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Nicotine Preference in Smokers as a Function of Smoking Abstinence

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PERKINS, K. A., J. E. GROBE, D. WEISS, C. FONTE AND A. CAGGIULA. *Nicotine preference in smokers as a function of smoking abstinence.* PHARMACOL BIOCHEM BEHAV **55**(2) 257–263, 1996.—Overnight smoking abstinence increases desire to smoke and intensity of smoking behavior in smokers, but it is not completely clear that this reflects an increase in reinforcement from the psychoactive effects of nicotine per se. We examined choice of nicotine vs. placebo via nasal spray (Study 1) and nicotine vs. nonnicotine cigarette puffs (Study 2) in separate groups of smokers during each of two sessions, following overnight abstinence vs. no abstinence. In each study, subjects followed a forced choice procedure in which they were instructed to self-administer six sprays/puffs from between the two nasal sprays/cigarettes every 15 min for 2 h following initial exposure to each. In Study 1, choice of nicotine spray (1.5 μg/kg per spray) increased significantly following abstinence vs. no abstinence (47± 6% vs. 34 ± 5%, respectively, $p < 0.05$). This shift in choice was more pronounced in the subset of smokers (choosers, $n = 9$ out of 24) who selected nicotine on more than 50% of choices on the abstinent day. Choosers exhibited greater responses to initial nicotine exposure on positive (e.g., pleasant, vigor) but not aversive (e.g., jittery, uneasy) subjective measures, suggesting that greater positive reinforcement from nicotine per se predicted subsequent choice. In Study 2, abstinence similarly increased choice of nicotine vs. nonnicotine cigarette puffs (82 ± 6% vs. 64 ± 8%, $p < 0.05$), although nearly all subjects (12 of 13) preferred the nicotine cigarette following abstinence. These results indicate that choice of nicotine per se, isolated from tobacco smoke, increases significantly after overnight tobacco abstinence. **Copyright © 1996 Elsevier Science Inc.**

Nicotine Tobacco Self-administration Drug choice Abstinence Smokers

ABSTINENCE from smoking increases desire to smoke [e.g. (18,20)], intensity of smoking behavior [probability of smoking, number of puffs, carbon monoxide boost, etc.; e.g. (7,31)], and the reinforcing value of smoking (18) in smokers. Although nicotine intake clearly reinforces tobacco smoking behavior in animals (32) as well as in humans (11,29), it is not necessarily certain for all smokers that increased smoking behavior after abstinence reflects an increase in reinforcement from nicotine per se (i.e., increased self-administration of nicotine). Overnight abstinence has been shown to increase preference for intake of nicotine from smoking (13,27). For example, Herskovic et al. (13) provided subjects with the opportunity to adjust on a puff-by-puff basis the amount of nicotine from tobacco smoking by using a device that allowed variable mixing of smoke from cigarettes differing in nicotine yield. Mean nicotine preference per puff during the single trial increased linearly with greater length of abstinence (none, 30 min, overnight), although number of puffs self-administered was no different between overnight abstinence vs. no abstinence (and greatest following 30-min abstinence). Nevertheless, no study has directly examined whether smokers will increase self-administration of nicotine alone, isolated from tobacco smoke, after a period of smoking abstinence. This is an important gap in the literature because increased preference for nicotine in smoke could be due to conditioned reinforcement from peripheral sensory effects [e.g., throat irritation; (28)] and not to psychoactive effects of nicotine.

The present research examined preference for nicotine intake via nasal spray in smokers as a function of overnight abstinence from smoking vs. no abstinence. A forced choice procedure was used, in which subjects were instructed to select from two different bottles (nicotine vs. placebo) to self-administer a specific number of sprays. Although conceptually similar to Herskovic et al. (13), this research focused on preference for nicotine in isolation rather than via smoking. It was hypothesized that the number of times nicotine spray was selected

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would increase with overnight abstinence, demonstrating increased preference for nicotine per se. We also sought to examine whether subjective responses to initial exposure may be associated with subsequent greater preference for nicotine vs. placebo, which could support the notion that choice was based on psychoactive effects of nicotine. Because preference for nicotine intake via smoking had not been studied with a similar forced choice procedure, we conducted a second study involving selection of nicotine vs. nonnicotine cigarette puffs as a function of overnight abstinence, for comparison with results from Study 1.

STUDY 1

Method

Subjects. Subjects were 24 smokers (8 men, 16 women) reporting a history of smoking at least 15 cigs/day for at least 1 year. Smokers expressing an interest in quitting smoking in the near future or those seeking assistance with smoking cessation were excluded from participation. All subjects were examined by physician to rule out current or past medical or psychiatric problems, and urine drug screens were obtained to exclude subjects with substance abuse problems (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and THC). Subjects were also excluded for excessive alcohol use ($\geq$ 15 drinks/week), determined by interview. Subject characteristics were as follows: age—22.8 $\pm$ 0.9 years; cigarettes/day—19.7 $\pm$ 1.0; number of years smoking—6.5 $\pm$ 1.0; nicotine yield of preferred cigarette (mg)—0.88 $\pm$ 0.05; Fagerstrom (4) score of nicotine dependence—4.8 $\pm$ 0.4.

