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Cigarette Desirability and Nicotine Preference in Smokers[1]

JOSEPH E HERSKOVIC,[2] JED E ROSE AND MURRAY E. JARVIK

Department of Psychiatry and Biobehavioral Sciences, The Neuropsychiatric Institute School of Medicine, University of California, Los Angeles, CA 90024 and Veterans Administration Medical Center, Los Angeles, CA 90073

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HERSKOVIC, J E, J E ROSE AND M E JARVIK *Cigarette desirability and nicotine preference in smokers* PHARMACOL BIOCHEM BEHAV 24(2) 171–175, 1986 —We conducted two experiments to explore the role of nicotine in the maintenance of cigarette smoking behavior In Experiment 1 we determined that, compared to 0 or 2 mg injections, an injection of 4 mg nicotine base into the filter of non-nicotine cigarettes significantly increased their desirability In Experiment 2, to determine how nicotine-seeking varied across a wide range of cigarette deprivation, we studied nicotine preference under three cigarette deprivation conditions overnight abstinence, 30 min deprivation, and immediately after smoking (satiation condition) Nicotine preference was assessed by allowing subjects to freely adjust the nicotine concentration of each puff using a smoke mixing device Nicotine preference was greatest after overnight deprivation Least after satiation, and intermediate after 30 min deprivation However, nicotine seeking increased as a function of cigarette deprivation despite the fact that higher nicotine puffs were rated as harsher, stronger and less desirable than lower nicotine puffs The results of both experiments suggest an inverted-U relationship between nicotine content and desirability

Cigarettes Deprivation Nicotine Reinforcement Satiation Smoking Tobacco Cigarette smokers

NICOTINE, the main psychopharmacologically active ingredient in cigarette smoke, has both rewarding and aversive properties in humans [9, 11, 21] and animals [3] It is known that nicotine alters the bioavailability of several behaviorally active neuroregulators, including beta-endorphin [14], which may produce temporary improvements in performance or affect [16] However, the reinforcing properties of nicotine have been difficult to demonstrate [16]

Some earlier attempts to investigate the reinforcing properties of nicotine have focused on trying to demonstrate that smokers will adjust their smoking habits when their systemic levels of nicotine are altered [6, 8, 13, 21] These so-called titration studies have been reviewed and criticized elsewhere [7,15] The findings that compensation occurs in both directions (though not to the same degree)—downwards to avoid excessive nicotine intake and upwards to avoid a reduction in nicotine intake—are consistent with the hypothesis that nicotine can be aversive as well as rewarding [21]

In another attempt to demonstrate the reinforcing properties of nicotine, strength, quality and smoking rate were measured as a function of nicotine content in experimental cigarettes [5] Adding nicotine to lettuce cigarettes did not affect any of these measures However, there was no verification of either the nicotine delivery of the cigarettes or subjects' compliance with the requirements of the study

To determine directly whether cigarette smoking has a nicotine-seeking component, we studied nicotine preference after cigarette deprivation and satiation using a smoke mixer which selectively varied nicotine delivery [18] We chose cigarette deprivation as the independent variable because it increases the tendency for subsequent smoking as reflected in latency to smoke, number of cigarettes smoked, and number of puffs [6,10] We reported that this increase in smoking is in part determined by a desire for nicotine because the average mixture chosen in the deprivation condition was significantly greater than in the satiation condition Further, because the average smoke mixture chosen in the deprivation condition was greater than 50% from the high nicotine side of the smoke mixer, we concluded that nicotine, in the concentrations studied, is reinforcing rather than aversive [18]

The present report was designed to further explore the reinforcing properties of nicotine and its role in the maintenance of cigarette smoking In Experiment 1 we corrected some of the procedural problems of the Goldfarb *et al* [5] study by verifying the "tar" and nicotine deliveries of the experimental cigarettes and by supervising the subjects in the laboratory instead of allowing them to record their responses at home We predicted that adding nicotine would increase the desirability of non-nicotine cigarettes

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[2]Requests for reprints should be addressed to Joseph E Herskovic, Veterans Administration Medical Center, Trailer 350, Mail Code 691/B151D, West Los Angeles, CA 90073

