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Acute tolerence to nicotine in smokers: lack of dissipation within 2 hours

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Abstract Greater understanding of development and dissipation of acute tolerance to nicotine may help explain temporal patterns of nicotine self-administration in smokers. The time course of dissipation of acute tolerance to nicotine was examined in 16 smokers (8M, 8F) participating in four sessions differing on pretreatment exposure or time interval prior to nicotine (20 μg/kg) challenge: placebo 30 min before, or nicotine (20 μg/kg) 30, 60, or 120 min before challenge. Nicotine and placebo were administered by measured-dose nasal spray. The measurement battery consisted of subjective, cardiovascular, thermal pain detection, and behavioral performance measures. Results demonstrated significant acute tolerance (i.e. smaller responses to nicotine challenge following nicotine versus placebo pretreatment) for most subjective measures and for heart rate. Acute tolerance dissipated with lengthening inter-dose interval for two subjective measures, dose strength and arousal, but there was no tolerance dissipation for other measures. In contrast, nicotine pretreatment resulted in acute sensitization of finger temperature (vasoconstriction) response, which dissipated with lengthening interval. No acute tolerance was observed for thermal pain detection or performance measures. These findings demonstrate that acute tolerance develops quickly to some subjective and cardiovascular effects of nicotine. However, acute tolerance to most effects did not dissipate over 2 h, suggesting that, following acute tolerance development during initial exposure, most smokers generally obtain similar magnitude of effects from each subsequent nicotine exposure (i.e. cigarettes smoked later in the day).

Key words Nicotine · Acute tolerance · Acute sensitization · Smokers · Inter-dose interval

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Introduction

Animal studies and recent research with humans indicate that repeated exposure to nicotine produces adaptation to its effects. Adaptation resulting in smaller responses to nicotine is termed tolerance, while greater responses with repeated exposure is termed sensitization (Kalant and Khanna 1990). Tolerance and sensitization are important to study, since they reflect physiological adaptation to nicotine and may be relevant to the onset and maintenance of nicotine self-administration in humans (i.e. smoking behavior in smokers).

Acute tolerance reflects short-term adaptation of the body to nicotine and may help explain typical temporal patterns of nicotine self-administration over the course of the day in smokers. Many smokers, especially those considered highly nicotine dependent, anecdotally report that their initial cigarette of the day provides the biggest "boost" or pleasure, and that succeeding cigarettes produce less effect (e.g., Fagerstrom 1978; West and Russell 1987; Pomerleau and Pomerleau 1992), suggesting acute tolerance development. If effects of nicotine are reduced as the latency since prior exposure decreases, smokers may pace their smoking in such a way as to optimize the effects of each cigarette while minimizing tobacco withdrawal (Kozlowski and Herman 1984; Russell 1989).

Evidence for acute tolerance to subjective (e.g. Perkins et al. 1993) and cardiovascular (Jones et al. 1978; Rosenberg et al. 1980; Porchet et al. 1988; Perkins et al. 1989) responses to repeated dosings with nicotine has been observed in humans, although

behavioral or cognitive performance tasks may show no acute tolerance and perhaps even acute sensitization (Sherwood et al. 1992; Perkins et al. 1994a). In order to relate acute nicotine tolerance to the temporal pattern of smoking in smokers, it is important to understand the time course of development and dissipation of acute tolerance. Porchet et al. (1988) have devised a very sophisticated model of pharmacodynamic tolerance to cardiovascular effects of intravenous nicotine. In applying this model to heart rate responding, they estimated a half-life of 35 min for the development and dissipation of acute tolerance following a single pretreatment dosing. However, it is unclear whether other effects of nicotine follow a similar pattern. Interestingly, the typical interval between cigarettes in smokers allowed to smoke ad lib in the natural environment has been observed in one study to be 36 min (Hatsukami et al. 1988). This would suggest that cigarettes are often smoked at a point of substantial acute tolerance. On the other hand, inter-cigarette intervals may be as long as 2 h on some occasions (Frederiksen and Frazier 1977; Morgan et al. 1985). Furthermore, given the recent widespread adoption of indoor smoking bans, longer intervals between cigarettes may be quite common today. Smokers may therefore be obtaining greater effects from cigarettes temporally spaced farther apart due to environmental restrictions on smoking than from cigarettes smoked closer together, as may occur in the absence of restrictions. Thus, it is possible that such restrictions on smoking may have the unintended effect of producing greater reinforcement from some exposures to smoking.