Nicotine/Placebo Dosing. Nicotine (1.5 μg/kg/spray) or placebo was provided by a nasal spray delivery procedure developed in our lab (19). This procedure has been found to produce reliable, dose-dependent increases in plasma nicotine (19,24,25). The nicotine dose per spray (0.1 mg for average-weight subject) was designed to be comparable to the amount of nicotine in a single puff from a cigarette. The nasal spray bottle delivered the designated amount of nicotine in saline, along with peppermint flavoring oil (Lorann Oils, Lansing, MI), which was used to mask the taste and smell of nicotine. To equate the placebo and nicotine sprays on immediate sensory effects, the placebo solution contained capsaicin (pepper extract), along with peppermint oil. Other details have been reported elsewhere (19,24,25).

Forced Choice Procedure. The procedure by which subjects chose nicotine vs. placebo sprays was adapted from that used by others in studying human choice behavior involving other drugs, such as caffeine (17), alcohol (3), and marijuana (2). Subjects were first presented with separate exposures to the two spray bottles, identified by the color of the tape attached to them as the orange and purple sprays. Color assigned to nicotine vs. placebo was counterbalanced between subjects. An experimenter, blind to the dose assigned to bottles, instructed subjects to administer to themselves six sprays from only one of the bottles (orange or purple), complete subjective effects forms, and then rest quietly for 15 min. They then repeated this procedure for the other spray (exposure trials). Order of nicotine vs. placebo spray exposure was counterbalanced between subjects. Subsequently, subjects were instructed to self-administer a total of six sprays from either or both bottles within a 3-min period (choice trial). All spray self-administrations were done under the observation of the experimenter, who maintained possession of spray bottles at all other times. Subjects repeated this selection of six sprays within 3 min every 15 min for 2 h (total of eight choice trials). Nicotine choice behavior was assessed by the percentage of total (n = 48) choices subjects chose the nicotine spray.

Because the spray bottle containing nicotine administered 1.5 μg/kg nicotine per spray, a maximum of 9 μg/kg could be obtained during each trial by subjects choosing nicotine spray for all six selections per trial. For the typical subject, this maximum approximated 0.6 mg, or somewhat less than the current nicotine yield of the average U.S. cigarette (5). This relatively small dose was used to increase the number of choice selections per session (i.e., vs. typical single choice, to increase flexibility of amount and pattern of nicotine self-administration) and because of the short, 15-min interval between choice trials, about half the typical interval between cigarettes in the natural environment (8).

Procedure. Subjects participated in two afternoon sessions (approx. 1300–1500 h), one following overnight ($\geq$ 12 h) abstinence from tobacco smoking and the other following no abstinence (i.e., ad lib smoking prior to the session). Subjects were considered compliant with instructions to remain abstinent if they had an expired-air carbon monoxide (COa) $\leq$ 13 ppm. On the no-abstinence day, subjects were instructed to smoke as they normally do prior to arriving at the session and then to smoke one cigarette of their preferred brand ad lib upon arrival and after every other choice trial (i.e., every 30 min) to minimize tobacco deprivation during the session.

During each session, subjects remained seated in a comfortable armchair. Following a 10-min quiet rest period and completion of subjective measures (baseline), subjects were given instructions on how to self-administer the spray bottles. Subjects then engaged in the two exposure trials (as described above) followed by the eight choice trials, one every 15 min, while the experimenter recorded the number of sprays self-administered from each bottle. Subjects were allowed to read quietly between trials.

Subjective measures of mood and desire to smoke were obtained at baseline and after each of the two exposure trials. Measures included: 1) visual analog scale (VAS) items of "Stimulated," "Head Rush," "Jittery," "Relaxed," "Pleasant," "Uneasy," "Alert," and "Urge to Smoke" (each ranging from 0 = not at all, 100 = very much); and 2) Profile of Mood States [POMS; (16)] scales of Tension (range = 0–32), Confusion (0–28), Vigor (0–32), and Fatigue (0–28), and the composite scale of Arousal [determined by subtracting Confusion and Fatigue from Tension plus Vigor; range = −56 to 64; (3)]. The VAS items and the POMS have been used extensively in studies of the acute effects of smoking or nicotine as well as other drugs [e.g. (3,23–25)].

Nicotine spray selections (percent of total) were compared between abstinence and no abstinence days and vs. 50% (chance) by t-test. Initial subjective responses to exposure trials of nicotine vs. placebo on the abstinence day were compared between nicotine spray choosers and nonchoosers (see below) using analysis of variance (ANOVA), with one between-subjects variable (chooser) and one within-subjects variable (dose). Follow-up comparisons were performed using Fisher's least significant difference t-test.

