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Effects of Acute Nicotine on Several Operant Behaviors in Rats

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POPKE, E. J., A. J. MAYORGA, C. M. FOGLE, AND M. G. PAULE. *Effects of acute nicotine on several operant behaviors in rats.* PHARMACOL BIOCHEM BEHAV **65**(2) 247–254, 2000.—The present experiment assessed nicotine's effects on complex cognitive processes using a variety of operant tasks in rats, including incremental repeated acquisition (IRA) to assess learning; conditioned position responding (CPR) to assess auditory, visual, and position discrimination; progressive ratio (PR) to assess motivation; temporal response differentiation (TRD) to assess timing; and differential reinforcement of low response rates (DRL) to assess timing and response inhibition. Acute nicotine administration (0.0, 0.3, 0.42, 0.56, 0.75, and 1.0 mg/kg, IP) increased IRA and CPR response rate without significantly altering accuracy. Nicotine had similar effects on response rate for PR. For TRD, nicotine had a U-shaped dose effect on accuracy, but failed to shift the mode of the TRD response distribution. For DRL, nicotine reduced accuracy and also shifted the mode of the DRL response initiation time distribution to the left. Nicotine produced an inverted U-shaped dose–effect curve for the overall number of "bursting" responses under both of these schedules. The results of this experiment suggest that nicotine can impair performance on some aspects of cognitive-behavioral performance, while simultaneously improving performance on others. © 2000 Elsevier Science Inc.

Nicotine Rats Operant behavior Cognitive function

THE effects of nicotine on behavioral models of cognitive performance are well documented (20). In animals, nicotine enhances water maze (37), radial arm maze (3,21), passive avoidance (4), and delayed matching-to-sample performance (11). In humans, nicotine improves stroop performance (26,30,37), word recall, and vigilance performance (12,32,40–43). The fact that nicotine can enhance these aspects of cognitive function has led to speculation that nicotine may be useful in treating cognitive-behavioral disorders (5,39). For example, nicotine has been shown to improve attention and reaction time in patients with Alzheimer's disease (18,33,44) and has shown potential for the treatment of schizophrenia (1), Tourette's syndrome (10,34) and Attention Deficit Hyperactivity Disorder (8,19).

Although nicotine has been shown to enhance performance of relatively simple behavioral tasks, its effects on the performance of more complex tasks is less clear. In rats, nicotine can improve radial-arm maze performance (21), but it has no effects on T-maze spatial alternation (22). These differential effects of nicotine have been interpreted to reflect the differential task demands imposed by T-maze and radial-arm maze, respectively (21). Specifically, it has been suggested that the T-maze is subject to more "proactive interference" than is the radial-arm maze, and therefore, may constitute a more complex behavioral problem. If this interpretation is correct, then these results suggest that nicotine's ability to enhance cognitive performance may be limited to relatively simple behavioral tasks. Spillich et al. (38), drew similar conclusions regarding the effects of nicotine (i.e., cigarette smoking) in a population of human smokers. Specifically, it was shown that nicotine did not alter performance on simple cognitive tasks involving signal detection or visual attention, and that nicotine actually impaired performance on more complex tasks involving text comprehension, short-term memory, and driving simulation. As was the case for maze learning, nicotine's enhancing effects on cognition in human smokers appear limited to relatively simple cognitive tasks. The purpose of the present experiment was to assess the effects of nicotine in rats using operant tasks of varying complexity that are thought to model different aspects of complex brain function. Tasks included: incremental repeated acquisition (IRA) to assess learning; conditioned position responding (CPR) to as-

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sess auditory, visual, and position discrimination; progressive ratio (PR) to assess motivation; temporal response differentiation (TRD) to assess timing behavior; and differential reinforcement of low response rates (DRL) to assess timing and response inhibition. The incremental repeated acquisition task requires subjects to perform a specific sequence of lever presses to receive reinforcement. Because the specific lever sequence is different for each test session, the incremental repeated acquisition task can provide an index of a subject's ability to "learn" novel sequences (7). The conditioned position responding task requires subjects to associate a given stimulus (here, either auditory or visual) with subsequent requirements for reinforcement (28,35,36). This task has been described as a "symbolic" matching-to-sample task (9), wherein specific visual or auditory stimuli serve as "symbols" for specific response locations. The progressive ratio task requires an incrementally greater number of responses (on a single operant lever) for subsequent reinforcers. This task has been used extensively to assess aspects of appetitive motivation (15,16) and the effects of drugs (14,31). The temporal response differentiation task requires subjects to make a continuous response on an operant lever for a fixed period of time to receive reinforcement. Such tasks have been used to assess subjects' ability to accurately estimate the passage of time (29). Finally, in the differential reinforcement of low response rates task, subjects are required to withhold responding for a fixed period of time to receive reinforcement. Like TRD, DRL tasks provide an assessment of subjects' ability to accurately estimate time and also of the subjects' ability to inhibit responding (6,17,19,25).

