Dissociation of Nicotine Tolerance from Tobacco Dependence in Humans

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ABSTRACT

Chronic functional tolerance to nicotine generally is believed to be associated with processes responsible for tobacco dependence. The dose-related effects of nicotine (0–20 μg/kg by nasal spray) on subjective, cardiovascular, and performance responses were compared among four groups varying in current or past dependence: dependent smokers (21 cigarettes per day for 20 years; n = 45), nondependent smokers (three cigarettes per day for 14 years; n = 12), former dependent smokers (mean of 7 years quit after smoking 25 cigarettes per day for 19 years; n = 17), and life-long nonsmokers (n = 19). Chronic tolerance was determined by a shift to the right, or flattening, of the dose-response curve relative to the curve for nonsmokers. Responses were corrected for plasma nicotine concentration to rule out dispositional tolerance. Chronic tolerance was observed for most subjective responses, but little or none for cardiovascular and performance effects. Tolerance was substantial and virtually identical between dependent and nondependent smokers, whereas tolerance of former smokers was intermediate between nonsmokers and dependent smokers. Identical chronic tolerance between dependent and nondependent smokers indicates that tolerance is not a linear function of smoking exposure and does not require presence of dependence. Thus, the wide variability in daily smoking rate among smokers cannot be attributed to differences in tolerance and must involve other processes of adaptation to nicotine. The modest reversal of tolerance in long-time former smokers suggests that such tolerance reversal is either limited or extremely slow after extended abstinence, despite loss of dependence. These results suggest there is no close link between nicotine tolerance and dependence and question the utility of tolerance as one of the criteria for defining dependence.

Nicotine is the primary constituent of tobacco that reinforces cigarette smoking behavior (Stolorman and Jarvis, 1995), the leading preventable cause of morbidity and mortality. The acute effects of nicotine responsible for initiation of smoking and onset of dependence are not specifically known but likely involve its influence on subjective mood (Henningfield et al., 1985; Perkins et al., 1997a,b; Jones et al., 1999). Subjective effects of nicotine, some of which may be similar to those of cocaine or other drugs of abuse (Henningfield et al., 1985; Jones et al., 1999), are associated with increased neuronal activity in nucleus accumbens, amygdala, and other brain regions believed to be involved in drug reinforcement and dependence (Stein et al., 1998).

After long-term exposure to tobacco smoking, many subjective effects of nicotine are attenuated (Perkins et al., 1994), reflecting chronic tolerance that is functional in nature (i.e., pharmacodynamic; due to reduced sensitivity of the body to a given blood level, rather than due to reduced blood levels themselves). Chronic tolerance also develops to the discriminative stimulus effects of nicotine (Perkins et al., 1997b), which may relate to its subjective effects. Functional tolerance to substances of abuse often is temporally related to escalating drug use and difficulty stopping drug use (Kalant and Khanna, 1990; Pratt, 1991), hallmarks of dependence. Current criteria for clinical diagnosis of drug dependence highlight the presence of tolerance (APA, 1994). Nicotine tolerance, therefore, may be critical to understanding the development of tobacco dependence (USDHHS, 1988). Drug tolerance also illustrates adaptive biological processes resulting from repeated drug intake, which may be relevant to understanding broader aspects of the body’s functioning (Kalant and Khanna, 1990). For example, nicotine exposure has been shown to produce down-regulation of nicotine receptor function and up-regulation of receptor density in some brain areas, depending on dose and duration of exposure (Marks et al., 1993; Breese et al., 1997).