Results

As shown at the top of Fig. 1, choice of nicotine spray was significantly greater following tobacco abstinence vs. no abstinence [47 vs. 34%, respectively, $t(23) = 2.21$, $p < 0.05$]. Choice on the abstinence day was not different from chance (50%), but choice on the no abstinence day was significantly

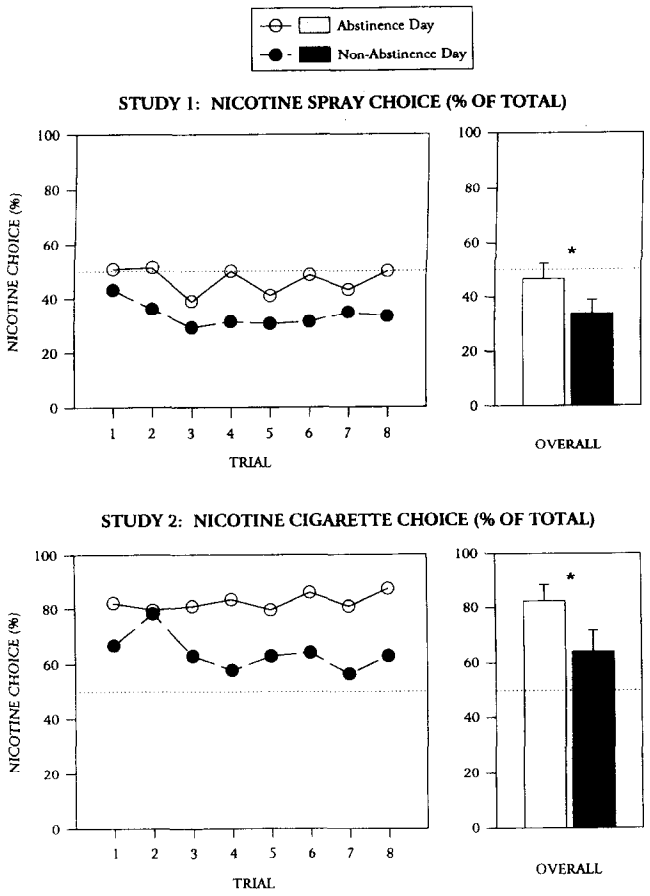

FIG. 1. Choice (percentage of total selections) of nicotine nasal sprays (Study 1; top) and of nicotine cigarette puffs (Study 2; bottom), across each trial and overall (mean ± SEM), following overnight tobacco abstinence vs. no abstinence. *$p < 0.05$ for overall comparison.

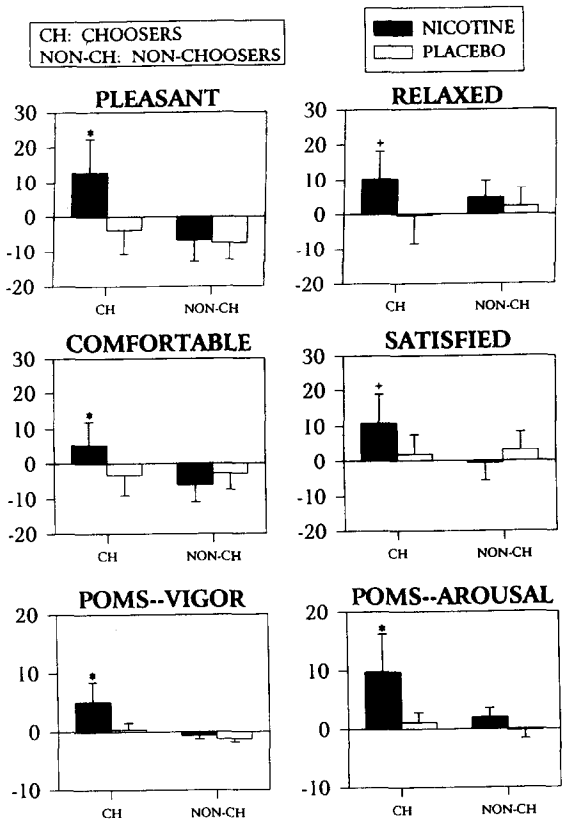

FIG. 2. Subjective responses (change from baseline) to initial exposure to nicotine vs. placebo nasal spray following overnight abstinence (Study 1). Responses shown are those that differentiated subjects who subsequently chose nicotine on more than 50% of selections (choosers, $n = 9$) from those who did not (nonchoosers, $n = 15$). *$p < 0.05$; +$p <$ 0.10 for difference in response to nicotine vs. placebo.

below chance, $t(23) = 3.12, p < 0.01$, suggesting aversion. The range of nicotine choices between subjects was 0–100% on the abstinence day and 0–83% on the no abstinence day. All subjects self-administered nicotine spray at least once on one of the days. Nine subjects (out of 24, 38%) selected nicotine on more than 50% of choices on the abstinence day, but fewer than half that (4 of 24, 17%) did so on the no abstinence day. Nicotine choice was stable across trials (see Fig. 1).