METHOD

Subjects

Subjects were 21 male Sprague–Dawley rats, approximately 6 months old and weighing roughly 325 g (324.6 ± 24.3 g) at the start of testing. Subjects were housed in 35.6 × 15.2 × 20.3 cm Plexiglas cages with absorbent wood-chip bedding. Temperature and humidity in the housing room was maintained at 21°C and at 45–55%, respectively. Food was available ad lib from weaning (postnatal day 22) through postnatal day 70. Beginning on Postnatal day 70, subjects were gradually food deprived to 80%–85% of their free-feeding body weight, and were maintained at this weight throughout the experiment. Water was available ad lib throughout.

Subjects in the present experiment had previously been trained to perform the operant tasks, and also had served in an earlier experiment to determine the effects of acute ethanol administration (0.5–3.0 g/kg ethanol administered twice weekly for 5 weeks) on operant task performance. Using the same subjects for multiple experiments eliminates the need to train new animals and maximizes the amount of useful data collected during each subject's life. Examination of subjects' behavioral performance (measured 2 weeks after the last ethanol administration and prior to the first nicotine administration) revealed no long-term residual effects of prior ethanol treatment. The time between the last ethanol exposure and the start of nicotine administration was 25 days.

Apparatus

Behavior was assessed using one of 12 identical operant test chambers. Each 24.6 × 22.9 × 21.0 cm chamber was housed in a sound-attenuating box equipped with a ventilating fan. The test panel contained three retractable levers (Stoelting, Co., #26446) each positioned under an array of nine stimulus lights (3 × 3). Food reinforcers (45-mg dustless precision food pellets, Bioserve, Frenchtown, NJ) were delivered into a feeding trough located immediately beneath the middle retractable lever. Each operant test panel was interfaced with a microcomputer that administered the behavioral tasks and recorded the behavioral responses. Each operant chamber was equipped with a house light that remained on for the duration of each behavioral task.

Behavioral Training

On postnatal day 90, subjects were divided into three groups, each of which was trained to perform one of three distinct sequences of operant tasks. The first group (n = 6) was trained to perform IRA, followed by CPR, followed by PR. The second group (n = 5) was trained to perform TRD, followed by CPR, followed by PR. The third group (n = 10) was trained to perform DRL, followed by CPR, followed by PR. At the start of training, subjects performed only the IRA, TRD, or DRL tasks during 50-min daily sessions (Monday–Friday). After behavioral stability had been achieved on these tasks, the duration of the tasks was shortened to 30 min and a 20-min CPR training task was added to the end of each session (total session time = 50 min). [Behavioral stability was assumed if the standard error for each task was not more than 15% of the mean of the percent task completed (reinforcers earned/reinforcers possible × 100) for seven consecutive sessions]. After behavioral stability was achieved on the CPR task, the length of the CPR task was reduced to 10 min and a 10-min PR task was added to the end of each session (total session time = 50 min). After subjects had met the stability criteria, the formal training phase was terminated, and drug treatments began. At no time during the experiment did subjects participate in more than one 50 min session per day.

Behavioral Testing

Learning task (IRA). The learning task required subjects to perform a specific sequence of lever presses to obtain reinforcers. At the beginning of each session, subjects could respond on any of the three retractable levers, but only responses to one of these resulted in reinforcer delivery. After 20 reinforcers were earned, a 1-min timeout was presented, followed by the presentation of an "incremented' two-lever sequence. At this level, a response on an additional lever was required before a response on the initial correct lever produced food. After the 20th errorless two-lever sequence, a 1-min timeout was followed by an incremented three-lever sequence. At this level, a specific sequence of three responses were required to produce reinforcement. After completing 20 errorless three-lever sequences, a four lever sequence was initiated, followed by a five-, and finally, a six-lever sequence, depending on the subject's performance. A total of 120 errorless sequences could be performed during a given IRA test session.