Experiment 2 was a replication and extension of the Rose *et al* [18] study of nicotine preference after cigarette deprivation and satiation Instead of two experimental conditions, 2 hr cigarette deprivation and satiation, we determined nicotine preference under three conditions overnight abstinence, 30 min deprivation, and satiation We have also changed the cigarettes used in the smoke mixer from University of Kentucky Tobacco Research cigarettes to commercial cigarettes with either enhanced or unaltered nicotine delivery because the commercial cigarettes more accurately reflect the "tar" and nicotine values to which smokers are accustomed (see METHOD) Also, the "tar" deliveries of the nicotine enhanced and unaltered commercial cigarettes are more similar than are those of the University of Kentucky high and low nicotine cigarettes Thus, in the present study, we were better able to vary nicotine independently of the non-nicotine components of smoke

EXPERIMENT 1

METHOD

Subjects

Eighteen smokers, 6 females and 12 males, were recruited from an advertisement in a local newspaper The data for females and males were combined because there were no sex differences on any of the dependent measures Subjects smoked an average of 25 7 (s d =9 5) cigarettes per day with an estimated nicotine delivery (Federal Trade Commission [FTC] method) of 1 0 (s d =0 2) mg Subjects ranged in age from 18–65 years (m=32 3) and had smoked cigarettes for an average of 15 6 years (range=3–40 years)

Cigarettes

Four types of cigarettes were administered a non-nicotine cigarette no longer commercially available in the United States (Triumph Smokes, Dallas, TX) injected with either 7 or 13 microliters of a 30% aqueous solution of nicotine base or 7 microliters of distilled water, or an unaltered Marlboro Lights The 5, 7, and 13 microliters of the 30% aqueous solution of nicotine base corresponded to 1 5, 2 0, and 4 0 mg of nicotine, respectively Nicotine base was obtained from SIGMA Chemical Company, St Louis, MO

Ten minutes prior to presentation, the Triumph cigarettes were injected axially approximately 1 cm into the cigarette filter with either the distilled water or nicotine solution The nicotine delivery of the injected experimental cigarettes was determined using an artificial smoking procedure similar to that used by the FTC [2] Puffs (35 cc) were taken every min to a butt length of 3 mm in excess of filter and overwrap and the smoke was trapped on Cambridge Filter pads and sent to the Clinical Psychopharmacology Laboratory at the Veterans Administration Medical Center Sepulveda for nicotine assay (2 samples of each cigarette) This assay yields nicotine values similar to those obtained by the FTC [2] (see Experiment 2) The nicotine delivery of the nicotine-injected cigarettes was enhanced from 0 mg to 0 56±0 12 mg (7 microliter injected) or 0 91±0 04 mg (13 microliter injected) The nicotine delivery of the water-injected cigarettes remained 0 mg The "tar' content of the Triumph cigarettes was about 24 4±1 7 mg, regardless of nicotine content The published nicotine and "tar' values for the Marlboro Lights are 0 74±0 04 mg and 10 7±0 3 mg, respectively [2]

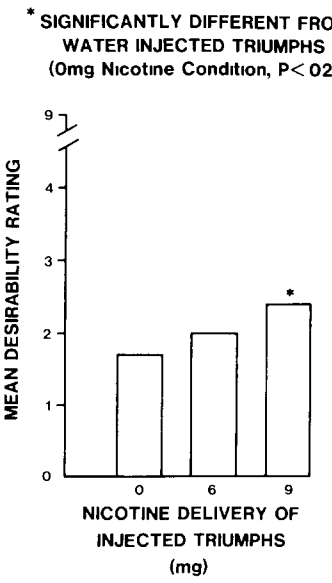

FIG 1 Mean desirability rating as a function of nicotine delivery for the three injected Triumph cigarettes The desirability score for each subject was defined as the mean rating of the three puffs The mean of these scores across subjects is plotted

Procedure

Subjects were tested individually for about 15 min in a completely within subjects design After giving their informed consent, each subject took three puffs from each of the four different types of cigarettes, for a total of 12 puffs The interpuff interval was 30 sec and to minimize possible cumulative dosing effects, the order of puffs was counterbalanced across subjects All cigarettes were visually disguised so that the brand names could not be identified Subjects rated the harshness, strength and desirability of each puff using ten-point scales ranging from "not at all" (0) to "extremely" (9)

