed by 15 s of a scrambled 2 mA shock. If the subject jumped onto the pole before the 5-s conditioned stimulus interval had elapsed (i.e., a conditioned avoidance response or CAR), he avoided the shock. If he jumped onto the pole during the shock (i.e., an escape), the shock and light stimulus were terminated. Subjects were given 10 trials per day for 12 days. A percent CAR was calculated for each daily session. Group differences in percent CARs were determined from four 3-day blocks and involved a two-way analysis of variance for repeated measures followed by a post hoc one-way analysis of variance for individual blocks when appropriate.

Lashley III Maze Testing

The Lashley III maze is an alternation task with a start and a goal box separated by six alleys (42,43). Overall dimensions of the maze were 75 cm wide, 187 cm long, and 30 cm high. To complete this maze, animals had to alternate left and right turns at each of the six doors. Although this is primarily a learning task, it requires animals to remember their previous days of maze experience to optimize performance. Animals were given 2 days of 15-min shaping trials in which food was placed liberally throughout the maze. Thereafter, food was placed only in the goal box and single 5-min trials were run each day for 25 days. Nicotine or saline vehicle injections were given 15 min prior to daily trials. Because animals must pass through a total of six doors and, therefore, can make a maximum of six alternation errors on any given trial, chance performance is three errors per trial. To achieve performance critieria for inclusion in the data analyses, animals were required to traverse the maze from start to goal box on at least 7 of the first 10 daily trials. Group differences in alternation errors were determined from four 5-day blocks of data collected from days 6 through 25. A two-way analysis of variance for repeated measures was utilized for statistical analyses, followed by a post hoc one-way analysis of variance for individual blocks when appropriate.

17-Arm Radial Maze Testing

In this task, animals are required to remember a baited set of 8 arms out of the 17 total arms (34). The maze's center platform was 87 cm in diameter and each of the 17 arms was 69 × 9 cm. A variety of extramaze cues were placed on the walls surrounding the maze, and geometric figures were painted on some maze surfaces to serve as intramaze cues. Before the initiation of testing, each animal was assigned to one of three eight-arm baited sets. Each of the 17 arms was included in at least one of the three sets to reduce possible odor cues. Animals were shaped for 2 days by allowing them to explore the maze for 15 min each day. For these shaping trials, food was placed throughout the maze and doors were closed to those arms not in an animal's baited set.

With all doors open, single daily trials of acquisition were begun on the third day. At the start of each trial, rats were placed on the center platform of the maze and permitted to choose among the 17 arms until all eight food rewards were taken or until 15 min had elapsed. Food was placed progressively further down the baited arms and arm choices were recorded beginning with a food reward location requiring the animal to place all four paws on the arm. Also beginning for animals at this food reward location, nicotine or saline vehicle injections were given 15 min before each daily trial for the 30 days of testing.

Statistical analysis was done on three sets of data according to Sengstock et al. (42). The first is a measure of general learning; the percent correct choices (i.e., entries into baited arms containing food) during the first eight arm choices. The second is a measure of short-term or working memory calculated from the first 12 choices; the percent of choices into

baited arms containing food out of the total number of choices made within the baited set. The third set of data is a measure of long term or reference memory and is also calculated from the first 12 choices; the percent correct choices in the baited set (containing or not containing food) over the total number of arm choices. Statistical analysis of all three measures of 17-arm maze testing involved a two-way analysis of variance for repeated measures, followed by a post hoc one-way analysis of variance for individual blocks when appropriate. For some groups, a one-way analysis of variance for repeated measures was utilized to determine performance improvement over time.

RESULTS

One-Way Active Avoidance

Aged vehicle-treated rats were severely deficient in the acquisition of one-way active avoidance behavior compared to the excellent learning of this task exhibited by young vehicle-treated animals (Fig. 1). A highly significant group effect, $F(1, 15) = 62.94$, $p < 0.001$, and group by blocks interaction, $F(3, 45) = 18.93$, $p < 0.001$, were present. Aged rats treated with nicotine prior to daily trials showed a substantial enhancement in acquisition compared to vehicle-treated aged animals (Fig. 1). The significant group effect, $F(1, 11) = 15.49$, $p < 0.005$, and group by blocks interaction, $F(3, 33) = 3.48$, $p < 0.05$, indicate that nicotine-treated aged rats exhibited a greater overall learning ability compared to aged controls and that their rate of learning was also greater. Nicotine treatment did not, however, improve the performance of aged rats to the level of young controls because statistical comparison between these two groups revealed both a significant group effect, $F(1, 14) = 17.41$, $p < 0.005$, and a group by blocks interaction, $F(3, 42) = 3.43$, $p < 0.05$.

