Psychopharmacology (1996) 128 : 221–226 © Springer-Verlag 1996

ORIGINAL INVESTIGATION

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Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers

Received: 11 August 1995 / Final version: 30 May 1996

Abstract The present study assessed the subjective and cardiovascular effects of intravenous nicotine in smokers and nonsmokers. Nonsmokers (n = 5) and smokers (n = 5) were administered a single dose of nicotine (0.75 or 1.5 mg) or saline on each of 3 days. The nicotine doses were given in ascending order in a double-blind fashion. Although smokers and nonsmokers manifested significant increases in systolic and diastolic blood pressure and heart rate 1 min after administration of all active test doses, the difference between peak heart rate and that measured at later times was greater in nonsmokers than in smokers. Nonsmokers and smokers also differed in subjective self-reports. In response to items on visual analogue scales indicative of positive effects (e.g., "good effects," "like drug," "use again," and "feel energetic"), smokers but not nonsmokers reported high scores (> 40) after nicotine injection. In addition, responses on the MBG and LSD subscales of the Addiction Research Center Inventory indicated that smokers experienced positive subjective effects after the test doses, whereas nonsmokers experienced disorientation. The fact that intravenous nicotine was not associated with positive subjective effects in nonsmokers indicates that repeated exposure is required to establish positive reinforcing effects of nicotine.

Key words Nicotine · Subjective responses · Cardiovascular responses · Non-smokers · Smokers

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Introduction

Nicotine is the active ingredient in tobacco that leads to addicition (US Department of Health and Human Services 1988), and its effects have been assessed in human subjects who habitually smoke tobacco cigarettes. Previous studies have demonstrated that nicotine produces dose-related changes in cardiovascular (Benowitz et al. 1982; Perkins et al. 1989, 1991) and electroencephalographic parameters (Kadoya et al. 1994) and in behavioral performance, particularly when research volunteers are deprived of the drug (Perkins et al. 1990; Parrott and Roberts 1991; Heishman et al. 1994). Acute administration of nicotine also produces pleasurable subjective effects (Henningfield et al. 1985; Perkins et al. 1993).

Substantially fewer studies have examined the effects of nicotine in nonsmokers, and the available literature suggests that these individuals respond differently to the drug than do experienced smokers. For example, when nicotine (15 μg/kg) is administered by measured-dose nasal spray, it impairs performance of a hand steadiness task to a greater extent in nonsmokers than in smokers (Perkins et al. 1990). In addition, when delivered in Polacrilex resin or tablets, nicotine improves the performance of nonsmokers on certain tasks involving memory and problem solving (Dunne et al. 1986), semantic relations (Provost and Woodward 1991), and rapid information processing (Wesnes and Warburton 1983). Greater performance-enhancing effects on the same tasks occur in nicotine-deprived smokers (Williams 1980; Snyder et al. 1988; Parrott and Winder 1989). Smokers and nonsmokers also manifest differences in subjective responses to nicotine. When nicotine was administered by nasal spray once every 30 min for 2 h, smokers and nonsmokers developed acute tolerance to subjective effects of a 30-μg/kg challenge dose; however, different measures showed tolerance in the two groups. Only the nonsmokers showed tolerance to dizziness and head rush, but the

smokers manifested tolerance to nicotine-induced increases in arousal and decreases in fatigue (Perkins et al. 1993).

Although, for research purposes, nicotine is often administered as an intranasal spray or in the form of Polacrilex resin, which is chewed, the rapid delivery of nicotine to the systemic circulation provided by inhalation of cigarette smoke may be most closely mimicked by rapid intravenous (IV) injection (Henningfield et al. 1985; Evans et al. 1993). Therefore, studies of the effects of nicotine given by the IV route could provide information relevant to the effects of smoking. To date, there has been no systematic study on the effect of IV nicotine in nonsmokers although previous research indicates that the administration of even highly addictive drugs, such as opiates, under controlled laboratory conditions is associated with a remarkably low incidence of iatrogenic dependence (Porter and Jick 1980; Schuster 1989).

