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Nicotine Blood Levels and Subjective Craving for Cigarettes

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JARVIK, M. E., D. C. MADSEN, R. E. OLMSTEAD, P. N. IWAMOTO-SCHAAP, J. L. ELINS AND N. L. BENOWITZ. *Nicotine blood levels and subjective craving for cigarettes.* PHARMACOL BIOCHEM BEHAV **66**(3) 553–558, 2000.—This study examined cigarette craving and blood nicotine levels in 11 male heavy smokers who were observed during 16 h of tobacco abstinence. Subjects rated their urge to smoke on a new brief 10-item questionnaire, Urge to Smoke (UTS), Schuh and Stitzer's four-item Visual Analog Scale (SSI), and a Strength of Urge to Smoke (SUTS) item. Testing occurred: 1) after 16 h (1700 h the night before to 0900 h the next morning) of abstinence from smoking; 2) after an ad lib smoking period following the 16 h abstinence; 3) every hour during 6 hours of abstinence; 4) and finally, after the 6 h abstinence, another ad lib smoking period. Thus, subjects smoked twice in each session. Blood plasma nicotine levels were measured before, after, and every 2 h during the 6-h abstinence period for a total of six measures. Blood pressure and heart rate were measured prior to each blood draw. There was a significant negative correlation between blood nicotine levels and craving for cigarettes on all craving questionnaires ($rs = -0.55$ to -0.78; $ps < 0.002$). Carbon monoxide was shown to correlate highly with nicotine blood levels ($rs = 0.83$ to 0.98 across subjects; $ps < 0.001$). Results are consistent with the hypothesis that "urge to smoke" reflects nicotine seeking in continuing smokers. © 2000 Elsevier Science Inc.

Nicotine Craving Withdrawal Cigarette Abstinence

SINCE nicotine was first isolated and named by Posselt and Reimann in 1828 (16) it has been suspected that nicotine has something to do with the urge to smoke. The senior author speculated 27 years ago that this tobacco alkaloid was the prime ingredient in tobacco providing the incentive for smoking (11). He wrote: "Nicotine is known to release catecholamines from their stores in the periphery, and it is reasonable to assume the same action would occur in the brain." Several years later, nicotine-mediated dopamine release was demonstrated in brain slices by Giorguieff et al. (5) and in living animals by Imperato et al. (10). The first experimental evidence that tobacco smoking might actually be a form of nicotine-seeking was provided by Johnston (14) who, in a series of anecdotal reports, observed that smokers found hypodermic and intravenous injections of nicotine to be pleasurable.

Nicotine replacement (gum, patch) has been generally shown to relieve smoking withdrawal symptoms, yet the evidence for relief of craving with nicotine replacement has been more equivocal (8). In fact, though "craving" or the urge to smoke was included as a symptom of nicotine withdrawal in DSM III (1), it was eliminated in DSM IV (2), because smokers often reported craving even during smoking. This observation may be more due to procedural issues rather than to true unreliability of the subjective experience. However, the variables that determine relapse may be quite different than those that determine smoking rate in a continuing smoker. Nicotine blood concentrations will be at zero within 8–12 h of abstinence, so, clearly, nicotine blood levels do not determine fluctuations in urge to smoke in smokers who have quit for a day or more.

The typical continuing smoker, however, rarely allows their nicotine blood levels to reach zero, and certainly never to remain there for very long. Unfortunately, acute, i.e., within day, studies of nicotine craving and withdrawal are rel-

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atively rare. Given that nicotine blood concentrations may fluctuate widely throughout the day, daily retrospective measures that are utilized in most cessation trials are not appropriate. A very careful study by Schuh and Stitzer (19) demonstrated that craving increased reliably over time within minutes after finishing a cigarette. They did not measure nicotine blood concentrations, however. Lunell et al. (15) showed that a nicotine inhaler reduced craving over 2 days in smokers who were not trying to quit, and did produce a negative correlation of nicotine blood levels and craving.

