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ORIGINAL INVESTIGATION

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Tolerance to repeated nicotine administration on performance, subjective, and physiological responses in nonsmokers

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Abstract *Rationale:* When administered acutely to nonsmokers, nicotine's effects on performance are inconsistent, perhaps because of suboptimal dosing or initial dysphoria that could interfere with performance. *Objective:* The purpose of this study was to determine if a range of nicotine doses administered for 8 days to nonsmokers would enhance psychomotor and cognitive abilities and to document the development of nicotine tolerance or sensitization. *Methods:* Twelve male volunteers, who reported ever smoking five cigarettes or less, participated in 8 consecutive experimental days in which they were administered four doses of nicotine polacrilex gum each day in this order: 0, 2, 4, and 8 mg. Performance, subjective, and physiological measures were assessed before and after each dose. *Results:* Plasma nicotine concentration ranged from 6.9 to 11.5 ng/ml following the 8 mg dose. Nicotine increased rate of responding and decreased response time on working memory (digit recall); however, accuracy was impaired. Nicotine also decreased accuracy on visual scanning and attention (two-letter search), and the 8 mg dose impaired gross motor coordination (circular lights). Tolerance did not develop to the performance impairing effects of nicotine. Nicotine produced dose-related increases in ratings of dysphoria and negative mood, including tension, anxiety, nervousness, turning of stomach, and sedation. Tolerance developed to some, but not all, of these aversive effects. Tolerance also was not observed to the increased cardiovascular measures. *Conclusion:* Although tolerance developed to some of the aversive effects of nicotine, performance enhancement was not observed. These data do not support the hypothesis that nicotine-induced performance enhancement contributes to the reinforcing effects of tobacco use during the early stages of dependence development.

Key words Nicotine · Human · Nonsmoker · Tolerance · Psychomotor · Cognition-Mood · Cardiovascular effect · Plasma nicotine concentration

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Introduction

The majority of studies investigating the effects of nicotine and tobacco on human performance have been conducted with smokers who were tobacco-abstinent for some period of time, typically overnight (Sherwood 1993; Heishman et al. 1994). In nicotine-dependent individuals, tobacco deprivation can produce attentional and cognitive impairment (Lyvers et al. 1994; Bell et al. 1999), which can be reversed to pre-deprivation levels by cigarette smoking or other forms of nicotine delivery (Snyder and Henningfield 1989; Parrott and Roberts 1991). Thus, in studies conducted with tobacco-abstinent smokers, it is difficult to distinguish between the effect of nicotine to *reverse* decrements and the potential of nicotine to *enhance* performance. The clearest demonstration of true enhancement is when nicotine improves performance over baseline levels in nonsmokers or in nonabstinent smokers (Heishman et al. 1994; Heishman 1998).

Although few in number compared with studies testing smokers, placebo-controlled studies testing nonsmokers or nonabstinent smokers have examined the effects of nicotine on a wide range of performance measures. These studies indicated that nicotine and smoking reliably enhanced finger tapping (West and Jarvis 1986;

Perkins et al. 1990, 1994), motor responses in brief tests of attention (Hindmarch et al. 1990; Kerr et al. 1991; Le Houezec et al. 1994), and performance in tests of sustained attention (Foulds et al. 1996; Levin et al. 1998; Mumenthaler et al. 1998). Previous reports of faster reaction time after smoking (West and Hack 1991) or nicotine (Kerr et al. 1991) on the Sternberg test, which measures retrieval from working memory, were not replicated by Foulds et al. (1996). Other studies have found that nicotine improved recognition memory in nonsmokers (Perkins et al. 1994) and recall memory in smokers who were tobacco abstinent for 1–2 h (Rusted et al. 1995, 1998).

In contrast to these beneficial effects, placebo-controlled studies have reported that nicotine either had no effect or impaired performance in nonsmokers or nonabstinent smokers on critical flicker frequency (Hindmarch et al. 1990; Kerr et al. 1991; Foulds et al. 1996), selective attention (Heishman et al. 1993; Perkins et al. 1994; Foulds et al. 1996), sustained attention (Wesnes et al. 1983; Wesnes and Warburton 1984), conditioned learning (Thornton et al. 1996), recall memory (Dunne et al. 1986; Hindmarch et al. 1990; Heishman et al. 1993), and other cognitive abilities, such as reasoning and arithmetic (Dunne et al. 1986; Heishman et al. 1993; Foulds et al. 1996). With such inconsistent findings, it is difficult to reach firm conclusions regarding the effects of nicotine on human performance for most behavioral domains.

One possible explanation for these inconsistent data is that, in some studies, the delivered dose of nicotine was not optimal to enhance performance. For example, Hindmarch et al. (1990) reported that 2 mg nicotine polacrilex gum produced measurable physiological and subjective effects, but had no effect on several performance measures. Perkins et al. (1994) reported that the nicotine dose-response function for finger tapping and memory was nonlinear with maximal behavioral effect in the 4–8 ng/ml plasma nicotine concentration range. In some studies (Wesnes et al. 1983; Wesnes and Warburton 1984), nicotine was administered orally in the form of 1.5-mg or 2-mg tablets, which were held in the mouth for 5 min, then swallowed. Effective buccal absorption of nicotine requires buffering of the delivery vehicle to increase salivary pH (US DHHS 1988), and swallowed nicotine is extensively converted to cotinine via first-pass metabolism (Benowitz et al. 1987). Thus, such oral dosing likely resulted in low bioavailability; plasma nicotine concentration was not reported.

Another possible reason for limited performance enhancement is that, in the majority of studies cited above, subjects typically received only one dose of nicotine during each experimental session. A potential consequence of such infrequent dosing is nicotine-induced dysphoria in nonsmokers (Hindmarch et al. 1990; Heishman et al. 1993), which may interfere with test performance. Initial exposure to cigarettes is typically reported as aversive (US DHHS 1988), and Perkins et al. (1993, 1994) have shown that smokers respond less to the dysphoric effects of nicotine (e.g., tense, dizzy, jittery, light-headed) than nonsmokers, demonstrating chronic tolerance. Thus, as tolerance develops to the dysphoric effects of nicotine with repeated exposure, performance enhancement might be more readily observed.

We addressed these limitations of previous research in the present study by administering ascending doses of nicotine polacrilex daily for 8 consecutive days to nonsmokers. A battery of performance tests, which assessed a range of human abilities, including gross motor coordination, visual attention, memory, reasoning, and problem solving, was administered before and after each nicotine dose. These tests were previously shown to be sensitive to the effects of tobacco abstinence in smokers and nicotine administration after tobacco deprivation (Snyder and Henningfield 1989; Bell et al. 1999). Subjective responses to the potential mood-enhancing and aversive effects of nicotine were assessed concurrently with the performance measures over the 8 days of nicotine administration. We postulated that if tolerance developed to the initial dysphoric effects of nicotine, performance enhancement would be observed. Nicotine plasma concentration was also measured to examine its relationship with the various pharmacodynamic measures.

Materials and methods

Subjects

Twelve healthy, male community volunteers, who ranged in age from 23 to 36 years (mean=31.4, SD=3.9), completed the study. One subject was discharged after experiencing an adverse reaction (nausea and vomiting) to nicotine on the first dosing day. Before the study, subjects were given thorough medical and psychiatric examinations and were interviewed about past and current drug use. Exclusionary criteria included ever smoking more than five cigarettes and a history of drug dependence. Three subjects reported never using any psychoactive substance. Four subjects reported limited past use of marijuana, and one subject reported current use of two joints per month. Two subjects reported past use of alcohol, and seven reported current use of alcohol, which averaged six beers or drinks per month. Two subjects reported past intranasal use of cocaine on less than five occasions. The study was approved by an Institutional Review Board. Subjects provided written informed consent according to guidelines for the protection of human subjects of the US Department of Health and Human Services and were paid for their participation. Subjects returned for follow-up visits up to 3 months after the study. All were in good health, and none reported having started smoking.

