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Nicotine Enhances Stimulus Detection Performance of Middle- and Old-Aged Rats: A Longitudinal Study

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GRILLY, D. M., B. B. SIMON AND E. D. LEVIN. *Nicotine enhances stimulus detection performance of middle- and old-aged rats: A longitudinal study.* PHARMACOL BIOCHEM BEHAV **65**(4) 665–670, 2000.—The effects of nicotine on sustained attention were tested in F344×BN male rats when they were chronologically middle and old aged. The rats (n = 11) were trained in a two-choice, stimulus detection task in which a press of one of two levers was reinforced with food, with the correct lever indicated by the position of a briefly illuminated light. They were tested when they were 24–25 and 34–35 months of age (i.e., at 60–68% and 85–95%, respectively of their expected median life span) after saline or 0.1–0.5 mg/kg doses of nicotine (SC). A significant dose-related improvement in percent correct choices and decrease in choice response times was found at both ages, and there was no significant main effect of age or an age by dose interaction. These results support the position that nicotine can enhance attentional processes in rats throughout their life span. Nicotine and other nicotinic agonists may have efficacy in the treatment of disorders such as Alzheimer's disease. © 2000 Elsevier Science Inc.

Aging Nicotine Performance Stimulus detection Attention Rats

IT has been well established that nicotine and nicotinic agonists can enhance the performance of humans in tasks designed to assess attentiveness (24,27,28,33,46,55–58). However, the effects of nicotine in rodents have not been as consistent in attention-dependent tasks, i.e., tasks that typically require animals to report by way of a choice response the detection of a visual stimulus, for example, its presence vs. absence, its presentation at a spatial location (either onset or offset), or a change in its location, that occurs periodically over time. Indeed, although some studies have found nicotine (in the 0.08 to 0.75 mg/kg dose range) to reliably improve performance of rats attention-dependent choice tasks (10,35,52), others have found that nicotine has little or no beneficial effects (5,54) or impairs performance (53). The nature of the rodent models to assess attention may explain the heterogeneity of correspondence to effects of nicotine on attention in humans.

Grilly and colleagues have developed a two-choice light detection procedure that is sensitive in demonstrating performance-enhancing effects of psychostimulant drugs. Several studies using this procedure have found improvements in performance (choice accuracy and speed) following low doses of the indirect dopamine agonist *d*-amphetamine (15,16,21), cocaine (12,16–19), and pemoline (unpublished observations), but not behaviorally relevant doses of morphine (13), opiate antagonists (13,15), the selective serotonin reuptake inhibitor fluoxetine (19), or the indirect serotonin/dopamine agonist 3,4-methylenedioxymethamphetamine (unpublished observations). The initial goal of the present research was to determine if nicotine improves the stimulus detection performance of middle-aged rats in a fashion similar to amphetamine, cocaine, and pemoline.

Upon determining that nicotine did enhance performance in a dose-related fashion, we determined if task performance would decline, and whether these dose-related effects would change when these same animals were chronologically old. Nicotinic cholinergic systems are involved with several important aspects of cognitive function including attention, learning, and memory (29,38). Although the available data are not always consistent with the hypothesis that normal aging in ro-

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dents robustly affects the function of the basal forebrain cholinergic system (47), there is some evidence for cholinergic degeneration, age-associated impairments in attention, and decline in response to nicotine in aged rats (23,34,48,54). Thus, one might expect that stimulus detection performance would decline, and that the performance-enhancing effects of nicotine would be attenuated with age. Conversely, older rats may be more susceptible to the performance-enhancing effects of nicotine, because acute nicotine exposure has been shown to improve working memory performance of aged rats but to not improve performance of young adult rats (30,59). Finally, because the rats in the present study had practiced the task regularly and had been maintained under food deprivation conditions from young adulthood, it was also possible that there would be no age differences in nicotine-induced improvements in performance. Numerous studies have shown that both life-long task experience/practice (2,3,6,9,32,43,51) and hypocaloric dietary restrictions (1,25,31,41,45) can dramatically reduce the neuropathological and performance deficits typically observed in aged rodents. Therefore, the present manuscript describes the results of assessing baseline performance with age, and the effects of nicotine on performance when assessed at middle and old age.