The present study examined pattern of acute tolerance across subjective, cardiovascular, behavioral performance, and antinociceptive (i.e. pain relief) responses to nicotine as well as the time course of dissipation of this acute tolerance. One difficulty in examining this question with humans is difficulty in controlling doses between subjects and across administrations within subjects. For example, reduced magnitude of responding to subsequent cigarettes during the day could reflect attenuated intensity of smoking topography (and therefore attenuated exposure to nicotine) rather than acute tolerance (Herning et al. 1983). In contrast, longer latency between cigarettes is often associated with greater smoking intensity and greater boost in plasma nicotine (Hatsukami et al. 1988), complicating interpretation of differential responding across cigarettes as a function of inter-cigarette interval. Another difficulty is the fact that tobacco smoke contains at least 3800 compounds other than nicotine (National Research Council 1986), and it cannot be clearly demonstrated that changes in responding to smoking reflect adaptation to nicotine per se. Inclusion of such smoke stimuli also allows for the possibility that magnitude of responding may be influenced by conditioned tolerance to nicotine via smoking (e.g. Epstein et al. 1991). To circumvent these problems, we employed a measured-dose method of administering nicotine per se, isolated from tobacco smoke, via nasal spray solution.

Materials and methods

Subjects

Subjects were eight male and eight female smokers with a minimum smoking history of 15 cigarettes/day for 1 year. Subjects reported that they routinely smoke within 60 min of waking in the morning and all but one reported smoking within 30 min, a characteristic linked to greater tobacco dependence (Kozlowski et al. 1981). All subjects were examined by physician to rule out presence of medical or psychiatric problems, and urine drug screens were obtained to exclude subjects with substance abuse problems. Male and female smokers were equated on mean ± SEM age (21.4 ± 0.8 versus 21.8 ± 0.6 years, respectively), number of cigarettes per day (20.0 ± 1.4 versus 19.9 ± 1.0), number of years smoking regularly (4.3 ± 1.0 versus 3.2 ± 0.4), nicotine content of preferred brand (0.8 ± 0.1 versus 0.9 ± 0.1 mg), and Fagerstrom Tolerance Questionnaire (1978) score (5.8 ± 0.6 versus 6.0 ± 0.5). As expected, males weighed more (75.5 ± 4.4 versus 64.5 ± 3.6 kg, respectively) and were taller (177.3 ± 3.7 versus 164.3 ± 2.4 cm) than females. However, in this study, doses were corrected for subject body weight to control for this difference between male and female smokers (see below).

Design

Using a within-subjects design, four conditions were presented to each subject, with order of conditions counter-balanced. Three conditions involved repeated presentation of nicotine every 30 min for 2 h (trials 1–4) during a session to induce acute tolerance (Perkins et al. 1994a). These three conditions differed in the time interval between trial 4 and a fifth, "challenge" trial involving the same dose: 30 min ("standard", same as interval between previous trials), 60 min, and 120 min. These intervals were selected based on naturalistic studies showing that inter-cigarette interval in ad lib smoking generally ranges from 30 to 120 min (e.g. Frederiksen and Frazier 1977; Morgan et al. 1985; Hatsukami et al. 1988). Dissipation of acute tolerance would be evidenced by larger responses to the challenge dose as a function of longer interval between trials 4 and 5. The fourth condition involved repeated presentation of placebo every 30 min for 2 h, followed 30 min later (standard interval) by the challenge trial of nicotine dosing. Response to the challenge dose in this session provided an assessment of maximal effect, or absence of acute tolerance. Comparison of magnitude of responding to the challenge dose during the three nicotine pretreatment conditions with responding during the placebo pretreatment condition determines whether dissipation of acute tolerance is complete (i.e. magnitude of responding is not different) or partial (magnitude is less than that for placebo condition). This design is very similar to that used in past animal (e.g. Stolerman et al. 1973) and human (Porchet et al. 1988) research on acute tolerance to nicotine.

Nicotine/placebo dosing method

Nicotine (20 μg/kg) and placebo (0 μg/kg) was administered by measured-dose nasal spray pump, a method developed in our laboratory and used in numerous studies (e.g. Perkins et al. 1986, 1989,1993, 1994a). Doses consisted of the designated amount of nicotine in saline solution containing peppermint oil (Lorann Oils,

Lansing, Mich.) to mask the taste and smell of nicotine. For the average subject, the dose of nicotine was approximately 1.3 mg, within the range of nicotine obtained from smoking a single typical cigarette (Benowitz et al. 1990). This method has been shown to produce dose-dependent increases in plasma nicotine and has been described previously in more detail (Perkins et al. 1986, 1989, 1994a).

Measurement battery

Subjects completed a battery of self-report subjective measures, cardiovascular assessment, behavioral performance tasks, and latency to thermal pain detection.