Nicotine Choosers. The nine subjects who selected nicotine spray on more than 50% of choices during the abstinence day were designated as nicotine choosers, and the remaining 15 were designated nonchoosers. Mean nicotine spray choice by choosers was 74% on the smoking abstinence day vs. 49% on the no-abstinence day, $t(8) = 1.90, p < 0.10$, for difference due to abstinence. The 74% choice on the abstinence day was significantly greater than chance, $t(8)=3.74, p < 0.01$, indicating actual preference for nicotine. Nonchoosers selected nicotine on 30% of choices on the abstinence day vs. 25% on the no abstinence day, both of which were significantly lower than chance, $t(15) = 5.16$ and 5.23, respectively, both $p < 0.005$, indicating aversion to nicotine spray on both days.

ANOVA results for subjective responses to the initial exposure trials of each spray (i.e., prior to choice trials) on the abstinence day indicated significant or nearly significant main effects of nicotine on increasing VAS items of Pleasant, $F(1, 21) = 4.47, p < 0.05$, Head Rush, $F(1, 21) = 7.33, p < 0.02$, Alert, $F(1, 21) = 3.54, p < 0.10$, Relaxed, $F(1, 21) = 3.50, p < 0.10$, and Jittery, $F(1, 21) = 3.06, p < 0.10$, as well as for POMS scales of Vigor, $F(1, 21) = 4.21, p = 0.05$, Arousal, $F(1, 21) = 4.34, p < 0.05$, and decreasing Fatigue, $F(1, 21) = 4.23, p = 0.05$. An interaction of nicotine/placebo × chooser/nonchooser was observed for VAS items of Comfortable, $F(1, 21) = 6.79, p < 0.02$, Satisfied, $F(1, 21) = 4.54, p < 0.05$, and Pleasant, $F(1, 21) = 3.68, p < 0.10$ (but not for POMS scales), suggesting that subjective responses to initial exposure may be associated with greater subsequent nicotine choice. Follow-up tests to the interactions indicated that choosers had significantly greater responses to nicotine vs. placebo spray on Pleasant and Comfortable and marginally greater response on Satisfied. Because of the importance of identifying subjective responses that may be predictive of nicotine choice, we conducted exploratory comparisons for other subjective effects. Choosers also had significantly greater responses to nicotine vs. placebo on POMS scales of Vigor and Arousal and marginally greater response on the VAS item of Relaxed. By contrast, nonchoosers had no significantly greater responses on any of these measures upon initial exposure to nicotine vs. placebo spray. These differential subjective responses in choosers and nonchoosers are presented in Fig. 2. In direct comparisons, differences between choosers and nonchoosers in subjective responses to initial nicotine vs. placebo spray exposures were

significant for Pleasant, Comfortable, Satisfied (all $p < 0.01$), and POMS-Vigor ($p < 0.05$), and nearly significant for Relaxed and POMS-Arousal (both $p < 0.10$). There were no differences in responses on aversive items (e.g., VAS-Jittery, VAS-Uneasy, POMS-Tension, POMS-Confusion) or on urge to smoke. There were also no differences between choosers and nonchoosers on smoking history characteristics (cigarettes/day, Fagerstrom score, etc.), suggesting no difference in degree of nicotine dependence.

STUDY 2

Results of Study 1 indicated a small but significant increase in choice of nicotine per se, in the absence of tobacco, following overnight abstinence in the group as a whole. To our knowledge, there are no comparable data for choice of nicotine vs. nonnicotine cigarette smoking as a function of abstinence using a similar forced-choice procedure and, thus, no adequate context in which to place results from Study 1. Therefore, we conducted a second study designed identically to Study 1, except for the method of nicotine delivery (smoking, instead of nasal spray).

Subjects. Subjects in Study 2 (seven men, six women) were comparable to those in Study 1 and recruited in similar fashion. Subject characteristics were as follows: age—20.5 ± 0.2 years; number of cigarettes/day—19.6 ± 1.1; years smoking—5.1 ± 0.6; nicotine yield of preferred cigarette (mg)—0.84 ± 0.07; Fagerstrom score—4.6 ± 0.5.

Nicotine vs. Nonnicotine Cigarettes. As in Study 1, the nicotine vs. nonnicotine cigarettes were identified as orange and purple, based on the tape wrapped around them. The nicotine cigarette was GPC® brand (1.2 mg nicotine yield), while the nonnicotine cigarette was Honey Rose® herbal brand. GPC brand was used as the nicotine cigarette because of its relatively high nicotine yield (for comparison with nonnicotine) and the infrequency with which it is mentioned as a preferred brand by subjects in our studies; we wanted to provide a nicotine cigarette that would not be recognized as similar in taste, etc., to subjects' preferred brands. Honey Rose was used as the nonnicotine cigarette because of its total lack of nicotine content, its very similar appearance to nicotine cigarettes, and its use in prior research by others as a placebo cigarette (6). Identifying marks on the cigarettes were covered by the colored tape wrapped around each.