General procedures

Subjects resided on the residential research unit of the National Institute on Drug Abuse for 3–4 weeks and participated individually in the protocol. Subjects were informed that the purpose of the study was to examine how nicotine affected their mood and performance of certain tests. During their participation, subjects were not allowed to consume any substances containing caffeine. Before the first experimental session, subjects practiced the cognitive and psychomotor tests until stable performance was achieved. Practice was distributed over 3–5 days and ranged from 17 to 58 trials for each test (mean across subjects=30.7, SD=10.5). Subjects then participated in ten consecutive daily experimental sessions. The first two sessions involved only placebo administration and

served to familiarize subjects with the procedures and various measures. Data from these two sessions are not reported. The remaining eight sessions were identical in procedure and involved administration of ascending doses of nicotine each day. These sessions will be numerically referred to as days 1–8.

Drug

Nicotine was administered in the form of polacrilex gum that was available in 2 and 4 mg doses and placebo (Marion Merrell Dow Inc., Kansas City, Mo., USA and Kabi Pharmacia, Helsingborg, Sweden). This gum has a bioavailability of about 50% (Benowitz et al. 1987). It was the same formulation currently marketed by SmithKline Beecham Consumer Healthcare in the US and by Pharmacia and Upjohn elsewhere. Nicotine polacrilex was chosen because it provided a controllable means of dose delivery and is characterized by low dependence potential and toxicity (US DHHS 1988), requisites for safe delivery of nicotine to nonsmokers.

Experimental procedures

The schedule of events during each experimental session are detailed in Table 1. Before and after each dose of nicotine, subjects completed various computerized subjective questionnaires and performed several psychomotor and cognitive tests. Physiological measures were taken before, during, and after each dose. At each drug administration, subjects were given two pieces of gum and instructed to chew once every 3 s for 15 min, according to a standardized recording of tones. On each day, four doses of nicotine were administered as follows: 1) 0900 hours: 0 mg (two pieces of placebo gum); 2) 1030 hours: 2 mg (one piece of 2 mg gum, one piece of placebo); 3) 1300 hours: 4 mg (two pieces of 2 mg gum); and 4) 1430 hours: 8 mg (two pieces of 4 mg gum). Following the protocol, subjects were observed for nicotine withdrawal signs and symptoms for 3–7 days before discharge from the research unit. No withdrawal was observed in any subject.

Table 1 Protocol of daily experimental sessions and presentation order of measures

0730	Breakfast
0830	Physiological measures (blood pressure, heart rate, skin temperature)
0845	Predose 1 measures (administered consecutively)
	Physiological measures
	Circular lights test
	Computerized performance tests
	Addiction Research Center Inventory (ARCI)
0900	Dose 1 administration: 0 mg nicotine
	Physiological measures taken every 3 min for 15 min
0915	Postdose 1 measures (administered consecutively, except where noted)
	Circular lights test
	Positive-Negative Questions (presented every 15 s for 3 min; 12 repetitions)
	Positive-Negative Questions (presented once, 60 s from last presentation)
	Positive-Negative Questions (presented once, 60 s from last presentation)
	Physiological measures
	Single Dose Questionnaire
	Desire-Strength Questions
	Physiological measures
	Positive-Negative Questions (presented once)
	Computerized performance tests
	Physiological measures
	Profile of Mood States
	Positive-Negative Questions (presented once)
	Physiological measures
	ARCI
	Positive-Negative Questions (presented once)
	Physiological measures
	Positive-Negative Questions (presented once)
	Physiological measures
0945	Blood sample 1
1000	Physiological measures
1015	Predose 2 measures (same as predose 1 measures)
1030	Dose 2 administration: 2 mg nicotine (same measures as dose 1)
1045	Postdose 2 measures (same as postdose 1 measures)
1115	Blood sample 2
1130	Physiological measures
	Lunch
1230	Physiological measures
1245	Predose 3 measures (same as predose 1 measures)
1300	Dose 3 administration: 4 mg nicotine (same measures as dose 1)
1315	Postdose 3 measures (same as postdose 1 measures)
1345	Blood sample 3
1400	Physiological measures
1415	Predose 4 measures (same as predose 1 measures)
1430	Dose 4 administration: 8 mg nicotine (same measures as dose 1)
1445	Postdose 4 measures (same as postdose 1 measures)
1515	Blood sample 4

Plasma nicotine and cotinine/residual nicotine

Blood samples were obtained through a heparinized catheter placed in an antecubital vein. Four blood samples were collected during each session (see Table 1). Immediately after obtaining each 10-ml sample, plasma was separated and frozen at –20°C. Plasma samples were analyzed for nicotine and cotinine using high-performance liquid-chromatography (HPLC) (Hariharan et al. 1988). The precision of the assay for nicotine in the concentration range 0–100 ng/ml was 6.6% and 8.0% within and between runs, respectively. The precision of the assay for cotinine in the concentration range 50–700 ng/ml was 3.8% and 4.3% within and between runs, respectively. Immediately after each dose, the chewed polacrilex was collected in a vial and frozen at –20°C. Gum samples were analyzed for residual nicotine content using HPLC by Marion Merrell Dow Inc. Extracted nicotine was estimated by subtracting the residual nicotine content from the stated nicotine content (0, 2, 4, or 8 mg) of each dose of polacrilex.

Physiological measures

Systolic and diastolic blood pressure, heart rate, and skin temperature were measured using an IVAC Vital-Check Monitor (Model 4000; IVAC Corporation, San Diego, Calif., USA).

Performance measures

Cognitive and psychomotor performance was assessed using four computerized tests and the circular lights test. The computerized tests required about 10 min to complete and were presented in the order listed below, with an inter-test interval of about 10 s. Each test contained a series of trials that were randomly chosen or varied. For each test, number of attempted trials, percent correct trials, and mean response time were recorded. Subjects were instructed to perform the tests as rapidly as possible, but not to sacrifice accuracy; they were paid $0.01 per correct response for each test. The two-letter search test assessed visual scanning, recognition, and attentional abilities. Each trial required subjects to determine whether two target letters were contained in a series of 20 letters presented below the target letters. The 20-letter series could contain neither, one, or both of the target letters. A maximum of 20 trials or 120 s was allowed. The logical reasoning test measured verbal information processing. Each trial presented the letter pair AB or BA and below it, a statement that correctly or incorrectly described the order of the letters. Subjects determined whether the statement was true or false. A maximum of 32 trials or 120 s was allowed. In the digit recall test, which measured working memory and attention, each trial began with a series of 9 random digits presented simultaneously for 1 s. The computer monitor went blank for 3 s, followed by the display of a different random series of eight of the original nine digits. Subjects determined the missing digit. A maximum of 20 trials or 120 s was allowed. In the serial addition/subtraction test, each trial involved the sequential presentation of two randomly selected digits and either a plus or minus sign, followed by a "?" prompt. Subjects performed the indicated addition or subtraction. A maximum of 50 trials or 180 s was allowed.

The circular lights test utilized a Wayne Computerized Saccadic Fixator (Model 287; Wayne Engineering; Northfield, Ill., USA) to assess gross eye-hand coordination. The device consisted of a wall-mounted panel (73.5×73.5×10.5 cm) that contained 33 button-lights arranged in three concentric circles. The height of the panel on the wall was adjusted such that each subject could comfortably reach the top of the panel while standing 0.5 m from the wall. Subjects began each test by pressing a green start button located in the upper right corner of the panel; this illuminated one of the 16 lights on the outer circle (72-cm diameter). Pressing the illuminated button-light extinguished that light, produced a brief tone, incremented the counter one digit, and resulted in the illumination of another light at a random location on the circle. Subjects could not view the digital counter and were instructed to earn as many points as possible; they were paid $0.01 per point. The score was the number of points during each 1-min test.