METHOD

Animals

The data from 11 surviving male F344×BN rats (Harlan–Sprague–Dawley, Inc., Indianapolis, IN) from an original cohort of 15 were used. They arrived in our lab at 60 days of age and housed in pairs in a colony maintained at 22°C and 50% humidity under a 12 L:12 D cycle (lights on 0800 h). Following a 40-day acclimation period in which food and water were freely available, food was restricted to approximately 12 g standard lab chow per day in addition to food earned during experimental and practice sessions (approximately 3.6 g). Rats were maintained at their young adult weights (mean middle-age weight = 375 g, mean old-age weight = 368 g) in this manner throughout this study. Training and test sessions were conducted between 1100 and 1600 h.

Middle age and old age in these rats were defined operationally in terms of chronological age at testing relative to their expected median life span. In our lab, we have determined the median life span of the F344×BN strain of male rat (n = 28), maintained under a food-restricted diet from young adulthood, to be approximately 37 months. Previous investigations on the life span of F344×BN males under somewhat more severe food restriction conditions than employed in our lab have indicated a median life span of 40 months (50). Thus, middle age in the rats employed in the present study was defined as 24–25 months, i.e., the age at which they were approximately 60–68% of their expected life span, and old age was defined as 34–35 months, i.e., the age at which they were approximately 85–95% of their expected median life span.

Prior to the middle-age nicotine tests of the present study, the animals had been tested at various ages following acute doses of *d*-amphetamine (three tests at 0.25, 0.50, and 0.75 mg/kg, and two tests with 1.0 mg/kg SC) and pemoline (one test each with 4, 6, 8, 10, 12, 14, 18, and 22 mg/kg PO); prior to the old-age nicotine tests, the rats were tested following 0.25, 0.50, and 0.75 mg/kg *d*-amphetamine (SC) and 4, 8, 14, and 22 mg/kg pemoline (PO). There were at least 7 days between the last of these drug exposures and the tests with nicotine. The "Principles of Laboratory Animal Care" (NIH publication No. 85-23, revised 1985) were followed, upon approval of the protocol from Cleveland State University's Animal Care and Use Committee.

Apparatus

Two operant chambers (Campden Instruments Ltd., rodent test chamber, model 410) were interfaced with microprocessors, which controlled experimental events and collected data. Two levers were located at one end of the chambers. Located between the two levers was a food tray, into which single 45-mg food pellets (Noyes Precision Pellets) were delivered as reinforcers. A microswitch was activated when the rat's head was inserted into the tray opening. The cue lights were located directly above each lever, and a house light was located in the middle of the ceiling. Further details of the apparatus can be found in another study (14).

Training and Testing Procedures

Prior to the nicotine tests, the animals had had considerable training on the stimulus detection task (median number of sessions = 66 over a 17–18-month period), which we have determined to be a critical factor in demonstrating the performance-enhancing effects of psychostimulants [see (20), for further details]. Test sessions were conducted with no illumination in the room containing the operant chambers. Each session consisted of 100 trials. Trials were initiated with the house light in the chamber coming on. Prior to cue light presentation, the rat had to have its head out of the food tray and had to refrain from pressing a lever for 1.0 s. The cue light above one of the levers was then briefly illuminated, and the first lever press upon cue light termination was recorded. If a lever was being pressed at the moment the cue light was terminated, it was recorded as the choice. Also, if no choice was made within 10 s of cue light termination, the trial was terminated and recorded as an omission trial. The duration of the cue light was set at a value for each individual animal prior to the two nicotine test series so that its baseline choice accuracy level (number of correct responses/number of choice trials × 100) was maintained between 75 and 88% over a minimum of four sessions, with at least 90 choice trials completed. The animals were given practice sessions two to three times per month between the two nicotine test series. At the time of the middle age drug tests, the cue durations ranged between 0.70 and 1.70 s (mean = 1.08 s) and the median number of task sessions was 66 (range = 61–101). At the time of the old-age drug tests, the cue durations ranged between 0.35 and 1.70 s (mean = 1.04), and the median number of task sessions was 96 (range = 85–118).

Drugs

Nicotine ditartrate (Sigma Chemical Company, St. Louis, MO) was dissolved in 0.9% sterile saline, and solutions were prepared so that all injections were given in a volume of 1.0 ml/kg. Injections in drug test sessions consisted of saline or 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg nicotine for all rats. For the middle-age tests, the three lower doses were tested first in a random order. Because the dose–response functions did not appear to have reached asymptotic levels with these doses, the two higher doses were then tested in a random order. Saline tests were conducted between the first two drug tests and before or after the last drug test (the mean scores of the two saline tests were derived for data analyses). For the old-age tests, the order of saline and drug treatments was randomly determined for each rat. Injections were given SC 20 min

prior to test sessions, and there was a minimum of 3 days between each test.