The objective of the present study was to assess and compare the subjective and cardiovascular effects of IV nicotine in nonsmokers and smokers. Subjects in each group were each administered a single dose of nicotine (0.75 or 1.5 mg) or saline on each of 3 days.

Materials and methods

Subjects

Nonsmokers (n = 5, four males, one female) and smokers (n = 5, four males, one female) 21–38 years of age (mean age = 31) participated in the experiment. None of the nonsmokers reported any use of tobacco products. Carbon monoxide (CO) levels in expired air from nonsmokers were all within the range of values expected from ambient exposure to cigarette smoke (< 6 ppm). Smokers reported smoking 15–40 cigarettes/day. No subject provided evidence of any history of illicit drug use. Abstinence from illicit substance abuse was verified on each day of the study by urinalysis that tested for use of illicit opiates and methadone, cannabinoids, cocaine, phencyclidine, amphetamines, barbiturates, and benzodiazepines.

Each subject gave written informed consent. All human studies were done in accordance with the declaration of Helsinki. The consent forms, as well as the experimental procedures, were approved by an Institutional Review Board in accordance with the Department of Health and Human Services guidelines for the protection of human subjects.

Procedures

Subjects were tested on 3 separate days approximately 1 week apart. They were required to abstain from drinking alcoholic beverages for 48 h and from caffeinated beverages for 12 h prior to each day of the study. Smokers also abstained from smoking for 12 h before starting each day of the study, and pre-test CO levels in expired air confirmed abstinence (mean value = 8.0 ppm). On each test day, subjects received one dose of *l*-nicotine bitartrate (National Medical Services, Willowgrove, PA.) dissolved in bacteriostatic saline or the saline alone. The test doses were infused over 10 s, via a catheter placed in a forearm vein. Unit doses were in a volume of 1 ml and contained either 0.0, 0.75 or 1.5 mg nicotine, expressed as the free base. In a previous study, these doses of nicotine produced dose-related cardiovascular and subjective effects in smokers (Henningfield et al. 1985). The three treatments were administered in pseudorandom order, such that nicotine doses were given in ascending order but the saline treatment was randomly inserted into the sequence. All dosing was double-blind. On each of the 3 test days, the subject sat upright in a comfortable recliner and the test compound (nicotine or saline) was administered. Participants received the dose in the afternoon 2–4 h after eating a light meal, and they did not eat during the session.

Heart rate, diastolic blood pressure, and systolic blood pressure were monitored at 60 min prior to each test injection; at 1, 3, and 5 min after the injection; and every 5 min thereafter until a total of 30 min had elapsed after drug administration.

The participants also completed three questionnaires, which were administered 60 min before (Pre-drug) and 30 min after (Post-drug) receiving the dose. Each subject was instructed to answer the post-drug questionnaire in terms of how the test injection made him/her feel during the 30-min interval after the dose. Seven 100-mm visual analogue scales (VAS) were used to assess "drug strength", "good effects", "bad effects", "drug liking", "drug high", "desire to use drug again", and "energy level". The degrees of "confusion", "fatigue", "vigor", "tension", "anger", and "depression" were measured with the Profile of Mood States (POMS) (McNair et al. 1971). Three scales from the Addiction Research Center Inventory (ARCI) were also used to assess the subjective responses typically produced by other drugs of abuse: the Morphine Benzedrine Group (MBG) scale assessed positive subjective effects; the Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale assessed fatigue and sedation, and the LSD Group scale assessed disorientation and weird feelings (Haertzen 1974). Finally, each subject was instructed to respond verbally to a beep prompt given every minute for 30 min by rating the strength of the drug effect on a scale from "0" to "4", in which "0" indicated no effect and "4" indicated a strong effect.

