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Comparison of Acute Subjective and Heart Rate Effects of Nicotine Intake via Tobacco Smoking Versus Nasal Spray

KENNETH A. PERKINS,*[1] JOAN E. SEXTON,* WILLIAM A. REYNOLDS, * JAMES E. GROBE,* CAROLYN FONTE* AND RICHARD L. STILLER†

*Western Psychiatric Institute & Clinic and †Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

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PERKINS, K. A., J. E. SEXTON, W. A. REYNOLDS, J. E. GROBE, C. FONTE AND R. L. STILLER. *Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking versus nasal spray.* PHARMACOL BIOCHEM BEHAV 47(2) 295–299, 1994.—Nicotine is the primary psychoactive constituent of tobacco smoke, but it is not clear whether the reinforcing effects of cigarette smoking can be attributed solely to nicotine intake. In this study, two groups of male and female smokers participated in three sessions involving intermittent exposure to moderate, low, or no nicotine doses via controlled tobacco smoking ("smoke," n = 20) or measured-dose nasal spray ("spray," n = 16). Visual analog scales of subjective effects (VAS) and heart rate (HR) were obtained within 5 min of each dosing. Plasma nicotine levels indicated comparable dosing between methods. For both methods, there were significant nicotine dose effects for most subjective measures and HR. More importantly, the pattern of effects across doses was virtually identical between methods, as nicotine intake via smoking or spray significantly increased HR and the VAS scales of Head Rush and Dizzy, decreased Hunger and Desire to Smoke, and had no effect on Comfortable, Jittery, or Relaxed. These results suggest that rapid nicotine uptake by novel methods may provide effects very similar to nicotine intake by smoking.

Nicotine Smoking Nasal spray Subjective effects Heart rate

NICOTINE is the primary psychoactive constituent of tobacco smoke (15). However, it is unclear whether the reinforcing effects of smoking are due solely to intake of nicotine per se. It may be that some of the 3800 other compounds in tobacco smoke (9) have significant psychoactive effects. Previous research has found that non-nicotine sensory stimuli of smoke may provide some reinforcement and reduce desire to smoke (14). These stimuli may have effects which are isodirectional to the effects of nicotine or are opposite of those of nicotine, altering the observed magnitude of responding to nicotine via smoking. Alternatively, or in addition, stimuli associated with smoking, such as the sight and smell of smoke, may come to act as conditioned stimuli for nicotine intake (14), fostering development of tolerance (reduced responding) to effects of nicotine via smoking (i.e., conditioned tolerance).

To our knowledge, very little research has directly compared the effects of nicotine administered by different methods or routes of administration. Henningfield et al. (6) found dose-dependent relationships between subjective effects and nicotine intake by either IV infusion or by smoking in male smokers with histories of drug abuse. Although effects were not directly compared between methods, the patterns of dose effects were generally similar. However, some responses, such as self-reported and observed "drug effects" and on a scale related to euphoria (MBG scale of Addiction Research Center Inventory), appeared to be greater at equivalent doses of IV versus smoked nicotine, while "desire to smoke" appeared to be suppressed more at low doses of smoked versus IV nicotine. These results suggest that novel forms of nicotine may produce greater responses on some measures, possibly because of the absence of conditioned stimuli (smoke) for nicotine, while other effects (desire to smoke) may be influenced more by these stimuli than by nicotine per se. Similarly, although we also found increases in subjective arousal following either tobacco smoking or nicotine nasal spray in male and female smokers, the increase appeared to be somewhat larger following the spray despite comparable increases in heart rate [i.e., similar apparent dosing (11)]. One problem with both of these studies is the absence of information on plasma nicotine concentrations to verify comparability of dosing between smoking and either comparison method (i.e., IV or spray).

The present investigation examined the subjective and

[1] Requests for reprints should be addressed to Kenneth A. Perkins, Western Psychiatric Institute & Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213.

heart rate effects of several nicotine doses presented by controlled tobacco smoking or by measured-dose nasal spray. Plasma samples were obtained to confirm comparability of dosing with each method.