Subjective Measures

The subjective measures included: 1) visual analog scale (VAS, ranging from 0 = not at all, 100 = very much) items of "Dose Strength", "Head Rush", "Jittery", and "Relaxed", 2) Profile of Mood States (POMS; McNair et al. 1971) scales of Tension (range = 0–32), Confusion (0–28), Vigor (0–32), and Fatigue (0–28), and the composite scale of Arousal (determined by subtracting Confusion and Fatigue from Tension plus Vigor; range = −56–64; deWit et al. 1989), and 3) the arousal portion of the Stress-Arousal Checklist (SACL-Arousal, Mackey 1980). These and similar scales have been used in previous studies of the subjective effects of nicotine and other drugs (e.g. Henningfield et al. 1985; Fischman and Foltin 1991; Perkins et al. 1993, 1994a).

Cardiovascular assessment

Heart rate (HR, in beats per min, or BPM) was assessed by feeding the EKG trace from a Grass Model 7P polygraph into a data acquisition board (DASH-16, Metrabyte, Taunton, Mass.) in an IBM AT-compatible computer, which counted the number of R-waves per min. Systolic (SBP) and diastolic blood pressure (DBP), in mmHg, were obtained automatically by Dinamap blood pressure recorder (Critikon, Tampa, Fla.). Finger temperature (in °C), a measure of vasoconstriction, was obtained from a thermistor probe (Model 427, Yellow Springs Instruments, Yellow Springs, Ohio) taped to the middle finger of the non-preferred hand. The probe was attached to a resistive bridge and connected to the data acquisition board, as described previously (Perkins et al. 1994b). These measures have been examined in previous human research on acute tolerance to nicotine (e.g. Rosenberg et al. 1980; Porchet et al. 1988; Perkins et al. 1994a) and may reflect acute sympathetic activation due to nicotine (Porchet et al. 1988).

Thermal pain detection

The procedure for assessing thermal pain detection has been described in detail elsewhere (Perkins et al. 1992, 1994b). Radiant heat is generated by a 1000-W tungsten-halogen quartz projection lamp, and its precise onset and offset are controlled by an electronic shutter operated by computer signals via the data acquisition board. Latency between shutter opening and subject's pressing a computer key associated with "pain", is recorded to the nearest 0.01 s by the computer's internal timer. Mean ± SEM latency in the absence of drug exposure is typically 37 ± 2 s (Perkins et al. 1994b).

Behavioral performance tasks

The behavioral performance tasks included finger-tapping speed, handsteadiness, and memory recognition. These tasks were employed because of previous research indicating their sensitivity to nicotine effects (USDHHS 1988; Perkins et al. 1994a). Each of these tasks, which are presented and scored by computer, has been used in previous studies and is described in detail elsewhere (Perkins et al. 1990, 1994a). Briefly, finger-tapping speed was assessed by instructing subjects to tap on one key of a keypad as quickly as possible for 30 s. Handsteadiness was determined by having subjects hold a metal stylus (2 mm in diameter) within a 3.0 mm hole without touching the sides of the hole for two 20-s periods. Length of contact was determined by computer to the nearest 0.01 s. Memory recognition was assessed by presenting a list of 20 one-syllable nouns all at once 5 min after dosing. Testing for recall occurred 15 min after dosing by presenting 40 words (20 original and 20 new), one at a time, and having subjects respond on one of two keys, representing "yes" or "no", as to whether the word was one of the original words in the list of 20.

For each of these performance tasks, a small monetary incentive contingent on performance was provided (e.g. $0.01 for each tap above 170) to help maintain motivation for good performance across the numerous trials.

Procedure

Subjects participated in one introductory session to learn the tasks and procedures and four experimental sessions, each following overnight abstinence from smoking, caffeine, and food. On each of the 5 days, subjects were first tested for expired-air carbon monoxide to confirm overnight smoking abstinence (CO ≤ 13 ppm). Following attachment of cardiovascular assessment equipment, subjects remained quiet for at least 10 min while resting in a comfortable armchair. Three practice trials with the measurement battery (except memory recognition, which for practical reasons could not be repeatedly assessed prior to dosing) were performed to generate stable predrug responding. A baseline assessment of subjective measures (except dose strength) was then obtained, followed by baseline measures of HR and BP and a baseline trial with the thermal pain detection and behavioral performance tasks (see above). Subjects were then administered 20 μg/kg nicotine (three sessions) or placebo (0 μg/kg, one session) every 30 min for 2 h (trials 1–4). Each dosing was followed by subjective and cardiovascular measures over the first 5 min and thermal pain latency and behavioral performance tasks during the subsequent 10 min. Subjects remained at quiet rest for the remainder of each trial until the next dosing.