ABBREVIATIONS: DSM, Diagnostic and Statistical Manual of Mental Disorders; POMS, profile of mood states; VAS, visual-analog scales; HR, heart rate; BP, blood pressure.
Chronic tolerance to nicotine in humans has been poorly characterized due to a relative absence of research, and many critical questions have not been addressed. Notably, despite its theoretical link to dependence, it is not known whether tobacco dependence must be present to demonstrate tolerance to nicotine. Nearly 10% of adult smokers do not meet clinical criteria for tobacco dependence. These smokers, referred to as nondependent smokers or “chippers”, typically smoke five or fewer cigarettes per day and do not experience withdrawal upon cessation (Shiffman et al., 1992; Owen et al., 1995). If tolerance is directly tied to dependence, these nondependent smokers should show no tolerance. According to one study, nondependent smokers show less tolerance to some cardiovascular responses of smoking, relative to dependent smokers (Shiffman et al., 1992). However, no study has compared their responses to those of nonsmokers to determine whether tolerance develops at all (i.e., relative to those naive to the drug and thus without any tolerance). Moreover, because chronic tolerance to nicotine is response-specific (Arcavi et al., 1994; Perkins et al., 1994), tolerance to cardiovascular responses may have little relationship with tolerance to drug effects likely to be more relevant to dependence, such as subjective mood responses (USDHHS, 1988). A finding of little tolerance in nondependent smokers would strengthen the importance of tolerance to understanding dependence and support the utility of tolerance as a criterion for defining dependence (APA, 1994). On the other hand, substantial tolerance in nondependent smokers would question the relevance of tolerance to defining dependence.

Another important question largely unaddressed in the human literature is the extent to which chronic tolerance reverses after extended abstinence from smoking (Kalant 1987), suggesting rapid reversal of chronic tolerance. However, tolerance to effects of such infusions may differ substantially from tolerance to rapid bolus uptake of nicotine (Kalant and Khanna, 1990), as occurs in tobacco smoking (USDHHS, 1988).

To determine the relationship of chronic tolerance with current or past tobacco dependence, we compared dose-response effects of acute bolus nicotine administration among current dependent smokers, nondependent smokers, formerly dependent smokers (“exsmokers”), and life-long nonsmokers. Subjective, cardiovascular, and behavioral performance measures were examined to determine whether the pattern of tolerance across groups was specific to only some responses or generalizable across several different nicotine effects. Responses were adjusted for plasma nicotine concentration to rule out variable dosing or dispositional tolerance as an explanation for group differences. We hypothesized that tolerance would be greater in dependent smokers than nondependent smokers, indicating that tolerance is directly related to amount of exposure to nicotine and may require dependence. We also hypothesized that tolerance would be less in exsmokers than dependent smokers, indicating that tolerance reverses after extended abstinence from smoking. Any differences between exsmokers and nonsmokers would indicate that this tolerance reversal is not complete. Limitations to this design are considered under Discussion, specifically the fact that humans differing in smoking history (which is self-selected, unlike in animal studies with randomly assigned subjects) may also differ in other ways very relevant to their acute responses to nicotine (e.g., genetics).

Materials and Methods

Subjects. All subjects were healthy adults at least 30 years of age, at which time smoking status is well established. Subjects were examined by physician to rule out current or recent medical or psychiatric problems contradicting participation, and urine drug screens were obtained to exclude subjects with substance abuse problems. To classify smoking status, all prospective subjects first completed a brief phone interview asking for “yes” or “no” responses to each of the seven DSM-IV criteria for tobacco dependence (APA, 1994), in addition to questions about amount and duration of smoking. An example item is, “Have you often had periods of days when you smoked a lot more than you intended to?” During a subsequent in-person screening session, subjects also completed a structured questionnaire addressing these same items in more detail (e.g., checking off each individual withdrawal symptom previously experienced) to help provide a reliable lifetime classification of dependent or nondependent smoker (or neither). Those who proceeded further in the screening process were required to respond consistently to both the phone interview and the in-person questionnaire. An earlier version of this questionnaire (“Cigarette Use Questionnaire”) is described by Downey and Kibbey (1995). Exsmokers completed these measures based on recall of their prior smoking behavior.