RESULTS AND DISCUSSION

Mean desirability rating as a function of nicotine delivery for the three injected Triumph cigarettes is shown in Fig 1 A one way Analysis of Variance (ANOVA) on desirability rating revealed a significant main effect of nicotine, $F(2,34)=3\ 31$, $p<0\ 05$ Post-hoc t-tests showed only one significant effect the 4 mg nicotine injected Triumphs were rated as more desirable than the water injected Triumphs, $t(17)=2\ 58$, $p<0\ 02$ Thus, adding 4 mg, and not 2 mg of nicotine to non-nicotine cigarettes significantly increased their desirability

Nicotine filter injections had no effect on either the harshness or strength ratings of the Triumph cigarettes, $F(2,34)=0\ 89$ and $1\ 18$, $p>0\ 20$, for harshness and strength, respectively Thus, all of the Triumph cigarettes, regardless of nicotine content, were rated as equivalently harsh and strong (at about 5) Perhaps these cigarettes were so undesirable that the bad taste overwhelmed the harshness and strength effect of the nicotine, although it is not clear why this did not happen in the Goldfarb *et al* [5] study where the cigarettes were equally undesirable but there was a significant effect of nicotine on strength

Compared to the Triumphs, a series of t-tests revealed that the Marlboro Lights were rated as the most desirable,

least harsh, and least strong of all the cigarettes tested ($p<0.001$ in all cases). The mean desirability, harshness and strength ratings of the Marlboro Lights were 4.63, 3.00 and 3.35, respectively. Marlboro Lights and Triumph cigarettes differ along many dimensions including nicotine content, the presence of flavor-enhancing additives, tobacco blends, curing, etc. Because of these differences the Marlboro Lights were included in the present study for comparison purposes only and not as another nicotine condition.

We conclude that nicotine can be rewarding because adding certain levels of nicotine to non-nicotine cigarettes significantly increased their desirability without affecting harshness or strength. However, the addition of nicotine does not make non-nicotine cigarettes as desirable as a popular commercial brand.

EXPERIMENT 2

METHOD

Subjects

Fifteen smokers, 8 females and 7 males, were recruited from an advertisement in a local newspaper. As was true in Experiment 1, the data for males and females were combined because there were no sex differences on any of the dependent measures. Subjects smoked an average of 23.7 (s.d. =7.4) cigarettes per day with an estimated nicotine delivery (FTC method) of 0.9 (s.d. =0.3) mg. Subjects ranged in age from 20–50 years (m=30.9) and had smoked cigarettes for an average of 15.3 years (range=3–32 years).

Apparatus

Cigarettes. To measure nicotine preference, we used high and low nicotine cigarettes in a smoke mixing device. To ensure that cigarettes differed only in nicotine delivery, we added either distilled water or a small amount of nicotine base (obtained from SIGMA Chemical Company, St. Louis, MO) to the filter of a commercial cigarette (Marlboro Lights 100's). Twenty microliters of water or a 30% aqueous solution of nicotine base corresponding to 6 mg of nicotine were injected axially approximately 1 cm into the cigarette filter. The nicotine delivery of the injected experimental cigarettes was determined as in Experiment 1. When smoked, the nicotine delivery of the nicotine-injected cigarette was enhanced from approximately 0.75±0.02 mg [2] to 1.5±0.1 mg. The nicotine delivery of the water-injected cigarette was about 0.73±0.03 mg. "Tar" delivery was unaffected by the filter injection technique and remained constant at about 10.6±0.3 mg.

Smoke mixing device. To control the nicotine delivery of each puff, subjects used one of four smoke mixers which were similar to one described previously [19]. These smoke mixers allowed subjects to blend smoke in graded amounts from the high and low nicotine cigarettes just described. By turning a knob, subjects could select any intermediate nicotine delivery desired. A dial reading ranging from 3.0 to 7.0 in 0.1 unit steps indicated the position of the knob on any given puff.