Statistics

Differences in drug effects between groups were determined by a three-way ANOVA, with Dose (0, 0.75, 1.5 mg nicotine) and Group (smokers, nonsmokers) taken as the factors and Time taken as the repeated measure. Dunnett's Test was performed for all post-hoc analyses when a statistically significant interaction was revealed by ANOVA. The criterion for significance was taken as $P < 0.05$.

Results

Cardiovascular responses

Figure 1 shows time courses of heart rate, systolic blood pressure, and diastolic blood pressure in response to saline and nicotine in nonsmokers and smokers. Table 1 lists all significant F values.

Heart rate

The significant Dose × Time interaction reflects the observation that smokers and nonsmokers showed significant increases in heart rate after either dose of nicotine but not saline, starting at 1 min after test injection and lasting for 15 min. The significant Group × Time interaction was due to the greater difference between heart rate at the peak, as compared with later times, in nonsmokers than in smokers.

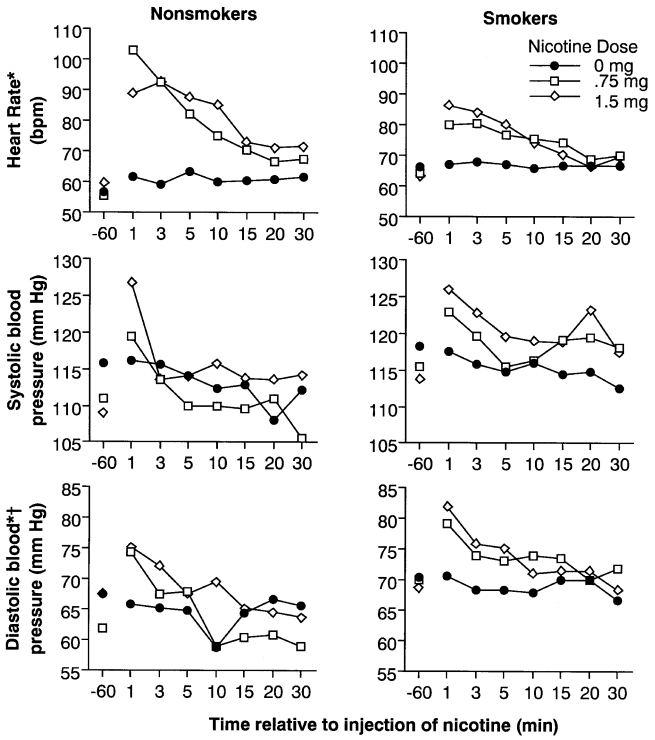

Fig. 1 Effects of nicotine on systolic blood pressure, diastolic blood pressure, and heart rate. Times indicated are minutes after the IV administration of each dose of nicotine (0.75 and 1.5 mg) and saline. *Left hand panels* are values of nonsmokers (n = 5); *right hand panels* are values of smokers (n = 5). ANOVA revealed significant effects of Time on all three measures in both groups. Significant Dose × Time interactions are indicated by an *asterisk* (*). Measures which showed a significant main effect of Group are indicated by a *dagger* (†)

Systolic blood pressure

Although there was no significant main effect or interaction involving Dose, both smokers and nonsmokers manifested an increase in systolic blood pressure during the first 3 min after the administration of either dose of nicotine but not saline. The significant main effect of Time reflected the finding that the highest systolic blood pressures were measured in both groups (within 3 min) after the administration of nicotine, after which values dropped to a steady level where they remained for the following 30 min.

Diastolic blood pressure

Smokers showed higher levels than nonsmokers in diastolic blood pressure (significant main effect of Group), irrespective of nicotine challenge. Moreover, a post-hoc analysis of the significant Dose × Time interaction indicated that both groups manifested significant increases in diastolic blood pressure as compared with baseline ($P < 0.0001$) during the first 3 min after the administration of either of the two doses of nicotine, and the difference between the response to nicotine and saline varied with time, as the diastolic pressure returned to or toward baseline.

Subjective responses

Figures 2, 3, 4, and 5 show the subjective responses by nonsmokers and smokers before and after the administration of saline and nicotine. Table 1 lists all significant F values.

