Pharmacology Biochemistry & Behavior, Vol. 32, pp. 677–681. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effects of Nicotine Gum and Tobacco Smoking on Human Avoidance Responding

DON R. CHEREK,[1] ROBERT H. BENNETT

Human Behavioral Pharmacology Laboratory, Department of Psychiatry and Behavioral Sciences University of Texas Medical School at Houston and University of Texas Mental Sciences Institute

THOMAS H. KELLY

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine

JOEL L. STEINBERG

Department of Psychiatry, University of Texas Health Science Center at Dallas

AND

NEAL L. BENOWITZ

Department of Medicine and Psychiatry, University of California, San Francisco

Received 24 June 1988

CHEREK, D. R., R. H. BENNETT, T. H. KELLY, J. L. STEINBERG AND N. L. BENOWITZ. *Effects of nicotine gum and tobacco smoking on human avoidance responding*. PHARMACOL BIOCHEM BEHAV **32**(3) 677–681, 1989.—Three male smokers were exposed to a free-operant avoidance schedule in which a lever press postponed a point subtraction on a counter for twenty seconds. Subtractions were scheduled to occur every 5 seconds in the absence of lever presses. Prior to each experimental session the subject was administered varying amounts of nicotine via either chewing nicotine gum or smoking low or high nicotine yield cigarettes. Smoking cigarettes resulted in increased avoidance responding relative to baseline nonsmoking rates. Chewing nicotine gum did not produce changes in avoidance responding, however, nicotine blood levels produced by chewing nicotine gum were similar to levels produced by smoking cigarettes. The differential responding determined by route of nicotine administration is discussed and the implications for use of nicotine gum as an adjunct for smoking cessation is addressed.

Nicotine Humans Avoidance Cigarette smoking Nicotine gum Route of administration Nicotine blood level

ANECDOTALLY, people report that they smoke more tobacco when they feel tense or anxious (1, 4, 8, 10). This commonly observed phenomenon has resulted in research interest regarding the relationship between cigarette smoking and stressful situations [e.g., (13, 16, 17)].

Research investigating self-administration of nicotine in stressful or anxiety-producing situations has revealed a positive relationship between stress and/or anxiety and nicotine self-administration. In one study, stressful conditions were produced by manipulating electric shock intensity and instructions. The number of cigarettes smoked and the number of puffs per cigarette increased with increases in the amount of operationally defined stress (16). In a study of irritability, subjects were exposed to periodic episodes of simulated aircraft overflights. Subjects who smoked high nicotine yield cigarettes reported less irritation than those who smoked low nicotine yield cigarettes (15). Aversiveness of

[1]Requests for reprints should be addressed to Don R. Cherek, Ph.D., Department of Psychiatry and Behavioral Sciences, Mental Sciences Institute, 1300 Moursund, Houston, TX 77030.

the situation has also been manipulated by presentation of blasts of white noise, which resulted in an increase in frequency and duration of cigarette puffs (11). More recently, an increase in cigarette puffing in response to increased intensity of industrial noise was observed in subjects performing an operant task (3).

This relationship between nicotine self-administration and stressful or aversive environments may be an important factor in the occurrence of relapse to smoking once an individual has ceased to smoke for a period of time. Data indicate that stressful or aversive environmental conditions are frequently a characteristic of the situations related to the resumption of smoking. In a series of studies investigating the situational variables associated with relapse, data indicated that the majority of incidents of relapse occurred in situations which precipitated anxiety, anger, frustration, or stress (18,19). Other researchers have found similar results (12).

The positive relationship between smoking and anxiety-producing and stress-producing environmental conditions suggests that smoking and nicotine self-administration may function to attenuate the characteristic response (i.e., anger, anxiety, aggression) elicited by aversive or stress-producing stimuli. Research supports this proposal. Cigarette smoking has been observed to reduce muscle tension and reflexive response (5) and to attenuate an aversive habituation of a startle response to loud acoustic stimuli (7). Nicotine has also been found to reduce aggressive operant responses occasioned by point loss presentation (2).

Though much research has indicated a relationship between nicotine self-administration and anxiety-producing and aversive environmental events, little research has investigated the behavioral effects of nicotine in aversive situations. The research reported here investigated the effects of nicotine administered by the chewing of nicotine gum and smoking cigarettes upon free operant responding maintained by avoidance of aversive stimulus presentation (point loss on a counter in which points were exchangeable for money).

