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Acute Reinforcing Effects of Low-Dose Nicotine Nasal Spray in Humans

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PERKINS, K. A., J. E. GROBE, A. CAGGIULA, A. S. WILSON AND R. L. STILLER. *Acute reinforcing effects of low-dose nicotine nasal spray in humans.* PHARMACOL BIOCHEM BEHAV **56**(2) 235–241, 1997.—Tobacco smoking behavior is reinforced by nicotine intake, but there has been little human research examining self-administration of nicotine per se, isolated from tobacco. In this study, 10 smokers (5 men, 5 women) who wanted to quit smoking sampled 0 (placebo), 0.75, and 1.5 ug/kg/spray nicotine via nasal spray during separate lab sessions before engaging in a free choice session, involving ad lib access to all three spray doses. Subjects also ad lib smoked during another session. For the group as a whole, neither nicotine spray dose was self-administered significantly more than placebo during the free choice session, suggesting low abuse potential. However, 4 of 10 subjects self-administered 1.5 ug/kg/spray on more than 50% of all sprays (vs. 33% chance) and were designated nicotine "choosers," while the others were "nonchoosers." Choosers responded to initial nicotine spray exposure during sampling sessions with greater positive subjective effects (similar to their responses to tobacco smoking), smoked more during the ad lib smoking session (i.e., self-administered more nicotine via tobacco smoking), and tended to be more heavily dependent smokers. They did not report greater withdrawal relief or less aversive effects from nicotine, suggesting their greater nicotine choice reflected greater positive reinforcement rather than negative reinforcement. These results are consistent with the few existing studies demonstrating that acute nicotine intake per se, in the absence of tobacco, may be reinforcing in some smokers. **Copyright © 1997 Elsevier Science Inc.**

Nicotine Humans Self-administration Reinforcement Tobacco dependence Subjective effects

NICOTINE is the ingredient in tobacco smoke most responsible for reinforcement of smoking behavior (32). The persistence of nicotine self-administration by tobacco smoking among humans is well known (10,29). Animal research and failed marketing efforts by tobacco companies have shown that tobacco smoking behavior is generally not maintained in the absence of nicotine (16,35). By the same token, human and animal studies have demonstrated maintenance of behavior reinforced by intravenous (i.v.) intake of nicotine alone, separate from other constituents of tobacco smoke (2,7,33).

Nevertheless, it is still somewhat unclear to what extent nicotine in isolation is reinforcing to humans. This lack of clarity has been used to support arguments that nicotine reinforces tobacco smoking behavior primarily because of its taste-enhancing or other peripheral sensory characteristics, rather than its psychoactive effects. Although past demonstration of nicotine self-administration by i.v. is consistent with a central, rather than peripheral, site of reinforcing action, only some smokers (especially those with histories of other drug abuse) have been shown to initially self-administer i.v. nicotine more than saline (7). Furthermore, Hughes et al. (13) found that nicotine polacrilex (i.e., via chewing gum) appeared to be aversive in current smokers, as well as in ex-smokers and never smokers, when subjects were kept blind to gum contents. We recently found that smokers increase their choice of nicotine vs. placebo nasal spray following overnight tobacco abstinence (25). However, these subjects engaged in a "forced-choice" procedure requiring them to self-administer a fixed number of sprays from either placebo or nicotine. Thus, it is unclear whether increased nicotine choice was due to an increase in positive reinforcement or a decrease in aversiveness from nicotine spray following tobacco abstinence. Despite recent studies on the clinical efficacy of nicotine nasal spray (30) and inhalers (31), in addition to the large clinical literature

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TABLE 1

SMOKING HISTORY CHARACTERISTICS OF INDIVIDUAL SUBJECTS

Subj. No.	Age	No. Cigarettes/Day	Nicotine Content of Preferred Brand (mg)	No. Yrs Smoker	Fagerstrom Score
Men:					
01	28	24	1.0	8	5
02	31	15	0.8	13	7
03	26	30	0.8	11	9
04	21	20	0.8	8	6
05	30	23	1.2	12	6
Women:					
51	40	20	1.1	28	6
52	39	20	0.7	25	5
53	35	40	0.8	21	9
54	36	20	0.9	21	6
55	20	22	0.8	8	6

on nicotine gum and patch (e.g., 28), we are aware of virtually no other controlled studies specifically examining whether nicotine per se is self-administered in humans.