VAS

Significant main effects of Dose and Time as well as significant Dose × Time interactions were demonstrated for each of the seven VAS measures (Fig. 2 and Table 1). The Dose × Time interaction was due to elevations in scores in both groups after the injection of nicotine as compared with pre-drug scores. Post hoc analyses of the Group × Time interactions reflected the fact that smokers, but not nonsmokers, gave high scores (> 40) on self-reports of "like drug", "good effects",

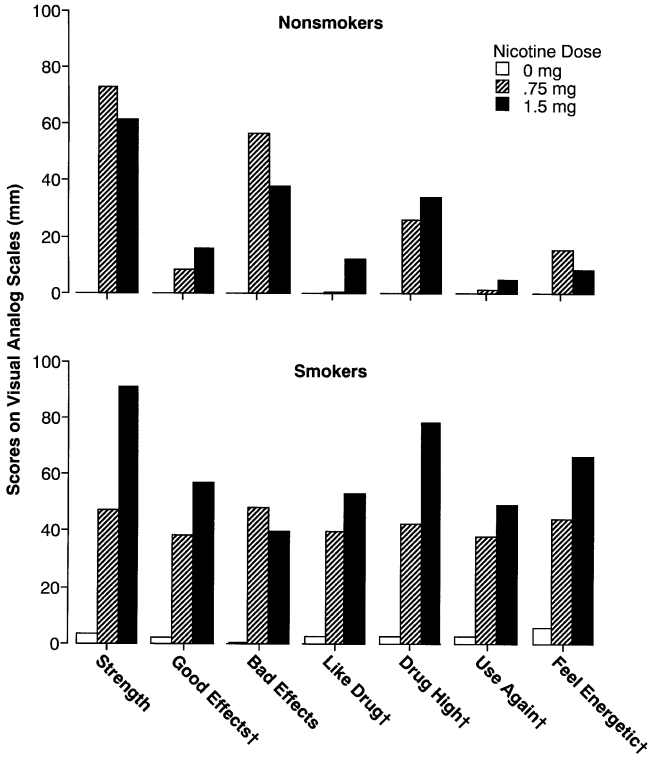

Fig. 2 Self-report scores on visual analog scales (*VAS*) given 30 min after the IV administration of each dose (0.75 mg, 1.5 mg) of nicotine and saline. *Top panel* shows scores of nonsmokers (n = 5), and *bottom panel* shows scores of smokers (n = 5). All seven measures obtained significant main effects of Dose and Time as well as significant Dose × Time interactions. There were no significant differences between active (0.75 and 1.5 mg) doses of nicotine; however, both active doses were significantly different from saline. *Daggers* (†) indicate measures which showed significant Group differences

