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Behavioral Performance Effects of Nicotine in Smokers and Nonsmokers[1]

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PERKINS, K. A., L. H. EPSTEIN, R. L. STILLER, J. E. SEXTON, T. D. DEBSKI AND R. G. JACOB. *Behavioral performance effects of nicotine in smokers and nonsmokers*. PHARMACOL BIOCHEM BEHAV **37**(1) 11–15, 1990.—Performance on finger-tapping and handsteadiness, tasks opposite in response requirements, was compared between male smokers and nonsmokers (n = 10 each) on two occasions, once following intake of nicotine (15 μg/kg) by measured-dose nasal spray and once following placebo. Compared with nonsmokers, smokers had significantly greater increase in finger-tapping speed due to nicotine. On the other hand, smokers tended to have improved performance on handsteadiness (i.e., less involuntary movement) due to nicotine, while nonsmokers had impaired performance, although this difference was not significant. Nicotine-induced changes in performance on each task were inversely related, suggesting specificity of the behavioral effects of nicotine depending on task demands, rather than a generalized effect. These effects of nicotine on behavioral performance may be important in understanding the reinforcing value of nicotine intake, and differences in effects as a function of smoking history may suggest chronic adaptation to nicotine.

Nicotine Performance Behavior Smokers Nonsmokers

NICOTINE has wide-ranging effects on behavioral task performance in animals and humans. Especially at lower doses, nicotine is often purported to be behaviorally "activating" in animals. Nicotine's effects in animals include increases in locomotion (4, 5, 14, 17, 20, 26, 31), tail tremor (8), body tremor (16), and responding for intracranial self-stimulation (27) or food reinforcement (34). Similar behavioral effects of tobacco smoking or nicotine intake via other means have been observed in humans, such as increases in maximal finger-tapping (33), avoidance responding (3), and hand tremor (15,29), improvement in simple and choice reaction time (10,18), and impairment in handsteadiness [i.e., decreased ability to inhibit motor movement; (7,32)]. Conversely, smoking abstinence has been associated with impaired reaction time (11) and improved handsteadiness (19). Although seemingly inconsequential in and of themselves, these effects may be useful indices of a more general behavioral activation induced by nicotine which may be a key to understanding its reinforcing value and addictive nature (25,35).

Tolerance (i.e., decreased response with repeated drug exposure) to behaviorally activating effects of nicotine has been demonstrated in animals (5), although sensitization (increased response with repeated drug exposure) has also been observed (14). In contrast, to our knowledge, there have been almost no studies of humans which have directly examined behavioral responses to nicotine in groups with vs. without extensive prior exposure to nicotine (i.e., smokers vs. nonsmokers). One study found increased finger-tapping following nicotine in nonsmokers but did not simultaneously examine smokers (33). Importantly, some older studies found no change or a decrease in finger-tapping in smokers after cigarette smoking (6), suggesting that chronic tolerance may develop to this behavioral activating effect. On the other hand, another recent study of females reported that nicotine gum improved speed and accuracy of choice reaction time performance in smokers but not in nonsmokers (10), perhaps suggesting sensitization. However, analysis of plasma nicotine revealed that nonsmokers' levels were less than half the nicotine levels of smokers (4.92 vs. 12.40 ng/ml, respectively, following 2 mg gum), demonstrating differential and possibly inadequate dosing. Therefore, it appears there has been no clear comparison of nicotine's behavioral effects in smokers and nonsmokers. Differences in these effects of nicotine may suggest that chronic nicotine exposure leads to alterations in behavioral responses to nicotine intake (tolerance or sensitization), alterations which may be associated with development of nicotine dependence (9,35).

In this study, the effects of nicotine on finger-tapping and handsteadiness were compared between male smokers and nonsmokers. These tasks were chosen because of their opposing response requirements (i.e., rapid motor movement in finger-tapping vs. inhibition of motor movement in handsteadiness), as well as their use in prior studies of nicotine and smoking, as noted previously. It was hypothesized that nicotine would improve rate of finger-tapping but impair handsteadiness, supporting a nonspecific activating effect of nicotine on simple behavioral performance tasks (32). Furthermore, smaller responses to nicotine in smokers would suggest tolerance while larger responses in smokers would suggest sensitization. In order to equate nicotine intake

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between these groups, nicotine was presented via measured-dose nasal spray pump, a method which has been shown to produce reliable, dose-dependent boosts in plasma nicotine (23,24).