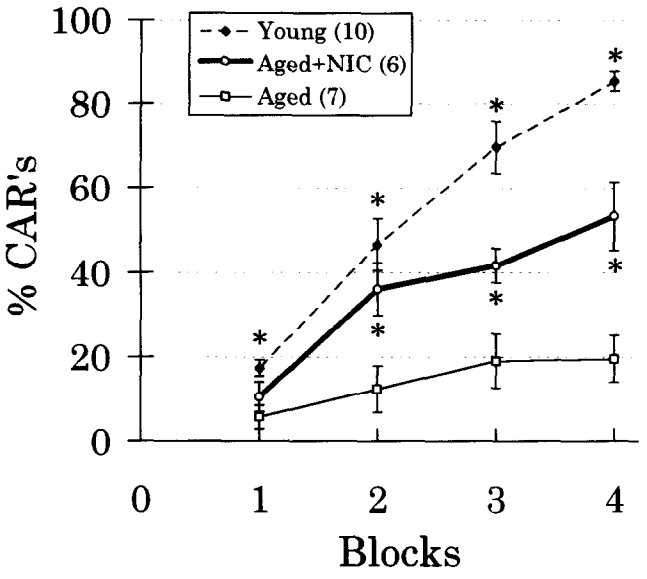

FIG. 1. One-way active avoidance acquisition for young adult rats, aged rats, and aged rats pretreated with nicotine (NIC; 0.2 mg/kg) 15 min prior to daily testing for 12 days. The number of animals in each group is indicated within parentheses. Astericks at individual 3-day time blocks indicate a significantly greater percentage of conditioned avoidance responses (CARs) for that group compared to the % CARs exhibited by aged control rats for that block ($p < 0.025$ or higher level of significance).

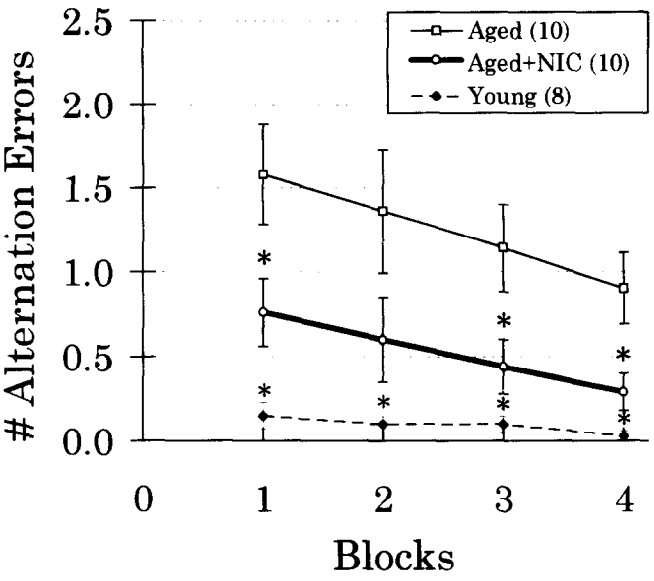

FIG. 2. Lashley III maze acquisition for young adult rats, aged rats, and aged rats pretreated with nicotine (NIC; 0.2 mg/kg) 15 min prior to daily testing. The number of animals in each group is indicated within parentheses. Astericks at individual 5-day time blocks indicate significantly fewer alternation errors for that group compared to errors exhibited by aged control rats for that block ($p < 0.05$ or higher level of significance).