Dependent smokers were those who met DSM-IV clinical criteria for tobacco dependence (three or more of the seven criteria) and had smoked at least 10 cigarettes per day for at least 10 years. They endorsed a mean of 5.0 ± 0.2 of the seven criteria for dependence, and 34 of 45 (76%) endorsed the criterion of “tolerance” (“a need for markedly increased amounts” or “markedly diminished effect with continued use of the same amount”). Nondependent smokers were those who did not meet the criteria for dependence (0–2 criteria); smoked six or fewer cigarettes per day but smoked on at least 5 days per week; and reported no past history of regularly smoking at a greater rate, similar to definitions used by others (Shiffman et al., 1992; Owen et al., 1995). They endorsed a mean of 1.7 ± 0.3 dependence criteria, but none endorsed the criterion of tolerance. Exsmokers reported meeting the same criteria as current dependent smokers when they were smoking but had been continuously abstinent (i.e., not even a puff) at least 1 year. Nonsmokers denied any history of daily smoking, and total lifetime exposure was (mean ± S.E.) 7.0 ± 2.6 cigarettes or other uses of tobacco (smokeless tobacco, pipes, etc.; maximum of 50 uses), with the most recent use being 12.8 ± 2.2 years earlier (minimum of 1 year earlier). Characteristics of each subject group are provided in Table 1. By design, total smoking exposure history and other indices of smoking (e.g., score on the Fagerstrom Test of Nicotine Dependence; Heatherton et al., 1991) were very similar between current dependent smokers and exsmokers, who had been abstinent for 6.7 ± 1.2 years, and very different between current dependent and nondependent smokers.

Smoking history information provided by each nondependent smoker and exsmoker was corroborated by phone interviews with two individuals long familiar with the subject (“collaterals”). Nine additional prospective subjects were excluded from participation after their collaterals failed to confirm their status as nondependent smokers (n = 7) or exsmokers who had quit at least 1 year earlier (n = 2), and they are not included in Table 1. Biochemical indices of recent smoking (expired-air carbon monoxide and plasma cotinine, a metabolite of nicotine) were obtained during screening and found to be consistent with subjects’ reported recent smoking history (Table 1).

Nicotine Administration. Nicotine (0, 10, 20 μg/kg) was administered with a nasal spray procedure developed in our laboratory that
TABLE 1
Demographic and smoking history characteristics of subject groups (mean ± S.E.)

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristic</th>
<th>Dependent Smokers</th>
<th>Nondependent Smokers</th>
<th>Exsmokers</th>
<th>Nonsmokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>38.3</td>
<td>1.4</td>
<td>33.8</td>
<td>1.1</td>
<td>42.5</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>18/27</td>
<td>3/9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>21.3</td>
<td>1.0</td>
<td>3.4</td>
<td>0.5</td>
<td>25.4b</td>
</tr>
<tr>
<td>Years smoking</td>
<td>20.3</td>
<td>1.4</td>
<td>13.7</td>
<td>1.4</td>
<td>18.5b</td>
</tr>
<tr>
<td>Cotinine (ng/ml)</td>
<td>225.8</td>
<td>29.0</td>
<td>50.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide (ppm)</td>
<td>28.8</td>
<td>2.4</td>
<td>6.8</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>FTND score&lt;sup&gt;c&lt;/sup&gt; (0–10)</td>
<td>5.1</td>
<td>0.3</td>
<td>0.8</td>
<td>0.3</td>
<td>6.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values for exsmokers reflect smoking exposure before they quit smoking.
<sup>b</sup> —, not applicable or below minimum detectable level (cotinine, <10 ng/ml).
<sup>c</sup> Fagerstrom Test of Nicotine Dependence (Heatherton et al., 1991).

provides reliable and rapidly absorbed (2–3 min) nicotine doses corrected for body weight (Perkins et al., 1994). A dose of 20 μg/kg nicotine by nasal spray is comparable to that obtained by a typical smoker from smoking between one-half and one cigarette (Perkins et al., 1994). Such a novel dosing method is necessary to examine functional tolerance to nicotine because of the ethical and practical difficulties of instructing nonsmokers and exsmokers to inhale measured amounts of tobacco smoke. Furthermore, because of its novelty, this method excludes influences due to familiarity with a tobacco product, such as cigarette smoking, which would be expected to enhance tolerance in smokers (i.e., behavioral or conditioned tolerance; Kalant and Khanna, 1990).