METHOD

Subjects

Subjects were male smokers and nonsmokers (n = 10 each), with groups comparable in terms of age (mean ± s.e.: 22.8 ± 1.2 vs. 21.5 ± 0.8 years, respectively) and body weight (74.9 ± 2.5 vs. 75.0 ± 2.0 kg). Minimum smoking history requirements for smokers was self-reported consumption of at least 15 cigarettes per day for one year or more, while nonsmokers were those with lifetime consumption of fewer than 20 cigarettes. The average smoking history for smokers was 19.9 ± 0.8 cigarettes per day for 5.4 ± 1.0 years, and the mean nicotine yield of their preferred brand was 0.95 ± .05 mg.

Tasks

Finger-tapping. Subjects were instructed to tap with the index finger of their preferred hand as fast as possible on one key of a computer keyboard for two 30-sec periods, separated by a 30-sec rest period. Each tap was recorded by computer, and the total number was presented on a computer screen at the end of each task period. This procedure was adapted from West and Jarvis (33). Task performance was the mean number of taps in the two 30-sec periods.

Handsteadiness. Handsteadiness was determined by use of the Gardner Steadiness Tester (Lafayette Instruments, Lafayette, IN). Subjects were instructed to use their preferred hand to hold a stylus (2 mm in diameter) within a 3.0 mm hole without touching the sides of the hole. Subjects were not allowed to support any part of their arm. Contact with the sides of the hole activated an auditory signal, which was designed to provide feedback to subjects to guide their performance. Length of time the stylus was in contact with sides during each of two 30-sec periods was determined electronically to the nearest 0.01 sec. This procedure was adapted from Frankenhauser *et al.* (7). Task performance was the mean amount of contact time for the two periods.

For both tasks, a modest performance-contingent monetary incentive was employed to maintain subject motivation for performance across trials. For finger-tapping, subjects received $0.01 for every 10 taps during both task periods of each trial. For handsteadiness, subjects received $0.01 for every sec *without* contact during both 30-sec task periods of each trial (i.e., incentive = 30 minus sec of contact). These incentive conditions were designed to provide similar amounts of reinforcement between tasks so that any differential effect of nicotine would not be due to motivational differences caused by unequal opportunity for monetary incentive. Prior to engaging in baseline trial attempts with each task (see below), subjects were provided with the incentive instructions and told that most subjects earn "a few dollars" for each task. During each session, subjects earned a mean total of $2.12 for finger-tapping and $2.05 for handsteadiness.

Nicotine and Placebo

Nicotine and placebo were presented via nasal spray pump, which produces reliable, dose-dependent increases in plasma nicotine (23,24). The nicotine dose was 15 μg/kg [mean of 1.1 mg, similar to nicotine consumption of most smokers from one cigarette (2)]. The dose consisted of 1.14 ml of 0.9% sodium chloride solution together with L-nicotine and peppermint flavoring oil (Lorann Oils, Lansing, MI), which was used to mask the smell of nicotine. The placebo (0 mg) contained only the sodium chloride solution with peppermint oil. This dosing method has been described elsewhere in more detail (21–24).

Procedure

Subjects participated in two sessions, one involving nicotine and the other involving placebo presentation, with the dose order counterbalanced. Sessions were scheduled at least one week apart to minimize carryover effects between sessions. Smokers were instructed to abstain from smoking for at least 12 hr prior to each of the 2 morning sessions. An expired-air CO of ≤13 ppm was used to confirm abstinence (1). All subjects were also instructed to abstain from caffeine and food intake for at least 8 hr before each session.