Lashley III Maze

Young vehicle-treated rats quickly learned to reduce their number of alternation errors to near zero by the end of the first test block (Fig. 2). By contrast, aged vehicle-treated rats made substantially more errors over the 20 days of testing, as indicated by a significant group effect, $F(1, 16) = 16.98$, $p < 0.001$. Aged rats pretreated with nicotine made markedly less alternation errors over the entire testing period compared to aged control rats because a group effect was present between these two groups, $F(1, 18) = 6.05$, $p < 0.025$. However, no group by blocks interaction was present, $F(3, 54) = 0.19$, $p > 0.05$, indicating that both aged groups improved their performance at the same rate. Although nicotine pretreatment did not reduce the overall number of errors exhibited by aged rats to the low numbers seen in young controls, the performance of aged, nicotine-treated rats was not significantly different from that of young controls for all blocks except block 1.

17-Arm Radial Maze

General learning. In comparison to the marked learning shown by young vehicle-treated rats in this task, aged vehicle-treated animals exhibited markedly poorer learning ability (Fig. 3). Both a group effect, $F(1, 16) = 61.00$, $p < 0.001$, and a group by blocks interaction, $F(5, 80) = 13.10$, $p < 0.005$, were present. It should be noted that the decrease in learning that occurred between blocks 1 and 2 for aged control animals was primarily a reflection of the food reward being placed further and further out on baited arms to where animals could neither see nor smell the reward from the center

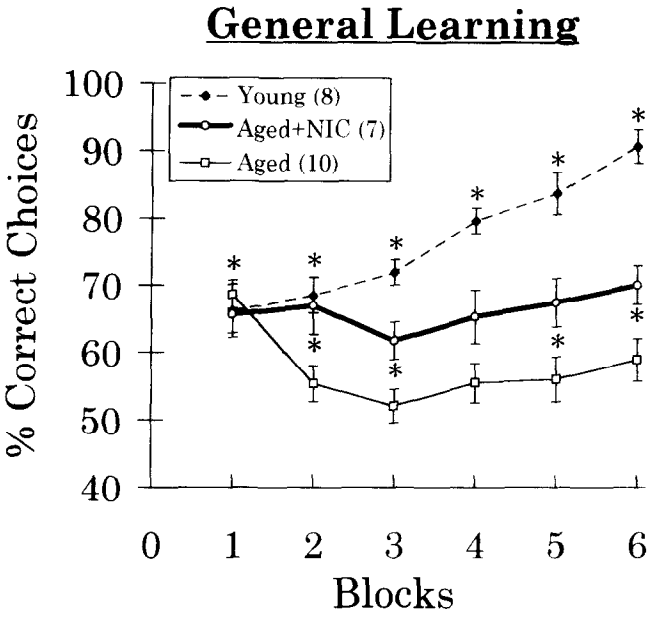

FIG. 3. General learning in the 17-arm radial maze for young adult rats, aged rats, and aged rats pretreated with nicotine (NIC; 0.2 mg/kg) 15 min prior to daily testing. Data are presented as percent of correct entries into baited arms (containing food) out of the first eight choices. The 30 days of data analysis are shown in six 5-day time blocks. Astericks at individual blocks indicate a significantly greater percent of correct choices for that group compared to aged control rats ($p < 0.05$ or higher level of significance). The number of animals in each group is indicated within parentheses.

platform. Aged rats treated with nicotine prior to daily testing exhibited a significantly greater level of overall performance compared to aged control rats (Fig. 3), as indicated by the presence of a group effect, $F(1, 15) = 9.78$, $p < 0.01$. For each of these aged groups, however, a one-way analysis of variance with repeated measures revealed no increase in performance through all six blocks of testing. Comparing the learning of aged nicotine-treated rats to that of young controls revealed a significant group effect, $F(1, 13) = 14.67$, $p < 0.005$, and a group by blocks interaction, $F(5, 65) = 4.81$, $p < 0.005$, indicating that the improved performance of aged rats treated with nicotine was still significantly below that of young controls.