Table 1 Main effects and interactions

Measure	Dose	Time	Dose × Time	Group	Group × Time
Cardiovascular					
Systolic blood pressure	n.s.	5.63 ($P < 0.0001$)	n.s.	n.s.	n.s.
Diastolic blood pressure	n.s.	7.89 ($P < 0.0001$)	2.30 ($P < 0.007$)	4.98 ($P < 0.04$)	n.s.
Heart rate	n.s.	22.66 ($P < 0.0001$)	5.09 ($P < 0.0001$)	n.s.	2.42 ($P < 0.02$)
Subjective responses					
Manual analogue scales					
Strength	19.25 ($P < 0.0001$)	73.95 ($P < 0.0001$)	18.88 ($P < 0.0001$)	n.s.	n.s.
Good effects	5.64 ($P < 0.03$)	20.46 ($P < 0.0002$)	5.95 ($P < 0.008$)	8.25 ($P < 0.009$)	7.29 ($P < 0.013$)
Bad effects	7.86 ($P < 0.003$)	30.58 ($P < 0.0001$)	8.3 ($P < 0.002$)	n.s.	n.s.
Like drug	4.21 ($P < 0.03$)	15.44 ($P < 0.0007$)	4.43 ($P < 0.02$)	10.20 ($P < 0.004$)	9.2 ($P < 0.006$)
Drug high	11.56 ($P < 0.0003$)	39.73 ($P < 0.0001$)	12.03 ($P < 0.0003$)	5.26 ($P < 0.03$)	4.45 ($P < 0.05$)
Use again	3.74 ($P < 0.04$)	15.30 ($P < 0.0007$)	3.97 ($P < 0.03$)	13.21 ($P < 0.001$)	11.85 ($P < 0.002$)
Feel energetic	5.06 ($P < 0.02$)	23.88 ($P < 0.0001$)	5.18 ($P < 0.01$)	11.45 ($P < 0.003$)	10.46 ($P < 0.004$)
Profile of mood states					
Confusion	n.s.	15.61 ($P < 0.0006$)	5.72 ($P < 0.01$)	n.s.	n.s.
Tension	n.s.	n.s.	4.06 ($P < 0.03$)	n.s.	n.s.
Depression	n.s.	n.s.	4.35 ($P < 0.03$)	n.s.	n.s.
Anger	n.s.	n.s.	4.03 ($P < 0.03$)	n.s.	n.s.
Vigor	n.s.	n.s.	n.s.	n.s.	n.s.
Fatigue	n.s.	n.s.	n.s.	n.s.	n.s.
ARCI					
MBG	n.s.	n.s.	n.s.	8.46 ($P < 0.008$)	n.s.
LSD	n.s.	62.94 ($P < 0.0001$)	10.21 ($P < 0.0007$)	4.77 ($P < 0.04$)	n.s.
PCAG	n.s.	n.s.	n.s.	n.s.	n.s.
Self-report of drug effect in response to beep prompt	11.22 ($P < 0.0008$)	50.52 ($P < 0.0001$)	12.41 ($P < 0.0001$)	n.s.	n.s.

[a] Numbers are significant F and P values

"use again", "drug high" and "feel energetic" as compared with pre-injection scores.

POMS

The test injections of nicotine had little effect on mood, as indicated by the POMS, in both smokers and nonsmokers. With the exception of "Vigor", both smokers and nonsmokers tended to report higher scores on all of the measures after an injection of nicotine.

ARCI

Significant main effects of Group were found for both the MBG scale, a measure of positive feelings and the LSD scale, a measure of disorientation. These main effects were due to the fact that smokers scored higher on the MBG scale and nonsmokers scored higher on the LSD scale. Despite no significant Group × Dose interaction, these results suggest that smokers and nonsmokers had qualitatively different experiences in response to nicotine. The PCAG scale did not show any significant effects.

Drug effect (beep prompt response)

Both smokers and nonsmokers experienced significantly stronger drug effects of both active test doses