Subjective measures

Five computerized questionnaires were completed. A short form of the Addiction Research Center Inventory (ARCI; Jasinski et al. 1968) consisted of 40 true-false items that comprised three scales: MBG, a measure of euphoria; PCAG, a measure of sedation; and LSD, a measure of dysphoria and psychotomimetic changes. The Single Dose Questionnaire (SDQ; Fraser et al. 1961) comprised four items: Do you feel the medicine? (yes-no); drug class identification (13 choices); rating of 13 drug symptoms from 0 (not at all) to 100 (extremely); and rating of drug liking from 0 (not at all) to 4 (an awful lot). The Profile of Mood States (POMS; McNair et al. 1971) consisted of 65 adjectives, which subjects rated on a 5-point scale from 0 (not at all) to 4 (extremely). Eight scales were measured: tension-anxiety, anger-hostility, fatigue, confusion-bewilderment, depression-dejection, vigor-activity, friendliness, and total mood disturbance. The Positive-Negative Effects questions consisted of two questions that were repeated frequently after each dose (see Table 1): “On a scale from 0 to 100 rate the degree of positive (negative) effects you obtained from this dose of the gum.” The “positive” question always preceded the “negative.” The Desire-Strength questions also consisted of two questions: “How strong is your desire to have another dose like you just had?” and “How strong was the dose you just had?” Subjective ratings from the first question were scored on a scale from –2 (strongly resist another dose) to 2 (strongly desire another dose) and from the second question on a scale from 0 (definitely a blank) to 4 (extremely strong dose).

Data analysis

Data for blood pressure, heart rate, skin temperature, the five performance tests, and the ARCI were analyzed by three-factor, repeated measures analysis of variance (ANOVA) with session day, nicotine dose, and trial (pre- and postdose) as factors. Predose and postdose data, rather than difference scores, were analyzed because a two-factor (session day×nicotine dose), repeated measures ANOVA on only predose data revealed significant effects on several measures, indicating a changing predose baseline during the ascending dosage regimen. For physiological measures, predose data consisted of the average of the three measurements taken 15 and 30 min and immediately before dosing; postdose data were an average of 11 measurements beginning 3 min and ending 45 min after dosing began. Performance and ARCI data consisted of the single predose and postdose assessments. Data for the Positive-Negative Questions, SDQ, Desire-Strength Questions, POMS, plasma nicotine and cotinine, and extracted nicotine consisted of postdose measurements only and were analyzed by two-factor, repeated measures ANOVA with session day and nicotine dose as factors. A mean score was calculated from the 18 postdose presentations of the Positive-Negative Questions.

A significant day×dose interaction would suggest the development of tolerance or sensitization to the effects of nicotine; however, to examine such changes more closely, post hoc tests using the Tukey method were used to compare postdose data across days (particularly days 1 and 8) within each nicotine dose and across doses within each day. To explore dose-response functions, post hoc comparisons were conducted on postdose data between each nicotine dose and placebo averaging over test days using two-tailed Dunnett's tests. Conservative F tests using adjusted probability levels (Huynh-Feldt correction) were used to interpret results of ANOVAs. Effects were considered statistically significant at $P<0.05$.

Table 2 Mean (SD) nicotine and cotinine plasma concentration (ng/ml) and extracted nicotine (mg) for each nicotine dose on 8 consecutive days of dosing

	Nicotine dose (mg)			
Test day	0	2	4	8
Day 1				
Nicotine[a]	0.1 (0.4)	1.3 (1.9)	4.0 (3.2)	11.5 (4.8)[c]
Cotinine[a]	10.8 (14.9)	5.1 (4.4)	10.8 (4.8)	17.0 (6.1)[e]
Extracted nicotine[b]	0.0 (0.0)	0.9 (0.4)	1.9 (0.7)[f]	4.7 (1.6)[c]
Day 2				
Nicotine	0.6 (1.8)	1.9 (2.7)	4.7 (4.2)	9.8 (6.7)[c]
Cotinine	22.8 (9.9)	26.2 (10.6)	29.2 (12.2)	41.2 (16.8)[c]
Extracted nicotine	0.0 (0.0)	0.7 (0.5)	1.7 (0.5)[f]	4.1 (1.2)[c]
Day 3				
Nicotine	0.0 (0.0)	1.7 (2.7)	3.6 (3.4)	7.4 (6.3)[d]
Cotinine	33.0 (14.9)	32.4 (13.6)	36.3 (13.8)	43.6 (15.3)[d]
Extracted nicotine	0.0 (0.0)	0.8 (0.4)	2.0 (0.9)[f]	3.4 (1.9)[c]
Day 4				
Nicotine	0.0 (0.0)	1.7 (2.2)	3.8 (3.2)	7.2 (6.0)[d]
Cotinine	38.5 (22.5)	36.4 (20.9)	37.8 (17.5)	45.6 (19.6)[e]
Extracted nicotine	0.0 (0.0)	1.0 (0.5)	1.8 (0.8)[f]	3.5 (1.5)[c]
Day 5				
Nicotine	0.0 (0.0)	0.9 (1.8)	3.3 (3.3)	7.2 (6.1)[d]
Cotinine	35.3 (20.7)	38.5 (21.0)	40.4 (20.0)	44.6 (23.2)[f]
Extracted nicotine	0.0 (0.0)	0.8 (0.4)	1.6 (0.6)[f]	3.7 (1.1)[c]
Day 6				
Nicotine	0.5 (1.5)	1.8 (2.9)	2.7 (3.2)	6.9 (6.4)[d]
Cotinine	38.8 (24.9)	38.9 (24.8)	40.5 (22.9)	46.2 (26.2)
Extracted nicotine	0.0 (0.0)	0.9 (0.5)	1.8 (0.9)[f]	4.2 (2.2)[c]
Day 7				
Nicotine	0.2 (0.4)	2.0 (2.9)	2.8 (3.2)	9.7 (12.5)[c]
Cotinine	37.5 (27.4)	41.3 (27.1)	42.3 (26.0)	48.0 (27.0)[f]
Extracted nicotine	0.0 (0.0)	0.8 (0.5)	1.8 (0.9)[f]	5.0 (1.8)[c]
Day 8				
Nicotine	0.0 (0.0)	0.8 (1.3)	2.8 (2.7)	9.6 (6.1)[c]
Cotinine	36.0 (23.2)	36.0 (22.8)	39.7 (20.0)	48.1 (28.0)[c]
Extracted nicotine	0.0 (0.0)	1.0 (0.6)	1.7 (1.0)[f]	4.0 (1.9)[c]

[a] Plasma samples obtained 30 min after the end of 15-min nicotine administration period
[b] Estimated from residual nicotine in chewed gum samples after 15-min administration period
[c] Significantly greater ($P<0.05$) than 0, 2, and 4 mg dose on same day
[d] Significantly greater ($P<0.01$) than 0 and 2 mg dose on same day
[e] Significantly greater ($P<0.01$) than 2 mg dose on same day
[f] Significantly greater ($P<0.01$) than 0 mg dose on same day

Results

Plasma nicotine and cotinine/extracted nicotine

Plasma nicotine concentration increased as a function of dose [$F(3,33)=25.78$, $P<0.001$] on each test day (Table 2). Post hoc comparisons indicated that nicotine concentration was greater than placebo at 4 mg ($P<0.05$) and 8 mg ($P<0.01$) nicotine, but not at the 2 mg dose. The day main effect and day×dose interaction were not significant.

Table 2 shows that plasma cotinine concentration also increased as a function of nicotine dose [$F(3,33)=34.38$, $P<0.001$]. Cotinine concentration was greater than placebo after 4 mg ($P<0.05$) and 8 mg ($P<0.001$) nicotine, but not after the 2 mg dose. A day main effect [$F(7,77)=15.52$, $P<0.001$] and marginal day×dose interaction ($P=0.095$) were explained by lower plasma cotinine concentration for all nicotine doses on day 1 ($P<0.001$) and for 0 mg ($P<0.001$), 2 mg ($P<0.01$), and 4 mg ($P<0.05$) nicotine on day 2 compared with days 3–8.