The present study investigated whether tobacco smokers without histories of other drug abuse would self-administer low-dose nicotine delivered by nasal spray. To reduce difficulties in interpreting results from the forced choice procedure, we employed an ad lib, "free choice" procedure similar to previous research with i.v. nicotine and nicotine gum, noted above. The nasal spray method administers nicotine in relatively rapid fashion (i.e., a few minutes to peak plasma nicotine concentration), much closer to that due to i.v. infusion than to gum or patch but still slower than tobacco smoking (22). The speed of a method's delivery of nicotine to the brain is important for studies of reinforcement since this speed is directly related to magnitude of reinforcing effects; methods delivering nicotine slowly to the brain, such as gum or transdermal patch, produce few positively reinforcing effects, while those delivering nicotine rapidly, such as inhalation (smoking) or i.v. infusion, are much more reinforcing (8). Wakasa et al. (33) recently demonstrated very clearly that speed of nicotine delivery is critical in determining whether i.v. nicotine will be self-administered in monkeys. Nasal spray delivery also precludes the possibility of reinforcement of use due to oral sensory or taste characteristics of nicotine (27).

METHODS

Subjects

Subjects were 10 tobacco smokers (5 male and 5 female). Eligible subjects were those expressing a desire to quit smoking within the next month and reporting a history of smoking at least 15 cigs/day for at least 5 yr. 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). Mean (range) characteristics for all 10 subjects were as follows: age — 30.6 yrs (20–40); smoking rate — 23.4 cigs/day (15–40); years smoking — 15.5 yrs (8–28); Fagerstrom Tolerance Questionnaire (4) score — 6.5 (5–9). The mean Fagerstrom score of 6.5 is comparable to that of smokers wanting to quit smoking (e.g., 17) and is higher than that typically seen in smokers not wanting to quit (4). Subjects are described individually in Table 1.

Nicotine/Placebo Dosing

Nicotine in doses of 0.75 ("very low") or 1.5 ug/kg/spray ("low"), along with placebo, was provided by a nasal spray delivery procedure developed in our lab (22). (This nasal spray delivery procedure is not the same as that examined in clinical trials by others (e.g., 30) but was developed by us for research purposes.) This procedure has been found to produce reliable, dose-dependent increases in plasma nicotine, and has the advantage of allowing adjustment of doses to correct for subject body weight (21–26). These small doses per spray were designed to reflect the amount of nicotine typically obtained from individual puffs on cigarettes. 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 (21–26).

Subjective Measures

Subjective measures were obtained to assess effects of nicotine vs. placebo sprays during initial sampling and to identify effects that may predict subsequent nicotine self-administration. These measures included: 1) visual analog scale (VAS) items of "Stimulated," "Head Rush," "Jittery," "Relaxed," "Pleasant," "Uneasy," "Alert," "Urge to Smoke," and "Liking of spray" (each ranging from 0 = not at all, 100 = very much); 2) Profile of Mood States (POMS; 18) scales of Tension (range = 0–32), Confusion (0–28), Vigor (0–32), and Fatigue (0–28), and the composite scale of Arousal (3), determined by subtracting Confusion and Fatigue from Tension plus Vigor (range= −56 to 64), and 3) tobacco withdrawal symptoms, adapted from Hughes et al. (11) and containing the following symptoms: irritable, anxious, difficulty concentrating, restless, impatient, hungry, depressed, and total withdrawal (average of all symptoms), each on a 0 (not at all) to 100 (extremely) scale. The VAS items and POMS have been used extensively in studies of the acute effects of smoking or nicotine, as well as other drugs (e.g., 6,21,25).