Behavioral Measures and Statistical Analyses

The following behavioral measures of task performance were derived for each animal in the drug tests: (1) choice accuracy (percentage correct choices); (2) choice response time (mean $\log_{10}$ of the time, in milliseconds, between cue light termination and a lever press); (3) the number of completed trials; and (4) food retrieval latency (mean $\log_{10}$ of the time, in milliseconds, between a correct choice and the animal's entry into the food tray). Minimum and maximum response times for a trial were 130 and 10,000 ms—the former due to constraints of the recording apparatus and the latter due to the constraints of the procedure. The first three measures are task performance measures of the type commonly assessed in stimulus detection tasks. The food retrieval latency measure is an indication of the animal's food-related motivation, for example, we have shown it to be sensitive to shifts in food deprivation time (17), exposure to anorectic drugs (19), and differences in reward pellet palatability (unpublished observations). Each of these measures was assessed by separate repeated-measures design ANOVAs, with two levels of age and six levels of drug treatment. For each age, planned comparisons with dependent measures *t*-tests were made between the saline tests and the five nicotine dose tests. A p-value of < 0.05 (two tailed) was considered significant.

RESULTS

To assess whether declines in stimulus detection task performance occurred in these rats as they aged, baseline levels of performance were determined after approximately 19, 32, 66, and 96 task sessions when the rats were 10–11, 18–19, 24–25, and 34–35 months of age, respectively. These levels were derived from saline tests conducted with the rats during two prior drug treatment series and the two present nicotine drug series. The mean performance measures across the four tests are shown in Table 1. As indicated, there was no evidence for a decline in task performance as a function of the animals' age/experience. In general, the cue durations required to maintain the animals' accuracy levels within the 75–88% criterion levels were either the same or shorter at 34–35 months of age than they were when the rats were 10–11 months of age. Also, the mean log choice response time decreased and the number of completed trials increased as a function of age/task experience.

Mean percent correct responses and log choice response times for the rats at middle and old age as a function of nicotine dose are shown in Fig. 1. There were dose-related improvements in both performance measures, i.e., an increase in percent correct responses and a decrease in log choice response times, with the performance measures reaching asymptotic levels between 0.3 and 0.5 mg/kg nicotine. Results from the two-way ANOVAs indicated a significant effect of dose on percent correct responses, $F(5, 50) = 13.38$, $p < 0.001$, and log choice response time, $F(5, 50) = 14.76$, $p < 0.001$. There were no obvious age-related differences in either measure, and there were no significant age effects or age by dose interaction with either measure (all Fs < 1.0). For both measures and ages the differences between saline and 0.3, 0.4, and 0.5 mg/kg nicotine doses were statistically significant (all ps < 0.036).

The mean number of trials completed at both ages and across all drug treatments ranged between 96 and 99, and there were no significant age or dose effects or an age by dose interaction (all Fs < 1.0). Although the animals' log food retrieval latency scores were somewhat lower when they were older, a difference that almost reached significance, $F(5, 50) = 4.75$, $p = 0.054$, there was no significant dose effect or age by dose interaction (all Fs < 1.29).

DISCUSSION

These results show that treatment with nicotine can significantly improve stimulus detection task performance accuracy and decrease choice response times in middle-aged and old rats, with the dose–response functions essentially being the same at both ages. These results are in accordance with findings from studies of vigilance and attention in young adult and aged humans reporting improved performance (both speed and accuracy) following nicotine treatment (24,27,28, 33,46,55–58).

These results replicate previous studies finding that nicotine can improve the performance of normal young adult rats in tasks requiring sustained attention (10,35). They extend these findings to include chronologically old rats that have been maintained under conditions expected to attenuate the behavioral and neurological consequences of aging. The present results contrast with previous studies finding nicotine-induced improvements in the working memory of aged rats, but not young adult rats (30,59); however, this may be due to the younger rats in the latter studies already operating at close to ceiling levels. These results also differ from studies with rodents reporting either minimal or no beneficial effects (5,54) or detrimental effects of nicotine on sustained attention (53). Although the effects of nicotine on the performance of rodents trained in tasks heavily dependent on attention have not been uniform, the effects of the classical nicotinic receptor antagonist mecamylamine and the mixed agonist/antagonist lobeline are clear—they disrupt various aspects of performance, for example, decreasing accuracy, increasing response omissions, and increasing response times (5,23,53). Therefore, although it has not been empirically tested, it would not be surprising for nicotinic antagonists to reverse the nicotine-