Conditioned position responding (CPR). In the conditioned position responding task, rats were trained to discriminate between two auditory stimuli [a high-frequency tone (1450 Hz) or a low frequency tone (350 Hz), each presented at 80 dB] or between two visual stimuli (all nine lights of the stimulus array illuminated vs. only the center three vertical lights illuminated). Each new trial began with the presentation of either a tone or the illumination of a stimulus light array. Subjects acknowledged this stimulus by pressing the center lever. Immediately following this "observing" response, cue lights above

both the left and right lever were illuminated. If the initial stimulus had been either the low-frequency tone or the illumination of only the center three lights, then a response on the left lever resulted in food delivery. If the initial stimulus had been either the high-frequency tone or the illumination of all nine stimulus lights, then a response on the right lever resulted in food delivery. Incorrect responses resulted in a 10-s timeout prior to the random presentation of the next auditory or visual stimulus. A maximum of 120 reinforcers could be earned during a given CPR test session.

Motivation task (PR). Only the far right retractable lever was used for this task. The first reinforcer of each test session was delivered after a single response on the operant lever. Subsequent reinforcers required an increase in the number of responses (i.e., the second reinforcer was delivered after two responses, the third after three responses, etc.). A maximum of 120 reinforcers could be earned during a given PR test session.

Timing task (TRD). For the timing task, only the left retractable lever was used. Subjects were required to hold the lever in the depressed position for at least 10, but not more than 14 s. Releasing the lever within this 10–14-s window resulted in food delivery (45-mg dustless precision food pellet, Bioserve, Frenchtown, NJ). Failure to release the lever within this 10–14 s window had no programmed consequences. A maximum of 120 reinforcers could be earned during a given TRD test session.

Timing and response inhibition task (DRL). For the timing and response inhibition task, only the center retractable lever was used. Subjects were required to withhold responding to this lever for at least 10, but not more than 14 s. The first response occurring within this 10–14-s window resulted in food delivery. Responses that occurred outside of this 10–14-s window were not reinforced, and resulted in the initiation of a new trial. A maximum of 120 reinforcers could be earned during a given DRL test session.

Drug Administration

Subjects received each dose of nicotine (0.0, 0.3, 0.42, 0.56, 0.75, and 1.0 mg/kg, prepared as base and administered IP) twice, in a randomized repeated measures design. These doses were selected to span a wide range of behavioral effects and to allow cross-species comparisons with other experiments conducted in our laboratory. Concentration of the nicotine solutions were varied across doses to ensure that the injection volumes would be equivalent in all conditions (1.0 ml/kg). Physiologic saline was used to prepare these solutions from nicotine hydrogen tartrate, and was administered as the control solution (1.0 ml/kg). Nicotine administration occurred 15 min prior to operant testing on Tuesdays and Fridays of each week. Testing without prior injection was conducted on Mondays and Wednesdays, and saline was administered on Thursdays. There were no behavioral test sessions conducted on Saturdays or Sundays.

Statistical Analyses

Learning (IRA) and conditioned position responding (CPR). Task accuracy and response rates were monitored for the learning and conditioned position responding tasks. Accuracy was calculated as the number of correct responses divided by the number of total responses multiplied by 100. Response rates indicate the number of responses made per second. For each of these end points, the effects of each duplicate dose of nicotine were averaged to derive a single value for each subject, at each dose. One-way repeated measures ANOVA were used to determine effects of nicotine across doses. Dunnett's post hoc tests were used to examine the effects of each dose of nicotine relative to saline control. A probability of 0.05 or less was used to determine statistical significance.

Motivation (PR). Response rate and break point were monitored for the motivation task. Response rate indicates the number of responses made per second. Break point indicates the number of responses required to earn the last reinforcer. As with the learning and conditioned position responding tasks, the effects of each duplicate dose of nicotine were averaged to derive a single value for each subject, at each dose. One-way repeated-measures ANOVA were used to determine effects of nicotine across doses. Dunnett's post hoc tests were used to examine the effects of each dose of nicotine relative to saline control. A probability of 0.05 or less was used to determine statistical significance.