Procedure

Subjects were among those inquiring about participation in research studies on effects of nicotine or smoking for pay-

ment and who expressed a desire to quit smoking within the coming month. This study was specifically described not as a smoking cessation study, but a study evaluating effects of nicotine sprays. Thus, these subjects did not contact the lab in order to seek treatment. However, as a benefit of participation, subjects were told they would be given counseling assistance for quitting smoking. Subjects were told that they would be given nasal sprays to freely use during lab sessions, and that at least one of them may contain nicotine. After the end of the study, subjects received payment for their participation and were provided with two 30-min individual counseling sessions to assist them in quitting smoking.

Subjects participated individually in five 4-hr afternoon sessions, each after 12-hr abstinence from smoking, which was confirmed by expired-air carbon monoxide < 13 ppm via Ecolyzer CO analyzer (Energetic Science, Hawthorne NY). Sessions took place in a small lab room equipped with a video camera for subject observation, along with television, radio, and magazines. Subjects were told that each session was designed to simulate a quiet afternoon in their own homes and that they could use any of the objects in the room to entertain themselves. Subjects remained seated in a comfortable armchair throughout each session.

Three of the first four sessions involved ad lib sampling of 0, 0.75, or 1.5 ug/kg/spray nicotine sprays ("sampling" sessions), with only one of the three sprays available per session. The remaining session of the first four involved ad lib tobacco smoking ("ad lib smoking" session) for comparison of nicotine intake with the spray sampling sessions. The order of these four conditions (three spray doses, one ad lib smoking) across sessions was counter-balanced between subjects. These three spray sampling sessions and one ad lib smoking session were followed by a fifth and final session involving free ad lib use of all three sprays ("free choice" session).

In each of the spray *sampling* sessions, subjects initially self-administered six sprays of the dose assigned for that session over a 3-min period, to introduce them to the effects of that dose and to ensure that they knew how to properly self-administer the nasal spray. Each spray bottle was distinguished by the color of tape wrapped around it (orange, white, purple), and assignment of colors to doses was counter-balanced between subjects. Then, subjects were instructed to self-administer as much of the spray as they wished over the subsequent 3 h. In the *ad lib smoking* session, subjects were instructed to simply smoke their preferred cigarettes as they wished for 3 h.

In the last, *free choice* session, subjects were initially exposed to six sprays of each of the three spray doses (containing the same color of tape as during sampling) to re-acquaint them with the effects of each dose. These three exposures were presented in random order, each over a 3-min period with 15 mins between exposures. Subjects were then instructed to self-administer as much of any of the three sprays as they wished over the subsequent 3 h.

Subjective measures were obtained at baseline (prior to initial spray exposure) and every 45 mins during the course of the 3-h self-administration period of each session. Spray self-administration and ad lib smoking were assessed by behavioral observation from videotapes of the session. Observers counted the number of times a subject used each of the sprays or puffed on a cigarette during each session. Observers were not present during the actual sessions they observed on tape. Most of the sessions (88%), randomly determined, were rated by two different raters to determine inter-rater reliability. Results showed virtually identical observations between raters ($r = 0.996$).

Finally, a blood sample was obtained at the end of each session to gauge nicotine exposure. The sample was collected into an EDTA tube, spun down to separate plasma, and stored at -60o C for later analysis. Plasma nicotine concentration was determined in the laboratory of Drs. Neal Benowitz and Peyton Jacob III by gas chromatography with nitrogen-phosphorus detection using 5-methylnicotine as the internal standard (15). Only one sample was obtained because multiple samples would have required an obtrusive indwelling catheter, and we have previously observed good reliability in plasma nicotine boosts with this spray method (22,24,26).