During both sessions, subjects were first introduced to each of the tasks via tape-recorded instructions. They engaged in two practice attempts with each task prior to the performance-contingent monetary incentive. They then engaged in two attempts of each with the incentive conditions in effect (baseline trial). Subsequently, subjects were presented with nicotine or placebo every 30 min for 2 hr (total of 4 presentations). Two attempts at each task followed each dose presentation (4 task trials), with handsteadiness occurring approximately 3 min after each presentation and finger-tapping two min later (5 min after dose presentation). After finishing each task attempt, subjects received feedback on their performance and amount of money "earned." Subjects rested quietly during the approx. 20–25 min prior to the next dose presentation and task trial.

This protocol was approved by the Institutional Review Board for Biomedical Research at the University of Pittsburgh.

Analyses

Change from predrug baseline trial performance to postdrug trials 1–4 on both measures was first analyzed by multivariate analysis of variance (MANOVA), involving status (smokers/nonsmokers) as between-subjects variable, and task (finger-tapping/handsteadiness) and dose (nicotine/placebo) as within-subjects variables. Performance on each individual task was analyzed by separate analyses of variance (ANOVAs) for each task. Paired comparisons were performed using Fisher's Least Significant Difference *t*-test procedure (12). The relationship between effects of nicotine on both tasks was determined by Pearson correlation of change from baseline due to nicotine.

RESULTS

There were no differences in baseline finger-tapping or handsteadiness performance among subjects as a function of smoking status or dose order. Mean ± s.e. baseline performance on finger-tapping was 207.5 ± 7.1 taps/30 sec for smokers and 214.7 ± 8.4 taps for nonsmokers. Mean baseline performance on handsteadiness was 10.21 ± 0.94 sec of contact/30 min for smokers and 11.13 ± 1.46 sec for nonsmokers. As planned, this baseline performance resulted in similar amounts of monetary reinforcement earned between the two tasks. For both baseline attempts at each task, subjects earned an average of 42.2 cents from finger-tapping and 38.6 cents from handsteadiness.

Results of the overall MANOVA of change in performance from baseline indicated significant main effects of Task, $F(1,18) = 11.98$, $p<0.005$, and Dose, $F(1,18) = 16.78$, $p<0.001$, but not of Status, $F(1,18)<1$. There were also significant interactions of Task × Status, $F(1,18) = 4.60$, $p<0.05$, of Task × Dose,

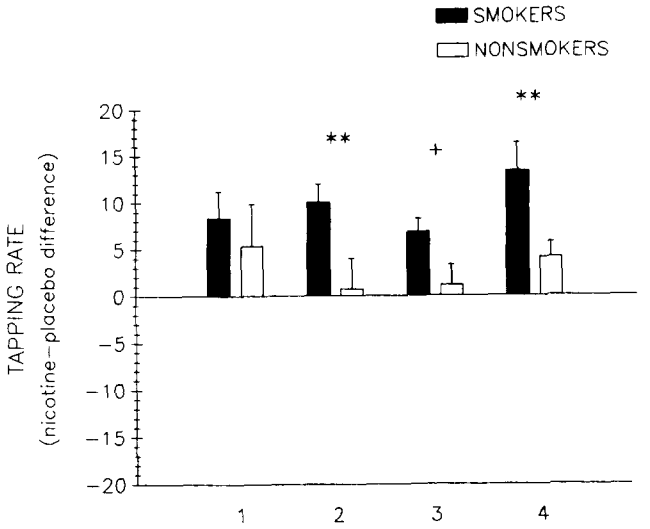

FIG. 1. Effects of nicotine on finger-tapping rate in smokers and nonsmokers across trials 1–4 (mean ± s.e. of difference from placebo control). Symbols indicate significance of difference between groups, $^{**}p<0.01$; $+p<0.10$.