Following the fourth trial of nicotine or placebo dosing, each session finished with a fifth, challenge trial involving 20 μg/kg nicotine. On the 3 days in which nicotine was presented during trials 1–4, this challenge dose was presented 30 min (standard interval), 60 min, or 120 min after trial 4. The challenge was presented 30 min following trial 4 on the day involving placebo dosing during trials 1–4. Subjects completed the subjective, cardiovascular, and behavioral performance measures in the same manner during trial 5 as in previous trials. A single blood sample was obtained after the last performance measure in order to provide some gauge of nicotine exposure during the challenge trial as a function of prechallenge conditions. Approximately 7 ml of whole blood were obtained from venipuncture of the antecubital vein, spun down immediately, and the plasma stored at −70°C for analysis. Plasma nicotine concentrations were determined by gas chromatography with nitrogen-phosphorus detection using 5-methylnicotine as the internal standard (Jacob et al. 1981).

Data analysis

Given the large number of dependent measures across the four response domains (subjective, cardiovascular, antinociception, performance), initial analysis of dissipation of acute tolerance involved

a series of multivariate analyses of variance (MANOVAs) to determine overall effects of condition (4) and gender. Separate MANOVAs were performed for subjective, cardiovascular, and performance measures. (Antinociception involved only one measure and was therefore analyzed by separate ANOVA.) The dependent variable in each analysis was difference from initial, pre-drug baseline (i.e. prior to trial 1) in response to the 20 μg/kg nicotine challenge dose (trial 5). Exceptions were absolute scores on the subjective measure of dose strength (where a baseline score was not possible) and the performance measure of memory recognition [for which the absolute challenge trial score was considered more reliable than change from baseline, based on previous research (Perkins et al. 1994a)]. Significant MANOVAs were followed up by analyses of variance (ANOVA) of individual measures. Follow-up comparisons using Fisher's least significant difference *t*-test (Huitema 1980) were performed between placebo pretreatment and each of the three nicotine pre-treatment conditions (30, 60, 120-min interval) to determine presence of acute tolerance to the challenge nicotine dose. Comparisons among the three nicotine pre-treatment conditions were also performed to determine whether dissipation occurred with lengthening inter-dose interval (i.e. greater responding following 60- or 120-min intervals versus 30-min interval) or whether acute tolerance development required inter-dose intervals longer than 30 min (i.e. smaller responding following 60- or 120-min intervals versus 30-min interval).

Results

Plasma nicotine concentrations were greatest for the 30-min (mean ± SEM = 17.2 ± 1.3 ng/ml) and 60-min (18.1 ± 1.3 ng/ml) intervals compared with the 120-min (13.7 ± 0.7 ng/ml) and placebo pretreatment conditions (5.7 ± 0.5 ng/ml), [$F(3,36) = 50.92$, $P < 0.001$]. These plasma nicotine differences due to pretreatment condition do not confound observations of acute tolerance, since smaller responding following nicotine pretreatment (30-, 60-, or 120-min inter-dose interval conditions) in spite of greater plasma nicotine levels is consistent with presence of acute tolerance. There were no significant effects of gender on plasma nicotine [$F(1,12)<1$].

MANOVA results of responses to the 20 μg/kg challenge trial indicated significant main effects of condition for subjective measures [$F(12,103) = 4.52$, $P < 0.001$], cardiovascular measures [$F(12,96) = 4.94$, $P < 0.001$], and performance tasks [$F(15,105) = 5.56$, $P < 0.001$]. There were no significant effects of gender, and subsequent analyses were conducted after collapsing across males and females.

Subjective effects

Significant effects of pretreatment condition were observed for the following subjective responses to the 20 μg/kg nicotine challenge: VAS items of Dose Strength, [$F(3,45) = 11.74$, $P < 0.001$], Head Rush [$F(3,45) = 7.99$, $P < 0.001$], and Relaxed [$F(3,45) = 7.57$, $P < 0.001$], SACL-Arousal [$F(3,45) = 3.10$, $P < 0.05$], and POMS scale of Tension [$F(3,45) = 4.47$, $P < 0.01$]. Nicotine challenge increased POMS-Vigor and decreased POMS-Fatigue, but there were no differences in these or any other subjective measures due to pretreatment condition. As shown in Fig. 1, nicotine pretreatment produced significant acute tolerance (i.e. placebo versus each nicotine pretreatment condition) to nicotine challenge effects of increased Dose Strength, Head Rush, Tension, Arousal (SACL), and to decreases in Relaxed. Furthermore, acute tolerance to Dose Strength partially dissipated with lengthening interval between nicotine pretreatment and challenge, as Dose Strength rating was significantly greater at 120-min versus 30-min intervals [$t = 2.55$, $P < 0.05$] (despite smaller plasma nicotine level). Dissipation of acute tolerance