METHOD

Subjects

Three males participated after giving their informed consent. Subjects were recruited through newspaper advertisements soliciting participation in behavioral research projects. These subjects were currently smoking tobacco and had done so for at least four years.

Subjects were given a physical exam and a diagnostic psychiatric interview prior to participation. Identification of any current or historical physical illness during this exam resulted in the exclusion of the subject. A detailed psychiatric interview was also conducted using the SADS-L (Schizophrenia and Affective Disorders Schedule-Lifetime) and a mental status exam. The discovery of any current or historical psychiatric illness including substance abuse and alcoholism resulted in the removal of the subject from the study.

We monitored the subject's drug usage outside the laboratory by using an extensive initial interview, urine analysis and breath alcohol testing. Subjects were excluded during the initial interviews if they reported use of any licit or illicit drug, except tobacco, caffeine, or alcohol. In addition, a urine sample was obtained prior to the first session and subjected to a complete drug screen analysis. Detection of any drug in the initial sample also resulted in the removal of the subject from the study. Periodically, additional urine samples were obtained and analyzed for drugs during the subject's participation. Alcohol drinking was monitored by having subjects provide a breath sample each day prior to the session. These breath samples were analyzed for alcohol content using an Intoximeter III. The presence of alcohol in the subject's breath sample resulted in the cancellation of that day's scheduled session. A second occurrence resulted in the removal of the subject from the study.

Instructions

Subjects were told that the research for which they had volunteered involved a study of the effects of nicotine gum and cigarettes on motor performance. Research subjects were taken into the experimental area and seated in front of a response console (BRS/LVE HT603) containing a response lever and a counter. The counter displayed eighty (80) points at the beginning of each session and subjects were told this represented a potential payment of eight dollars (1 point = 10 cents). Pressing the lever on the console avoided reductions in this point total scheduled to occur at various times during the experimental session. No other instructions concerning the avoidance schedule were provided.

Avoidance Schedule

The avoidance schedule was a free-operant avoidance schedule in which the absence of a lever press resulted in point subtractions scheduled to occur every five seconds. A lever press postponed the next scheduled point subtraction by twenty seconds. Each point subtraction decreased the total on the display counter by one point, i.e., ten cents. Each point subtraction was accompanied by a brief illumination of a stimulus light located below the counter and produced an audible auditory click.

Nicotine Treatments

Subjects participated daily in thirty-minute experimental sessions, Monday through Friday. Each subject participated in up to 151 sessions. Subjects arrived at the experimental area one hour prior to the scheduled session time and were provided with water to drink and reading materials.

Subjects were exposed to alternating baseline and nicotine treatment conditions. Under baseline conditions, subjects were not allowed to smoke during the hour preceding nor during the experimental session. The number of baseline sessions between treatment conditions varied and was determined by the stability of the lever pressing. The nicotine treatments consisted of chewing nicotine gum, smoking a low nicotine delivery cigarette, and smoking a high nicotine delivery cigarette. The nicotine treatments were experienced in the following order: nicotine gum, low nicotine delivery cigarette, high nicotine delivery cigarette.

During nicotine gum treatment, subjects were given two pieces of gum to chew 60 minutes prior to the session. After 30 minutes, subjects expectorated the gum, and were given two additional pieces to chew for the remaining 30 minutes prior to the session. The experimental session began immediately following the expectoration of the second two pieces of gum.

Each of the four pieces of gum were either placebo or contained 2 mg of nicotine (Nicorette). There were four conditions of nicotine gum administration defined by the amount of nicotine in the four pieces of gum. In the placebo condition, all four gum pieces were placebo, the 2 mg condition consisted of two placebo pieces during the initial 30 minutes and one piece of placebo and one piece of active nicotine gum during the second 30 minutes. The 4 mg condition consisted of two placebo pieces during the first