Many clinical smoking cessation studies have demonstrated a causal connection between plasma nicotine levels and urge to smoke by showing that subjects who receive nicotine replacement show less craving than subjects receiving placebos (4,18). The purpose of the present study was to extend the work of Schuh and Stitzer (19) by examining the relationship between craving and the level of nicotine in the blood during 6 h of abstinence. It was hypothesized that, within individuals, subjective reports of craving would be inversely related to nicotine blood concentrations.

METHOD

Preliminary Study

A pilot study was first conducted to develop a small set of subjective craving questions that 1) were internally consistent (reliable), and 2) strongly changed when participants were abstinent. Twenty-one subjects were recruited from the West Los Angeles Veterans Affairs Medical Center. All were male with a mean age of 40.8 years old (SD = 6.2; range = 30–51), a mean number of cigarettes smoked per day of 23.3 (SD = 7.8; range = 11–40), and a mean number of years smoking of 19.2 (SD = 9.7; range = 2–33). Mean educational level was 14 years (SD = 3.9; range = 13–20). Participants were told that they would be required to not smoke for either 16 or 24 h. Two subjects were disqualified for noncompliance.

This study was reviewed and approved by the institution's Human Subjects Subcommittee and, thus, in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All subjects were paid $30 in Veterans Canteen Service (VCS) scrip for their participation.

Upon arrival at the laboratory in the evening (1700 h) subjects gave written informed consent and completed three different craving questionnaires: Shiffman/Jarvik [SJWS, (21)], Questions on Smoking Urges [QSU; (22)], and the Hughes Withdrawal Scale [HWS; (8)]. Exhaled carbon monoxide levels were measured, and the subjects were instructed to remain abstinent for the next 16 h. At the end of 16 h subjects returned to our laboratory (at 0900 h) and responded to the questionnaire battery. Subjects in the 16-h condition (n = 15) were then allowed to smoke ad lib. After the smoking period, subjects completed the questionnaire battery again, were paid, and released. Subjects in the 24-h condition (n = 6) did not smoke at the 16-h mark, but expired air carbon monoxide samples were taken for abstinence verification, and subjects completed the questionnaire battery. At the 20-h mark (1300 h), subjects again returned for abstinence verification by expired air carbon monoxide. The procedure at the end of the 24-h abstinence condition was identical to that for the 16-h group: questionnaires followed by ad lib smoking followed by questionnaires.

Individual items from the three craving scales (SJWS, QSU, HWS) were examined for changes over time and intercorrelation. A new brief 10-item questionnaire, Urge to Smoke (UTS), was created based on those 10 items that showed the greatest change over the 16-h period and had high item-total correlations with a summary score that included all craving items (i.e., withdrawal items form the SJWS and HWS were not included in the summary score). Items from all three questionnaires are ranked in Table 1 with mean items scores, pre- and post-16 h of abstinence and standard errors.

Main Study

Subjects. Eleven heavy smoking male patients in good general health between the ages of 35 and 51 were recruited at the West Los Angeles Veterans Affairs Medical Center. No subjects from the preliminary study were included in the main study. Subjects smoked at least 20 cigarettes per day for the past 5 years, and had their smoking status verified by carbon monoxide (CO >20 ppm). Exclusionary criteria included diabetes, major medical or psychological disorders, and/or use of psychotropic drugs. All subjects' medical records were reviewed before they were accepted into the study. Subjects' mean age was 41.3 years old (SD = 4.9; range = 35–51) and mean educational level was 13.4 years (SD = 1.2; range = 11–15). With regard to smoking behavior, the mean number of cigarettes smoked was 27.8 per day (SD = 8.9; range = 16–40), mean number of years smoking was 24.3 (SD = 6.5; range = 15–34), mean baseline cotinine was 199 ng/ml (SD = 97; range = 108–373), and mean Fagerström Test for Nicotine Dependence scores [FTND, (7)] was 6.1 (SD = 2.2; range 4–7). No subjects were disqualified during this study.