Timing (TRD) and timing and response inhibition (DRL). Prior to analysis, TRD and DRL responses were classified as either "targeted" responses or "bursting" responses. "Targeted" responses were defined as those having durations (TRD) or interresponse times (DRL) of 3 s or more. "Bursting" responses, on the other hand, were defined as those having durations (TRD) or interresponse times (DRL) of less than 3 s. Accuracy of targeted responses was defined as: [(correct targeted responses/total targeted responses) $\times$ 100], and was analyzed using one-way ANOVA for repeated measures. The total number of bursting responses was analyzed separately from "targeted" responses using one-way ANOVA for repeated measures. Dunnett's a posteriori comparisons were used to compare each dose condition to control. To examine changes in the mode of the distributions of TRD and DRL responses, a Wilcoxon matched-pairs, signed-rank test was used (23). A probability of 0.05 or less was used to determine statistical significance.

RESULTS

The results for each of the five operant tasks are summarized in Table 1. For the learning task (Fig. 1), there were no significant effects of nicotine on accuracy, but nicotine produced an inverted U-shaped dose–effect curve for response rate, $F(5, 25) = 7.44$, $p < 0.001$. This pattern of results suggests that subjects responded faster following nicotine treatment than they did following saline treatment, but that there

TABLE 1

Task	End Point	0.3 mg/kg	0.42 mg/kg	0.56 mg/kg	0.75 mg/kg	1.0 mg/kg
IRA	Accuracy					
	Response rate		↑			
CPR	Accuracy					
	Response rate	↑	↑	↑	↑	↑
PR	Response rate	↑	↑	↑	↑	↑
	Break Point			↑		↑
TRD	Accuracy	↓	↓	↓	↓	↓
	Response rate					
DRL	Accuracy	↓	↓	↓	↓	↓
	Response rate	↑	↑	↑	↑	

Arrows denote significant increases (↑) or decreases (↓) from saline ($p < 0.05$).

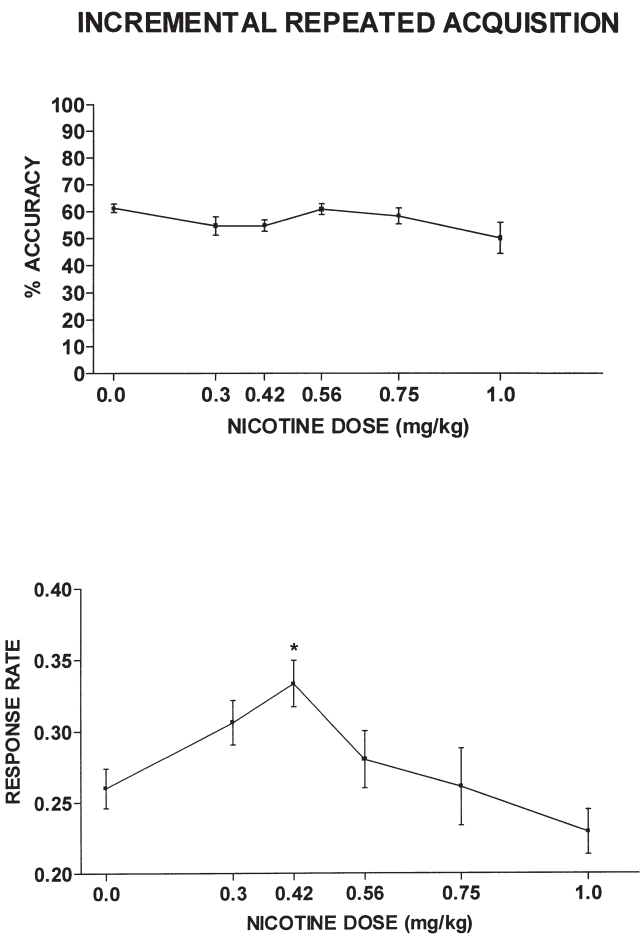

FIG. 1. Effects of nicotine on IRA accuracy and response rate (mean ± SEM). *Denotes significant difference from 0.0 mg/kg nicotine.