Table 2 also shows that extracted nicotine increased in an orderly dose-dependent manner on each day of nicotine dosing [$F(3,33)=150.58$, $P<0.001$]. The day main effect and day×dose interaction were not significant. Across test days, mean (SD) extracted nicotine was 0.86 mg (0.48) for the 2 mg dose (43%), 1.77 mg (0.79) for the 4 mg dose (44%), and 4.07 mg (1.71) for the 8 mg dose (51%). Extracted nicotine was greater than placebo for all active doses ($P<0.01$).

Performance measures

Nicotine increased the number of attempted trials [$F(3,33)=21.65$, $P<0.001$) and decreased response time [$F(3,33)=12.21$, $P<0.001$] in a dose-related manner on

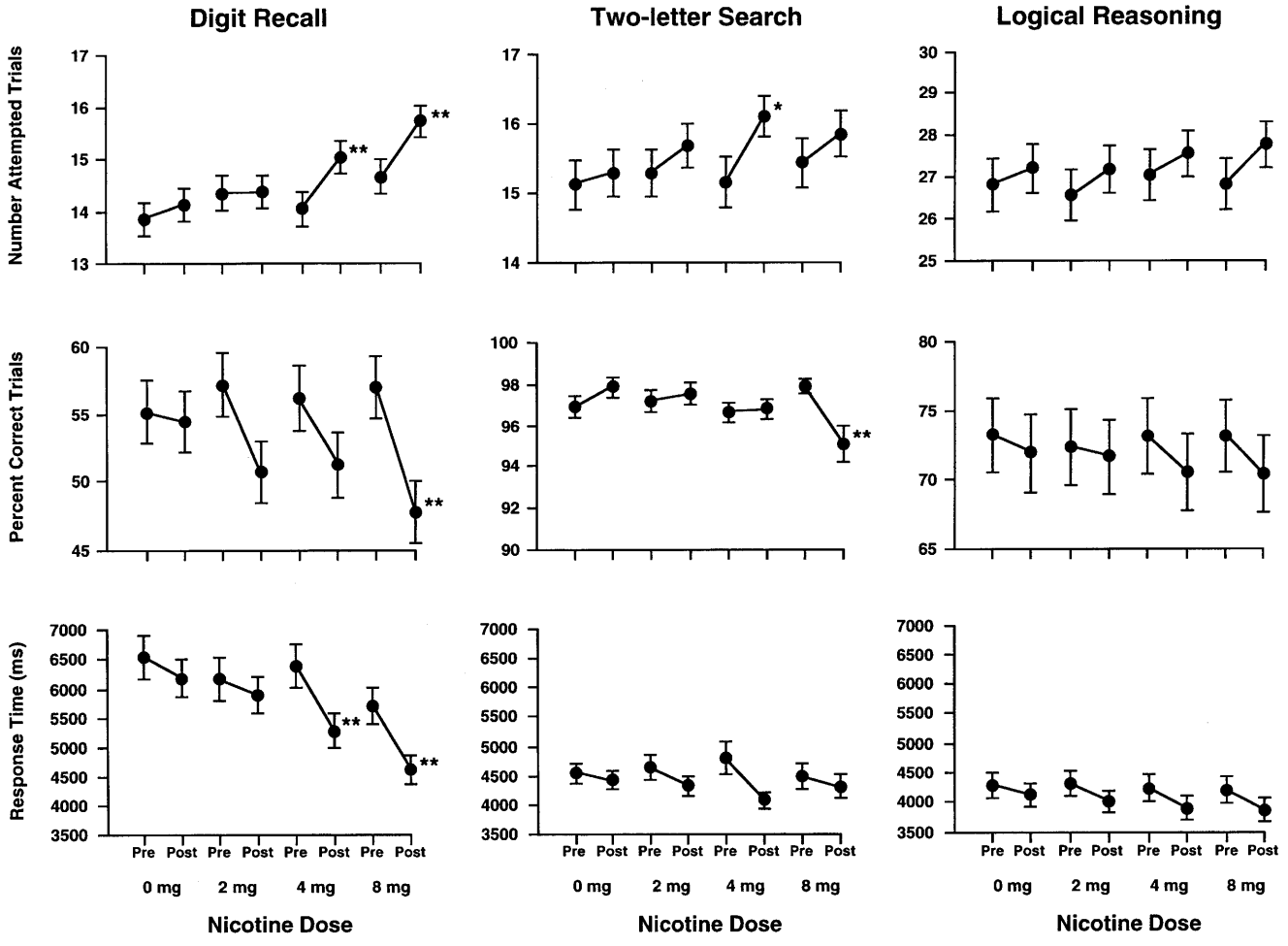

Fig. 1 Cognitive performance on the digit recall, two-letter search, and logical reasoning tests as a function of predose and postdose nicotine polacrilex administration. *Top row* shows number of attempted trials, *middle row* shows percent correct trials, and *bottom row* shows mean response time. Each data point represents the mean (±SEM) of 12 subjects averaged over 8 consecutive days of nicotine dosing. Significant differences between postdose nicotine data and placebo are indicated by **P*<0.05 and ***P*<0.01

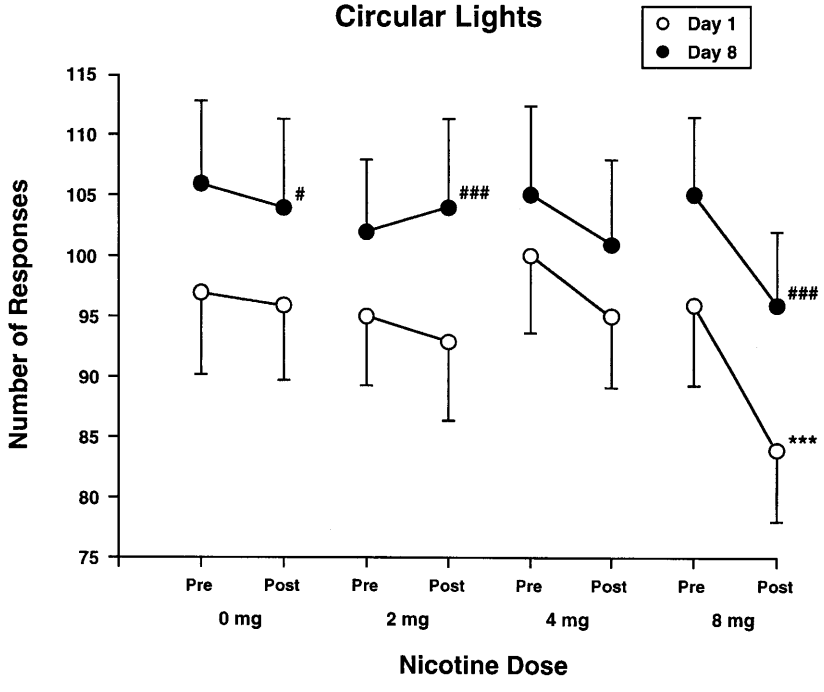

Fig. 2 Performance on the circular lights test as a function of predose and postdose nicotine polacrilex administration on the first (day 1) and last (day 8) day of nicotine dosing. Each data point represents the mean (±SEM) of 12 subjects. Significant differences between postdose nicotine data and placebo within the same day are indicated by ****P*<0.001. Significant differences between postdose data on day 1 versus day 8 within each dose are indicated by #*P*<0.05 and ###*P*<0.001