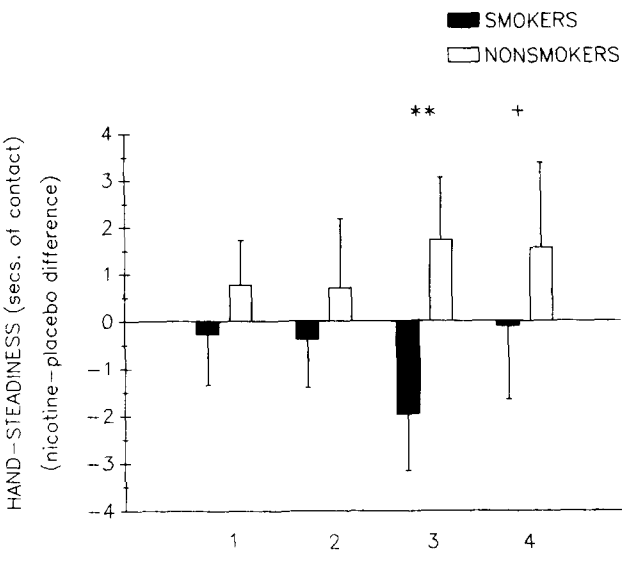

FIG. 2. Effects of nicotine on handsteadiness smokers and nonsmokers across trials 1–4 (mean ± s.e. of difference from placebo control). Symbols indicate significance of difference between groups, $^{**}p<0.01$; $+p<0.10$.

$F(1,18)=9.62$, $p<0.01$, and of Task × Status × Dose, $F(1,18)=5.03$, $p<0.05$. Thus, nicotine had differential effects on performance between smokers and nonsmokers depending on the task. The overall Status × Dose interaction was not significant, $F(1,18)=2.41$.

Finger-Tapping

ANOVA results revealed that finger-tapping was significantly increased by nicotine, $F(1,18)=16.24$, $p<0.001$, as shown in Fig. 1. However, the significant Status × Dose interaction, $F(1,18)=4.81$, $p<0.05$, indicated that this effect of nicotine varied as a function of smoking status. Comparisons showed that the increase due to nicotine was significant for smokers ($t=2.20$, $p<0.05$) but not for nonsmokers ($t<1$). The consistency of nicotine's effects across subjects was indicated by the fact that across the 4 trials all 10 smokers had higher rates of finger-tapping following nicotine vs. placebo, and 7 of 10 nonsmokers also had higher rates following nicotine.

Handsteadiness

There was no significant main effect of Dose on handsteadiness, $F(1,18)<1$, as nicotine did not consistently improve or impair handsteadiness relative to placebo. However, although the Dose × Status interaction was not significant, $F(1,18)=1.21$, nicotine tended to improve handsteadiness in smokers but impair handsteadiness in nonsmokers, as shown in Fig. 2. Exploratory analyses indicated that this difference did reach significance during Trial 3, $t=3.93$, $p<0.01$, and was marginally significant during Trial 4, $t=1.77$, $p<0.10$. Across the 4 trials, 6 of the 10 smokers had improved handsteadiness following nicotine vs. placebo, while 7 of the 10 nonsmokers had impaired handsteadiness following nicotine.

There was a marginally significant relationship between the effects of nicotine on finger-tapping and handsteadiness, $r(19)=-.31$, $p<0.10$, suggesting that the greater the increase in finger-tapping due to nicotine, the lesser the impairment in handsteadiness.

DISCUSSION

These findings indicate that, compared with nonsmokers, smokers may exhibit differential behavioral responses to nicotine depending on the task demands. For finger-tapping, which was predicted to be enhanced by nicotine, smokers showed greater improvement in performance due to nicotine than did nonsmokers. For handsteadiness, which was predicted to be impaired by nicotine, smokers showed slightly improved performance following nicotine while nonsmokers showed slightly impaired performance, although this difference was not significant. Thus, smokers may show sensitization to the performance-enhancing effects of nicotine but may tend to minimize the impairing effects of nicotine (perhaps reflecting tolerance).