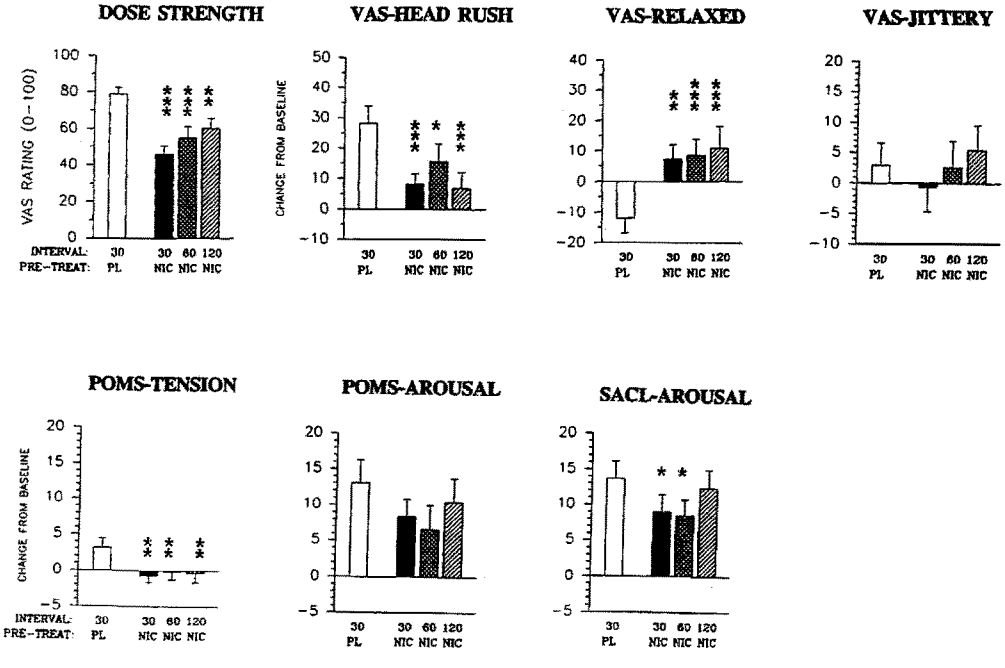

Fig. 1 Mean ± SEM subjective responses to 20 μg/kg nicotine challenge (trial 5) as a function of prior dosing during trials 1–4 (*pre-treat*: placebo or 20 μg/kg) and/or interval since trial 4 (30, 60, 120 min). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for difference from placebo pretreatment

to SACL-Arousal was nearly significant between the 30- and 120-min ($t = 1.69$, $P < 0.10$) and between 60- and 120-min ($t = 1.92$, $P < 0.10$) intervals. However, there was no other evidence of acute tolerance dissipation with lengthening interval between pretreatment and challenge, suggesting that inter-dose intervals longer than 2 h are needed to see such dissipation to the other subjective effects showing acute tolerance (i.e. increase in Head Rush and POMS-Tension, and decrease in Relaxed).

Cardiovascular

Heart rate and finger temperature were significantly influenced by pretreatment condition, [$F(3,45) = 7.09$, $P < 0.001$ and $F(3,42) = 3.47$, $P < 0.05$, respectively], as shown in Fig. 2. There were no significant effects of condition on systolic or diastolic blood pressure responses to nicotine challenge (mean ± SE increases of 11.9 ± 1.5 and 7.7 ± 1.4 mmHg, respectively, for all conditions). For HR, acute tolerance was observed for each of the three nicotine versus placebo pretreatment conditions. However, there were no significant differences among the three interval conditions, indicating no dissipation of acute tolerance to HR response. For finger temperature, a different pattern emerged. Decrease in finger temperature (i.e. vasoconstriction) was greatest at the 30-min interval, indicating maximal response to nicotine. Thus, there was no evidence of acute tolerance, and results suggested acute sensitization to vasoconstrictive effects of nicotine. This effect of nicotine at 30-min interval was significantly reduced at the 60-min interval, ($t = 2.22$, $P < 0.05$) (despite similar plasma nicotine level), and the 120-min interval, ($t = 2.89$, $P < 0.01$), which were not significantly different from placebo pretreatment, indicating complete dissipation of acute sensitization.