This study was reviewed and approved by the institution's Human Subjects Subcommittee, and thus in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All subjects were paid $75 in VCS scrip for their participation.

Design

The study utilized a repeated measures ABAB design with abstinence as condition A and smoking ad lib as condition B. All subjects experienced the same procedure (order of conditions). Observed measures (time series) of primary interest were subjective craving for cigarettes, nicotine blood concentrations, and expired CO concentrations. Ancillary measures included heart rate, blood pressure, cotinine blood concentrations, cotinine saliva concentrations, and subjective measures other than craving (e.g., hunger, withdrawal symptoms). It was felt that these measures might provide additional information concerning the validity of the key variables, but no specific hypotheses were generated concerning these items.

Materials

Expired breath carbon monoxide was measured using a Bedfont EC50 Microsmokerlyzer II. Heart rate and blood pressure were measured automatically by a Datascope Accutorr. Marlboro king size filtered cigarettes (hardpack) were provided to subjects for smoking sessions. The protocol schedule was maintained using a Psion 3a multitasking handheld computer that signaled the research assistants precisely when assessments were to be done.

Measures

Background measures. One time only background questionnaires included the Fagerstrom Test for Nicotine Dependence [FTND, (7)], the Smoking Motivation Questionnaire [SMQ, (17)], the Reasons for Quitting [RFQ, (3)], and the

TABLE 1

CRAVING ITEMS RANKED BY SIGNIFICANCE IN CHANGE FROM TIME 1 TO TIME 2

Item #	Question	*t*-Value	Time 1	Time 2	SE Time 1	SE Time 2
sj 1	If you could smoke freely, would you like a cigarette this minute?	−16.87	1.667	6.7333	0.252	2.63
sj 20	Do you have an urge to smoke a cigarette right now?	−14.48	1.8667	6.7333	0.3065	0.1533
tiff 19	I have an urge for a cigarette	−13.54	1.7333	6.5333	0.3712	0.1652
sj 17	Do you miss a cigarette?	−11.8	1.7333	6.6	0.2282	0.235
tiff 16	I crave a cigarette right now	−10.87	1.2	5.8	0.1069	0.4386
tiff 21	I am going to smoke as soon as possible	−8.66	1.6	5.8667	0.2895	0.4458
tiff 10	All I want right now is a cigarette	−8.49	1.2	5.3333	0.1069	0.4847
tiff 5	I don't want to smoke now	−7.05	2.6667	6.9333	0.6068	0.0667
tiff 13	I have no desire for a cigarette now	−6.93	2.8667	6.6	0.5509	0.235
tiff 2	Nothing would be better than smoking a cigarette right now	−6.63	1.9333	4.9333	0.4079	0.5387
tiff 8	Smoking a cigarette would not be a pleasant	−6.18	3.1333	6.5333	0.5243	0.2364
tiff 12	Even it were possible, I wouldn't smoke now	−6.12	2.0667	5.9333	0.5021	0.4925
hugh 1	Desire to smoke	−5.85	1.3333	3.0667	0.2906	0.2667
tiff 7	If I were offered a cigarette, I would smoke it immediately	−5.61	1.8667	5.6667	0.4563	0.5989
tiff 1	I would be less irritable now if I could smoke	−5.57	2.2667	5.6	0.4306	0.5327
sj 10	Are you thinking of cigarettes more than usual?	−5.33	2.3333	5.7333	0.504	0.5297
sj 22	Would you find a cigarette unpleasant right now?	−5.26	3.4	6.6667	0.592	0.2108
tiff 4	I will smoke as soon as I get the chance	−4.67	2.1333	6.0667	0.4667	0.5207
sj 14	If you were permitted to smoke, would you refuse a cigarette right now?	−4.05	3.3333	6.4667	0.6449	0.4008
tiff 25	I would do almost anything for a cigarette now	−3.76	1.0667	3.2	0.0667	0.5707
tiff 15	Smoking now would make things seem just perfect	−3.74	1.8	4.0667	0.3677	0.6208
tiff 17	I would not enjoy a cigarette right now	−3.59	2.6667	5.7333	0.5989	0.5474
tiff 22	A cigarette would not be very satisfying now	−3.53	2.6667	5.4667	0.4646	0.6464
tiff 18	A cigarette would not taste good now	−3.13	3	5.5333	0.5164	0.6239
tiff 6	If I were offered a cigarette, I would smoke it immediately	−3.03	1.8	3.5333	0.243	0.5152
tiff 3	I am not missing smoking right now	−3	3.1333	5.9333	0.6752	0.4522
tiff 24	If I were smoking now I could think more clearly	−2.98	1.8	3.5333	0.2795	0.5925
tiff 26	Right now, I am not making plans to smoke	−2.8	2.4667	5.667	0.5333	0.5729
tiff 11	Smoking right now would make me feel less tired	−2.43	1.5333	2.9333	0.2364	0.4925
tiff 14	My desire to smoke seems overpowering	−2.16	2.2667	4	0.5021	0.5164
tiff 20	I could control things better right now if I could smoke	−1.79	1.8667	3.1333	0.3634	0.5595
tiff 9	If I were smoking this minute, I would feel less bored	−1.7	2.7333	3.8667	0.5207	0.5762
sj 8	Smoking a cigarette would not be pleasant	0	6.8667	6.8667	0.0909	0.0909
tiff 23	If I had a lit cigarette in my hand, I probably wouldn't smoke it	0.82	5.0667	5.7333	0.4727	0.5646