These differences due to smoking history seem rather inconsistent with a straightforward pharmacological explanation of tolerance or sensitization, which would presumably predict smaller or larger responses, respectively, to nicotine in smokers vs. nonsmokers regardless of task. Although speculative, an alternative explanation may be possible from consideration of the "reinforcement loss" hypothesis of behavioral tolerance (28). In presenting this hypothesis, Schuster *et al.* (28) proposed that tolerance to a drug effect may depend on whether or not the drug impacts on an organism's ability to maintain adequate reinforcement-contingent performance. Tolerance would occur when the drug's effect on performance led to a decrease in reinforcement (i.e., impaired performance) and would not occur when the drug's effect led to no changes or an increase in reinforcement (i.e., unaffected or enhanced performance). Somewhat consistent with this notion, there was some evidence of tolerance, albeit weak, to the impairing effects of nicotine on handsteadiness but no tolerance, and in fact evidence of sensitization, to the performance-enhancing effects of nicotine on finger-tapping. From a reinforcement standpoint, therefore, smokers would seem better able to minimize nicotine-induced loss of reinforcement and maximize nicotine-induced enhancement of reinforcement, at least within the current paradigm. Interestingly, animal research has demonstrated that chronic nicotine treatment produces tolerance to nicotine's initial depressant effects of behavior but apparent sensitization to the

subsequent increase in behavior later in the session (4). However, relevance of the reinforcement loss hypothesis to interpreting the differences between smokers and nonsmokers in the present study requires several assumptions, including equal past exposure between groups to situations in which improved behavioral performance related to finger-tapping and handsteadiness was reinforcing or beneficial in some way. Additional research is needed to support this possible relationship between reinforcement loss and behavioral response to nicotine, including the use of tasks which show greater nicotine-induced impairment in performance.

These results are also not consistent with the notion that nicotine intake results in generalized behavioral activation. Such an effect would be expected to produce increased motor activity during both tasks, resulting in impaired handsteadiness (i.e., increased contact time) as well as increased finger-tapping rate. These changes would be expected to result in a positive correlation between performance on the two following nicotine. However, we found that finger-tapping and handsteadiness effects of nicotine were not positively related and, in fact, tended to be negatively correlated, suggesting differential effects of nicotine on activation depending on the task. Specificity of behavioral effects of nicotine has been reported in the animal literature [e.g., (17, 26, 27)] but may not be as fully appreciated in studies of humans (30).

Although smokers were abstinent from smoking for at least 12 hr prior to each session, any mild tobacco withdrawal is unlikely to have influenced these results since there were no differences between groups in task performance during predrug baseline. Lack of significant effects of nicotine on performance of nonsmokers may have been due to the relatively small sample size of 10 or to an insufficient number of trials with nicotine. However, differential intake of nicotine between smokers and nonsmokers, a problem in past research [e.g., (10)], is not a likely explanation, given our past findings of reliable dosing with this measured-dose procedure (23,24). Moreover, we have recently found that, compared with smokers, nonsmokers exhibit similar or greater heart rate responses to nicotine spray (unpublished observations), further indicating equal dosing between groups since heart rate is quite sensitive to nicotine dose (23,24). Finally, the use here of an interdose interval of 30 min allowed for greater dissipation of plasma nicotine prior to subsequent presentations. This 30-min interval is longer than that used in our other studies in which no accumulation of plasma nicotine occurred across four dose presentations separated by 20 min (24).

The findings reported here are limited by the extent to which our measured-dose method of nicotine administration simulates nicotine intake via cigarette smoking. In addition, nicotine was noncontingently administered in this study, while the usual self-administration of nicotine by smoking may produce different behavioral effects in smokers than those observed here (18). Nevertheless, these results may indicate how chronic nicotine exposure (i.e., smoking history) leads smokers to differentially adapt to the various behavioral effects of nicotine in order to take advantage of its "positive" effects on performance without suffering from concurrent "negative" effects. Nicotine could thus serve a useful coping function for smokers (25). Further research is necessary to clarify the consistency of these differences as a function of smoking status. Larger differences may be found with groups varying more widely on nicotine exposure (i.e., older smokers and nonsmokers). Conversely, these differences may recede over time after smokers stop smoking. In addition, nicotine dose may be an important mediating variable worth examining, as differences in other responses to nicotine as a function of smoking history have been shown to be dose-dependent (24). Similar comparisons between smokers and nonsmokers in effects of nicotine on performance on other types of behavioral or cognitive tasks may indicate the extent to which smokers adapt to nicotine-induced alterations in functioning, adaptation which may be important in the development of nicotine dependence.

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