Reference (long-term) memory. Reference memory of young vehicle-treated rats improved significantly throughout testing to attain almost 90% correct choices (Fig. 4). In sharp contrast, aged vehicle-treated animals exhibited poor reference memory, performing at or near chance levels throughout the 30-day testing period. In fact, a one-way analysis of variance with repeated measures revealed that aged, vehicle-treated rats failed to improve their performance throughout the six blocks of testing. Comparing young and aged vehicle-treated rats, a highly significant group effect was present, $F(1, 16) = 71.88$, $p < 0.001$, as was a group by blocks interaction, $F(5, 80) = 11.99$, $p < 0.001$. Aged animals pretreated with nicotine had significantly better reference memory compared to aged control rats (Fig. 4); both a group effect, $F(1, 15) = 15.41$, $p < 0.005$, and a group by blocks interaction, $F(5, 75) = 3.74$, $p < 0.005$, were evident. Nonetheless, reference memory in aged nicotine-treated rats was significantly below that of young control rats, as revealed by a significant group effect, $F(1, 13) = 9.95$, $p < 0.01$, and a group by blocks interaction, $F(5, 65) = 6.75$, $p < 0.005$. Furthermore, a one-way analysis of variance for repeated measures indicated that aged nicotine-treated rats did not improve their reference memory throughout the six blocks of testing.

Working (short-term) memory. Working memory in aged vehicle-treated rats was statistically below that of young vehicle-treated rats over the entire test period (Fig. 5), as indicated by the presence of a group effect, $F(1, 16) = 25.62$, $p < 0.005$. However, both aged and young groups exhibited a high level of working memory performance throughout all six blocks of testing because their overall percent correct choices were 89% and 95%, respectively. Nicotine pretreatment did not further improve the already high level of performance shown by aged animals (Fig. 5); statistical analysis of working memory in aged nicotine-treated rats vs. aged controls revealed no group effect, $F(1, 15) = 2.39$, $p > 0.05$, and no group by blocks interaction, $F(5, 75) = 0.67$, $p > 0.05$. Moreover, nicotine pretreatment did not improve the working memory of aged rats to the level of young controls as demonstrated by a significant group effect, $F(1, 13) = 20.03$, $p < 0.005$.

DISCUSSION

The results of this study demonstrate that chronic nicotine administration can attenuate, though not eliminate, learning and memory impairments associated with normal brain aging in the rat. Nicotine's cognition-enhancing ability was observed in three divergent behavioral tasks (one-way active avoidance,

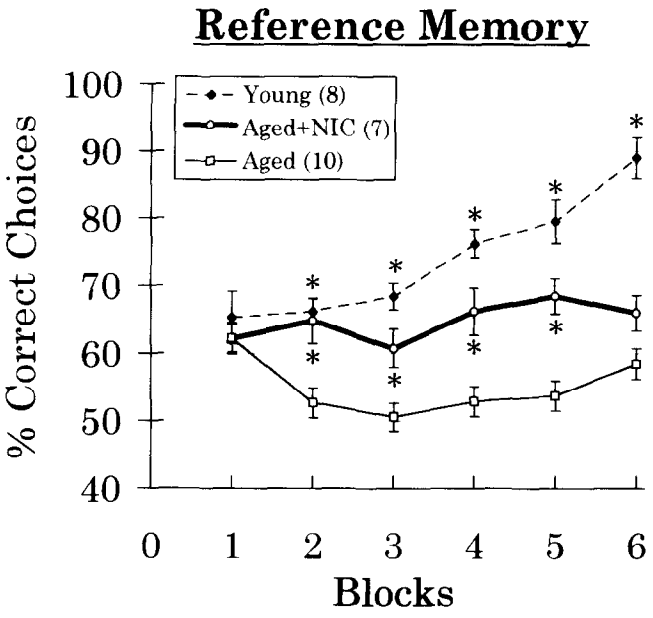

FIG. 4. Reference (long-term) memory in the 17-arm radial maze for young adult rats, aged rats, and aged rats pretreated with nicotine (NIC; 0.2 mg/kg) 15 min prior to daily testing. Data were calculated as the percent correct entries into arms of the baited set out of the first 12 choices. The 30 days of data analysis are shown in six 5-day time blocks. Astericks at individual blocks indicate significantly greater reference memory for that group compared to aged control rats for that block ($p < 0.01$ or higher level of significance). Numbers in parentheses indicate number of animals.