To verify dosing and rule out dispositional tolerance (that due to differences in drug kinetics), a blood sample was obtained by venipuncture at the end of each session and analyzed for plasma nicotine concentration by gas chromatography with nitrogen-phosphorus detection using 5-methylnicotine as the internal standard (Jacob et al., 1981). Results showed very similar mean nicotine concentrations across groups (as shown later in the figures), except between nonsmokers and dependent smokers following 20 μg/kg nicotine (9.0 ± 0.9 versus 11.8 ± 0.6 ng/ml, respectively). Values for exsmokers (11.0 ± 0.7 ng/ml) and nondependent smokers (10.2 ± 1.4 ng/ml) were intermediate between the other two groups. The difference between nonsmokers and dependent smokers is consistent with previous research showing faster nicotine clearance, resulting in lower blood values, in nonsmokers compared with smokers (Benowitz and Jacob, 1993; Perkins et al., 1994). Analyses of group differences used plasma nicotine as a covariate to correct for any differences in exposure to nicotine (under Data Presentation and Statistical Analyses).

Tolerance Battery of Measures. Subjective effects measures included the profile of mood states (POMS; McNair et al., 1971) and a series of visual-analog scale (VAS) items, which have been used in similar research (Perkins et al., 1994; Jones et al., 1999) and related to nicotine self-administration behavior in smokers (Perkins et al., 1997a,b). POMS scales included tension, vigor, depression, confusion, and arousal. VAS items included stimulated, alert, sedated, tired, pleasant, jittery, relaxed, comfortable, head rush, and feel drug.

Cardiovascular responses consisted of heart rate (HR, in beats per minute), systolic and diastolic blood pressure (BP, in mm Hg), and skin temperature (°C). HR and BP were obtained automatically by Dinamap blood pressure recorder (Critikon Inc., Tampa FL). Finger temperature, a measure of vasoconstriction, was determined by a thermistor probe (Yellow Springs Instruments, Yellow Springs, OH) taped to the middle finger of the nonpreferred hand.

Performance tasks involved finger-tapping speed, memory recognition, hand steadiness, and rapid information-processing. Finger-tapping required tapping with the index finger on one key of a computer keypad as quickly as possible for 60 s. Hand steadiness was assessed by the Gardner Steadiness Tester (Lafayette Instruments, Lafayette, IN). Subjects were required to 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. Contact with the hole was signaled by auditory tone feedback. Duration of contact was determined by computer to the nearest 0.01 s. Memory recognition was assessed by presenting at one time a list of 20 one-syllable nouns 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. The preceding tasks are described elsewhere in more detail (Perkins et al., 1994). For the Sternberg rapid information-processing task, subjects were given one or five “target” letters to retain in short-term memory. They then were to respond as quickly as possible to a series of letter pairs, indicating whether the given letter pair did (“hits”) or did not (“correct rejections”) contain a target letter. The difference in reaction time between the one- and five-letter trials was the primary measure of memory scanning speed (information processing; Schneider and Shiffrin, 1977). Responding has been shown to be improved (i.e., faster) by nicotine under distracting conditions involving auditory presentation of nontarget letters (Grobe et al., 1998). This task was presented in the current study under both distracting and nondistracting conditions in random order following each dose administration.

Procedures. Subjects participated in three sessions, one for each nicotine dose (0, 10, 20 μg/kg by nasal spray). For determination of tolerance, doses were presented on separate days, and the order of the three doses across days was counter-balanced. Expired-air carbon monoxide was assessed in all subjects before each session to verify overnight (>14-h) abstinence from smoking in the current smokers (carbon monoxide ≤ 13 ppm). This abstinence requirement minimized the possibility that attenuated responses to nicotine in smokers could be attributed to acute tolerance (due to residual effects of very recent nicotine exposure) rather than to chronic tolerance (Kalant and Khanna, 1990).