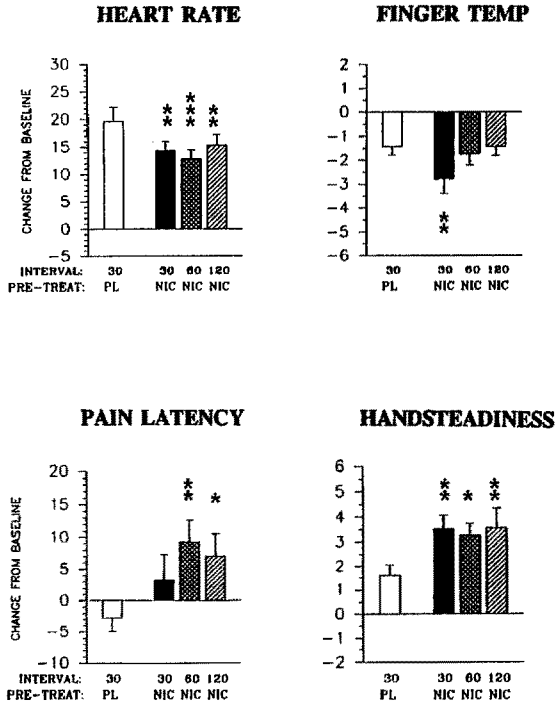

Fig. 2 Mean ± SEM heart rate (BPM), finger temperature (°C), thermal pain detection latency (in s) and handsteadiness (seconds of contact) responses to nicotine challenge dosing as a function of prior dosing during trials 1–4 and/or interval since trial 4. Other details as in Fig. 1. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for difference from placebo pretreatment

Antinociception

The effect of pretreatment condition was also significant for thermal pain latency [$F(3,45) = 2.98$, $P < 0.05$]. Similar to finger temperature, pain latencies following nicotine challenge were longer with nicotine pretreatment compared with placebo pretreatment, indicating no acute tolerance, as also shown in Fig. 2. However, this effect actually increased (non-significantly), rather than dissipated, with longer interval between nicotine dosings, suggesting greater antinociceptive effects (and possibly sensitization) with longer delay between nicotine dosing. Alternatively, there was no increase in latency due to nicotine challenge in the placebo pretreatment condition, suggesting that longer latency in the nicotine pretreatment conditions may be due to greater accumulation of nicotine. Previous research has shown antinociceptive effects of nicotine only at relatively high doses (Perkins et al. 1994b).

Behavioral performance

The effect of condition was significant for handsteadiness [$F(3,45) = 4.64$, $P < 0.01$], as also shown in Fig. 2, but not for finger-tapping (mean increases of 4.4 ± 2.2 for all four conditions) or memory recognition (mean percent correct of 76.2 ± 2.6 for all conditions). Nicotine acutely impaired handsteadiness, as found previously (Perkins et al. 1994a), and this impairment was exacerbated by nicotine pretreatment, regardless of interval prior to challenge. As with antinociception, this greater response following nicotine pretreatment could be due to sensitization or to greater accumulation of nicotine. Nicotine challenge dosing generally increased finger-tapping rate above pre-drug baseline, regardless of pretreatment condition, but there was no clear dissipation of these effects with longer inter-dose interval.

Discussion

Compared with placebo pretreatment, nicotine pretreatment generally resulted in reduced subjective

and heart rate responding of tobacco smokers to a nicotine challenge dose, thus demonstrating rapid acute tolerance to nicotine's effects on these measures. However, there was no evidence of acute tolerance to thermal pain detection or behavioral task performance. These results are consistent with the few previous studies examining acute tolerance during repeated exposures to nicotine per se in humans (Jones et al. 1978; Rosenberg et al. 1980; Porchet et al. 1988; Perkins et al. 1993, 1994a). They also verify that the appearance and magnitude of acute tolerance varies greatly depending on the response domain of interest (Perkins 1994a).

However, the main question addressed in this study was on whether or not acute tolerance dissipates with lengthening interval prior to nicotine challenge. Subjective effects of dose strength and arousal, previously found to be sensitive to prior chronic as well as acute exposure to nicotine (Perkins et al. 1993, 1994a), showed maximal acute tolerance when the nicotine challenge dose was administered 30 and/or 60 min after previous dosing. The magnitude of this tolerance was partially (dose strength) or completely (arousal) dissipated when nicotine administration was delayed to 120 min after previous dosing. These results suggest that widely spaced cigarette smoking produces greater responses in a few selected effects of nicotine which may be reinforcing. Use of measures more closely associated with drug reinforcement, such as "Liking", may have provided even stronger evidence (e.g. Henningfield et al. 1985; deWit et al. 1989).