Smoker's Beliefs Questionnaire (SBQ, Olmstead, unpublished data).

Biochemical measures. Breath samples were assessed for carbon monoxide content. Blood samples (10 ml) were assayed for nicotine and cotinine concentrations.

Subjective repeated measures. Repeated measure questionnaires included 1) the Urge to Smoke questionnaire [UTS); 2) a modified version of the Shiffman/Jarvik Withdrawal scale (21), which contained only the noncraving-related withdrawal items (SJWS-NC); 3) a 10 point Likert Hunger scale; 4) Schuh and Stitzer's index, a four-item visual analog scale [SSI; (19)]; 5) the Hughes Withdrawal Scale (8); and 6) a single-item Strength of the Urge to Smoke (SUTS).

Procedure

Subjects visited the laboratory at 1700 h the night before their scheduled experimental session to sign informed consent forms and complete background questionnaires. At this time they produced an expired breath carbon monoxide (CO) sample after a breath hold time of 20 s. They were then instructed to remain abstinent overnight, and informed that they would be allowed to smoke cigarettes the following morning. Subjects returned the following morning for CO validation of smoking abstinence. Only those with CO levels <8 ppm (12,13) were allowed to continue in the study (no participants failed to meet the criterion).

Subjects were then transported to the West Los Angeles Veterans Affairs Medical Center's Clinical Research Center (CRC). When subjects arrived at the CRC they completed the subjective and physiological battery. Next, a catheter (Insyte) was implanted into an arm vein and 10 ml of blood was drawn. Immediately thereafter subjects were allowed to smoke as many cigarettes as they wished ad lib until they voluntarily stopped (the range was one to six cigarettes; time taken to smoke ranged from 6 to 20 min). Blood was taken precisely 2 min after their final cigarette. Subsequent blood samples were taken every 2 h. Catheters were flushed with heparin solution after every blood draw. A minimum of 3 ml in "uptake" blood was drawn before each 10-ml sample of blood was collected. Biochemical measures (saliva cotinine and exhaled carbon monoxide) preceded each blood draw. Subjective measures were taken every hour. At the end of 6 h of abstinence (blood draw #5) subjects were again allowed to smoke ad lib until they no longer wanted to smoke (range = 1 to 6 cigarettes; smoking time range = 4 to 29 min). A final blood sample was taken 2 min after the subject's final cigarette. Final biochemical and subjective batteries accompanied

the final blood draw. During the 6 h on the ward, subjects watched television and played games (e.g., cards, dominos).