The procedure for each session was identical, except for the particular dose administered. Following attachment of BP cuff and finger thermistor probe, subjects remained quiet for at least 30 min while resting in a comfortable armchair. A baseline assessment of subjective measures was then obtained, followed by baseline measures of cardiovascular responses and then the performance measures. This sequence of measures was repeated following each of three dose administrations, one every 30 min. Dosing took 2 min, followed by subjective and cardiovascular assessment during minute 3 to 7 postdosing, and the performance measures during minute 8 to 22 postdosing. Subjects rested comfortably until the subsequent dose administration.

All subjects provided informed consent after the nature and consequences of participation were explained. This research was approved by the Institutional Review Board of the University of Pittsburgh Medical Center.
Data Presentation and Statistical Analysis. Response to each dose (0, 10, 20 μg/kg) was defined by change from predose baseline to the postdose mean of responses across the three dose administrations per session. Dose-response curves of nicotine with each measure were plotted by group as a function of mean plasma nicotine concentration. Tolerance was defined as a shift to the right, or flattening, of the curve, for the groups with current or past smoking exposure relative to that for nonsmokers. The statistical significance of this tolerance was determined by the interaction of smoking status group by nicotine dose in the analyses of covariance, using plasma nicotine concentration as the covariate. Follow-up comparisons, using Fisher’s least-significant difference t tests (Huitema, 1980), identified significant differences between nonsmokers (referent group) and the other groups at specific doses. Additional comparisons were conducted between dependent and nondependent smokers to determine whether tolerance required the presence of dependence and was related to amount of smoking exposure. Comparisons between exsmokers and dependent smokers determined whether tolerance reversed after extended abstinence.

Results

Subjective Effects. Analyses identified significant group by nicotine dose interactions for 9 of the 15 subjective effects scales: POMS scales of tension (P < 0.01), depression (P < 0.01), and confusion (P < 0.001), and VAS items of head rush (P < 0.001), jittery (P < 0.01), feel drug (P < 0.05), pleasant (P < 0.05), comfortable (P < 0.05), and relaxed (P < 0.05).

Dependent smokers were tolerant (i.e., had significantly smaller responses than nonsmokers) to all nine of these effects, as shown in Fig. 1. Nondependent smokers also showed significant tolerance to all nine effects and did not differ from dependent smokers on these or any of the other subjective effects measures.

Exsmokers generally showed intermediate tolerance. Responses of exsmokers were greater (i.e., less tolerance) than those of dependent smokers on six of the nine measures following either 10 or 20 μg/kg nicotine (POMS scales of tension and confusion; VAS items of pleasant, relaxed, jittery, and comfortable). However, this possible reversal of tolerance in exsmokers was only partial, since their responses were significantly smaller than those of nonsmokers on three of the nine measures (VAS items of head rush, relaxed, and comfortable) following 10 μg/kg nicotine and seven of nine (all but VAS items of pleasant and relaxed) following 20 μg/kg nicotine (Fig. 1).

Cardiovascular Effects. In contrast with the substantial tolerance to subjective effects of nicotine, no evidence of tolerance was found for any of the four cardiovascular effects. Nicotine dose significantly increased HR and systolic and diastolic BP (all P < 0.001, Fig. 2), but not finger temperature. However, no interactions of group by dose were significant.

Performance Effects. Group by dose interactions were observed for hand steadiness (P < 0.05), memory recognition (P < 0.05), and one component of the Sternberg task (correct rejections under nondistracting conditions; P < 0.05), but not for finger-tapping (main effect of dose only; P < 0.001). As shown in Fig. 3, tolerance to hand steadiness effects was significant in dependent smokers, but not in nondependent smokers or exsmokers. Reversal of tolerance was significant in exsmokers for hand steadiness response to 10 μg/kg only. Despite the significant interactions, tolerance was not observed for memory recognition and the Sternberg task, since responses of the groups with current or past exposure to smoking were similar to, or greater than, those of nonsmokers (Fig. 3). The improvement in memory recognition in dependent smokers following nicotine was fully reversed in exsmokers.