Procedure. Subjects participated in two sessions, following overnight smoking abstinence vs. no abstinence, as described previously for Study 1. On the no abstinence day, subjects smoked as they normally do prior to the session. They then smoked one of their preferred brand of cigarettes ad lib upon arrival and after every other choice trial (every 30 min) to minimize tobacco deprivation, as in Study 1. The choice procedure was also similar to that of Study 1, except subjects chose from between nicotine vs. nonnicotine cigarette puffs. During each session, subjects were first exposed to six puffs of each of the two cigarette types (nicotine vs. nonnicotine exposure trials) followed by eight choice trials of six puff selections from between the two cigarettes. Exposure and choice trials occurred once every 15 min under the observation of an experimenter blind to the color assignment of each cigarette.

During each trial, each of the six smoke puffs were consumed within 3 min according to instructions on a computer monitor to standardize the duration of each puff. Subjects were first instructed to light both cigarettes without inhaling and place them in a large ashtray. They then signalled to the experimenter when they had made their choice of which cigarette they preferred for their next puff and followed the computer instructions, which indicated when they should inhale, hold the puff for 3 s, and then exhale. Subjects then made their next choice of cigarette, followed the computer instructions for the next puff, and so on for each of the six puffs. Subjects could wait up to 30 s between puffs. A similar procedure has been employed in several previous studies of controlled smoke exposure (18,23,25).

Results

Choice results for nicotine vs. nonnicotine cigarette puffs are presented in the bottom of Fig. 1, to compare directly with choice results for nicotine vs. placebo spray from Study 1. Similar to results for Study 1, choice of nicotine cigarette puffs was greater on the abstinence vs. no abstinence day [82 vs. 64%, $t(12) = 2.33$, $p < 0.05$]. However, in contrast with Study 1, choice of nicotine cigarettes was significantly greater than 50% (i.e., preferred) in the group as a whole on the abstinence day, $t(12) = 5.49$, $p < 0.001$, but not on the no abstinence day, $t(12) = 1.78$, $p = 0.10$. The range of nicotine cigarette choice between subjects was 27–100% on the abstinence day and 21–96% on the no-abstinence day. On the abstinence day, nearly all subjects (12 of 13, 92% of sample) selected the nicotine cigarette on more than 50% of choices and all but two subjects (11 of 13, 85%) selected the nicotine cigarette on at least 75% of choices, compared with 9 of 13 (69%) and 6 of 13 (46%), respectively, on the no-abstinence day. Also, similar to Study 1, nicotine choice remained stable across trials.

Given the relatively high degree of nicotine cigarette choice and the small sample size from this study, it was not possible to divide subjects into choosers vs. nonchoosers of nicotine cigarettes. Nevertheless, these results provide useful data on the influence of overnight tobacco abstinence on nicotine cigarette choice with which to compare effects of abstinence on nicotine spray choice in Study 1.

GENERAL DISCUSSION

Results of Study 1 indicate that choice of nicotine per se, isolated from tobacco smoke, significantly increases after overnight smoking abstinence vs. no abstinence in smokers not trying to quit. Although most subjects did not display an absolute preference for nicotine spray, this shift in choice was very similar in magnitude to the increase in choice of nicotine cigarette puffs observed in Study 2, suggesting some generalizability in the influence of brief tobacco abstinence on nicotine reinforcement via nasal spray and cigarette smoking. Further supporting this notion is the result of a recent study showing an association between amount of ad lib smoking behavior and amount of ad lib nicotine spray self-administration in smokers (21). Our findings also replicate Herskovic et al. (13), who showed increased preference for nicotine via smoking following abstinence, and extends these results to preference for nicotine per se, in the absence of smoking.

It is possible our results underestimate the effect of abstinence on increasing choice of nicotine via spray or smoking. Subjects in both studies received nicotine during the initial exposure trials of both sessions and, thus, were not as deprived during subsequent choice trials of the abstinence day as they would have been without such exposure. This exposure was necessary to allow subjects to identify each of the two sprays/cigarettes prior to determining their preference during choice trials. Exposure to each on a previous day could have mini-

mized this potential problem. On the other hand, nicotine choice percentages were fairly stable across trials (Fig. 1), suggesting that immediately preceding exposure had little influence on choice.