Analysis

The time series for blood nicotine concentration, craving scales (UTS, VAS), and CO concentrations were intercorrelated for each subject across time (six observations that profiled sequential events: after overnight abstinence, 2 min after smoking to satiety, after 2 h of abstinence, after 4 h of abstinence, after 6 h abstinence, 2 min after smoking to satiety after the 6-h abstinence period). The series were also analyzed for trends over the middle four observations, which represented the change from smoking to satiety through 6 h of abstinence. Using repeated measures analyses of variance (rANOVA), linear ($X = \beta_0 + \beta_1 t$), linear + quadratic ($X = \beta_0 + \beta_1 t + \beta_2 t^2$), and exponential ($X = \beta_0 e^{-\beta_1 t}$) trends were examined. The effects of smoking on craving and the biochemical assessments were also analyzed.

RESULTS

Figure 1 shows the pattern of plasma nicotine concentrations and expired CO concentrations. The pattern for CO closely mirrors that of nicotine with increases after smoking and monotonic dissipation during abstinence. The correlations within subjects between nicotine and CO concentrations ranged from 0.83 to 0.98 (all $p < 0.05$).

Craving for cigarettes increased significantly after overnight abstinence [e.g., UTS: $t(10) = 16.61$, $p < 0.001$; SSI: $t(10) = 8.92$, $p < 0.001$]. It then significantly decreased after ad lib smoking [UTS: $t(10) = 4.05$, $p < 0.003$; SSI: $t(10) = 6.35$, $p < 0.001$]. Over the observed 6-h abstinence period craving generally increased but unlike the biochemical measures, this trend was not monotonic for every subject. Figure 2 shows the mean trend over time (for the mean of the UTS Likert scale; the SSI and SUTS evidenced similar patterns) and the data for two unusual cases. One individual (Subj. A) showed consistently high craving even immediately after the first smoking period; the other individual (Subj. B) indicated fairly low craving even several hours into the abstinence period. Overall, there was a significant negative relationship between blood nicotine levels and craving for cigarettes on all of the various craving questionnaires (individual *r*s range = −0.55 to −0.78; *p*s < 0.05).

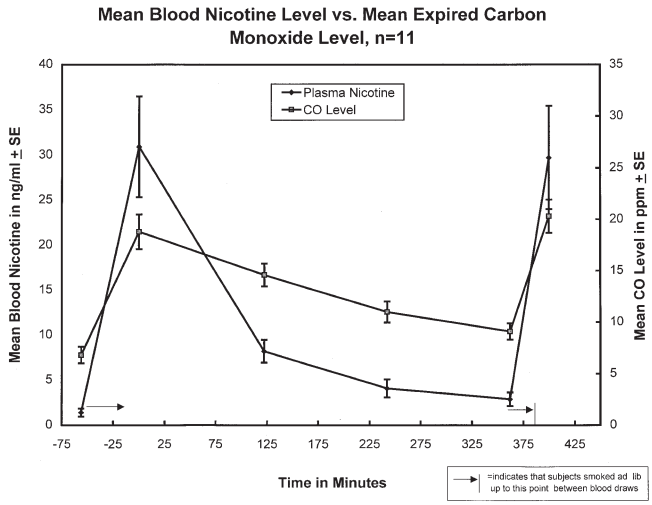

FIG. 1. Mean blood nicotine level vs. mean expired carbon monoxide level, $n = 11$.