Expired air CO measurement. Expired air CO levels were measured with an electrochemical analyzer (Ecolyzer Model A) when subjects entered the laboratory after overnight smoking abstinence and before and after each nicotine preference determination [12]. Samples were collected after 20 sec of breath holding and discarding the first 500 cc of expirate to eliminate dead space air from the sample [22].

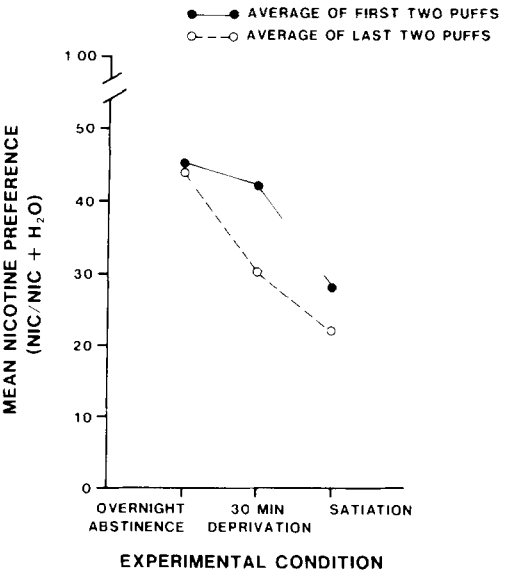

FIG. 2. Mean nicotine preference for the average of the first (closed circles) and last (open circles) two puffs as a function of experimental condition.

Procedure

Subjects were tested in a within subjects experimental design either individually or in groups of up to four individuals, depending on subject availability. When group testing was conducted, subjects were separated from each other by cardboard partitions and communication among subjects was discouraged.

Subjects entered the laboratory at 9 a.m. after having abstained from cigarette smoking for 12 hours. After obtaining informed consent, overnight abstinence was checked by measuring expired air CO level. With one exception, the expired air CO level for all subjects was less than 20 ppm. The subject whose level was 32 ppm assured us that she had not had a cigarette in 12 hours. Further, because her CO levels were raised significantly by smoking through the mixer (up to 58 ppm) we concluded that she probably had complied with the overnight abstinence requirement.

We then showed subjects how to use the smoke mixers and allowed them to practice turning the knob with unlit cigarettes. This was followed by the first nicotine preference determination (overnight deprivation condition). All nicotine preference determinations consisted of lighting the cigarettes and taking a puff from the middle, low and high settings of the smoke mixer and then smoking freely for 10 min, adjusting the nicotine delivery of each puff to the level desired. The sides of the mixer in which the high and low nicotine cigarettes were placed were randomly assigned. Subjects recorded the mixer dial reading to the nearest 0.1 unit and rated the strength, harshness, and desirability of each puff using ten-point scales ranging from "not at all" (0) to "extremely" (9).

This was followed by another nicotine preference determination (30 min deprivation condition). For the first seven subjects only, nicotine preference was determined three additional times at 30 min intervals. Analysis of variance of the four 30 min deprivation conditions revealed no significant differences in either nicotine preference or number of puffs

A previous study also reported no differences in a number of smoking variables when subjects smoked at 30 min intervals [1] Therefore, for the final eight smokers, the three additional 30 min deprivation nicotine preference determinations were eliminated Thus, for all 15 subjects, the 30 min deprivation condition was defined as the nicotine preference determination made 30 min after the overnight deprivation condition

Finally, 30 min later, all 15 subjects took ten paced puffs (one puff every 30 sec for 5 min) from an uninjected Marlboro Light 100 which was not placed in the mixer This was followed immediately by the final nicotine preference determination (the satiation condition)

Data Analysis

We calculated two measures of nicotine preference—average nicotine preference of the first two puffs and average nicotine preference of the last two puffs—and one estimate of total smoke intake (number of voluntary puffs) for each of the three experimental conditions (overnight deprivation, 30 min deprivation, and satiation)

Average nicotine preference was defined as the mean preference for the high nicotine cigarette as calculated from the dial settings recorded for each puff Nicotine preference was expressed as the proportion of smoke from the high nicotine cigarette divided by the total amount of smoke flowing through the mixer The dial settings were transformed into flow ratios using calibration curves relating dial reading to the proportion of air flowing through each side of the mixer Air flow was measured with Gilmont spherical float flowmeters during calibration tests for each of the four smoke mixers