METHODS

Subjects

Subjects were two separate groups of male and female smokers, one which was exposed to controlled tobacco smoking ("smoke," n = 20, 10 male and 10 female) and another which was exposed to nasal spray nicotine ("spray," n = 16, 8 male and 8 female). Eligible for the study were smokers who smoked at least 15 cigarettes per day for at least one year and who denied use of other forms of tobacco. There were no differences between groups in age (21.4 ± 0.6 vs. 21.1 ± 0.6 yrs for smoke vs. spray, respectively) and body weight (65.6 ± 2.1 vs. 66.6 ± 3.0 kg), but compared with spray subjects, smoke subjects smoked slightly fewer cigarettes per day (18.7 ± 0.8 vs. 21.4 ± 1.1), $F(1, 32) = 4.17$, $p < .05$, and had lower Fagerstrom (1) Tolerance Questionnaire scores (5.8 ± 0.4 vs. 6.9 ± 0.4), $F(1, 32) = 4.80$, $p < .05$. Except for body weight, there were no differences due to gender. All denied any serious current health problems or medication use, and all denied any history of substance abuse or psychiatric difficulties.

Subjective Measures

Subjective responses to nicotine were assessed by 100-mm visual analog scales (VAS; 0 = *not at all* and 100 = *extremely*) of "Head Rush," "Jittery," "Dizzy," "Comfortable," "Relaxed," "Hunger," and "Desire to Smoke." These were developed based on previous research on the subjective effects of nicotine (15). Scales such as these have been widely used in studies of the subjective effects of nicotine [e.g. (12)] as well as other drugs (2).

Heart Rate

Silver/silver chloride electrodes were attached to each subject for heart rate (HR) measurement. HR (in bpm) was determined by counting R-waves over a 2-min period from the EKG trace displayed on a Grass Model 7P polygraph.

Controlled Nicotine Exposure via Smoking ("Smoke" Group)

Smoke subjects received controlled exposure to their usual cigarette (mean = 0.76 ± 0.03 mg nicotine yield, range = 0.7–1.1 mg), a very low-nicotine-yield cigarette (Carlton Ultra Lights = 0.1 mg nicotine), or an unlit cigarette (sham). The brand name on each cigarette was obscured by adhesive tape. A similar procedure of computerized instructions for controlling smoking/sham-smoking exposure was described in a previous study (12). Briefly, this procedure involves instructing subjects by a video monitor to puff on cue using the cigarette designated for that day (lit for usual or very low nicotine, unlit for sham) once every 20 s for ~2.5 min (total of eight puffs) per exposure. It is designed to manipulate nicotine exposure between conditions but also standardize exposure across subjects within conditions.

Nicotine Dosing ("Spray" Group)

Nicotine (10 or 20 μg per kg of subject's body weight) and placebo (0 μg) were administered to spray subjects by measured-dose nasal spray pump, a method developed in our lab and used in numerous studies. Each dose presentation consisted of 1.14 ml of 0.9% sodium chloride solution together with the designated amount of L-nicotine and peppermint flavoring oil (Lorann Oils, Lansing, MI), which was used to mask the taste and smell of nicotine. This method has been shown to produce nearly linear, dose-dependent increases in plasma nicotine and has been described previously in more detail (10,13).

Procedure

Subjects in both groups (smoke or spray) participated in three sessions on three separate days, one for each nicotine dose (moderate dose = usual cigarette or 20 μg/kg spray, low dose = very low nicotine cigarette or 10 μg/kg spray; no nicotine = sham-smoking or placebo spray), with the order of doses counterbalanced between subjects within each group. On each day, subjects came to the lab following overnight abstinence from smoking, caffeine, and food. Smoking abstinence was verified by expired-air CO less than 13 ppm. At the end of a 30-min period of quiet rest, baseline HR and subjective measures were obtained. Following this initial, predose baseline assessment, nicotine doses were presented by controlled tobacco smoking (smoke group) or nasal spray (spray), as described above, once every 30 min for 2 h. HR and subjective measures were assessed during the 5 min following each presentation, beginning 1 min postdosing. During the interval between assessments and the subsequent dose presentation, subjects remained seated and watched travel and nature videotapes to maintain their attention.