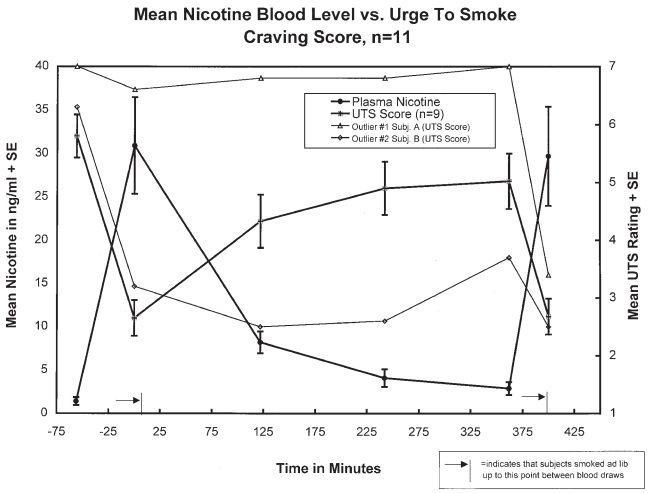

FIG. 2. Mean nicotine blood level vs. urge to smoke craving score, $n = 11$.

Slopes for nicotine, CO, and questionnaire scores were examined with trend analysis. Specifically the 6-h abstinence phase data (four assessments) were fit with linear, linear + quadratic, and exponential functions. As expected, the nicotine blood concentrations and CO values over time were best fit to an exponential function; the means of the estimates for $t_{1/2}$ were 107.5 min (SD = 21.7) and 328.8 min (SD = 86.4) for nicotine and CO, respectively. The mean SSI, UTS, and SUTS scores also appeared to best fit an exponential trend. In contrast, the HWS and the SJWS-NC did not appear to fit any of the three types of trends (i.e., statistical tests for trends were not significant).

Finally, exponential coefficients (β_1 from $X = \beta_0 e^{-\beta_1 t}$) for nicotine elimination rate and craving (mean UTS) change rate were calculated for each individual. The two rate parameters were negatively correlated ($r = -0.11$, NS), indicating that those who eliminated nicotine at faster rates had slower increases in subjective craving reports. The scatter plot of these values is shown in Fig. 3. Two outliers emerged. One of these was expected: this was the subject who indicated high levels of craving even postsmoking (Subj. A in Fig. 2), so very little change in craving occurred; this person was also one of the slowest metabolizers of nicotine (labeled "outlier #1" in Fig. 3). The other subject's metabolism of nicotine was not particularly unusual; however, his rate of craving increase was clearly the fastest. An examination of the data indicated that this was the only subject who began at full satiety (zero craving) after smoking and reached the maximum of the craving scales at the end of the 6-h period; otherwise, there was nothing distinguishing about this individual (labeled "outlier #2" Subj. C). With the two outliers removed, the magnitude of the correlation between the craving change parameter and the nicotine change parameter increased to $r = -0.49$ ($p < 0.20$).

Although the finding was not statistically significant, the apparent negative relationship between craving change rate and nicotine elimination rate was counterintuitive (i.e., we would expect that those who eliminate nicotine faster should crave faster). We examined the correlations among nicotine elimination rate, initial nicotine concentration (2 min after

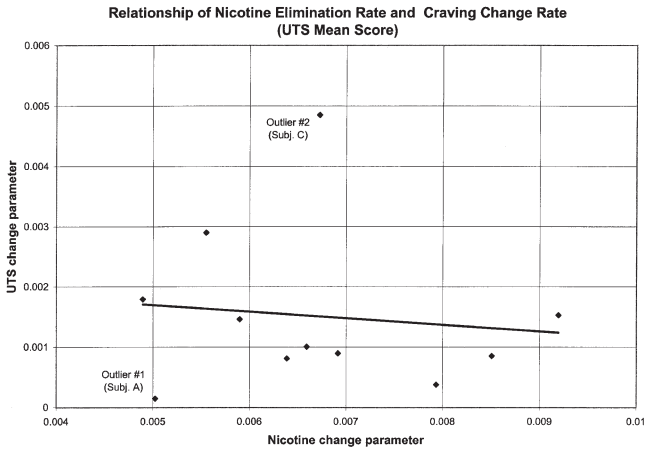

FIG. 3. Relationship of nicotine elimination rate and craving change rate (UTS mean score).