Data Analyses

Initial analyses compared amount of spray use and subjective responses across the three sampling sessions (0, 0.75, and 1.5 ug/kg/spray) using within-subjects analyses of variance (ANOVA). Amount of self-administration of each of the three sprays (very low and low dose vs. placebo) during the free choice session was the primary dependent measure. Amount of spray use during the free choice session was initially analyzed using a within-subjects ANOVA, with dose (3 levels) as the factor. We then identified "choosers" of the low nicotine dose (1.5 ug/kg/spray) by selecting those who self-administered that dose more than 50% of the time on the free choice day (33% would be random self-administration). (Selection of the 0.75 ug/kg dose was low by all but one subject and thus was not used to identify "choosers.") Subjective responses to the very low and low doses vs. placebo during the respective sampling sessions were compared between these "choosers" and the remaining subjects, who were considered "nonchoosers," using mixed between-subjects (chooser/nonchooser) and within-subjects (dose) ANOVAs. Differences between these subgroups in responses to particular doses were determined by Fisher's least significant difference *t*-test (14). Differences between choosers and nonchoosers on smoking history and ad lib smoking during the smoking session were determined by *t*-tests. Finally, subjective responses during the ad lib smoking session were presented in figures for comparison with responses to nasal sprays but were not included in analyses because of the lack of any comparable "placebo" smoking condition. Data are presented as mean ± SEM.

RESULTS

Sampling Sessions

During the respective sampling sessions, subjects self-administered a mean ± SEM of 47.6 ± 8.8, 34.7 ± 9.6, and 31.0 ± 9.1 sprays of placebo, very low (0.75 ug/kg/spray), and low (1.5 ug/kg/spray) dose nicotine spray, respectively, $F(2, 16) = 4.22$, $p < .05$. Sampling of placebo spray exceeded that of very low or low nicotine spray ($p < .05$ for both vs. placebo). End-of-session plasma nicotine levels reflected the different doses self-administered: placebo — 1.0 ± 0.02, very low dose — 5.5 ± 1.3, and low dose — 8.3 ± 1.9 ng/ml. For comparison, these subjects self-administered 49.4 ± 5.3 cigarette puffs from 5.2 ± 0.4 cigarettes during the ad lib smoking session, which resulted in substantially higher mean plasma nicotine, 21.7 ± 2.9 ng/ml.

Free Choice Session

In the free choice session, subjects self-administered a total of 33.1 ± 6.4 sprays. Of these, 12.9 ± 4.6 sprays (39% of total) were placebo, 6.3 ± 2.5 sprays (19%) were very low dose (0.75

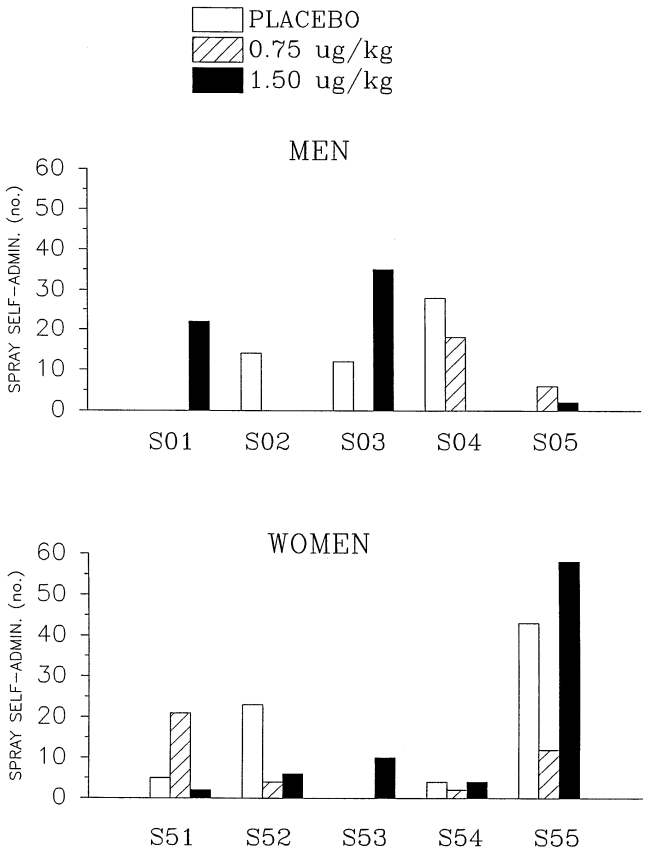

FIG. 1. Number of ad lib uses of 0 (placebo), 0.75 (very low), and 1.5 (low) ug/kg/spray nicotine nasal sprays on the free choice day for each individual subject.