To assess comparability of nicotine dosing between methods, a blood sample was collected into an EDTA tube approximately 10 min after the last dosing (i.e., after completion of measures). Samples were obtained from all smoke subjects and a randomly selected subsample of six spray subjects. We have previously found very good reliability of dosing with the spray method, with minimal interindividual variability (10). Thus, results from a subsample were assumed to provide an accurate measure of mean plasma nicotine for the spray group as a whole, as in previous studies [e.g. (10)]. The reliability of the controlled smoking procedure is less clear, and therefore samples were obtained from all smoke subjects. Plasma nicotine concentration was determined in the laboratory of Drs. Neal Benowitz and Peyton Jacob III at San Francisco General Hospital by gas chromatography with nitrogen-phosphorus detection using 5-methylnicotine as the internal standard (8).

Data Analysis

The initial, predose baseline values for each measure were first compared between groups using analysis of variance (ANOVA). Responses to the methods themselves, in the absence of nicotine intake (i.e., no nicotine condition in each group), were then directly compared by ANOVA of change from baseline to the mean of postsham (smoke group) or postplacebo spray (spray group) presentations. Method (smoke vs. spray) and subject gender were the between-subjects factors. Subjective and HR effects due to nicotine intake were then analyzed for each method separately using similar ANOVAs of change from initial, predose baseline to the mean of postdose (no nicotine, low, moderate) responses. For each ANOVA, the within-subjects factor was dose (no, low, moderate) and the between-subjects factor was subject gender. Follow-up comparisons were performed with Fisher's least significant difference t test (7). Comparability of meth-