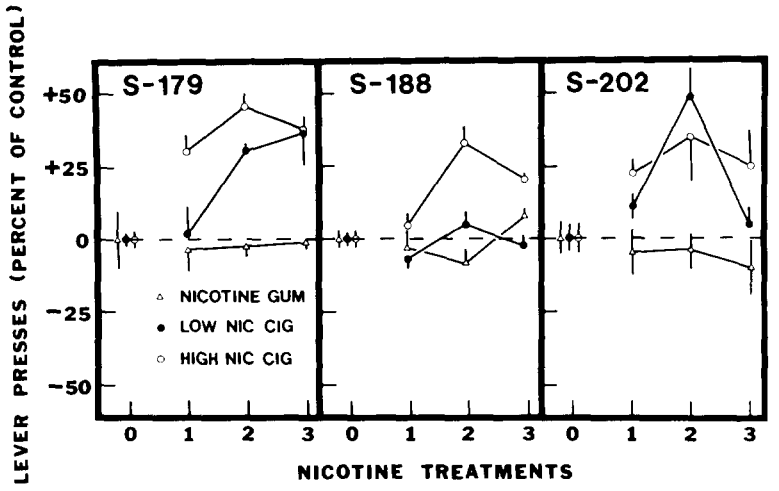

FIG. 1. The number of lever presses per session are shown for all three subjects. Data points are expressed as a percentage change from mean placebo values set at zero. Drug data points represent the mean of three different sessions. The vertical lines at each data point represent ± S.E.M. Nicotine treatments were: Nicotine gum (triangle), low nicotine delivery cigarettes (closed circles) and high nicotine delivery cigarettes (open circles). Nicotine treatments (0) refers to placebo gum or nonsmoking baseline conditions. Nicotine treatments (1) refers to chewing 2 mg of nicotine gum or taking 7 puffs on a low or high nicotine delivery cigarette. Nicotine treatments (2) refers to chewing 4 mg nicotine gum or taking 15 puffs on low or high nicotine delivery cigarettes. Nicotine treatments (3) refers to chewing 8 mg nicotine gum or taking 30 puffs on low or high nicotine cigarettes.

30 minutes and 2 active nicotine pieces during the second thirty minutes, and during the 8 mg condition the subject chewed two active nicotine pieces of gum during both thirty-minute periods.

During nicotine cigarette treatment conditions, subjects were required to take 7, 15, or 30 puffs on cigarettes (University of Kentucky research cigarettes) immediately prior to the session. The puffs were regulated such that one puff occurred every 30 seconds. In the 7 puff condition, seven puffs were taken from one cigarette, in the 15 puff condition 7 puffs were taken from one cigarette and 8 puffs were taken from a second cigarette, and the thirty puff condition consisted of 10 puffs from each of three cigarettes. Two types of research cigarettes were employed which differed only in the nicotine yield (no difference in tar content or carbon monoxide delivery). One cigarette had a 0.42 mg yield of nicotine (low) and the other had a 2.14 mg yield (high).

Each of the gum doses and different numbers of puffs on high and low nicotine delivery cigarettes were administered on three separate occasions. One administration of each of the gum doses or number of puffs constituted one block. Subjects were exposed to three blocks with nicotine gum before proceeding to low and then high nicotine delivery cigarettes. The order of presentation within each block was randomly selected. Nicotine gum doses and number of puffs were selected to allow maximum nicotine exposure (8 mg gum and 30 consecutive puffs) without producing nicotine toxicity. The highest and lowest available nicotine delivery research cigarettes were used.

In order to assess the effects of the various treatments on nicotine and cotinine plasma levels, blood samples were obtained on particular days. These samples were obtained just prior to nicotine treatment, immediately following the treatment, and thirty (30) minutes later. Each ten (10) ml sample of blood was collected in a EDTA containing vacutainer using a heparin lock. All samples were centrifuged and 3 to 3½ ml of plasma drawn off and stored at −20 degrees C. until analyzed. Analysis was performed by gas chromatography method (9).

RESULTS

Subjects S-179 participated in 151 total sessions, S-188 participated in 116 sessions, and S-202 experienced a total of 106 sessions. All three subjects developed a very stable pattern of avoidance responding which was maintained over sessions. Subjects S-179 initially produced a high rate of responding, but over the first 20 sessions his response rate decreased to a relatively moderate rate comparable to that of the other subjects. Subjects spent longer periods of time in the initial gum condition (70, 46 and 43 sessions) because of time required to obtain stable responding. Shorter amounts of time were spent in the low nicotine cigarette (39, 29 and 29 sessions) and high nicotine cigarette (31, 41 and 34 sessions) conditions. Subject S-179 emitted a range of response rates of 7.5–19.6 resp/min. Response rates for Subject S-188 and S-202 ranged from 2.9 to 3.9 resp/min and 15.6 to 21.1 resp/min respectively. All subjects lost points over the course of the experiment. Subject S-179 lost 10 total points over 7 different sessions, while S-188 lost 5 total points over 4 sessions, and S-202 lost a total of 6 points over 5 sessions. All point losses occurred during the baseline sessions and occurred at various points during the course of the experiment.