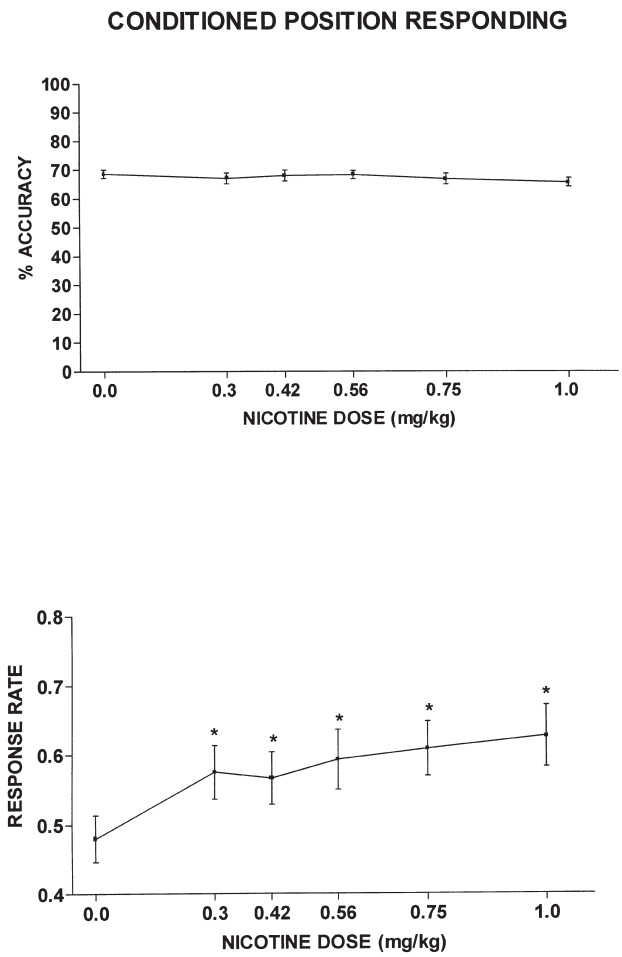

FIG. 2. Effects of nicotine on CPR accuracy and response rate (mean ± SEM). *Denotes significant difference from 0.0 mg/kg nicotine.

was no concomitant effect on accuracy. On average, subjects were able to reach the three lever sequence during a given test session. Nicotine did not alter the IRA sequence level achieved.

A similar pattern of results was seen for the conditioned position responding task (Fig. 2) as was seen for the learning task. Specifically, there were no significant effects of nicotine on accuracy, but nicotine dose dependently increased response rates, $F(5, 100) = 11.30$, $p < 0.0001$. This pattern of results was the same regardless of whether the task was paired with the timing task (TRD), the timing and response inhibition task (DRL), or the learning task (IRA). Similarly, this pattern of results was the same regardless of whether the auditory or visual stimulus was used.

For the motivation task (Fig. 3), nicotine dose dependently increased response rates, $F(5, 80) = 4.404$, $p < 0.01$, and also increased PR break point, $F(5, 80) = 2.763$, $p < 0.05$. As was the case for the conditioned position responding task, this pattern of results was the same regardless of the specific pairings of tasks.

For the timing task (Fig. 4), nicotine had a U-shaped effect on accuracy, $F(5, 20) = 12.74$, $p < 0.0001$. These effects were significant for all but the highest dose of nicotine tested ($p < 0.05$). In addition, there was an inverted U-shaped dose effect of nicotine on the number of bursting responses, $F(5, 20) = 4.271$, $p < 0.01$, with the effect of 0.42 mg/kg differing significantly from vehicle control ($p < 0.05$). There were no effects of nicotine to shift the mode of the TRD response duration distribution.

The effects of nicotine on the response inhibition task (Fig. 5) were similar to those seen for the timing task. Specifically, nicotine had a U-shaped dose effect on accuracy, $F(5, 45) = 13.36$, $p < 0.0001$, with significant effects observed at all but the highest dose of nicotine tested ($p < 0.05$). In addition, there was an inverted U-shaped dose effect of nicotine on the number of bursting responses, $F(5, 45) = 5.482$, $p < 0.01$ with the effects of 0.3 and 0.56 mg/kg differing significantly from vehicle control ($p < 0.05$). Unlike the results for TRD, however, nicotine also had an inverted U-shaped dose effect on the mode of the interresponse time distribution for DRL with low doses of nicotine reducing the modal interresponse time and the highest dose having no effect on modal interresponse time ($p < 0.05$).