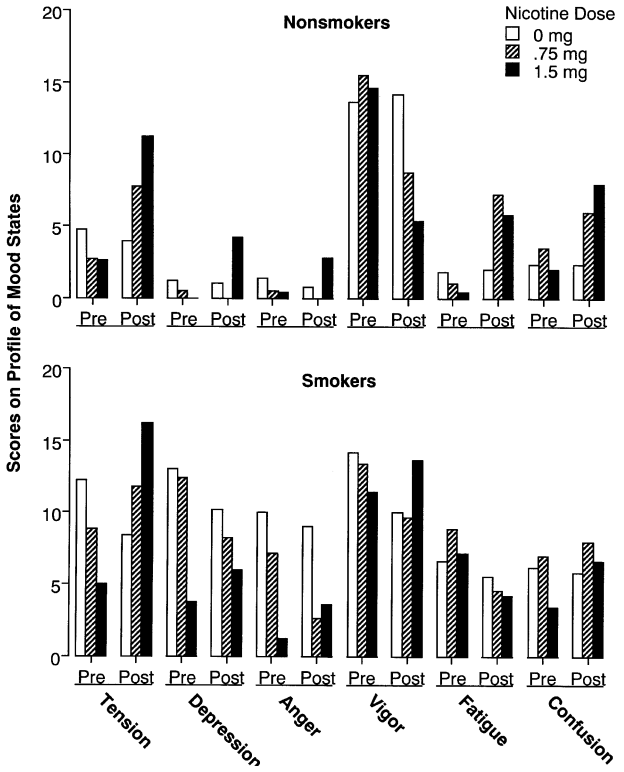

Fig. 3 Self-report scores on Profile of Mood States (POMS) given 60 min before (*Pre*) and 30 min after (*Post*) the IV administration of each dose of nicotine (0.75 and 1.5 mg) and saline. *Top panel* shows scores of nonsmokers ($n = 5$) and *bottom panel* shows scores of smokers ($n = 5$)

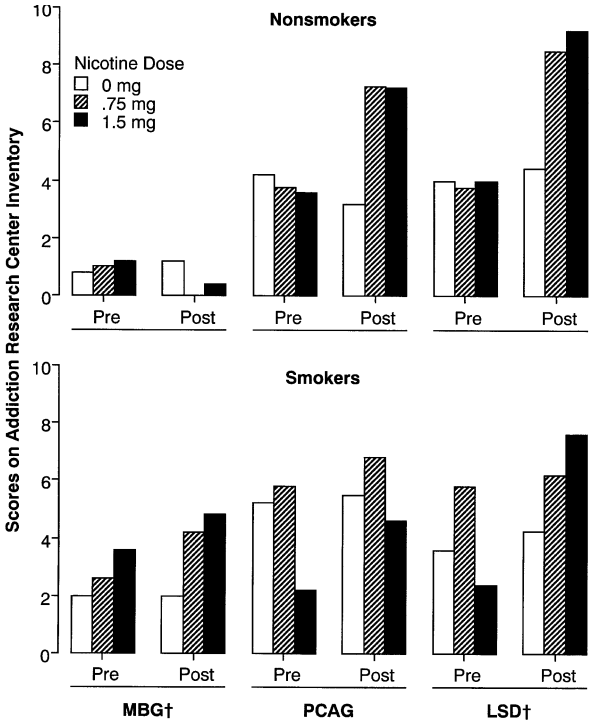

Fig. 4 Self-report scores on Addiction Research Center Inventory (*ARCI*) given 60 min before (*Pre*) and 30 min after (*Post*) the IV administration of each dose of nicotine (0.75 and 1.5 mg) and saline. *Top panel* shows scores of nonsmokers ($n = 5$) and *bottom panel* shows scores of smokers ($n = 5$). The *daggers* (†) indicate measures that showed significant main effects of Group. Whereas smokers reported greater positive subjective effects (*MBG*) than nonsmokers, nonsmokers reported greater feelings of disorientation (*LSD*)