Discussion

Processes of adaptation to chronic nicotine intake that lead to dependence are not apparent, but chronic tolerance has long been assumed to play a key role (USDHHS, 1988; Pratt, 1991; APA, 1994). However, this study challenges the notion of any strong link between nicotine tolerance and dependence in humans, and the findings have several important implications for our understanding of tobacco dependence and smoking behavior.

First, tolerance to subjective effects of nicotine was virtually identical between dependent and nondependent smokers, indicating that tolerance is not a linear function of amount of prior smoking exposure and does not require the presence of dependence. Consequently, tolerance to these effects of nicotine may fully develop with even modest regular exposure of just a few cigarettes per day. Such exposure, however, is apparently insufficient to produce tobacco dependence in these smokers, as determined by DSM-IV criteria, indicating dissociation between adaptive processes responsible for tolerance versus dependence. The equivalent tolerance between dependent and nondependent smokers is particularly surprising given the fact that the vast majority of the dependent smokers but not a single nondependent smoker endorsed the “tolerance” criterion from DSM-IV.

Second, this finding also suggests that the wide variability in daily smoking rate among smokers (USDHHS, 1988; Owen et al., 1995) cannot be attributed to differences in chronic tolerance to nicotine, and the cause of this important individual difference must lie elsewhere. Perhaps consistent with this notion, recent in vitro research indicates that activation of nicotinic acetylcholine receptors on dopamine neurons in the ventral tegmental area (which are thought to be involved in the rewarding effects of nicotine) can desensitize very quickly, producing acute tolerance. However, this action also can induce long-term potentiation of excitatory glutamatergic inputs to these neurons well beyond the duration of the desensitization (Mansvelder and McGehee, 2000), thus possibly accounting for reports that nicotine can induce prolonged release of dopamine from these neurons at its target site in the nucleus accumbens. This might suggest that desensitization (and tolerance) produced by nicotine can be uncoupled from its capacity to produce long-term excitation of brain reward areas.

Third, reversal of tolerance appears to be very limited, or very slow, following extended abstinence from smoking and presumed elimination of dependence. Tolerance to subjective effects of nicotine was moderate in exsmokers, who had been abstinent an average of nearly 7 years, because dose-response curves generally were shifted to the right, relative to those for nonsmokers, but usually not as far right as those for currently dependent and nondependent smokers. These results are consistent with one study (Hughes et al., 1989), but not another (Hughes et al., 2000), of tolerance to nicotine in long-time exsmokers, both of which examined the subjective effects of nicotine gum in exsmokers versus current smokers.
and nonsmokers. Preclinical research suggests that lengthy nicotine exposure can produce a "persistent inactivation" of nicotinic receptors that may be irreversible (Reitstetter et al., 1999). Thus, mechanisms responsible for at least some of these subjective effects may never fully regain the same degree of sensitivity to nicotine as that exhibited during
initial exposure (e.g., teens experimenting with tobacco). Such incomplete tolerance reversal may help explain why many exsmokers who relapse can rapidly resume smoking at a high rate, often within days or weeks, after even extended abstinence (Norregaard et al., 1992), whereas those initially naive to smoking invariably require at least a few years to escalate to high-rate smoking (McNeill et al., 1989).

The finding of substantial chronic tolerance to most sub-

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**Fig. 2.** Dose-dependent relationship of nicotine with cardiovascular responses of systolic and diastolic BP (in mm Hg) and HR (in beats per minute). Nonsmokers (○), exsmokers (△), nondependent smokers (□), dependent smokers (◇). The interaction of dose by group was not significant for any measure. Other details as in Fig. 1.