A subset of subjects appeared to show absolute preference for nicotine spray on the smoking abstinence day. Several positive subjective responses to initial nicotine spray exposure on the abstinence day—increased pleasant, comfortable, relaxed, satisfied, vigor, and arousal—differentiated smokers who subsequently self-administered the nicotine spray more than placebo (choosers) from those who did not (nonchoosers). Because responses to aversive effects and decline in urge to smoke did not differentiate these groups, choosers appeared to select nicotine over placebo for its positive reinforcing effects. This explanation must remain tentative, however, because we did not include a measure of withdrawal; association of withdrawal relief with nicotine choice would support a negative reinforcement explanation. In addition, nonchoosers selected nicotine on significantly less than 50% of choices on both days, indicating aversion. Nevertheless, our findings are remarkably similar to another recent study, of smokers interested in quitting, that identified those more likely to ad lib self-administer nicotine vs. placebo spray in a free choice procedure on the basis of positive subjective responses to initial exposure (alert, pleasant, relaxed, satisfied, vigor, and arousal) and not aversive effects or withdrawal relief (21). Similarity of results between forced choice vs. free choice procedures confirms previous research with other drugs indicating comparability of the methods for determining preference [e.g. (17)].

Despite the behavior of choosers, nicotine spray was not preferred over placebo spray by the group as a whole in Study 1, while nicotine cigarette puffs were preferred over nonnicotine cigarette puffs in Study 2. This finding is perhaps consistent with other evidence that, in addition to nicotine's central effects, sensory effects from nicotine and nonnicotine constituents of smoking may contribute to smoking reinforcement (1,28). Yet, although Studies 1 and 2 were very similar in procedure, it is difficult to directly compare absolute preferences for nicotine between these two studies for a number of reasons. First, despite attempts to control nicotine exposure via smoking, we did not directly compare actual amount of nicotine exposure from one controlled puff with that from one nicotine spray (e.g., by plasma nicotine analyses). Thus, dosing per presentation (spray, puff) may have differed, and actual amount of nicotine exposure could have been similar between spray and smoke deliveries in spite of very different nicotine choice percentage. In this case, selection of nicotine spray at a rate less than 50% could reflect satiation (or avoidance of toxic effects of excessive nicotine) rather than lack of preference for nicotine. However, for this to explain the lower rate of nicotine spray vs. cigarette puff choices, nicotine delivery per spray would have had to be greater than that per puff. This is unlikely because of prior data showing the opposite, that this dose of nicotine spray (1.5 μg/kg/spray) generally delivers less nicotine to the body than the same number of puffs via controlled puffing of a nicotine cigarette similar to that used here (25). In addition, a satiation explanation would predict decreasing nicotine choice across trials (i.e., as satiation increased), but we found stable choice across trials in both studies.

Second, reduced preference for nicotine spray vs. cigarettes may have been due to slower speed of nicotine delivery via spray. Speed of nicotine delivery has been directly related to magnitude of reinforcement from nicotine intake (12,30). This possibility may be strengthened by the observation that nicotine via gum, which is even slower than nasal spray, is aversive (i.e., self-administered significantly less than placebo) in smokers not trying to quit, even when abstinent overnight from smoking (15).

Third, the nonnicotine herbal cigarette used here was not ideal for direct comparison with a commercially available nicotine cigarette. Herbal cigarettes may be noticeably different from nicotine cigarettes in aspects other than nicotine content, such as in taste and smell, which can influence smoking behavior and reinforcement (1,28). Thus, subjects' strong familiarity with tobacco (i.e., nicotine-containing) cigarettes may have fostered their greater choice of nicotine cigarettes, as evidenced by high nicotine cigarette preference even on the no abstinence day, while all were unfamiliar with nicotine via nasal spray. Greater availability of nonnicotine tobacco cigarettes may allow for better determination of nicotine vs. nonnicotine reinforcement via smoking (1).

There are other limitations to Study 1 that may reduce the generalizability of these results. Only single sessions of tobacco abstinence and no abstinence occurred, and reliability of nicotine spray preference under these conditions is not known. It is also possible that even nonchoosers would prefer nicotine over placebo spray if given more extensive access to the nicotine spray. Other research has shown that smokers initially preferring intravenous (IV) saline over nicotine increase their preference for IV nicotine over subsequent sessions (10). In addition, the relatively low rate of nicotine spray selection in this study may be specific to the subjects of this study, who were young, not very dependent, and did not want to quit smoking. Smokers who are older, more dependent, and/or who want to quit may show greater preference for nicotine vs. placebo nasal spray (22). Subjects with histories of other drug abuse, who were screened out of the present studies, may also more readily prefer nicotine spray, as shown previously with IV nicotine vs. saline (10).