DISCUSSION

The present experiment examined the effects of nicotine on several behavioral tasks that are thought to model differ-

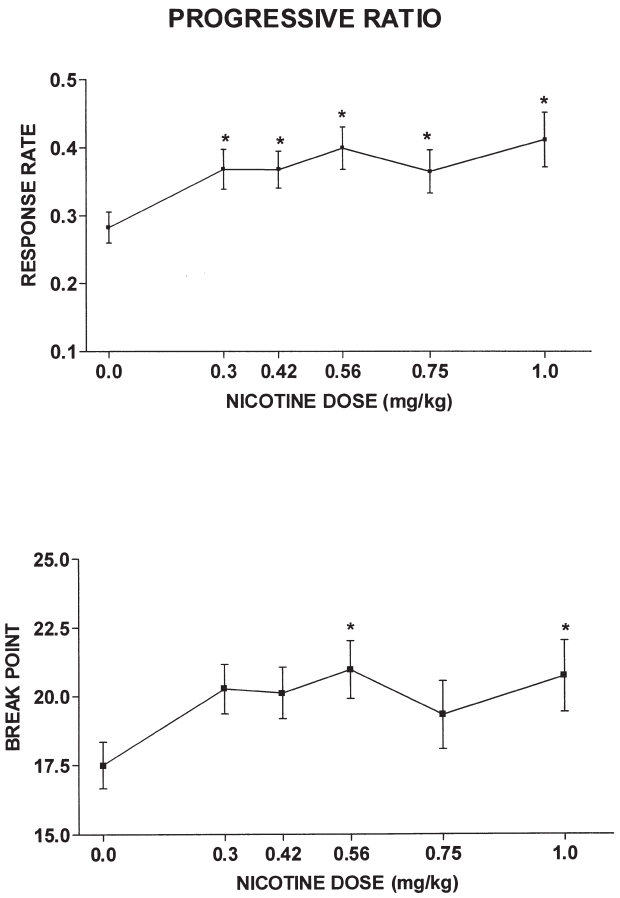

FIG. 3. Effects of nicotine on PR response rate and break point (mean ± SEM). *Denotes significant difference from 0.0 mg/kg nicotine.

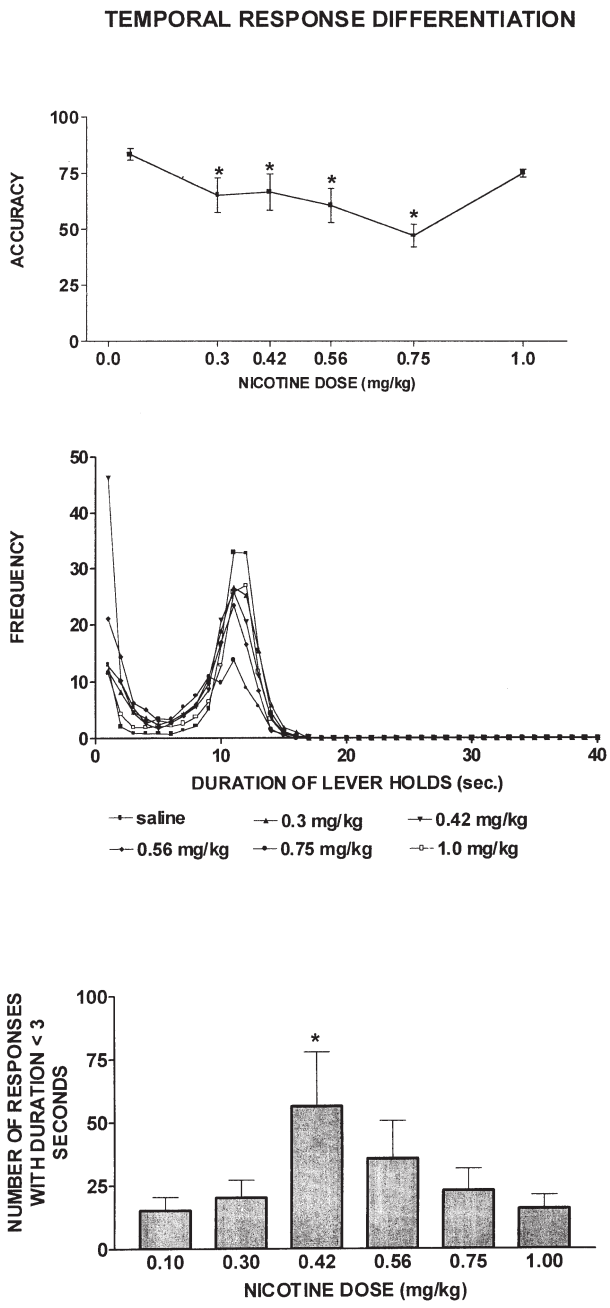

FIG. 4. Effects of nicotine on TRD accuracy (mean ± SEM), the distribution of TRD response times, and TRD "bursting" (mean ± SEM). *Denotes significant difference from 0.0 mg/kg nicotine.