**Fig. 3.** Dose-dependent relationship of nicotine with behavioral performance responses. The interaction of dose by group was significant for hand steadiness (seconds of contact time), memory recognition (number correctly recalled out of 40), and one component of the Sternberg rapid information-processing task (correct rejections under nondistraction conditions; in milliseconds). Negative values for the Sternberg task indicate faster reaction time. Other details as in Fig. 1.
jective effects of nicotine but little or none to cardiovascular and performance responses (except hand steadiness) supports the notion that tolerance is response-specific (Arcavi et al., 1994; Perkins et al., 1994). Although the timing of the performance tasks later in the battery could have reduced the chances of observing tolerance to those measures, this seems unlikely given that the hand steadiness task, which did show tolerance, was performed after finger-tapping, which did not. Moreover, we observed a similar lack of tolerance to cardiovascular measures, which were obtained concurrently with subjective measures that did show tolerance. Underlying mechanisms responsible for subjective effects of nicotine must show substantial chronic adaptation with repeated exposure, whereas mechanisms responsible for cardiovascular and most performance effects do not. Notably, we saw little evidence of sensitization, or increased sensitivity to nicotine due to past exposure, which would result in a shift to the left in dose-response curves of smokers compared with nonsmokers (Kalant and Khanna, 1990), although memory recognition was improved by nicotine in dependent smokers only.

A limitation of this research is one common to virtually all human studies of chronic tolerance to drugs of abuse, lack of random assignment of subjects to differential smoking histories. Unlike research with animals, where subjects can be randomly assigned to chronic drug histories, smoking histories are not randomly distributed within the human population, and factors (other than tolerance) covarying with smoking status may influence acute responses to nicotine. Yet, groups were recruited in the same manner from the same general population, and our results of tolerance to acute bolus doses of nicotine are generally consistent with extensive well controlled, randomized research in rodents (Stoler- man, 1999). Moreover, ethical and practical alternative strategies for examining chronic tolerance in humans are not apparent.

Other explanations for these findings are also possible but, in our view, not very likely. Tolerance to subjective effects in dependent and nondependent smokers was not due to residual nicotine from recent smoking since sessions were preceded by a minimum 14-h duration of smoking abstinence, equal to at least five half-lives of nicotine (approx. 2–2.5 h; Lee et al., 1987). Differences observed here were not due to differences in nicotine exposure during testing (e.g., dispositional tolerance) since doses were corrected for body weight and responses were corrected for plasma nicotine levels. It is possible that tolerance to effects of nicotine other than those examined in this study may be critical to development of dependence, even if tolerance to the subjective effects assessed here were not. Some of the effects to which smokers were tolerant could be viewed as somewhat aversive. Tolerance to aversive effects could allow pleasurable effects to be more prominently experienced, and tolerance to those pleasurable effects may not occur. However, even so, our findings of no differences in tolerance between dependent and nondependent smokers would still question a direct link between nicotine tolerance and dependence. Generalizability of these findings across other routes of nicotine administration could help clarify whether our results are specific to nicotine by nasal spray or are more broadly relevant to effects of nicotine per se, isolated from tobacco smoke.

Our main finding is that nicotine tolerance is not directly associated with tobacco dependence and, thus, processes responsible for each must involve differing actions of nicotine. The degree to which these results generalize to tolerance versus dependence on other drugs of abuse is unclear but warrants examination. A similar lack of association of tolerance with dependence in studies of other drugs of abuse could cast doubt on the utility of tolerance as one of the DSM-IV criteria for drug dependence (APA, 1994), as may be the case for tobacco dependence based on our results. Future studies of nicotine effects on receptor function, neurotransmitter activity, and specific areas of brain activation (Breese et al., 1997; Stein et al., 1998; Reistetter et al., 1999; Mansvelder and McGehee, 2000) as a function of nicotine tolerance versus tobacco dependence could help explain the dissociation found here between these two apparently different forms of chronic adaptation to nicotine. Results of this work could increase our understanding of mechanisms involved in dependence, providing directions for improving the treatment and prevention of smoking.

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References


habits in relapsed subjects from a smoking cessation trial after one year. Br J Addict 87:1189–1194.

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