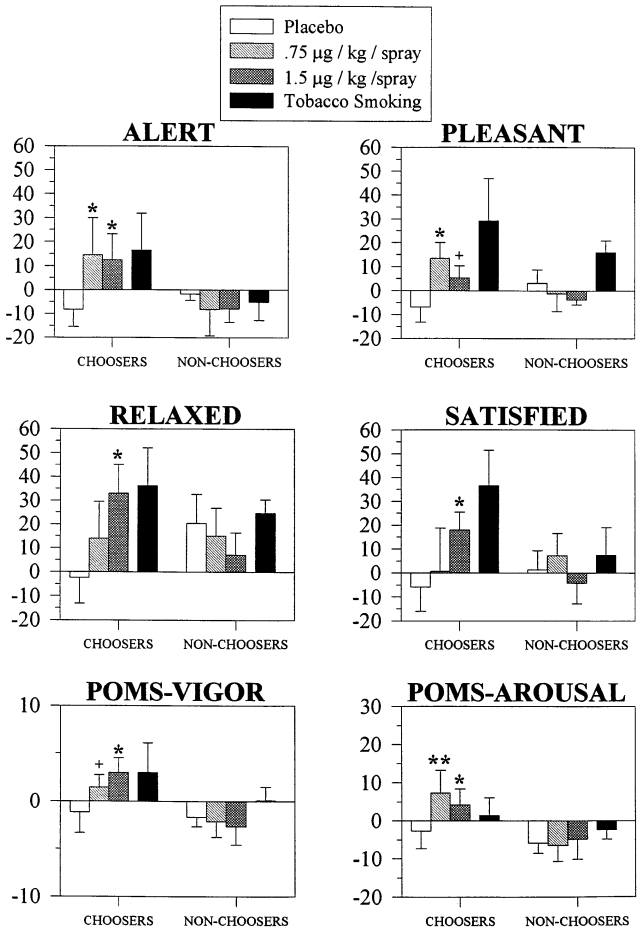

FIG. 2. Mean ± SEM changes in subjective measures from initial baseline following ad lib use of 0 (placebo), 0.75, and 1.5 ug/kg/spray nicotine nasal sprays during the respective spray sampling sessions, for choosers ($n = 4$) and non-choosers ($n = 6$). $^{**}p < .01$; $^{*}p < .05$; $^{\pm}p < .10$ for difference from placebo. Subjective changes due to tobacco smoking during the ad lib smoking session are provided for comparison only.

ug/kg/spray), and 13.9 ± 6.1 sprays (42%) were low dose nicotine (1.5 ug/kg/spray), $F(2, 16) = 4.13$, $p < .05$, with the very low dose administered significantly less than placebo or low dose. However, there was wide variability across subjects in spray self-administration during the free choice session, as shown in Fig.1, with some subjects showing clear preference for low nicotine spray, and others not.

Nicotine Choosers vs. Nonchoosers

Four subjects met the criterion of greater than 50% low dose nicotine self-administration during the free choice session and were identified as nicotine "choosers" (Ss #1,3,53,55). The other six were designated "nonchoosers." Self-administration rates of placebo, very low, and low dose nicotine during the free choice session were 13.8 ± 10.2, 3.0 ± 3.0, and 31.3 ± 10.3 sprays, respectively for choosers vs. 12.3 ± 4.6, 8.5 ± 3.6, and 2.3 ± 1.0 sprays, respectively, for nonchoosers. End-of-session plasma nicotine levels on the free choice day reflected this differential self-administration of nicotine spray (7.9 ± 2.2 vs. 3.3 ± 0.9 ng/ml for choosers vs. nonchoosers, respectively; $t = 2.30$, $p = .05$).