ent aspects of complex brain function in rats. The results indicate effects of nicotine to alter performance on all tasks but in different ways and at different doses. Performance on the timing (TRD) and response inhibition (DRL) tasks was disrupted following nicotine administration, with even the lowest dose tested significantly reducing task accuracy. The reductions in accuracy seen under the TRD schedule resulted from a reduction in targeted responding, and was not accompanied by a shift in the mode of the TRD response distribution. The reductions in accuracy seen under the DRL schedule however, resulted from a leftward shift in the mode of the interresponse time distribution, and may reflect an impairment in subjects' ability to withhold responding. Performance on the conditioned position responding (CPR) and learning (IRA) tasks was not impaired by nicotine.

The fact that nicotine had different effects on these operant tasks suggests that distinct cognitive abilities, as modeled by the operant behaviors examined here, may be differentially sensitive to the effects of nicotine. It has previously been postulated that the differential effects of nicotine on cognitive performance may be linked to differences in task complexity, with very simple task performance being facilitated by nicotine and more difficult task performance being impaired by nicotine (22,38). This postulate is supported by reports of differential effects of nicotine on maze performance in rats and on differential effects of nicotine on complex cognitive tasks in humans. In the present experiment, motivation (as indexed by PR performance) was increased by nicotine, whereas performance of timing (as indexed by TRD) and response inhibition (as indexed by DRL) tasks was disrupted by nicotine. Learning (IRA) and visual, auditory, and auditory position discrimination (CPR) were largely unaffected by nicotine. Although it is possible that the differential effects of nicotine on these tasks reflect differences in task complexity, there are

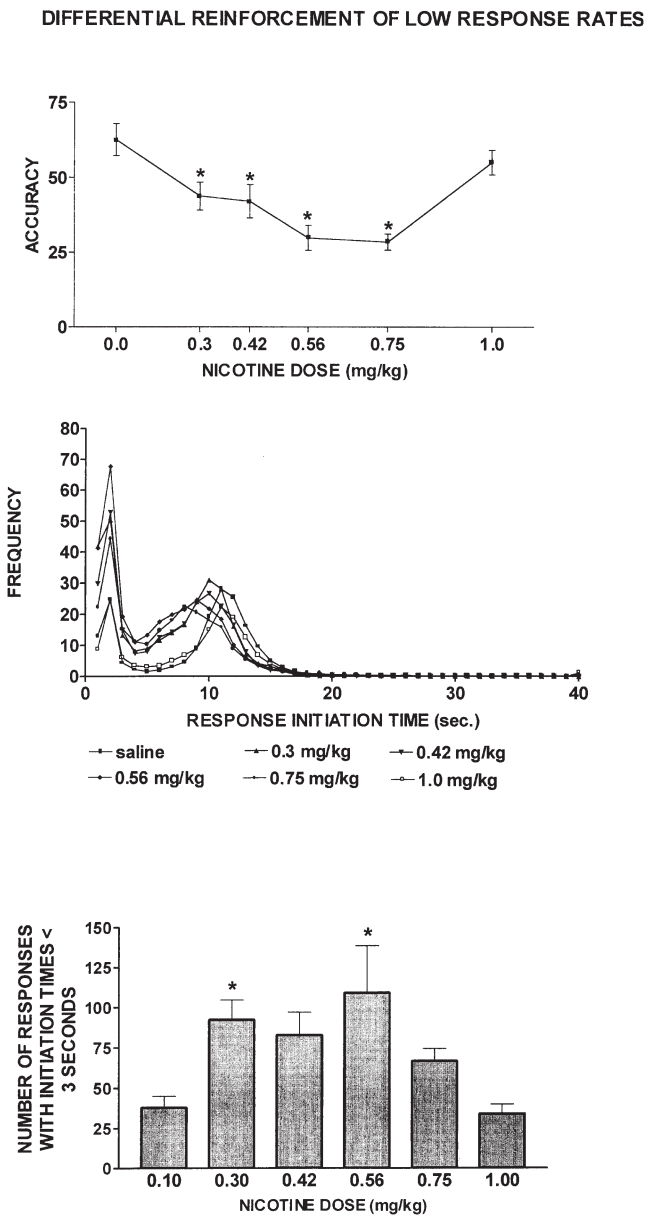

FIG. 5. Effects of nicotine on DRL accuracy (mean ± SEM), the distribution of DRL response times, and DRL "bursting" (mean ± SEM). *Denotes significant difference from 0.0 mg/kg nicotine.