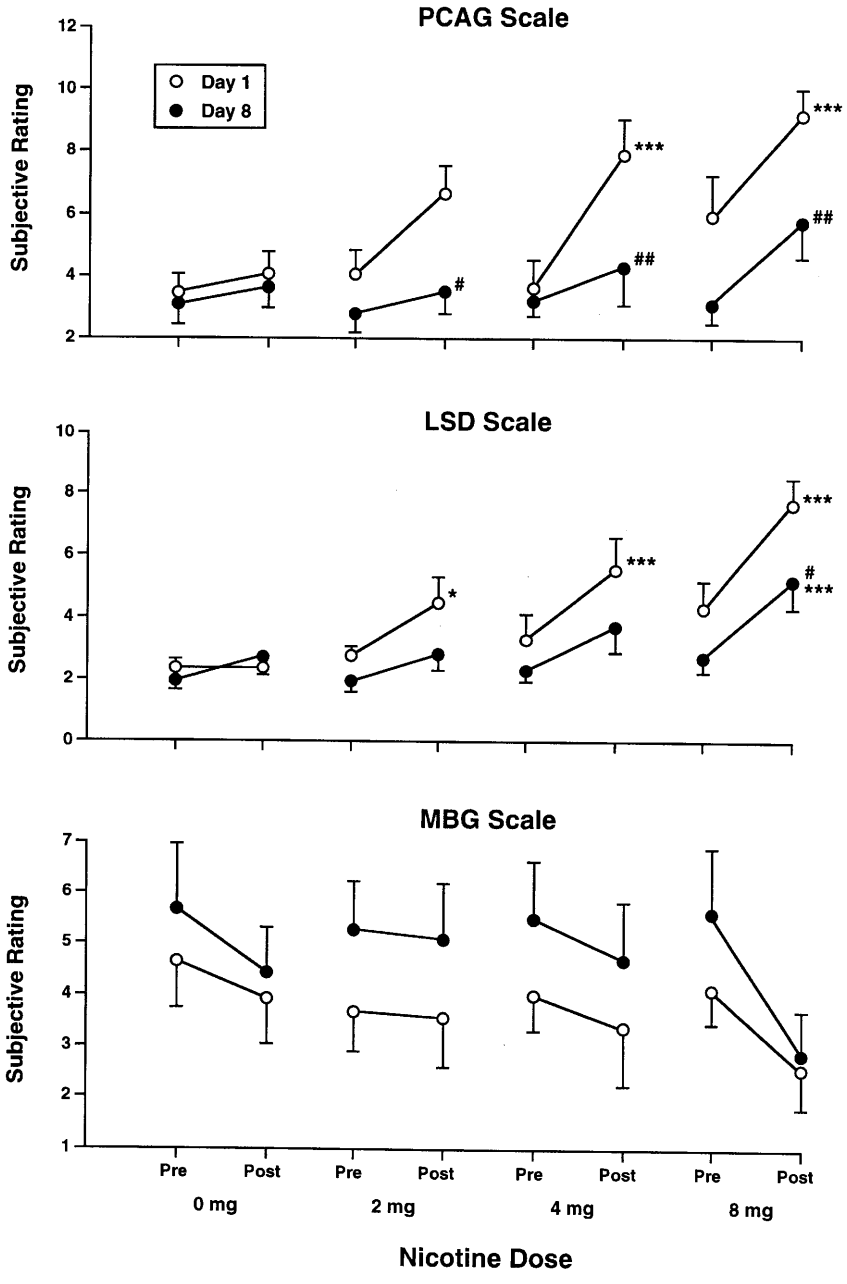

Fig. 3 Subjective responses on the ARCI as a function of predose and postdose nicotine polacrilex administration on the first (day 1) and last (day 8) day of nicotine dosing. Each data point represents the mean (±SEM) of 12 subjects. If the SEM is not visible, it is less than the radius of the symbol. Significant differences between postdose nicotine data and placebo within the same day are indicated by **P*<0.05 and ****P*<0.001. Significant differences between postdose data on day 1 versus day 8 within each dose are indicated by #*P*<0.05 and ##*P*<0.01. Significant differences between active nicotine and placebo averaged over 8 days of nicotine dosing were: PCAG: 4 and 8 mg (*P*<0.01), LSD: 4 and 8 mg (*P*<0.01), and MBG: 8 mg (*P*<0.01)

the digit recall test (Fig. 1). A dose×trial interaction [$F(3,33)=6.02$, $P<0.01$] was also obtained for attempted trials. In contrast, nicotine reduced percent correct responding [dose×trial interaction, $F(3,33)=3.19$, $P<0.05$]. The day×dose interaction was not significant for any measure on the digit recall test.

There was a dose×trial interaction [$F(3,33)=6.95$, $P<0.01$] for percent correct trials on the two-letter search test (Fig. 1). Number of attempted trials was increased and response time was decreased from predose to postdose at 4 mg nicotine on days 1 and 4 only, resulting in a day×trial interaction for both measures ($P<0.05$). The day×dose interaction was not significant for any measure on the two-letter search test.

On the logical reasoning test, decreases were observed from predose to postdose in percent correct responding [trial main effect, $F(1,11)=22.05$, $P<0.001$] and response time [trial main effect, $F(1,11)=4.88$, $P<0.05$] (Fig. 1). These decreases were seen across days for all nicotine doses including placebo. Nicotine had no effect on the serial addition/subtraction test.

Figure 2 shows that performance on the circular lights test was impaired by nicotine [dose main effect, $F(3,33)=7.55$, $P<0.01$; dose×trial interaction, $F(3,33)=8.65$, $P<0.001$]. Impairment was observed exclusively after the 8 mg dose ($P<0.01$), which decreased scores compared with placebo on Days 1, 2, and 4 ($P<0.001$). Although the day×dose interaction was not

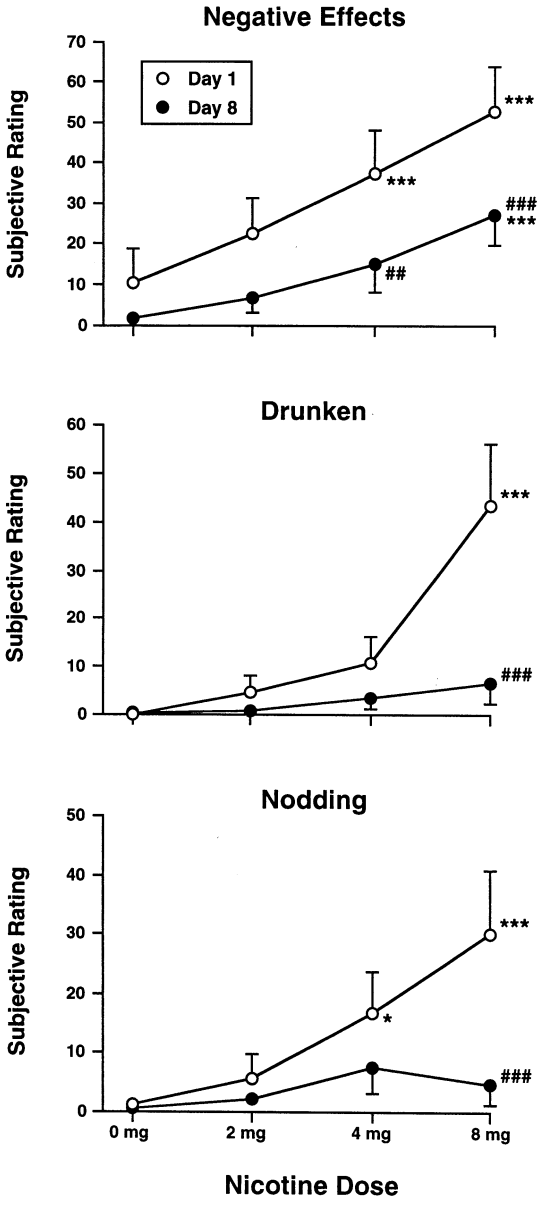

Fig. 4 Subjective responses to the item, "On a scale from 0 to 100 rate the degree of negative effects you obtained from this dose of the gum" and two drug symptoms from the SDQ, drunken and nodding, as a function of nicotine polacrilex administration on the first (day 1) and last (day 8) day of nicotine dosing. Each data point represents the mean (±SEM) of 12 subjects. If the SEM is not visible, it is less than the radius of the symbol. Significant differences between active nicotine and placebo within the same day are indicated by **P*<0.05 and ****P*<0.001. Significant differences between day 1 and day 8 within each dose are indicated by ##*P*<0.01 and ###*P*<0.001. Significant differences between active nicotine and placebo averaged over 8 days of nicotine dosing were: negative effects: 4 and 8 mg (*P*<0.01), drunken: 8 mg (*P*<0.01), and nodding: 4 and 8 mg (*P*<0.01)

significant, scores after the 8 mg dose on days 5–8 were not different from placebo, suggesting the development of tolerance. That scores at 8 mg on days 5–8 were greater than the 8 mg score on day 1 (*P*<0.001), which would also suggest tolerance, was due to the fact that performance improved over test days for all doses [day main effect, $F(7,77)=6.06$, $P<0.001$].