Choosers and nonchoosers were compared on subjective responses to nicotine vs. placebo sprays during the respective sampling sessions of each to determine whether any of these responses to initial exposure may differentiate the groups and thus predict subsequent nicotine self-administration during the free choice session. Despite the small samples of each, choosers were found to have significantly greater increases than non-choosers on most of the positive effects of nicotine vs. placebo: VAS items of alert, pleasant, relaxed, and satisfied; and POMS scales of vigor and arousal. These group differences are shown in Fig. 2. Interestingly, choosers appeared to have similar responses to tobacco smoking during the ad lib smoking session (also shown in Fig. 2 for comparison) as to the low nicotine dose. However, there were no differences between groups in effects of nicotine on "liking" and "urge to smoke." There were also no differences in effects of nicotine on attenuating total withdrawal or individual withdrawal symptoms, except perhaps for "difficulty concentrating" (see Fig. 3). Importantly, choosers and non-choosers also did not differ on aversive effects of nicotine (e.g., increases in VAS-jittery, POMS-Tension; data not shown), indicating that it was greater positive responses to nicotine in choosers — and not greater aversive responses to nicotine in non-choosers — which differentiated the groups. There were no differences between groups in baseline levels of subjective and withdrawal mea-

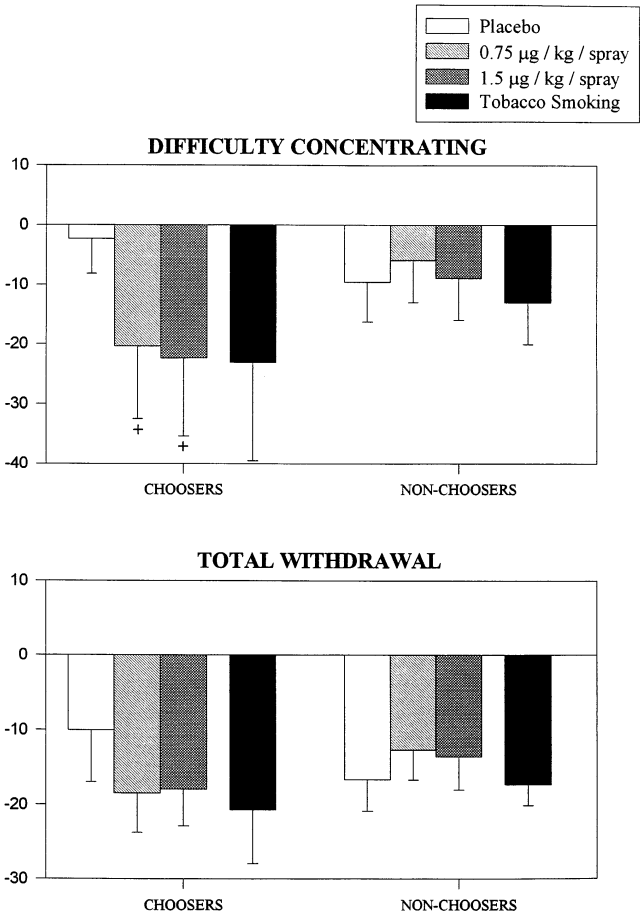

FIG. 3. Mean ± SEM changes in the withdrawal symptom of "difficulty concentrating" and in total withdrawal from initial baseline following ad lib use of 0 (placebo), 0.75, and 1.5 ug/kg/spray nicotine nasal sprays during the respective spray sampling sessions, for choosers (n = 4) and non-choosers (n = 6). $\pm p < .10$ for difference from placebo. Changes in withdrawal due to tobacco smoking during the ad lib smoking session are provided for comparison only.

sures, so differential responding to nicotine was not confounded by any possible baseline differences. This differential responding to nicotine between groups could also not be explained by lack of adequate initial exposure to nicotine doses in non-choosers during the sampling sessions. Although choosers self-administered more low nicotine, very low nicotine, and placebo sprays (means of 41.3, 46.0, and 59.3, respectively) during the respective sampling sessions than did non-choosers (24.2, 27.2, and 39.8, respectively), non-choosers still obtained substantial exposure to nicotine that should have allowed for positive effects to occur if they existed for these subjects. (These sprays were in addition to the six sprays subjects were instructed to self-administer at the beginning of each sampling session.)