several alternative explanations that cannot be conclusively ruled out. It is possible, for example, that the timing (TRD) and response inhibition (DRL) tasks appear most sensitive to the effects of nicotine because they were always performed first, when rats are maximally food deprived and when plasma levels of nicotine are presumably high. Although this explanation may account for the high sensitivities of TRD and DRL, it cannot account for the fact that the learning (IRA) task, which was also performed first, was almost completely insensitive to nicotine. Further, this explanation cannot account for the fact that the motivation (PR) task was significantly affected by nicotine despite the fact that it was always run last. Pilot studies conducted in our laboratory indicate that performance on these operant tasks is unaffected by the order of task presentation (i.e., performance does not change when the order of task presentation is changed). Nonetheless, future experiments, using a counterbalanced order of task presentation, will be required before unequivocal conclusions can be drawn regarding the respective roles of order and task complexity to mediate nicotine's effects.

An alternative explanation for the differential effects of nicotine on the performance of these operant tasks may involve differences in the neural substrates that influence each of these complex operant behaviors. Timing behavior, for example, such as that modeled by TRD performance, is thought to be influenced by dopaminergic circuitry through the basal ganglia (26). Because nicotine is known to influence dopaminergic function in this region (13,24,27), it is possible that the effects of nicotine reported here result from its interaction with the dopaminergic systems involved with temporal discrimination. The fact that nicotine did not alter accuracy on the learning (IRA) or the conditioned position responding (CPR) task suggests that the specific abilities required to perform these tasks may involve brain areas or neural processes that are only minimally affected by nicotine, or that are equipped with sufficient neural redundancy so as to compensate for some of its cognitive–behavioral effects. Future experiments using nicotinic antagonists to block nicotine's primary pharmacologic effects, or using other receptor antagonists to block nicotine's downstream pharmacologic effects, will help to further clarify the mechanisms that underlie effects of nicotine on these complex behavioral processes.

One particularly noteworthy result of the present experiment are the effect of nicotine on response inhibition (DRL) and the apparent dissociation between the effects of nicotine on DRL and TRD. For DRL, nicotine produced a clear, leftward shift in the distribution of response latencies, an effect that was not seen for TRD. This pattern of results indicates an impairment in subjects' response inhibition or "waiting capacity" (6), without an alteration in subjects' ability to perceive time. The apparent effects of nicotine to impair response inhibition may have important implications for nicotine's potential as a therapeutic agent. Levin et al. (23) has reported that transdermal nicotine (7.0 mg/day–21.0 mg/day) improves attention and alleviates clinician-rated symptoms in patients with attention deficit hyperactivity disorder, a disorder that is also characterized by impairments in response inhibition (2). The results of the present experiment suggest that, under certain conditions, nicotine may impair response inhibition in a way that may exacerbate, rather than improve some of the symptoms of ADHD. Future clinical trials with nicotine should consider the potential of nicotine to impair response inhibition when assessing nicotine's therapeutic potential.

In summary, the present experiment examined the effects of nicotine on the performance of operant tasks that are thought to model different aspects of complex brain function. Nicotine dose dependently impaired subjects' ability to perform tasks that require accurate time perception (TRD) and the ability to inhibit responding (DRL), but had no effect on the ability of subjects to perform a learning task (IRA) or to perform a conditioned position responding task (CPR). Nicotine enhanced the rate of responding and break point for the motivation (PR) task. The fact that nicotine did not uniformly alter performance of these operant tasks suggests that distinct cognitive abilities, as modeled by the behaviors chosen here, are differentially sensitive to the effects of nicotine. This pat-

tern of effects may be linked to differences in task complexity, method of task presentation, or differences in the neural substrates that underlie the performance of these operant tasks. One particularly noteworthy result of the present experiment is the fact that nicotine produced an apparent impairment in response inhibition. Because nicotine has been offered as a potential treatment for cognitive–behavioral disorders, many of which are characterized by impairments in response inhibition, findings that nicotine can disrupt response inhibition may be relevant to nicotine's potential as a therapeutic agent.

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