smoking to satiety), craving change rate, and initial craving rating (coincident with initial nicotine concentration); these are shown in Table 2. Initial craving level was negatively correlated with craving change and positively correlated with nicotine elimination rate though the latter relationship was stronger. The correlation between initial nicotine level with craving change rate appeared to be moderately positive, indicating that those with higher initial levels of nicotine increased in craving faster. Initial nicotine level appeared to be unrelated to the speed of nicotine elimination and to initial craving level.

Secondary analyses uncovered no strong relationships of the ancillary variables to the primary variables. For example, the correlation between blood nicotine levels and blood pressure averaged 0.21 (range = −0.42 to 0.91) and 0.30 (range = −0.30 to 0.83) for systolic and diastolic blood pressure, respectively. Only three correlations could be considered statistically significant at $p < 0.05$ (two in the case of SBP and one in the case of DBP). Within-subject correlations for nicotine blood concentration and heart rate averaged 0.18 (range = −0.55 to 0.74) with none reaching statistical significance. Likewise, the degree of reported withdrawal (SJWS-NC, HWS) was low and nearly constant, and hence, was unrelated to the other variables.

DISCUSSION

The present study conceptually replicated and extended the findings of Schuh and Stitzer (19). Six hours of cigarette smoking deprivation caused a monotonic increase in cigarette craving that was accompanied by a monotonic decrease in blood nicotine levels. The acute relationship between blood nicotine and urge to smoke in continuing smokers is rarely studied. Although the observed correlation may be a spurious effect of the synchronicity of two monotonic time series, establishing a correlation is a first step in determining causation. Moreover, it was found that the subjective experience, often labeled as inconsistent, was fairly uniform across subjects; approximately 80% of the participants followed the expected pattern.

TABLE 2

CORRELATIONS AMONG INITIAL NICOTINE CONCENTRATION,* NICOTINE ELIMINATION, INITIAL MEAN UTS,* AND UTS CHANGE ($n = 9$)

	Initial Nicotine*	Nicotine Elimination Rate†	Initial Craving*
Nicotine elimination rate†	−0.05		
Initial Craving*	−0.17	0.70‡	
Craving Change Rate†	0.47	−0.49	−0.48

*Value two minutes after smoking to satiety
†Estimated exponential slope: β_1 from $X = \beta_0 e^{-\beta_1 t}$.
‡$p < 0.05$.

The unexpected correlation shown in Fig. 3 (between nicotine elimination rate and craving change rate) may be explained by the combination of the negative correlation found for initial craving and craving change rate and the positive correlation between nicotine elimination rate and initial craving. The former correlation is most likely a measurement artifact, i.e., those who start at a higher level on the scale have a more restricted range within which change can occur. Unfortunately, this effect appeared with both the Likert measures and the visual analogue measures so that some other item format may be required to reduce or eliminate this artifact. The latter correlation indicates that those who eliminate nicotine faster tend not to report as much reduction in craving after smoking freely. This is more interesting. Although subjects were instructed to smoke until they were satisfied, some individuals never achieved a clearly low craving level, and more commonly, these were the subjects who eliminated nicotine at the fastest rates. One explanation is that these subjects were completely satiated immediately after smoking, and that after 5 min, when they responded to the craving measures, they were no longer satiated. There was little time for much nicotine to be eliminated (5 min in the face of an average 108-min half-life), so such a rapid change in satiety could not be chiefly related to nicotine blood concentrations. It also may be that these individuals are more likely to experience the feeling that their preferred nicotine levels are not easily maintained due to their increased metabolism, and thus, have learned to feel a consistent lack of satiation. Nicotine elimination rate was not strongly related to the FTND ($r = 0.28$, NS), so this lack of smoking satiety may be mostly independent of the degree of dependence. In any case, judgement should be reserved until these correlations are replicated, preferably in a larger sample.