Subjective measures

ARCI

Nicotine dose-dependently increased scores on the PCAG [$F(3,33)=7.23$, $P<0.01$] and LSD [$F(3,33)=15.79$, $P<0.001$] scales and decreased scores on the MBG scale [$F(3,33)=6.30$, $P<0.01$] (Fig. 3). Significant dose×trial interactions were also obtained for the PCAG [$F(3,33)=8.00$, $P<0.001$], LSD [$F(3,33)=9.41$, $P<0.001$], and MBG [$F(3,33)=6.22$, $P<0.01$] scales, such that post-dose changes were greatest at the 4 and 8 mg doses. For each scale, the trial main effect was significant ($P<0.01$), and the day main effect was significant for the PCAG scale ($P<0.01$). The day×dose interaction was not significant for any scale. However, tolerance to the effects of nicotine on the PCAG scale was suggested because post-dose scores on day 8 were less than scores on day 1 ($P<0.05$), and day 8 scores for all doses were not significantly greater than 0 mg on day 8 (Fig. 3).

Positive-negative effects

There was a day [$F(7,77)=5.26$, $P<0.001$] and dose [$F(3,33)=17.74$, $P<0.001$] main effect for the Negative Effects question. Although the day×dose interaction was not significant, Figure 4 indicates that tolerance partially developed to the negative effects of nicotine. Scores on day 8 were less than those on day 1 at the 4 and 8 mg doses. The Positive Effects question was not affected by nicotine.

Desire-strength

Nicotine produced dose-dependent increases in ratings of dose strength [$F(3,33)=33.85$, $P<0.001$]. Scores after the 2, 4, and 8 mg doses were greater than placebo ($P<0.01$). Although there was a day×dose interaction [$F(21,231)=1.74$, $P<0.05$], there were no differences across days for any of the doses, indicating no tolerance development. Further, strength ratings at the 8 mg dose were greater than respective 0 mg scores on all test days ($P<0.05$). Nicotine had no effect on ratings of desire for another dose.

POMS

Nicotine increased scores on tension-anxiety [$F(3,33)=4.29$, $P<0.05$] and total mood disturbance [$F(3,33)=3.75$, $P<0.05$]. Tension-anxiety score at the 4 and 8 mg doses was greater than that at 0 mg ($P<0.05$), and total mood disturbance score was greater than place-

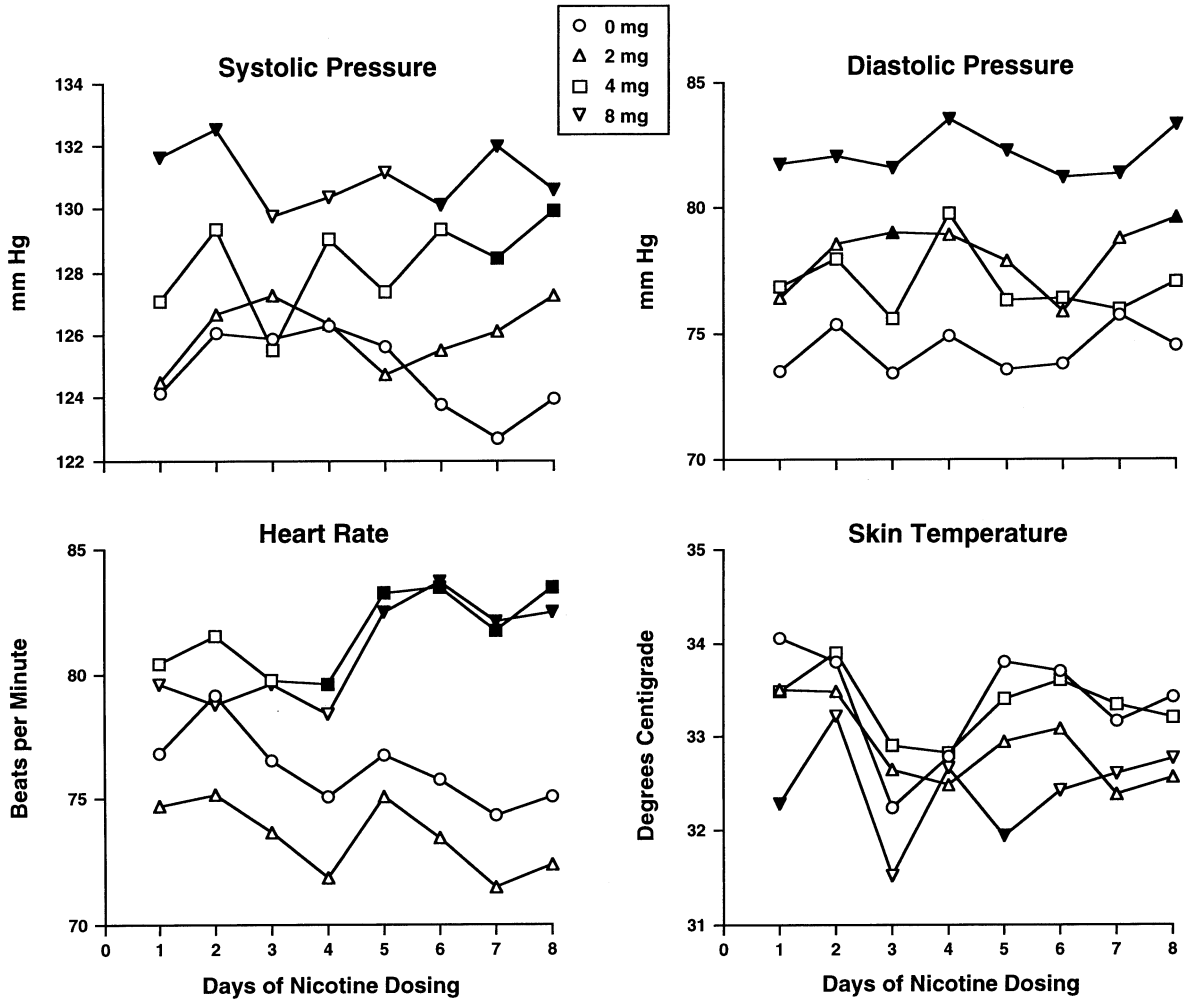

Fig. 5 Physiological measures as a function of postdose nicotine polacrilex administration and 8 days of nicotine dosing. Each data point represents the mean of 12 subjects; SEM was omitted for clarity. Significant (P<0.05) differences between active nicotine and placebo within the same day are indicated by *filled symbols*. There were no significant differences between day 1 and day 8 within each dose. Significant differences between active nicotine and placebo averaged over 8 days of nicotine dosing were: systolic pressure: 4 and 8 mg (P<0.01), diastolic pressure: 2, 4, and 8 mg (P<0.01), heart rate: 2, 4, and 8 mg (P<0.01), and skin temperature: 8 mg (P<0.01)

bo only after 8 mg nicotine (P<0.05). Nicotine produced a trend toward increased scores on depression-dejection (P=0.07) and fatigue-inertia (P=0.09). Nicotine did not affect the other POMS scales, and there was no day×dose interaction on any of the scales.