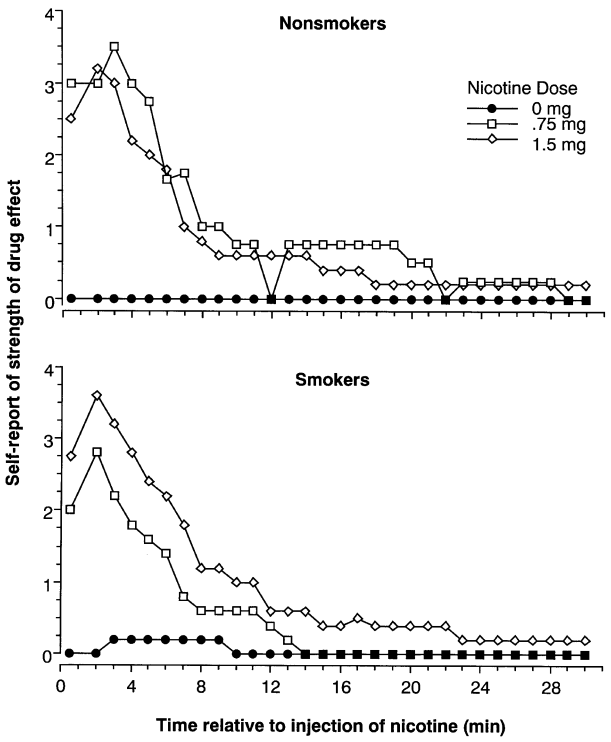

Fig. 5 Self-report of strength of drug effect given every minute for 30 min after the IV administration of each dose of nicotine (0.75 and 1.5 mg) or saline. *Top panel* shows scores of nonsmokers ($n = 5$), and *bottom panel* shows scores of smokers ($n = 5$). ANOVA revealed significant effects of Dose and Time as well as significant Dose × Time interactions

when compared with those of saline (Fig. 4). Both groups also reported the strongest drug effects between 1 and 5 min after the IV injection, with peak effects occurring within 2–3 min. In addition, starting at about 11 min after the 1.5-mg dose of nicotine, the drug effect reported by both groups gradually declined to a steady but non-zero score.

Discussion

Both smokers and nonsmokers manifested increases relative to baseline in heart rate and blood pressure, 1–5 min after the administration of nicotine. A significant Group × Time interaction in heart rate reflected the fact that the two groups differed in peak heart rate. That is, heart rate was higher immediately after injection of nicotine in nonsmokers than in smokers. The two groups also differed in diastolic blood pressure, with smokers showing higher levels than non smokers, irrespective of nicotine challenge. Moreover, nicotine produced transient effects to increase diastolic and systolic pressure in both groups, and the effects decayed over time. Despite differences between the two groups in peak heart rate after the test injections, no significant main effects of Dose and no Group × Dose interactions on cardiovascular parameters were observed. This absence may be due to the small sample size.

Nonsmokers gave qualitatively different subjective responses from smokers. Although no significant Group × Dose interaction was found, all the VAS measures associated with positive qualities showed group differences. Whereas smokers assigned high scores to positive measures (i.e. “good effects of the drug”, “liking the drug”, “desire to use the drug again”, and “feeling energetic”) of their experience following the nicotine injections, nonsmokers reported low scores on the same measures. An indication that smokers experienced qualitatively different subjective feelings than nonsmokers was also presented by results obtained from the ARCI scales. Smokers scored high on the MBG scale, which generally measures positive subjective feelings, and nonsmokers scored high on the LSD scale, which reflects disorientation, awareness of bodily sensations, and weird feelings (Haertzen 1974; Muntaner et al. 1989).

The findings from this study are consistent with previous reports on the cardiovascular and subjective effects of nicotine. For example, when given to smokers, nicotine increases heart rate and blood pressure whether it is administered intravenously (Henningfield et al. 1985), in gum (Nemeth-Coslett et al. 1986), or as

an aerosol spray (Perkins et al. 1986). Furthermore, smokers report pleasurable effects when nicotine is given through any of those routes (Johnston and Glasg 1942; Henningfield et al. 1985; Nemeth-Coslett et al. 1986, 1988; Perkins et al. 1993). Our results also concur with studies of the subjective effects of nicotine in aerosol spray in nonsmokers (Perkins et al. 1993). As in our study, nonsmokers experienced more negative effects (jittery, light-headed, dizzy, head rush) than did smokers, but they reported fewer positive effects (vigor, arousal).

The data suggest that nicotine may be more like barbiturates, morphine, and alcohol than amphetamines in that repeated exposure may be required to establish reinforcing effects. Lasagna et al. (1955) reported that when drug-naive human volunteers were given either amphetamine, heroin, or morphine, the opiates produced unpleasant effects in 75% of the subjects on the first administration, but repeated exposure to the drug finally produced the experience of euphoria. In the present study, most nonsmokers tended to report liking nicotine less than did smokers and tended to report no desire to use the drug again. This finding is consistent with evidence from previous studies, indicating that nicotine is one of several drugs which is not liked on the first administration (Haertzen et al. 1983).

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