The relationship between nicotine blood concentrations and carbon monoxide concentrations was expected to be positive, though the large magnitudes observed were perhaps more due to the specific procedure. The rate of CO elimination is generally two to three times slower than nicotine elimination, and while nicotine elimination is fairly consistent within an individual, the half-life for CO can greatly vary by level of activity (e.g., as little as 2 h during exercise and up to 8 h during sleep). Thus, such high correlations probably would not occur under a paradigm that includes more smoking periods and shorter durations of abstinence. In such a case, nicotine levels would be expected to fluctuate with greater amplitude than CO; in fact, CO might appear as more of a constant or even as monotonically increasing, depending on the frequency of measurements. When fluctuations are expected rather than monotonic changes, the difference in level of quantification for expired CO measurements (via Bedfont MicroSmokelyzer) compared to blood nicotine concentrations (via gas chromatography) also works to attenuate observed correlations.

There are several limitations of this study. The fact that the data from most of the subjects followed a very similar pattern is encouraging, but there were three subjects, who in one way or

another represented serious deviations from the normative group. The small sample restricts the opportunity to capture uncommon or rare patterns so that a complete typography is not possible. The prevalence of cases counter to our theory requires further study. Considering the brand of cigarette utilized in the protocol, most normally smoked this exact brand (7 out of 11) or one much like it (Camel regulars, 3 out of 11), but there was one participant who normally smoked menthol cigarettes (Salem). While the menthol smoker was not an outlier in this case, it is possible that the use of a standardized cigarette may have moderated the craving response. Finally, the pattern of abstinence studied here would not be typical for most smokers who usually smoke at least once an hour if allowed. Accurate assessment of the nicotine blood concentration and craving relationship in normal ad lib smoking would require a larger number of blood draws and assays making such a study difficult to execute.

It can be argued that, in recent years, there has been a move away from the view of the supremacy of nicotine as the key to understanding subjective desire to smoke. The generally low rates of success with nicotine replacement products set the stage for the development of nonnicotine treatments for smoking cessation such as bupropion. Others have focused upon secondary reinforcers. For example Westman et al. (23) compared the craving reduction of a regular cigarette, a denicotinized cigarette paired with an intravenous steady infusion of nicotine, denicotinized cigarette with intravenous pulses of nicotine, and a denicotinized cigarette with intravenous saline in overnight abstinent smokers. The denicotinized cigarette with saline provided as much craving relief as a regular cigarette. However, the denicotinized/saline condition also generated the largest CO boost, possibly compensatory behavior indicating nicotine seeking, nonetheless. Recent work by Schuh et al. (20), using denicotinized cigarettes, has shown that, for a subset of people, tar yield may have some effect on preference and satisfaction (hence satiety) ratings. Earlier work (6,9), however, indicates that nicotine content is more important than tar in preference ratings. In any case, these studies only measured acute satisfaction, and do not speak to the needs of smokers over a longer period. Clearly, the lack of success of low nicotine cigarettes in the marketplace indicates that reinforcers other than nicotine lack durability in the maintenance of smoking.

To some degree, craving may be the result of psychological factors independent of pharmacologic state, but we posit that self-reported craving is, in part, an accurate, though individually standardized, appraisal of blood nicotine levels in continuing smokers. Our data are supportive of this theory, but cannot confirm causation. Our position is that the relationship between nicotine and craving is, in fact, substantial but remains ill-delineated. Experiments based upon the present paradigm but which include experimental manipulations such as nicotine-free tobacco cigarettes or nicotine given in a fashion that duplicates smoking pharmacokinetics are the next step.

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