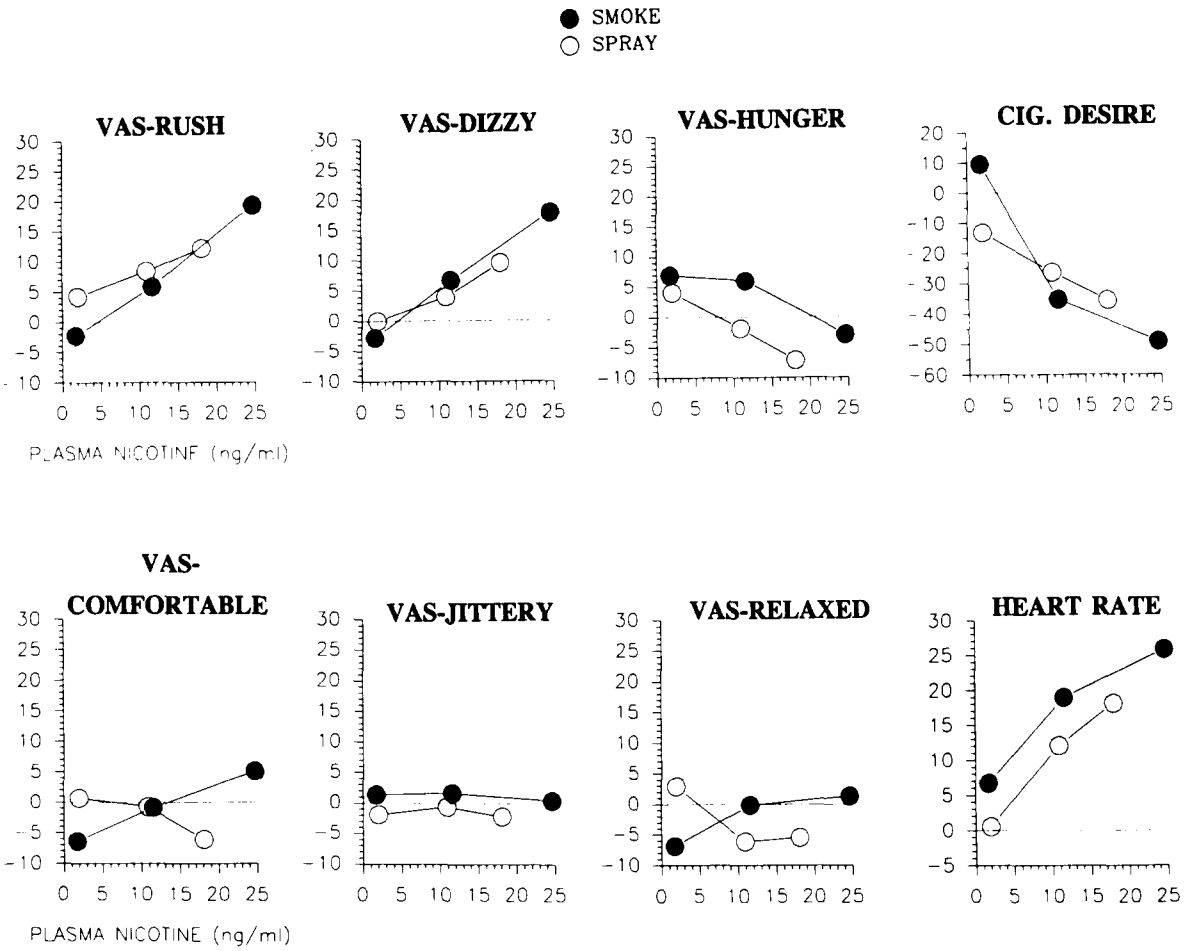

FIG. 1. Mean change from baseline in subjective and heart rate measures due to no, low, or moderate levels of nicotine intake via controlled tobacco smoking ("smoke"; sham, very low yield, or usual cigarette) versus nasal spray ("spray"; 0, 10, or 20 μg/kg nicotine).

ods was determined by similarity of ANOVA results, as in Henningfield et al. (6), and by graphic presentation of responses by plasma nicotine concentration. [Effects of nicotine intake via the different methods were determined by separate, parallel analyses, as in Henningfield et al. (6), rather than in a single direct analysis controlling for plasma nicotine levels, because of the uncertain validity of some of the assumptions required of such an analysis. Specifically, equivalent regression slopes between methods could not be assumed, and analyses of responses to the no-nicotine condition of each method suggested an intercept of zero could also not be assumed for all measures across methods (see Results)].

RESULTS

Comparability of Nicotine Dosing via Smoking Versus Spray

Plasma nicotine analyses confirmed roughly comparable nicotine dosing via smoking versus nasal spray, although the "moderate" dose produced greater plasma nicotine in smoke versus spray. Usual cigarette, very low cigarette, and sham exposures resulted in mean ± SE plasma nicotine concentrations of 24.7 ± 1.9, 11.6 ± 1.2, and 1.7 ± 0.4 ng/ml, respectively, while 20, 10, and 0 μg/kg nicotine by nasal spray resulted in concentrations of 18.1 ± 2.9, 10.9 ± 0.8, and 2.0 ± 0.2 ng/ml, respectively.

Subjective Responses

There were no significant differences between groups in baseline measures, except that smoke subjects had higher baseline Hunger scores than spray subjects (69.8 ± 4.9 vs. 51.5 ± 6.9) $F(1, 32) = 7.18$, $p < .02$. An explanation for this difference is not clear, since subjects in both groups were required to maintain the same overnight abstinence from food, smoking, and caffeine. In directly comparing responses to the methods per se (i.e., in the absence of nicotine intake), sham-smoking (smoke group) was associated with lower Head Rush scores, $F(1, 32) = 7.47$, $p = .01$, and greater Desire to Smoke scores, $F(1, 32) = 21.31$, $p < .001$, than placebo spray (spray group), as indicated in Fig. 1. The Method × Gender interaction was also significant for Comfortable, $F(1, 32) = 4.35$, $p < .05$, and Relaxed scores, $F(1, 32) = 3.99$, $p = .05$, as females responded to sham-smoking with sharp declines in each measure relative to their response to placebo spray, and males did not respond on either measure to either method, as shown in Fig. 2. Although there were no other differences between methods per se, these different effects