The results of these studies also point out difficulties in interpreting findings with the forced choice procedure. Because the procedure requires subjects to select one or the other option, it is often not clear whether an increase in relative preference for drug actually reflects: 1) an increase in the reinforcing value of that drug, 2) a decrease in the aversive effects of the drug, or 3) a decrease in the reinforcing value of the other option (e.g., placebo spray, nonnicotine cigarette). Therefore, for the group of subjects in Study 1 as a whole, it is possible that overnight abstinence decreased the aversiveness of nicotine spray since selection of nicotine spray was significantly less than 50% on the no abstinence day and increased to near 50% on the abstinence day. However, this explanation is not likely when results for choosers and nonchoosers are examined separately. For nicotine choosers, abstinence did appear to increase the reinforcing value of nicotine spray, because preference for nicotine was near 50% on the no abstinence day (49%) but significantly above 50% on the abstinence day (74%). Yet, for nonchoosers, preference for nicotine spray was significantly below 50% on both days (25% and 30%, respectively). Similar to results for choosers in Study 1, overnight abstinence in Study 2 increased the reinforcing value of nicotine cigarette puffs in all subjects, as shown previously using a different procedure (18). Selection of nicotine puffs was not significantly different from 50% on the no-abstinence day but increased significantly on the abstinence day. Therefore, despite potential difficulties in interpreting forced choice results, our findings indicate that tobacco abstinence clearly increases preference for nicotine per

se, isolated from tobacco, in a subset of smokers and increases preference for nicotine cigarette puffs in smokers in general.

Aside from examining the influence of tobacco abstinence on nicotine choice in smokers varying in tobacco dependence and desire to quit, future research should determine whether environmental manipulations may increase or decrease nicotine choice. For example, tobacco smoking desire and behavior have sometimes been shown to increase following acute stress (20,26) as well as in response to psychomotor performance demands (9). Demonstration of increased nicotine choice under these same conditions would be important in understanding whether the increased smoking may be due to greater reinforcement from nicotine per se rather than from nonnicotine stimuli associated with tobacco smoking (1,28). Nicotine self-administration by gum has also been shown to increase or decrease depending on whether smokers trying to quit were informed or kept blind to gum contents (14). Similar manipulations of information about spray contents may also influence nicotine spray choice. Finally, this procedure may have utility in assessing the influence of brief abstinence on preference for other chronically used drugs, such as caffeine (17) and alcohol (3).

In summary, overnight tobacco abstinence was shown to significantly increase choice of nicotine per se, isolated from tobacco smoking, in smokers not trying to quit smoking. The magnitude of this effect of abstinence on nicotine spray choice was similar to its effect on nicotine cigarette choice, suggesting some generalizability between methods of nicotine self-administration. Although smokers in general may not initially prefer nicotine vs. placebo spray, a subset of subjects, who experience greater positive subjective effects from nicotine spray, appear to prefer nicotine spray following overnight abstinence. Future research should examine choice of nicotine vs. placebo in subjects varying in dependence and desire to quit smoking, as well as changes in choice as a function of environmental manipulations known to influence tobacco smoking (e.g., stress) or nicotine intake by other means (e.g., instructions about drug identification).