On the other hand, the majority of subjective effects showed no dissipation of acute tolerance with lengthening interval prior to nicotine challenge, and some showed no acute tolerance at all. Similar lack of acute tolerance dissipation was observed for heart rate, although finger temperature (vasoconstriction) effects of nicotine were acutely sensitized by prior nicotine exposure, and this sensitization dissipated with lengthening inter-dose interval. Performance effects of nicotine uniformly showed no acute tolerance and tended to increase following nicotine pretreatment. Therefore, these results indicate that only a few of nicotine's many effects appear to be influenced by the rather narrow differences in inter-dose interval typically experienced by smokers during the course of a day. In any case, this differential pattern of acute tolerance dissipation across responses suggests differential mechanisms responsible for that tolerance (Porchet et al. 1988; Perkins et al. 1994a).

It is important to note that the findings observed in this study may be specific to the nicotine dose, dosing pattern, and measures used, and examination of dissipation with other dosing procedures or other effects may reveal different results. For example, Porchet et al. (1988) found partial dissipation of acute tolerance to HR effects within 2 h and complete dissipation 3 h after previous nicotine exposure. However, that study involved one pretreatment exposure and administered nicotine by slow intravenous infusion, compared with four pretreatment exposures via nasal spray in the current study. Furthermore, although nicotine was administered in the absence of tobacco smoke stimuli for methodological reasons, the pattern of acute tolerance development and dissipation to effects of tobacco smoking may be different from effects of nicotine per se.

Nevertheless, most dependent smokers wait no longer than 2 h between cigarettes (Frederiksen and Frazier 1977; Morgan et al. 1985). Therefore, our results would suggest that, following acute tolerance development during initial nicotine exposure from their first cigarettes of the day, smokers experience generally similar effects from each subsequent cigarette (with some exceptions, e.g. SACL-Arousal). One implication of these results is related to environmental restrictions on smoking which reduce frequency and increase spacing between smoking exposures. These data suggest that subjective and physiological effects of nicotine derived from smoking under conditions of temporal restrictions would not be significantly different from nicotine effects derived during more frequent smoking.

Given little evidence of acute tolerance dissipation with a 2-h inter-dose interval, it would be important to examine tolerance dissipation over longer intervals between nicotine exposures. Smokers differ in their frequency and patterns of smoking over the course of a day (e.g. Frederiksen and Frazier 1977; Morgan et al. 1985; Russell 1989), and a minority of smokers often smoke less frequently than once every 2 h (e.g. Shiffman et al. 1992). Thus, differential rates of acute tolerance development and dissipation between individuals may help explain these very different smoking patterns (Russell 1989). It is also possible that such tolerance dissipation (chronic as well as acute) may help explain early relapse during initial attempts to stop smoking or "cut down". Greater reinforcement during subsequent exposure to nicotine after a short period of abstinence could possibly account for the "priming" effect of acute drug intake on precipitating drug relapse (deWit and Stewart 1981), a phenomenon which has recently been observed in cigarette smokers trying to quit (Chornock et al. 1992).

In summary, nicotine pretreatment produced acute tolerance to most subjective effects and to heart rate response to nicotine challenge, but partial or complete tolerance dissipation within 2 h was observed only with subjective measures of dose strength and arousal. These findings suggest that 1- or 2-h intervals between cigarettes may not significantly increase the reinforcing effects of smoking. Future research should examine longer intervals between cigarettes, given individual differences in smoking patterns and the possible relevance of tolerance dissipation to early smoking relapse.

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References

Benowitz NL, Porchet H, Jacob P (1990) Pharmacokinetics, metabolism, and pharmacodynamics of nicotine. In: Wonnacott S, Russell MAH, Stolerman IP (eds) Nicotine psychopharmacology: molecular, cellular, and behavioural aspects. Oxford University Press, New York, pp 112–157

Chornock WM, Stitzer ML, Gross J, Leischow S (1992) Experimental model of smoking re-exposure: effects on relapse. Psychopharmacology 108:495–500

deWit H, Stewart J (1981) Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 75:134–143

deWit H, Pierri J, Johanson CE (1989) Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharmacol Biochem Behav 33:205–213

Epstein LH, Caggiula AC, Perkins KA, McKenzie SJ, Smith JA (1991) Conditioned tolerance to the heart rate effects of smoking. Pharmacol Biochem Behav 39:15–19

Fagerstrom KO (1978) Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav 3:235–241

Fischman MW, Foltin RW (1991) Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. Br J Addict 86:1563–1570

Frederiksen LW, Frazier M (1977) Temporal distribution of smoking. Addict Behav 2:187–192

Hatsukami DK, Pickens RW, Svikis DS, Hughes JR (1988) Smoking topography and nicotine blood levels. Addict Behav 13:91–95

Henningfield JE, Miyasato K, Jasinski DR (1985) Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther 234:1–12

Herning RI, Jones RT, Benowitz NL, Mines AH (1983) How a cigarette is smoked determines blood nicotine levels. Clin Pharmacol Ther 33:84–90