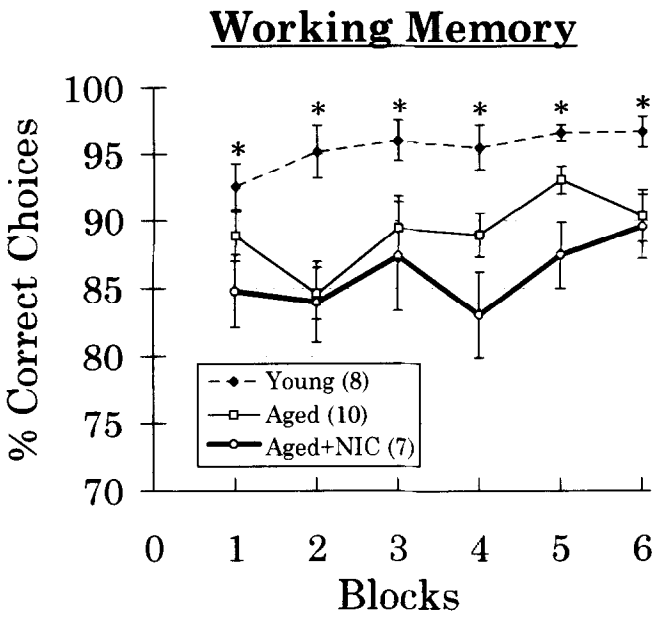

FIG. 5. Working (short-term) memory in the 17-arm radial maze for young adult rats, aged rats, and aged rats pretreated with nicotine (NIC; 0.2 mg/kg) 15 min prior to daily testing. Data were calculated from the first 12 entries as the percent correct choices into baited arms (containing food) over the total number of choices within the baited set. The 30 days of data analysis are shown in six 5-day time blocks. Astericks at individual blocks indicate significantly different working memory for that group compared to aged control rats ($p < 0.05$ or higher level of significance). The number of animals in each group is indicated within parentheses.

Lashley III maze, and 17-arm radial maze) in which aged rats were injected with nicotine prior to as many as 30 daily test sessions. Although numerous earlier studies have documented nicotine-enhanced cognitive performance in normal young adult rats or those with cholinergic lesions (10,20,26,28), the present study is the first to report improved acquisition and memory retention following nicotine administration to aged rats. These results are consistent with the only other study that investigated the cognition-enhancing potential of nicotine in an aged animal (6), wherein a nicotine-induced improvement in delayed matching was reported in aged rhesus monkeys.

In rats and other experimental animals, aging itself brings about impairments of learning and memory in a variety of tasks including passive/active avoidance (17,34,38,50), cognitive mapping (18,22,23), and spatial discrimination (13,14, 21,46). In the present study, the very poor acquisition exhibited by aged rats in one-way active avoidance testing is consistent with results from earlier studies utilizing similar versions of this task (38,50). Additionally, results from the present study establish the Lashley III maze as an age-sensitive cognitive mapping task (i.e., a task in which the correct choice sequence can be internalized and, consequently, does not require external sensory cues). Aged rats were clearly impaired in Lashley III maze acquisition compared to young adults, as indicated by their greater number of alternation errors over the entire 20-day test period. Previous studies involving other cognitive mapping tasks, such as the 14 unit T-maze (18, 22,23), have also revealed acquisitional impairments in aged rats.

Particularly affected by aging is the performance of rodents in complex spatial discrimination or place learning tasks such as the 8- and 12-arm radial mazes (22,46), the Morris water maze (13,14,36), and the holeboard (45). The present study utilized a highly complex 17-arm radial maze in determining that aged rats are substantially impaired in general learning and reference (long-term) memory aspects of this task, but only mildly impaired in working (short-term) memory in comparison to young adults. Moreover, aged rats did not improve their performance on any aspect of this task over the entire 30-day test period. These 17-arm radial maze results are consistent with earlier studies involving less complex radial or holeboard mazes, in which aged rats were shown to be greatly impaired in acquisition or reference memory, but not impaired (or only mildly so) in working memory (21,45,46).