TABLE 1

(MEAN ± 1 SD) BASELINE PERFORMANCE MEASURES OF THE RATS AS A FUNCTION OF AGE AND MEDIAN NUMBER OF STIMULUS DETECTION TASK SESSIONS

Age (months)	Task Sessions	Cue Duration (s)	Percent Correct Responses	Log Choice Response Time	Log Food Retrieval Latency	Trials Completed
10–11	19	1.21 (± 0.29)	81.8 (± 4.1)	2.88 (± 0.21)	2.90 (± 0.15)	85.2 (± 16.8)
18–19	32	1.26 (± 0.37)	82.2 (± 5.7)	2.82 (± 0.18)	3.01 (± 0.10)	92.8 (± 7.6)
24–25	66	1.08 (± 0.40)	82.4 (± 4.8)	2.81 (± 0.09)	2.98 (± 0.14)	98.1 (± 1.7)
34–35	96	1.04 (± 0.45)	83.1 (± 6.9)	2.79 (± 0.14)	2.93 (± 0.27)	96.3 (± 9.7)

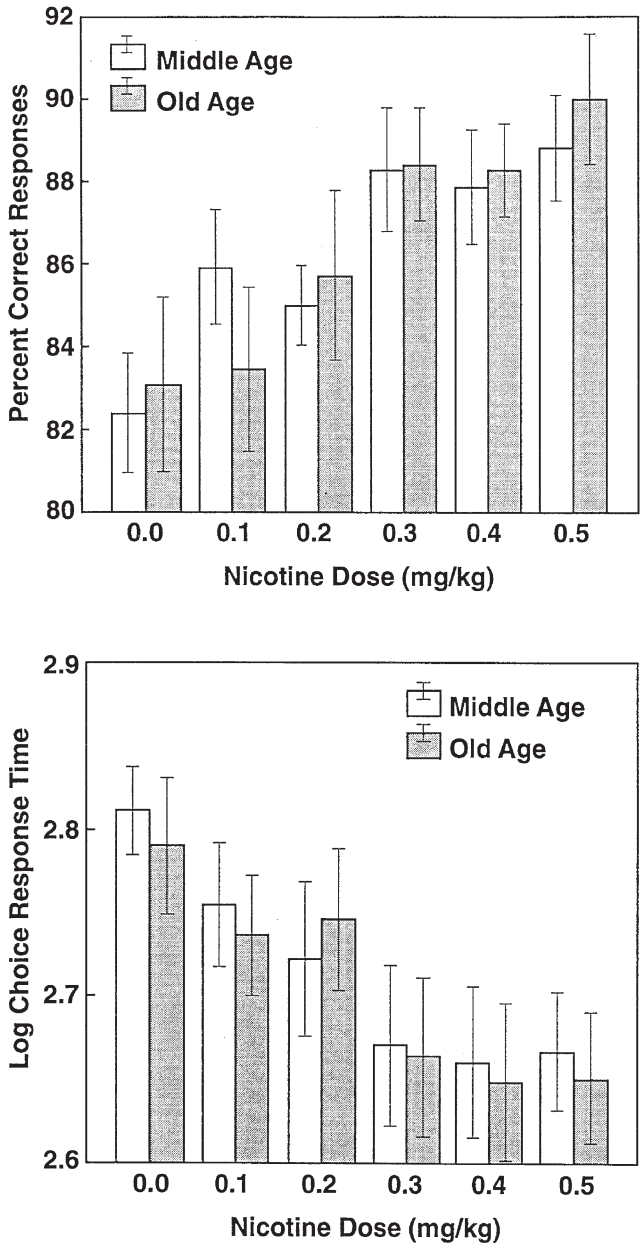

FIG. 1. Mean percent choice accuracy (upper panel) and $\log_{10}$ choice response time (lower panel) as a function of the rat's age at testing and dose of nicotine. Error bars indicate ± 1 SEM.

induced improvements in performance that we observed in the present study.