Huitema B (1980) Analysis of covariance and alternatives. Wiley, New York

Jacob P, Wilson M, Benowitz NL (1981) Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. J Chromatogr 222:61–70

Jones RT, Farrell TR, Herning RI (1978) Tobacco smoking and nicotine tolerance. In: Krasnegor NA (ed) Self-administration of abuse substances: methods for study. US Govt Printing Office, Washington DC, pp 202–208

Kalant H, Khanna JM (1990) Methods for the study of tolerance. In: Adler M, Cowan A (ed) Modern methods in pharmacology, vol. 6. Wiley-Liss, New York, pp 43–66

Kozlowski LT, Herman CP (1984) The interaction of psychosocial and biological determinants of tobacco use: more on the boundary model. J Appl Soc Psychol 14:244–256

Kozlowski LT, Director J, Harford MA (1981) Tobacco dependence, restraint, and time to the first cigarette of the day. Addict Behav 6:307–312

Mackey CJ (1980) The measurement of mood and psychophysiological activity using self-report techniques. In: Martin I, Venables PH, (eds), Techniques in psychophysiology. Wiley, New York, pp 501–562

McNair DM, Loor M, Droppelman LF (1971) Profile of mood states. Educational and Testing Service, San Diego, Calif.,

Morgan SF, Gust SW, Pickens RW, Champagne SE, Hughes JR (1985) Temporal patterns of smoking topography in the natural environment. Int J Addict 20:613–621

National Research Council (1986) Environmental tobacco smoke: measuring exposures and health effects. National Academy Press, Washington D.C.

Perkins KA, Epstein LH, Stiller R, Jennings JR, Christiansen C, McCarthy T (1986) An aerosol spray alternative to cigarette smoking in the study of the behavioral and physiological effects of nicotine. Behav Res Methods Instr Comput 18:420–426

Perkins KA, Epstein LH, Stiller RL, Marks BL, Jacob RG (1989) Chronic and acute tolerance to the heart rate effects of nicotine. Psychopharmacology 97:529–534

Perkins KA, Epstein LH, Stiller RL, Sexton JE, Debski T, Jacob RG (1990) Behavioral performance effects of nicotine in smokers and nonsmokers. Pharmacol Biochem Behav 37:11–15

Perkins KA, Grobe JE, Jennings JR, Epstein LH, Elash C (1992) A technique for rapid, reliable assessment of thermal pain threshold in humans. Behav Res Methods Instr Comput 24:60–66

Perkins KA, Grobe JE, Epstein LH, Caggiula AC, Stiller RL, Jacob RG (1993) Chronic and acute tolerance to subjective effects of nicotine. Pharmacol Biochem Behav 45:375–381

Perkins KA, Grobe JE, Fonte C, Goettler J, Caggiula AR, Reynolds WA, Stiller RL, Scierka A, Jacob RG (1994a) Chronic and acute tolerance to subjective, behavioral, and cardiovascular effects of nicotine in humans. J Pharmacol Exp Ther 27

Perkins KA, Grobe JE, Stiller RL, Scierka A, Goettler J, Reynolds WA, Jennings JR (1994b) Effects of nicotine on thermal pain detection in humans. Exper Clin Psychopharmacol 2:95–106

Pomerleau CS, Pomerleau OF (1992) Euphoriant effects of nicotine in smokers. Psychopharmacology 108:460–465

Porchet HC, Benowitz NL, Sheiner LB (1988) Pharmacodynamic model of tolerance: application to nicotine. J Pharmacol Exp Ther 244:231–236

Rosenberg J, Benowitz NL, Jacob P, Wilson KM (1980) Disposition kinetics and effects of intravenous nicotine. Clin Pharmacol Ther 28:517–522

Russell MAH (1989) Subjective and behavioural effects of nicotine in humans: some sources of individual variation. Prog Brain Res 79:289–302

Sherwood N, Kerr JS, Hindmarch I (1992) Psychomotor performance in smokers following single and repeated doses of nicotine gum. Psychopharmacology 108:432–436

Shiffman S, Zettler-Segal M, Kassel J, Paty J, Benowitz NL, O'Brien G (1992) Nicotine elimination and tolerance in non-dependent cigarette smokers. Psychopharmacology 109:449–456

Stolerman IP, Fink R, Jarvik ME (1973) Acute and chronic tolerance to nicotine measured by activity in rats. Psychopharmacology 30:329–342

US Department of Health and Human Services (1988) The health consequences of smoking: nicotine addiction. A Report of the Surgeon General. US Government Printing Office, Washington D.C.

West RJ, Russell MAH (1987) Cardiovascular and subjective effects of smoking before and after 24 hr of abstinence from cigarettes. Psychopharmacology 92:118–121