Results of the present study clearly indicate nicotine's broad cognition-enhancing ability in aged rats over the diversity of an avoidance task, a cognitive mapping task, and a spatial discrimination task. For example, pretreatment of aged rats with nicotine resulted in substantial improvements in the acquisition of both one-way active avoidance pole jumping and Lashley III maze. Young adult rats have previously been shown to exhibit enhanced performance in active avoidance and Lashley III maze following nicotine treatment (11,12). Nicotine-induced improvements in general learning and reference memory aspects of 17-arm radial maze testing further exemplify nicotine's broad cognition-enhancing ability in aged rats. Interestingly, nicotine administration did not improve the already high level of working memory exhibited by aged rats in this task. This result might have been unexpected in view of earlier eight-arm radial maze studies reporting that the same nicotine pretreatment (0.2 mg/kg) improves working memory of trained young adult rats (25,29). Variables such as subject age, sex, and degree of maze experience could explain nicotine's ability, or inability, to affect working memory in radial maze testing.

The cognitive improvements induced by nicotine pretreatment in aged rats during this study's one-way active avoidance, Lashley III maze, and 17-arm radial maze testing may involve a nicotine receptor-induced increase in the generalized level of alertness/attention (24). Alternatively, nicotine receptor activation may be specifically facilitating higher integrative function, as suggested from studies showing that posttrial nicotine administration can enhance cognitive function (5,19). In any event, the cognition-enhancing ability of nicotine pretreatment in aged (22-24-month-old) rats over three diverse tasks appears to have occurred in animals with an anatomically intact nucleus basalis cholinergic system. This is suggested from our recent studies comparing 3-month and 24-month-old rats in which no age-related decreases in neocortical ChAT activity, AChE activity, or nicotine receptor densities were observed (49), and an age-related atrophy (but no loss) of nucleus basalis neurons was evident (8). Although the brain sites and mechanism(s) of action of chronic nicotine treatment for induction of cognitive enhancement in such aged animals are unknown, nicotine's cognitive actions most likely involve: a) activation of postsynaptic nicotinic receptors to depolarize postsynaptic neurons, b) activation of presynaptic nicotinic receptors on cholinergic nerve terminals to enhance acetylcholine release, and/or c) activation of presynaptic nicotinic receptors on dopamineric, noradrenergic, serotoninergic, or GABAergic nerve terminals to induce release of their respective neurotransmitters (48). Interestingly, several studies report that nicotine can exert cognition-enhancing effects even in young adult rats in which the septo-hippocampal and/or

the nucleus basalis cholinergic systems have been compromised by excitotoxic lesions or knife cuts (10,20,28,44).

Despite the chronic administration of nicotine to aged rats of this study for either 12, 25, or 30 days (depending on which of the three cognitive tasks was being evaluated), no behavioral desensitization occurred during the 12-30-day test period. Rather, nicotine pretreatment was continously effective in enhancing the cognitive performance of aged rats over the entire test period for all three cognitive tasks. In fact, nicotine-treated aged animals were usually still performing at a significantly higher level than aged control animals at the end of cognitive testing. Previous studies involving young adult rats in an eight-arm radial maze also revealed continuous cognition-enhancing effects of nicotine over 3-4 weeks of administration (27,29). Although the mechanism(s) for such persistent cognitive effects of nicotine is not understood, chronic nicotine administration induces an upregulation of nicotine binding sites in several brain regions, particularly neocortex (30,41). To what extent this receptor upregulation is involved in the persistent cognition-enhancing effects of chronic nicotine treatment remains unclear.

In senile dementia of the Alzheimer's type (SDAT), nicotinic receptor binding sites are substantially reduced in the neocortex and hippocampus (1,37,40). It has, thus, been suggested that stimulation of the remaining nicotinic receptors might lessen cognitive impairments due to cholinergic neuron dysfunction. An increasing number of clinical studies have, in fact, found encouraging enhancements in the attention and information processing of SDAT patients following nicotine administration (24,33,39,47). However, the present study clearly indicates the ability of chronic nicotine treatment to enhance the cognitive performance of normal aged rats, suggesting that chronic nicotine or nicotinic agonist administration may be of considerable clinical benefit in the treatment of age-associated memory impairment. To this end, the demonstrated cognition-enhancing abilities of nicotine in aged rats for the three tasks of this study could serve as a reference for evaluating the potential of newly synthesized nicotinic agonists to treat age-associated memory impairment.

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