SDQ

Nicotine produced dose-related increases on the question, Do you feel the medicine? [F(3,33)=13.46, P<0.001). Scores after the 2, 4, and 8 mg doses were greater than placebo (P<0.01). A day×dose interaction [F(21,231)=2.09, P<0.01] was explained by relatively flat dose-response functions on days 4 and 5 only. There was no difference between scores on days 1 and 8, and scores after the 8 mg dose were greater (P<0.05) than placebo on each day, except days 4 and 5, indicating lack of tolerance development.

Drug class identifications for tobacco, alcohol, and placebo predominated. Averaged over days for 0, 2, 4, and 8 mg nicotine, respectively, percentage of tobacco identification was 30, 47, 51, and 58%; percentage of alcohol identification was 6, 10, 19, and 23%; and percentage of placebo identification was 59, 32, 22, 4%.

Of the 13 drug symptoms, five showed increased scores as a function of nicotine dose: high (P<0.01), drunken (P<0.01), nodding (P<0.01), nervous (P<0.05), and turning stomach (P<0.01). Two symptoms, drunken (day×dose interaction, P<0.05) and nodding showed evidence of tolerance (Fig. 4). Nicotine decreased ratings of relaxed (P<0.05) and produced an increased trend on sleepy (P=0.06), coasting (P=0.07), and skin itchy (P=0.08). The remaining symptoms, drive, normal, soapbox, and pleasant sick, were not affected by nicotine. Nicotine also had no effect on the drug liking item.

Physiological measures

Figure 5 shows postdose data from four physiological measures as a function of nicotine dose and session day. Nicotine increased systolic [$F(3,33)=7.98$, $P<0.001$] and diastolic [$F(3,33)=20.46$, $P<0.001$] blood pressure and mean arterial pressure [$F(3,33)=7.43$, $P<0.01$, data not shown]. Nicotine also altered heart rate [$F(3,33)=22.83$, $P<0.001$]. The day×dose interaction for heart rate approached significance ($P=0.08$), with increases on days 5–8 at 4 and 8 mg compared with placebo ($P<0.001$) (Fig. 5). There was a dose×trial interaction ($P<0.01$) for all measures, indicating greater postdose changes after 4 and 8 mg nicotine compared with lower doses.

Discussion

The main purpose of this study was to determine if nicotine would enhance psychomotor and cognitive abilities in nonsmokers using a range of nicotine doses and a repeated dosing regimen that would allow the development of tolerance to the initial dysphoric effects of nicotine. Although tolerance developed to some of the aversive effects of nicotine, no overall performance enhancing effects of nicotine were observed. Nicotine actually impaired gross motor coordination, working memory, visual scanning and recognition, and attention. These data do not support the hypothesis that performance-enhancing effects of nicotine contribute to the reinforcing effects of tobacco use during the early stages of dependence development.

Initial nicotine dosing

Nicotine produced dose-related increases in subjective ratings of dysphoria and negative mood, which is consistent with previous studies of nonsmokers administered nicotine polacrilex (Heishman et al. 1993), nicotine nasal spray (Perkins et al. 1993, 1994), and subcutaneous or intravenous nicotine injections (Russell et al. 1990; Soria et al. 1996; Foulds et al. 1997). Subjects reported decreased relaxation and increased tension, anxiety, nervousness, turning of stomach, drunkenness, and overall negative ratings. Nicotine also increased scores on the LSD scale of the ARCI, which assesses dysphoria and somatic changes (e.g., *I feel anxious and upset*, *Some parts of my body are tingling*, *I have a disturbance in my stomach*). Consistent with its low abuse liability (Nemeth-Coslett and Henningfield 1986; Nemeth-Coslett et al. 1987), nicotine polacrilex decreased scores on the MBG (euphoria) scale of the ARCI and had no effect on ratings of drug liking. Nicotine also produced a sedative effect, as reflected by increased scores on the PCAG scale and ratings of nodding. This finding is consistent with nicotine-induced decreases in ratings of vigor and arousal in nonsmokers (Perkins et al. 1993; Soria et al. 1996) and the depressant effect of nicotine on locomotor activity in nontolerant animals (Clarke and Kumar 1983).

Using tests that assessed a range of cognitive and psychomotor abilities, we found that nicotine did not enhance performance. Achieving an optimal dose of nicotine may be critical to observe performance enhancement because human (Perkins et al. 1994) and animal (Levin 1992) studies have shown that lower nicotine doses can improve and higher doses impair performance. However, we did not observe enhancement across a range of plasma nicotine concentration.

The effect of nicotine and smoking on human memory is inconsistent. Nicotine has been reported to enhance (Perkins et al. 1994; Phillips and Fox 1998), have no effect on (Heishman et al. 1993; Foulds et al. 1996) or impair (Dunne et al. 1986) memory recall or recognition in nonsmokers. Interestingly, on the digit recall test, nicotine increased number of attempted trials and decreased response time (enhancement), but impaired correct responding, suggesting a trade-off between response speed and accuracy. Using the same test, Foulds et al. (1996) reported an identical speed-accuracy trade-off in nonsmokers administered subcutaneous injections of nicotine. Enhanced response speed is a reliable effect of nicotine across behavioral domains (Heishman et al. 1994), including the Sternberg test of retrieval of information from working memory (Kerr et al. 1991; West and Hack 1991). Enhanced speed on the digit recall test occurred at the 4 and 8 mg doses, which produced average plasma nicotine concentration of 3.5 and 8.7 ng/ml, respectively. Perkins et al. (1994) reported that plasma nicotine concentration in the range of 4–6 ng/ml was associated with improved recognition memory (typically easier than recall memory tested in the present study) and faster motor speed in finger tapping, whereas plasma concentration greater than 8 ng/ml produced decrements in motor responding and memory. After 8 mg nicotine in the present study, plasma nicotine concentration ranged from 6.9 to 11.5 ng/ml, and response speed was improved, but accuracy on the digit recall test was significantly impaired.

In addition to assessing working memory, the digit recall test requires attention to the rapidly presented stimuli. The two-letter search test is a measure of selective attention and visual scanning. Nicotine decreased accuracy on both tests, suggesting an impairment of attentional abilities. The enhanced response speed observed on the digit recall test could be interpreted as an improvement in attention; however, enhanced speed (increased attempted trials and decreased response time) on the two-letter search test was seen only at the 4 mg dose on days 1 and 4. The lack of general enhancement by nicotine on tests assessing attention is surprising because nicotine reliably improves motor responding in tests of attention in nonsmokers (Kerr et al. 1991; Le Houezec et al. 1994; Perkins et al. 1994; Foulds et al. 1996).

Nicotine had no effect on verbal information processing, as assessed by the logical reasoning test, which is consistent with previous studies of nonsmokers using the same test (Heishman et al. 1993; Foulds et al. 1996) or

similar reasoning tests (Dunne et al. 1986). Foulds et al. (1996) reported that nicotine enhanced response time and accuracy on a rapid visual information processing (RVIP) test that requires considerable sustained attention to detect three consecutive even or odd digits presented singly at 600-ms intervals for 10 min. Although frequently cited as a test that demonstrates the cognitive-enhancing effects of nicotine (e.g., Warburton 1992), the four other studies using the RVIP test with nonsmokers or nonabstinent smokers found that smoking or nicotine had no effect on performance (Heishman et al. 1994). The other test in this study involving information processing, serial addition/subtraction, was not affected by nicotine. The relatively few studies examining the effects of smoking or nicotine on cognitive processes, such as reasoning, problem solving, and mathematical abilities, have reported inconsistent findings, leading Sherwood (1993, p. 167) to conclude, "As yet there appears no clear consensus on how nicotine affects the processes involved in the manipulation of information."