It is likely that the differences among the studies investigating nicotine's effects on attention in rats depend on factors such as nicotine dose, strain of rat, the nature of the task, and level of training (29). The nature of the task appears to be particularly relevant, because the three basically negative reports on nicotine's effects on attention-dependent performance involved tasks that required the animals to report the presence vs. absence of a light stimulus, and the three positive reports involved tasks that required the animals to report the location of a light. The importance of the animals' level of training in determining whether psychostimulant-induced improvements in stimulus detection tasks will be observed has been demonstrated by (20), who found that as choice behavior in the task became more strongly controlled by the stimulus-reinforcement contingencies the facilitation effects of low doses of amphetamine became more apparent, and the disruptive effects of somewhat higher doses became less apparent.

Whether our findings with respect to nicotine's ability to enhance stimulus detection performance as a function of task training are applicable to other tasks, particularly those suggested to assess sustained attention in animals, is unclear. Because the procedure initiates trials with the onset of a house light, which is followed a second or so later by a cue light, one might argue that the task requires minimal "sustained attention" on the part of the rat. However, we argue that the task taps some aspect of visual attention process (as opposed to more complicated processes like memory, learning, or discrimination ability) because: (1) the cue for correct choice responses is presented briefly; (2) lengthening (or shortening) the cue duration improves (or disrupts) choice performance in a monotonic manner (49); and (3) conditions that increase (or decrease) the general arousal level of the rat improves (or disrupts) choice performance (17). Furthermore, even if one assumes that our task does not demand a particularly high level of a rat's attentional resources, it is sufficiently demanding that the rat's baseline "error rate" of approximately 18% is considerably greater than the error rate they obtain (less than 5%) if the cue light were to stay on until the animal makes a choice response. Finally, essentially the same results with nicotine have been obtained using a modified version of the present task in which the house light off-time between trials was decreased to 1.3 s, and the interval between the house light onset and the cue light onset varied randomly between 3, 7, and 11 s across trials (unpublished observations).

The improvement in choice accuracy in this task we have observed with low doses of stimulants is not likely due to their motor-enhancing effects because the levers only become operative after the cue light terminates and become inoperative after the first lever press. Thus, while an increase in motor output could potentially shorten choice response time, it would not necessarily enhance choice accuracy; it might actually decrease it because of the animal's indiscriminate rapid pressing of the levers, a phenomenon we have observed in some rats administered higher doses of stimulants (e.g., 1.0 mg/kg *d*-amphetamine).

The lack of any reliable declines in stimulus detection task performance in these rats from young adulthood to a relatively advanced age was surprising. In fact, only one rat required an increase in its cue duration from middle to old age (from 0.70 to 1.0 s) to maintain its accuracy levels between 75–88% correct, whereas three rats required cue duration decreases between 0.15–0.35 s to maintain their baseline performance within these criteria. This phenomenon contrasts with a large body of literature indicating impairments in reaction time, cognitive functioning, and attention in rats as they reach senescence (4,11,23,26,34,36,54). However, in contrast to most of these studies in which cross-sectional designs were used, the rats in the present longitudinal study practiced the task on a regular basis throughout their adult life span, and were maintained on a substantial hypocaloric dietary regimen throughout this time. As noted earlier, individually both of these conditions have been demonstrated to substantially attenuate the detrimental effects of chronological aging in rodents in a wide variety of behavioral domains (1–6,9,25,31, 32,40–43,45,51). Which of these two factors contributed to the

lack of deterioration in performance in these rats and whether their protective effects may have been synergistic is unknown, because, to our knowledge, studies have not adequately addressed this issue.

The finding that nicotine improved performance in very old, but physically healthy rats contrast with results from previous studies with this procedure investigating the effects of the indirect dopamine agonists cocaine (12) and amphetamine (21). Because the performance-enhancing properties of these drugs were reduced considerably in aged rats, the latter studies suggested that there are qualitative changes in the effects of stimulants as rats age. The differences between nicotine and amphetamine or cocaine may be due to differences in the involvement of dopaminergic and nicotinic cholinergic systems in memory and other behaviors of rodents. The difference may also be due to a more substantial deterioration in brain dopaminergic than cholinergic systems that occurs with normal aging in rodents (7,22,37,44,47,60). And although nicotine's ability to increase extraneuronal levels of dopamine is shared by cocaine and amphetamine (8,39), nicotine may have fewer behaviorally disruptive effects than more potent dopaminergic stimulants. Thus, it may be easier to demonstrate task performance improvements in old animals following nicotine.

These results support the position that nicotine can enhance attentional processes in rats throughout most of their life span, as is commonly found in humans, which may partially account for its long-term abuse in humans. These results also suggest that nicotinic agonists may have efficacy in the treatment of attentional deficit disorders.

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