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REFERENCES

1. Butschky, M. F.; Bailey, D.; Henningfield, J. E.; Pickworth, W. B. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. Pharmacol. Biochem. Behav. 50:91–96; 1995.
2. Chait, L. D.; Burke, K. A. Preference for high- vs. low-potency marijuana. Pharmacol. Biochem. Behav. 49:643–647; 1994.
3. deWit, H.; McCracken, S. G. Ethanol self-administration in males with and without an alcoholic first-degree relative. Alcohol. Clin. Exp. Res. 14:63–70; 1990.
4. Fagerstrom, K.-O.; Schneider, N. G. Measuring nicotine dependence: A review of the Fagerstrom Tolerance Questionnaire. J. Behav. Med. 12:159–182; 1989.
5. Federal Trade Commission. Tar, nicotine, and carbon monoxide of the smoke of 534 varieties of domestic cigarettes. Washington, DC: Federal Trade Commission; 1992.
6. Gilbert, D.; Meliska, C. J.; Williams, C. L.; Jensen, R. A. Subjective correlates of cigarette-smoking-induced elevations of peripheral beta-endorphin and cortisol. Psychopharmacology (Berlin) 106: 275–281; 1992.
7. Griffiths, R. R.; Henningfield, J. E.; Bigelow, G. E. Human cigarette smoking: Manipulation of number of puffs per bout, interbout interval and nicotine dose. J. Pharmacol. Exp. Ther. 220:256–265; 1982.
8. Hatsukami, D. K.; Pickens, R. W.; Svikis, D. S.; Hughes, J. R. Smoking topography and nicotine blood levels. Addict. Behav. 13:91–95; 1988.
9. Heishman, S. J.; Taylor, R. C.; Henningfield, J. E. Nicotine and smoking: A review of effects on human performance. Exp. Clin. Psychopharmacol. 2:345–395; 1994.
10. Henningfield, J. E.; Goldberg, S. R. Control of behavior by intravenous nicotine injections in human subjects. Pharmacol. Biochem. Behav. 19:1021–1026; 1983.
11. Henningfield, J. E.; Goldberg, S. R. Pharmacologic determinants of tobacco self-administration by humans. Pharmacol. Biochem. Behav. 30:221–226; 1988.
12. Henningfield, J. E.; Keenan, R. Nicotine delivery kinetics and abuse liability. J. Consult. Clin. Psychol. 61:743–750; 1993.
13. Herskovic, J. E.; Rose, J. E.; Jarvik, M. E. Cigarette desirability and nicotine preference in smokers. Pharmacol. Biochem. Behav. 24:171–175; 1986.
14. Hughes, J. R.; Pickens, R. W.; Spring, W.; Keenan, R. M. Instructions control whether nicotine will serve as a reinforcer. J. Pharmacol. Exp. Ther. 235:106–112; 1985.
15. Hughes, J. R.; Strickler, G.; King, D.; Higgins, S. T.; Fenwick, J. W.; Gulliver, S. B.; Mireault. G. Smoking history, instructions and the effects of nicotine: Two pilot studies. Pharmacol. Biochem. Behav. 34:149–155; 1989.
16. McNair, D. M.; Loor, M.; Droppelman, L. F. Profile of mood states. San Diego CA: Educational and Testing Service; 1971.
17. Oliveto, A. H.; Hughes, J. R.; Higgins, S. T.; Bickel, W. K.; Pepper, S. L.; Shea, P. J.; Fenwick, J. W. Forced-choice vs. free-choice procedures: Caffeine self-administration in humans. Psychopharmacology (Berlin) 109:85–91; 1992.
18. Perkins, K. A.; Epstein, L. H.; Grobe, J. E.; Fonte, C. Tobacco abstinence, smoking cues, and the reinforcing value of smoking. Pharmacol. Biochem. Behav. 47:107–112; 1994.
19. Perkins, K. A.; Epstein, L. H.; Stiller, R. L.; Jennings, J. R.; Christiansen, C.; McCarthy, T. An aerosol spray alternative to cigarette smoking in the study of the behavioral and physiological effects of nicotine. Behav. Res. Methods Instrum. Comput. 18: 420–426; 1986.
20. Perkins, K. A.; Grobe, J. E. Increased desire to smoke during acute stress. Br. J. Addict. 87:1037–1040; 1992.
21. Perkins, K. A.; Grobe, J. E.; Caggiula, A. R.; Wilson, A.; Stiller, R. L. Acute reinforcing effects of low-dose nicotine nasal spray in humans. Pharmacol. Biochem. Behav. (in press).
22. Perkins, K. A.; Grobe, J. E.; D'Amico, D.; Fonte, C.; Wilson, A.;Stiller, R. L. Low-dose nicotine nasal spray use and effects during initial smoking cessation. Exp. Clin. Psychopharmacol. 4:157–165; 1996.
23. Perkins, K. A.; Grobe, J. E.; Fonte, C.; Breus, M. 'Paradoxical' effects of smoking on subjective stress vs. cardiovascular arousal in males and females. Pharmacol. Biochem. Behav. 42:301–311; 1992.
24. Perkins, K. A.; Grobe, J. E.; Fonte, C.; Goettler, J.; Caggiula, A. R.; Reynolds, W. A.; Stiller, R. L.; Scierka, A.; Jacob, R. Chronic and acute tolerance to subjective, behavioral, and cardiovascular effects of nicotine in humans. J. Pharmacol. Exp. Ther. 270:628–638; 1994.
25. Perkins, K. A.; Sexton, J. E.; Reynolds, W. A.; Grobe, J. E.; Fonte, C.; Stiller, R. L. Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking vs. nasal spray. Pharmacol. Biochem. Behav. 47:295–299; 1994.

26. Rose, J. E.; Ananda, S.; Jarvik, M. E. Cigarette smoking during anxiety-provoking and monotonous tasks. Addict. Behav. 8:353–359; 1983.
27. Rose, J. E.; Jarvik, M. E.; Ananda, S. Nicotine preference increases after cigarette deprivation. Pharmacol. Biochem. Behav. 20: 55–58; 1984.
28. Rose, J. E.; Levin, E. D. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br. J. Addict. 86:605–609; 1991.
29. Stolerman, I. P.; Jarvis, M. J. The scientific case that nicotine is addictive. Psychopharmacology (Berlin) 117:2–10; 1995.
30. Wakasa, Y.; Takada, K.; Yanagita, T. Reinforcing effect as a function of infusion speed in intravenous self-administration of nicotine in rhesus monkeys. Jpn. J. Psychopharmacol. 15:53–59; 1995.
31. West, R. J.; Russell, M. A. H. Cardiovascular and subjective effects of smoking before and after 24 h of abstinence from cigarettes. Psychopharmacology (Berlin) 92:118–121; 1987.
32. Yanagita, T.; Ando, K.; Kato, S.; Takada, K. Psychopharmacological studies on nicotine and tobacco smoking in rhesus monkeys. Psychopharmacol. Bull. 19:409–412; 1983.