Figure 1 illustrates the effects of the three nicotine treatments upon lever pressing maintained by avoidance of point loss for each subject. The lever pressing of subject S-179 was more variable under placebo gum conditions than under nonsmoking conditions. This subject emitted a much wider range of reponse rates which were more variable early in the study. Lever presses during the

TABLE 1

PLASMA CONCENTRATIONS OF NICOTINE AND COTININE (ng per ml)

Subject No.	Initial Values		After Treatment		30 Minutes Later	
	Nicotine	Cotinine	Nicotine	Cotinine	Nicotine	Cotinine
S-179						
30 puffs High Nic	21.7	249.7	47.2	280.9	35.7	281.9
30 puffs Low Nic	30.3	279.3	42.1	341.5	27.6	273.7
8 mg Nic Gum	36.2	258.5	45.2	294.8	38.6	295.6
S-188						
30 puffs High Nic	20.5	446.4	40.0	435.3	36.2	435.9
30 puffs Low Nic	25.3	372.6	29.7	417.6	27.3	430.7
8 mg Nic Gum	20.5	330.2	33.7	340.4	27.5	349.1
S-202						
30 puffs High Nic	<1.0	112.1	23.2	108.1	20.2	144.7
30 puffs Low Nic	1.5	129.3	5.1	132.3	3.8	139.9
8 mg Nic Gum	<1.0	129.9	5.1	123.1	3.4	134.1

nicotine gum treatments are expressed as a percent of responding during placebo gum conditions. Lever presses during the smoking conditions (low nic cig and high nic cig) are expressed as function of the nonsmoking baseline conditions. See the figure legend for further description of the figure. Chewing nicotine gum at various doses of nicotine for 60 minutes prior to the experimental sessions did not result in changes in avoidance responding in any of the subjects. Smoking the low nicotine delivery cigarettes (7, 15, 30 puffs) produced increased avoidance responding in two of the three subjects. Smoking the high nicotine delivery cigarettes increased avoidance responding in all subjects. The thirty puff condition produced slight decreases in responding in comparison to the 15 puff condition in all subjects in the high nicotine delivery cigarette condition. The decrease in responding in the 30 puff condition in relation to the 15 puff condition was observed in the low nicotine delivery cigarette condition in two of the subjects. Inspection of cumulative records indicated that increases in response rate appeared to persist throughout the session, with no evidence of decreased responding later in those sessions. Repeated measures ANOVA analysis indicated a significant main effect of smoking high nicotine delivery cigarettes, $F(3,6) = 4.87$, $p<0.05$, while the effects of chewing nicotine gum and smoking low nicotine delivery cigarettes were not significant.

The results of the nicotine and cotinine analysis of blood samples for the subjects are shown in Table 1. Blood samples were taken before and after the largest dose of nicotine gum and prior to and following the 30 puff procedure in both the low nicotine delivery and high nicotine delivery cigarette conditions only. Cotinine levels indicated that our subjects were low (S-202), moderate (S-179), and high (S-188) nicotine users. For subjects S-188 and S-179 chewing the 8 mg dose of nicotine gum resulted in nicotine blood levels similar to those obtained in the two smoking conditions while, for subject S-202 the 8 mg dose nicotine gum produced a nicotine blood level similar to that obtained in the low nicotine delivery cigarette condition which was smaller than the high nicotine delivery cigarette condition. These similar blood levels obtained via gum administration, however, were not associated with measurable behavioral effects. All subjects showed increases in nicotine blood levels following smoking cigarettes, with the greatest changes following administration of the high nicotine delivery cigarettes. The low nicotine delivery cigarette condition resulted in a 11.8 ng/ml increase in subject S-179 but only minimal increases in the other two subjects. It is interesting to note that the high nicotine using subject (S-188) had no increase in avoidance responding following the smoking of the low nicotine delivery cigarettes. Smoking the high nicotine delivery cigarettes produced much larger increases in nicotine blood levels (25.5, 19.5, 23.2 ng/ml) and was accompanied by increases in avoidance responding in all subjects. The correlation between changes in avoidance responding and changes in plasma concentrations of nicotine was not significant ($r = .12$, N.S.).