Other comparisons indicated that nicotine spray choosers were more highly nicotine dependent than nonchoosers. Compared with nonchoosers, choosers typically smoked more per day (29.0 ± 4.0 vs. 19.7 ± 1.1 cigarettes/day; $t = 2.70$, $p < .03$) and had a slightly higher Fagerstrom nicotine dependence score (7.3 ± 1.0 vs. 6.0 ± 0.3; $t = 1.43$, n.s.). In addition, choosers tended to self-administer more cigarette puffs (60.8 ± 6.1 vs. 41.8 ± 6.3 puffs; $t = 2.06$, $p < .08$) from more cigarettes (6.0 ± 0.4 vs. 4.7 ± 0.5; $t = 1.91$, $p < .10$) during the ad lib smoking session, resulting in significantly higher end-of-session plasma nicotine levels (29.2 ± 3.6 vs. 16.6 ± 2.8 ng/ml; $t = 2.78$, $p < .03$). These observations suggest generalizability in the strength of nicotine self-administration across different methods and routes of administration (i.e., those self-administering nicotine spray to a greater extent also self-administered more nicotine via tobacco smoke).

DISCUSSION

Results of this study indicate that reinforcement from nicotine per se, in the absence of tobacco and in the novel form of a nasal spray, is variable between tobacco smokers. Although the low nicotine dose (1.5 ug/kg/spray) was self-administered more than the very low dose or placebo during the free choice session, there was no significant difference between this dose and placebo (42% vs. 39% of all sprays, respectively). Thus, for the group of smokers as a whole, low dose nicotine nasal spray could not clearly be demonstrated in this acute lab study to be reinforcing, as defined by self-administration to a significantly greater extent than vehicle (34).

However, nicotine by nasal spray did appear to be reinforcing in a subset of subjects, those 4 out of 10 identified as nicotine "choosers." Notably, compared with nonchoosers, choosers tended to be more highly nicotine dependent, to self-administer nicotine via tobacco smoking more on the ad lib smoking day, and to respond to the low nicotine dose with more positive subjective effects during initial sampling (similar to their responses to smoking on the ad lib smoking day). Yet, there were no differences between choosers and nonchoosers in effects of nicotine on attenuating withdrawal symptoms (except perhaps for difficulty concentrating), suggesting that their greater nicotine self-administration reflected greater positive reinforcement from nicotine and not greater negative reinforcement (i.e., withdrawal relief). Furthermore, it is unlikely that nonchoosers avoided nicotine because of its possible aversive effects, since there were no differences between choosers and nonchoosers in effects of nicotine on aversive subjective measures. Moreover, compared with choosers, nonchoosers did not report significantly different subjective responses to placebo and did not self-administer placebo at a greater rate during the free choice session. Therefore, nicotine nonchoosers cannot be alternatively described as "placebo choosers."

These results are remarkably consistent with a previous study of nicotine nasal spray self-administration in smokers not interested in quitting (25). In that study, we found that those who were subsequently choosers of nasal spray nicotine (n = 9 out of 24) in a forced choice (rather than ad lib free choice) procedure also reported greater positive effects during initial exposure and no difference in aversive effects, compared with nonchoosers. This consistency of results between studies extend to the specific scales differentiating choosers and nonchoosers: VAS items of Pleasant, Relaxed, and Satisfied, and POMS scales of Vigor and Arousal. (VAS Alert also differentiated subgroups in the current study, while VAS Comfortable differentiated subgroups in the forced choice study.) Therefore, despite differences in procedures assessing reinforcement (free choice vs. forced choice) and in the samples examined (those wanting to quit vs. those not wanting to quit), these two studies found that virtually identical positive (and not aversive) subjective responses to initial exposure predict subsequent nicotine spray self-administration.

Clear evidence of reinforcement from nicotine per se in a subset of smokers is comparable to findings from studies of other methods of nicotine administration. As noted previously, Henningfield and Goldberg (7) found that only some smokers would reliably respond for i.v. nicotine vs. saline upon initial exposure in the lab. Other research suggests variability in nicotine reinforcement by gum, with some subjects demonstrating clear preference for nicotine vs. placebo gum and others demonstrating clear preference for placebo over nicotine (12). Thus, our results do not appear to be specific to nicotine self-administration by nasal spray, suggesting generalizability across methods and routes of administration. This generalization may even extend to nicotine intake by tobacco smoke inhalation, as evidenced by the greater ad lib smoking behavior in nicotine nasal spray choosers vs. nonchoosers and the similarity in subjective responses to low dose nicotine vs. smoking in the choosers. Our results also go beyond the few previous studies to identify characteristics (greater nicotine dependence) and responses to initial nicotine spray exposure (greater positive subjective effects) that are predictive of subsequent nicotine self-administration. Similar variability in self-administration across subjects and comparable associations between subjective effects and self-administration have also been observed for other drugs (e.g., methylphenidate; 1).