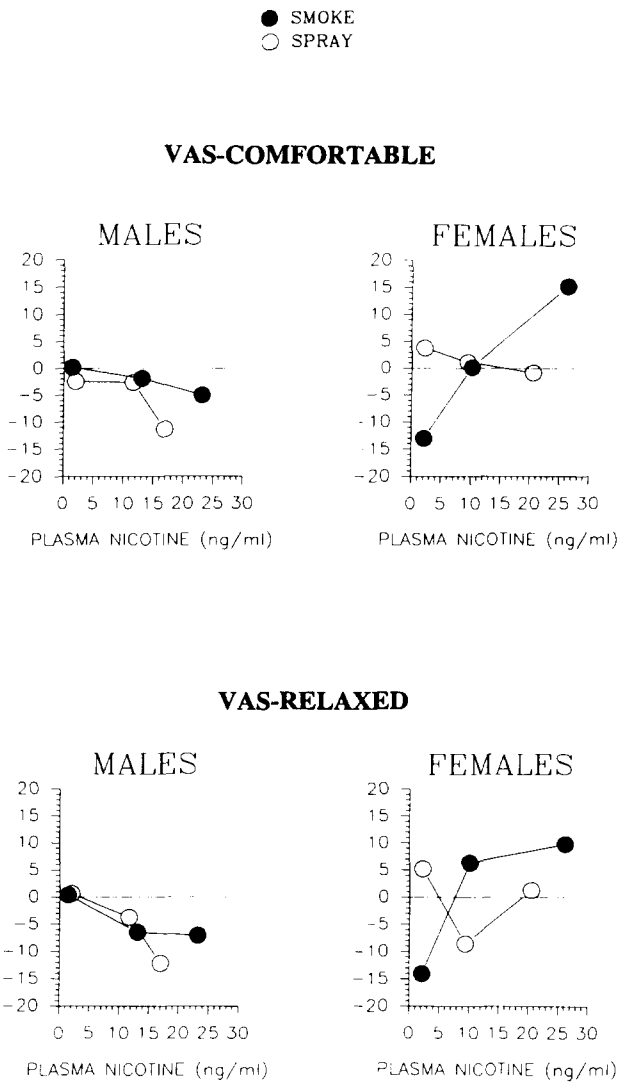

FIG. 2. Mean change from baseline in visual analog scale (VAS) measures of "Comfortable" and "Relaxed" due to nicotine intake via controlled tobacco smoking (smoke) versus nasal spray (spray) in male and female smokers.

of sham-smoking versus placebo spray indicated that direct comparison of nicotine responses between methods, controlling for nicotine plasma levels, may not be valid, as noted above.

Separate analyses of nicotine dose effects for each method revealed two patterns of virtually identical results across measures. As shown in Fig. 1, nicotine dosing via tobacco smoking (i.e., smoke group) produced significant increases in VAS scales of Head Rush, $F(2, 36) = 13.07, p < .001$, and Dizzy, $F(2, 36) = 13.56, p < .001$, and significant decreases in Hunger, $F(2, 36) = 5.61, p < .01$, and Desire to Smoke, $F(2, 36) = 40.01, p < .001$. There were no significant dose effects via smoking for Comfortable, $F(2, 36) = 2.30, p > .10$; Jittery, $F(2, 36) < 1$; and Relaxed, $F(2, 36) < 1$. As also shown in Fig. 1, nicotine dosing via nasal spray (i.e., spray group) also produced significant increases in VAS scales of Head Rush, $F(2, 28) = 4.62, p < .02$, and Dizzy, $F(2, 28) = 10.42, p < .001$, and significant decreases in Hunger, $F(2, 28) = 4.03, p < .05$, and Desire to Smoke, $F(2, 28) = 9.80, p < .001$. There were no dose effects via spray for Comfortable, $F(2, 28) = 1.65$, NS; Jittery $F(2, 28) < 1$; and Relaxed, $F(2, 28) = 2.13, p > .10$.

There were no significant main effects of gender on responses to nicotine for any measure with either method. However, significant Dose × Gender interactions were observed with smoking for Comfortable, $F(2, 36) = 4.83, p < .02$, and Relaxed scores, $F(2, 36) = 3.41, p < .05$. As shown in Fig. 2, these interactions were both due to the greater increase across doses in females versus males: sham versus usual cigarette, $t(18) = 4.38, p < .001$ for Comfortable; $t(18) = 3.39, p < .01$ for Relaxed. Much of this differential effect due to gender appeared to be due to females' decline from baseline in each measure in response to the sham-smoking condition, as noted previously.