Subjects completed the Profile of Moods States (POMS) questionnaire at the end of each session. A MANOVA analysis was performed on the POMS scores for the six categories (Tension, Depression, Confusion, Vigor, Anger, and Fatigue). The results were not significant at the .05 level, however, the thirty-minute period between nicotine administration and administration of the POMS may have attenuated any nicotine effect upon mood possibly detected by the questionnaire.

DISCUSSION

Overall, the data suggest that the effect of nicotine upon avoidance responding is related to dose amount and also the route of administration. Chewing the nicotine gum increased nicotine blood levels to levels similar to the smoking conditions but these levels were not associated with changes in responding. The smoking of the low nicotine delivery cigarette resulted in a substantial increase in nicotine blood level in one subject and small changes in the other two subjects. This smoking condition resulted in increases in responding in two subjects. The high nicotine delivery cigarette produced increased responding in all subjects, though the 30 puff condition resulted in fewer responses in each subject relative to the 15 puff condition.

Previous research with nicotine administration using human subjects has investigated nicotine effects upon various behavioral measures and tasks. In general, nicotine administration with experienced smokers improves performance [for review see (6,20)]. Reaction time is shorter and performance is maintained for a longer period of time. In vigilance tasks, smoking improved performance and maintained this level of performance over time. The effects of nicotine upon temporal discrimination has been found to produce an overestimation of the interval duration (underestimation of the elapsed time, subjects responded too soon).

These data support previous findings that nicotine improves performance on a behavioral task, however, the route of administration, dosage level, and amount of previous experience with nicotine modulates this performance improvment. Oral administration of nicotine via gum produced no behavioral effect while smoking improved performance (e.g., no point losses during smoking sessions, increased responding during smoking sessions). Similar increases in avoidance responding have been observed in animal studies (6).

The basis for nicotine effects upon avoidance responding is not well determined. Nicotine may produce more responding via a stimulation effect or an attenuation of the temporal discrimination behavior of the subject either of which would result in shorter interresponse times. The nicotine may also serve to stimulate vigilance to maintain "on task" performance thus decreasing probability of lapses in responding, i.e., long interresponse times.

Regardless of the mechanism underlying the behavioral effects associated with increased nicotine blood levels, the increased responding and the consequent improved avoidance of point loss are most likely the result of a direct CNS effect which is only observed by inhalation route of administration. Though the nicotine blood levels in both routes of administration (smoking and chewing gum) were comparable, performance enhancement was observed only following smoking of the cigarettes (inhalation route of administration). There may be two possible explanations for this differential behavioral effect at comparable nicotine blood levels. The arterial levels and brain levels of nicotine are underestimated by venous blood levels following cigarette smoking (a relatively more rapid dosing rate) in contrast to levels resulting from nicotine gum chewing, a relatively slower dosing procedure [see (14)]. A second explanation may be that the psychoactive effects of nicotine are more pronounced with a rapid rise in brain levels of nicotine associated with inhalation in contrast to a slower rate of rise resulting from gum chewing. This slower rate may also be associated with the development of acute tolerance.

Although these data are based upon only three subjects, the results may have implications for the use of nicotine gum as an adjunct to smoking cessation. The enhancement and maintenance of performance may be a salient factor maintaining tobacco smoking. The use of nicotine gum as an alternative source of nicotine, though diminishing some of the withdrawal symptoms, cannot be expected to produce the behavioral effects observed from smoking. Thus, the employment of nicotine gum as a substitute for smoking may not be an effective treatment strategy for smokers who are required to maintain performance levels for long periods of time on repetitive tasks.

In conclusion, the present research investigated the behavioral effects of nicotine in an aversive situation operationally defined as avoidance of point loss. Nicotine administration via smoking increased both nicotine blood levels and responding maintained by avoidance of point loss and dosage level modulated this increase. In contrast, chewing nicotine gum increased nicotine blood levels comparable to increases observed resulting from smoking without producing any behavioral effects.

ACKNOWLEDGEMENT

This research was supported in part by PHS Grant DA 04044 from the National Institute on Drug Abuse.

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