The 8 mg dose of nicotine impaired performance on the circular lights test. To our knowledge, this is the first report of nicotine's effect on gross motor coordination. In general, smoking or nicotine produces motor activation, such that locomotor activity in tolerant animals is increased (Clarke and Kumar 1983), and in nonsmoking humans, finger tapping rate is increased (West and Jarvis 1986; Perkins et al. 1990). Perkins et al. (1994) reported that lower nicotine doses increased and higher doses decreased finger tapping rate. Perkins et al. suggested that the decreased response rate was consistent with higher doses of nicotine producing blockade of peripheral ganglia. However, ganglionic blockade would be unlikely in the absence of overt signs of nicotine overdose. The most parsimonious explanation is that decreased gross (present study) and fine (Perkins et al. 1994) motor responding after high nicotine doses was secondary to increased dysphoria observed in both studies.

Nicotine increased all cardiovascular measures in a dose-related manner. Consistent with previous studies of nicotine in nonsmokers (Heishman et al. 1993; Perkins et al. 1994; Soria et al. 1996), we observed significant increases in systolic and diastolic blood pressure after 4 and 8 mg nicotine. Average increases of 3 and 6 mm Hg in systolic pressure and 3 and 8 mm Hg in diastolic pressure after 4 and 8 mg nicotine, respectively, were comparable to those seen in smokers after smoking one tobacco cigarette (Benowitz et al. 1988). Average heart rate increases of 5.5 beats/min after 4 mg nicotine and 4.7 beats/min after 8 mg nicotine were consistent with increases of 5–14 beats/min following administration to nonsmokers of nicotine polacrilex (Nyberg et al. 1982; Heishman et al. 1993), subcutaneous nicotine (Russell et al. 1990; Le Houezec et al. 1994; Foulds et al. 1997), and nicotine nasal spray (Perkins et al. 1994). The decrease in skin temperature was consistent with the effects of nicotine in smokers (Benowitz et al. 1982) and nonsmokers (Heishman et al. 1993) and reflects nicotine's peripheral vasoconstrictive effect.

Repeated nicotine dosing

Nicotine polacrilex produced orderly, dose-dependent increases in plasma nicotine and cotinine concentration on each day of dosing. Extracted nicotine, as estimated by residual nicotine content in the chewed gum, was about half of the administered dose, confirming previous data (Benowitz et al. 1987; Nemeth-Coslett et al. 1987, 1988). The actual systemic dose of nicotine was probably less because of expectoration and swallowing (Benowitz et al. 1987). Plasma nicotine concentration and extracted nicotine did not vary significantly over the 8 test days, suggesting that pharmacokinetic tolerance can be ruled out as a mechanism for any observed tolerance.

Chronic tolerance (i.e., less responsivity in smokers compared with nonsmokers) and acute tolerance (i.e., reduced responsivity to nicotine during a single session) in smokers and nonsmokers have been demonstrated for many of nicotine's effects, including cardiovascular, subjective, and performance (Perkins et al. 1989, 1993, 1994, 1995; Russell et al. 1990; Arcavi et al. 1994; Fattinger et al. 1997). We were interested in whether tolerance would develop to the aversive effects of nicotine in nonsmokers, which might mask the performance-enhancing effects of nicotine. Over 8 days of nicotine administration, tolerance developed to some, but not all, of the subjective aversive effects. By day 8, subjects were not as sedated as on day 1, as assessed by the PCAG scale and ratings of nodding (SDQ). Acute tolerance to the sedative effect of nicotine in nonsmokers was not observed (Perkins et al. 1993, 1994), suggesting that repeated dosing for more than 1 day is required to observe tolerance (cf., Stolerman et al. 1973; Clarke and Kumar 1983). The other subjective measures showing tolerance were overall negative effects and ratings of drunken; the latter was interpreted as feeling "woozy" or "dizzy." In contrast, tolerance did not develop to ratings of nervous, turning stomach, tension, and the LSD scale. Tolerance may never fully develop to some dysphoric effects because nonabstinent smokers can experience dizziness and nausea when they are exposed to high doses of nicotine (Houtsmuller and Stitzer 1999).

Although tolerance developed to some of the aversive effects of nicotine, we did not observe performance enhancement. The two cognitive tests that were the most sensitive to nicotine, digit recall and two-letter search, showed no evidence of tolerance to either performance speed or accuracy. In contrast, tolerance to the psychomotor impairing effect of nicotine on the circular lights test was suggested. Performance after 8 mg nicotine on days 5–8 was not different from placebo on the same days. However, a definitive conclusion regarding psychomotor tolerance is not possible because the day×dose interaction was not significant, and performance on the circular lights test improved with practice over the 8 test days. Perkins et al. (1994) found no evidence for acute or chronic tolerance to nicotine-induced impairment in hand steadiness, and observed acute sensitization (im-

proved accuracy) in recognition memory. These findings and those of the present study suggest that acquired tolerance to the psychomotor and cognitive impairing effects of nicotine requires repeated dosing for more than 8 days and that tolerance development may vary as a function of performance test.

Acute (Perkins et al. 1991, 1994, 1995; Arcavi et al. 1994; Fattinger et al. 1997) and chronic (Perkins et al. 1989, 1994) tolerance to the cardiovascular (increased heart rate and blood pressure) effects of nicotine in humans have been observed. However, the repeated dosing schedule in the present study revealed no tolerance to the effects of nicotine on any physiological measure. Interestingly, heart rate was increased to a higher level after 4 and 8 mg nicotine on days 5–8 compared with days 1–4 (Fig. 5). Whether this enhanced responding represents sensitization is unclear. Sensitization to the blood pressure, but not heart rate, effects of nicotine has been observed in rats (Cruz and Vidrio 1997). Sensitization is characterized by progressively increasing responsivity (Strakowski and Sax 1998), yet heart rate remained constantly elevated on days 5–8. However, a further increase may have been observed with continued dosing beyond 8 days. If this elevated heart rate (8–9 beats/min over placebo) were maintained with continued nicotine administration, it would suggest that the increased heart rate seen in smokers (Benowitz et al. 1984) originates within the first week of daily nicotine exposure.

Limitations and conclusions

Several factors limit the conclusions of this study. The absence of 8 days of only placebo dosing and the use of an ascending, rather than a randomized, dose schedule present the possibility that results were due to time of day or fatigue, rather than nicotine. However, analysis of the blinded placebo session before nicotine dosing began indicated a decrease in PCAG (sedation) scores ($P<0.05$) over the course of the day, suggesting that fatigue was not a confounding factor. Concerns about the safety of our research volunteers and the tolerability of nicotine in nonsmokers dictated that we administer the doses in ascending order each day. We have used an ascending dosing procedure successfully in the past (Heishman et al. 1993), and, except for the one participant who experienced an adverse reaction and was discharged, all subjects tolerated the nicotine doses with relatively minor adverse symptoms.

Several other issues limit the generality of the findings. The slow absorption of nicotine via polacrilex may not produce similar subjective and performance effects compared with the rapid nicotine absorption of inhaled cigarette smoke. However, the dysphoric effects of nicotine observed in the present study were similar to those seen in beginning smokers, and studies have reported lack of performance enhancement after rapidly delivered nicotine via smoking or injection (see Introduction). Our findings in nonsmoking men may not generalize to women given recent evidence of gender differences in smoking and responses to nicotine (Benowitz and Hatsukami 1998; Perkins et al. 1999). Finally, our results may not generalize to the early stages of nicotine dependence in adolescents who may differ from adult nonsmokers along psychological, environmental, biological, and genetic dimensions.

In summary, over the course of 8 days, tolerance developed to some of the aversive effects of nicotine in nonsmokers, but not to increased cardiovascular measures or psychomotor and cognitive impairment. Repeated exposure to nicotine for more than 8 days may be required to observe complete tolerance to initial nicotine-induced dysphoria and to demonstrate potential performance enhancement. Although this dosing paradigm only approximated the initiation of cigarette smoking, the finding that nicotine failed to enhance performance in nonsmokers suggests that people do not begin smoking for its purported cognitive benefits.

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