Heart Rate Effects

The relationships between plasma nicotine and HR for smoking and nasal spray are also presented in the lower right panel of Fig. 1. Sham-smoking (smoke group) was associated with greater HR response than placebo spray (spray group), $F(1, 32) = 32.23, p < .001$, suggesting the possibility that puffing behavior itself may have an immediate effect on HR. Significant nicotine dose effects on HR were observed for both smoke, $F(2, 36) = 84.61, p < .001$, and spray, $F(2, 28) = 59.13, p < .001$. However, the puffing effect of smoking appeared to displace HR upward equally across doses, parallel to spray. There were no significant main or interaction effects involving gender.

DISCUSSION

The results of this exploratory study suggest that nicotine administration by controlled tobacco smoking or by nasal spray has very similar effects in smokers. Nicotine intake via tobacco smoking or nasal spray significantly increased heart rate and the subjective measures of Head Rush and Dizzy, decreased Hunger and Desire to Smoke, and had no effect on Comfortable, Jittery, or Relaxed. This observation is generally consistent with Henningfield et al. (6), who found comparable subjective effects of nicotine dosing via intravenous infusion versus controlled inhalation. The present study adds to this very sparse literature by employing a comparison method other than IV and by providing dose–response effects of nicotine by each method plotted by plasma nicotine concentrations. Notably, smoked versus IV cocaine has also been shown to produce generally similar subjective and cardiovascular effects in humans (3), suggesting generalizability of results across drugs.

On the other hand, the equality of effects between methods was not complete. In the absence of any nicotine intake, placebo spray had essentially no effect, while sham-smoking increased Desire to Smoke and decreased Head Rush. Sham-smoking also decreased Comfortable and Relaxed scores in females but not males. Thus, the behavior of puffing on an unlit cigarette may be a "cue" (14), or discriminative stimulus, for tobacco smoking, increasing the salience of tobacco deprivation in these overnight-deprived smokers more than that following placebo spray exposure. The discomfort caused by the presence of this cue in the absence of nicotine availability may be greater in female than in male smokers. Sham-smoking also acutely increased HR during the 2-min HR measurement period, suggesting that puffing behavior alone may

briefly elevate HR in addition to the well-known and perhaps longer lasting effects of nicotine on HR. Nevertheless, despite these effects of sham-smoking, the lack of differences between methods in responses to nicotine suggests that the effects of tobacco smoking on these measures are primarily due to nicotine intake per se and not other, non-nicotine influences, although non-nicotine influences may exert other effects not assessed here.

A limitation of this study was the use of a between-subjects design rather than comparing the effects of nicotine-dosing methods within subjects, although the two groups of subjects were generally comparable. Although availability of plasma nicotine concentrations allowed for determination of similarity of nicotine dosing with each method, another potential shortcoming was the use of a single postdose plasma sample for this purpose. Despite possibly similar patterns of plasma nicotine after dosing with each method (4,10,15), it is highly likely that arterial nicotine concentrations during the first 5 min after dosing, when measures in this study were obtained, are much higher with tobacco smoking (5) compared with nasal spray (or almost any other delivery method). Thus, arterial (and brain) nicotine concentrations may have been much greater following controlled smoking versus nasal spray. Because of the practical difficulties in obtaining arterial drug concentrations (5), this potential problem may not be easily addressed. Nevertheless, given a possible difference in nicotine delivery to the arterial circulation, it is even more surprising that essentially no differences in effects were observed between methods.

Additional studies are needed to directly compare nicotine intake via tobacco smoking versus other methods to replicate these findings and to identify other responses to nicotine which may (or may not) differ depending on the method. A broader array of subjective and physiological, as well as behavioral, responses should be examined. Such research may identify methods of nicotine administration which produce dose-related effects even more similar than those of nasal spray to those of tobacco smoking. Results of these studies may be useful in identifying new promising nicotine replacement therapies (4) as well as classes of smokers more likely to respond favorably to these treatments (13).

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