The average nicotine preference for the first two voluntary puffs (after the three mandatory puffs) was assumed to reflect a "hunger" for nicotine and the average preference for the last two puffs was assumed to represent the most desired level because by then, subjects had a chance to sample different dial settings

All mandatory and voluntary puffs were included in calculating the slopes of the regression lines relating subjective ratings to the proportion of smoke from the high nicotine cigarette

RESULTS AND DISCUSSION

Figure 2 shows the mean nicotine preference for the average of the first and last two puffs as a function of experimental condition The value of both measures was greatest after overnight deprivation, least after satiation, and intermediate after 30 min deprivation A 2 (first vs last puffs) by 3 (deprivation) ANOVA revealed a significant main effect of deprivation, $F(2,28)=3\ 87$, $p<0\ 05$ Neither the main effect of puffs nor the interaction was significant indicating that although the effect of deprivation seemed somewhat stronger for the average of the last two puffs (Fig 2), there was no difference in nicotine preference between the first and last puffs Thus, we have replicated, over a wider range of deprivation conditions, our previous finding that nicotine preference increases after cigarette deprivation [18]

The mean number of puffs were 8 5 (s d =2 4), 11 1 (s d=2 3), and 9 6 (s d =3 4) for the overnight deprivation, 30 min deprivation, and satiation conditions, respectively The one-way ANOVA for puffing was significant, $F(2,28)=6\ 06$, $p<0\ 01$ Post-hoc t-tests revealed only one significant difference subjects took more puffs after 30 min deprivation than after overnight deprivation, $t(14)=3\ 98$, $p<0\ 01$

There are at least two possible explanations of the difference in puffing between the overnight and 30 min deprivation conditions First, a lack of acute tolerance to nicotine's effects after overnight deprivation may have occurred That is, subjects may have been more sensitive to the pharmacological effects of nicotine after overnight deprivation and therefore took fewer puffs than after 30 min deprivation when some acute tolerance level is reached Second, although the subjects did prefer the highest concentrations of nicotine in the overnight deprivation condition, this condition was the first time they ever used the smoke mixer with lit cigarettes and they may have been tentative about taking too many puffs In our previous study, subjects were tested on two separate days, thus novelty of the apparatus was not a significant factor in the 2 hr deprivation condition [18] In that study, subjects took significantly more puffs after deprivation than after satiation In the present study, subjects took more puffs after 30 min deprivation (where novelty of the apparatus was not a factor) than after satiation Although this result was not statistically significant, it is consistent with our previous findings

As in our previous study [18], the slopes of the regression lines relating perceived harshness, strength and desirability to the proportion of smoke from the high nicotine cigarette did not differ across experimental conditions ($p>0\ 5$ in all cases) The mean slopes for harshness and strength ranged from 3 4 to 4 2 The mean slopes for desirability were $-1\ 3$, $-1\ 1$, and $-1\ 4$ for the overnight deprivation, 30 min deprivation, and satiation conditions, respectively The positive slopes indicate that higher nicotine puffs were rated harsher and stronger than lower nicotine puffs In a previous study, Rose [17] also reported positive strength versus nicotine slopes The negative desirability slopes indicate that some smokers liked lower nicotine puffs more than higher nicotine puffs

The perception of nicotine in smoke might be affected by other factors such as "tar" [4] For example, in a previous study [17] and in Experiment 1 of the present study we used high "tar" cigarettes and found that variations in nicotine had very little effect on perceived strength In contrast, in Experiment 2 we used relatively low "tar" cigarettes and found that variations in nicotine had large effects on perceived strength Such findings suggest that "tar" may play a role in modulating the strength of nicotine, and cast doubt on the suggestion that smokers will accept low-"tar," medium nicotine cigarettes as an alternative to higher "tar" brands [20]

In sum, nicotine seeking increased as a function of cigarette deprivation despite the fact that higher nicotine puffs were rated as harsher, stronger and less desirable than lower nicotine puffs This finding is analogous to the findings that intravenous nicotine self-administration continues to occur in some smokers despite drug induced illness [9,11] Overall, the results of both experiments suggest an inverted-U relationship between nicotine content and desirability

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