On the other hand, there are several aspects of the current study that may limit these conclusions. First, our sample size of 10 smokers was small, reducing our power to identify reliable differences in self-administration between doses and factors predictive of nicotine self-administration. However, the overall difference in low nicotine vs. placebo self-administration during the free choice session was so small (42% vs. 39%) that a substantially greater sample size may still not have revealed a statistically significant difference between the two sprays. In addition, our sample size was sufficient for conventional statistical analyses to reveal significant differences in responses to nicotine between subsequent choosers and nonchoosers of nicotine. Furthermore, the number of smokers in our sample was comparable to that in Henningfield and Goldberg (7) and in Hughes et al. (12), both of which also identified individual variability in robustness of nicotine self-administration by i.v. and gum, respectively. Nevertheless, repeat testing of nicotine vs. placebo self-administration would have enabled us to determine the reliablity of our differentiation of subjects into choosers vs. nonchoosers of nicotine.

Second, it is possible that even nonchoosers may have exhibited greater self-administration of nicotine vs. placebo spray if given more extended access to them. Notably, Henningfield and Goldberg (7) found that smokers who did not initially self-administer i.v. nicotine gradually increased their rate of nicotine-reinforced responding over seven sessions. Thus, rather than nonchoosers being incapable of experiencing reinforcement from nasal spray nicotine, they may simply require a longer period of access in order to acquire nicotine spray self-administration. Similar individual differences in rate of acquisition of tobacco smoke self-administration among teens may also exist (19).

Third, greater positive responses of choosers to initial low dose exposure during sampling may have been due to their greater ad lib self-dosing in that session, rather than to any stable individual differences in subjective effects of nicotine. However, the close similarity in results between the current study, involving ad lib initial exposure, and our previous study (25), involving fixed initial exposure, reduces the likelihood of this alternative explanation. This similarity of results between studies also argues against the notion that choosers in the current study self-administered sprays to a greater degree only to obtain greater sensory stimulation (e.g., 27) and not for nicotine per se. If sensory stimulation, rather than nicotine, had been the source of reinforcement, there should have been no difference between subgroups in subjective effects following fixed initial exposure in our forced choice study (25) and no specificity of choosers' spray selection during the free choice session of the current study.

Finally, another potential limitation was the low doses employed (0.75 and 1.5 ug/kg/spray). It is conceivable that these doses were too small to provide substantial reinforcing effects over and above placebo in all subjects (e.g., unable to be discriminated from placebo). However, this explanation would predict comparable rates of self-administration between placebo vs. very low-dose nicotine spray, while we observed that very-low dose nicotine was self-administered significantly less than placebo (and less than low dose nicotine). These doses were designed to simulate amount of nicotine per cigarette puff (20), to give subjects better control over the amount and pattern of nicotine self-administration, as is possible with cigarette smoking. Nevertheless, studies employing larger doses per spray, such as the 0.5 mg/spray (approx. 10 and 5 times greater than our very low and low dose, respectively) in Sutherland et al. (30), may reveal more robust acute self-administration of nasal spray nicotine in smokers under the lab conditions employed in this study.

Further research should examine other factors that may be related to self-administration of nicotine per se, including factors that can be easily manipulable, such as information to subjects regarding spray contents. Such information has been shown to greatly influence rate of nicotine gum self-administration (12, 13). It would also be important to examine other environmental influences on nicotine spray self-administration, such as psychological stress or concurrent drug use, to clarify whether factors associated with increased tobacco smoking also increase reinforcement from nicotine per se (32).

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