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Subjective correlates of cigarette-smoking-induced elevations of peripheral beta-endorphin and cortisol

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Abstract. Two experiments assessed subjective and hormonal effects of smoking cigarettes with three different nicotine deliveries. In experiment 1, 12 males smoked two cigarettes on three different occasions: (1) nicotine-free; (2) their own brand (1.0 mg FTC-estimated nicotine delivery); or (3) 2.4 mg FTC nicotine cigarettes. In experiment 2, 12 males smoked cigarettes of comparable nicotine yield using a quantified smoke delivery system (QSDS). Blood was sampled 2 min after each cigarette completion. Relative to nicotine-free smoking, plasma beta-endorphin (BE) and serum cortisol concentrations increased after quasi-ad libitum smoking of 2.4 mg, but not after 1.0 mg nicotine cigarettes. Self-reported malaise (nausea, sickness, and unpleasantness) also increased after smoking 2.4 mg nicotine cigarettes; subjective distress was correlated with changes in blood BE and cortisol. Smoking 1.0 mg cigarettes did not increase BE or cortisol, or subjective distress. QSDS smoking produced hormonal and subjective effects similar to quasi-ad libitum smoking; however, correlations between neuromodulator concentrations and mood were non-significant. These findings suggest that the elevated levels of plasma BE and cortisol reported in some smoking studies may not be characteristic effects of normal smoking.

Key words: Nicotine – Smoking – Beta-endorphin – Cortisol – Nausea – Affect – Reinforcement – Neuromodulators

Studies reporting that nicotine administration elevates blood concentrations of pituitary and adrenal neuromodulators in humans (Pomerleau et al. 1983; Novack and Allen-Rowlands 1985; Seyler et al. 1986) and infrahumans (Balfour et al. 1975; Conte-DeVolx et al. 1981; Cam and Bassett 1984) have recently attracted theoretical and experimental attention. Evidence suggesting that cigarette smoking may elevate plasma concentrations of the endogenous opioid, beta-endorphin (BE), has prompted some investigators to propose that tobacco use may be motivated by nicotine-induced release of endogenous opiate-like neuromodulators (Henningfield et al. 1981; Pomerleau and Pomerleau 1984). Reports indicating that the opiate antagonist, naloxone, reduces cigarette smoking (Karrass and Kane 1980; Gorelick et al. 1989) support this view, but not all studies confirm this finding (Nemeth-Coslett and Griffiths 1986).

While there is some evidence for involvement of an opiate-like neuromodulator in smoking, it is also well established that physiological stress can elevate peripheral levels of the endorphins (Akil et al. 1979) and cortisol (Selye 1976). This is important because most laboratory studies of smoking and neuromodulators have required subjects to smoke high-nicotine-delivery cigarettes rapidly, after overnight (10–16 h) smoking abstinence. The consequences of rapid ingestion of high doses of nicotine by smokers whose nicotine tolerance has been diminished by prolonged smoking abstinence may not be representative of normal smoking (Benowitz 1988; Gilbert and Welser 1989). For example, rapid smoking, and smoking the first cigarette of the day frequently lead to nausea and subjective distress even in habitual smokers (Silvette et al. 1962; Kozlowski et al. 1981). Furthermore, models implicating neuromodulators in the positive reinforcement of smoking (e.g., Pomerleau and Pomerleau 1984) have predicted positive correlations between peripheral neuromodulator concentrations and self-reported states of pleasure/positive affect; yet, in some studies where subjective states have been assessed, smoking-induced elevation of plasma BE, cortisol, and other neuromodulators has been associated with nausea (e.g., Seyler et al. 1984, 1986). Thus, an alternative hypothesis that could account for much of the earlier data (Gilbert and Welser 1989) is that smoking-induced neuromodulator elevation after rapid smoking results from physiological and subjective distress (nausea, sickness, etc.).

Based on these considerations, we hypothesized that rapid smoking of two strong cigarettes after several

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hours of smoking deprivation would produce organismic distress, feelings of discomfort and negative affect, and elevated peripheral BE and cortisol levels. In contrast, smoking more normal-nicotine-delivery cigarettes at a normal rate was not expected to produce subjective distress, nor to elevate peripheral neuromodulator concentrations.

Previous studies of smoking-induced neuromodulator changes have not systematically assessed subjective states with psychometric instruments. The present studies were designed to measure endocrinological consequences of cigarette smoking in conjunction with psychometrically assessed affective states. A quasi-ad libitum smoking procedure was used in the first study. To provide more precise control of nicotine ingestion, a system for delivering quantified doses of smoke was used in the second study.

Experiment 1

Materials and methods

Subjects. Twelve Caucasian males, aged 21–35, and weighing 160–180 pounds were recruited by local newspaper advertisements. They had been smokers for 2.5–20 years ($\bar{X}=9.7$ years), and were currently smokers of at least 15 per day of Camel Filter® or Marlboro® 85 mm cigarettes ($\bar{X}=24.0$/day, SD = 9.6). Male Caucasians were used in order to replicate previous studies and because the small number of participants used made extensions to other populations infeasible.

Procedure. Requirements of the study were explained and a breath carbon monoxide (CO) sample, obtained from each subject, was evaluated (Catalyst Research CO monitor, Model 1000) during a late afternoon orientation session, before the first experimental session. Subjects were tested on 3 different days, separated by 48 h. Subjects abstained from smoking from midnight before the 1:00 p.m. and 3:00 p.m. sessions (minimum of 13–15 h smoking abstinence). Abstinence was verified by measuring expired CO levels at the start of each test session, and confirmed by subsequent baseline plasma nicotine assays (see Results). On each test day they smoked two cigarettes of the following types: A nicotine-free herbal cigarette (Honey Rose®); their own cigarette – either a Camel Filter® or Marlboro® regular (FTC–estimated 1.0 mg nicotine deliveries); or a high-nicotine (2.4 mg FTC–estimated nicotine delivery), Kentucky Reference (2R1) cigarette. All subjects participated under all smoking conditions, the order of testing being counterbalanced according to a Latin Square, with subjects randomly assigned to one of the following orders: (A) High, Own, Nicotine-free ($N=4$); Own, Nicotine-free, High ($N=4$); or Nicotine-free, High, Own ($N=4$). Subjects were instructed to smoke normally, at their own pace, except that they were required to smoke each 2.4 mg cigarette for exactly 5 min, with 10 min between the lighting of cigarettes. This 10-min interval replicates procedures typically used in previous studies reporting elevated neuromodulator concentrations after smoking high-nicotine cigarettes (e.g., Seyler 1984, 1986). To approximate more normal smoking conditions, the 1.0 mg and 0.0 mg cigarettes were smoked to 8 mm above the filter overwrap, with 30 min between lightings of the two cigarettes.

Before smoking, baseline blood samples, taken 45 min after insertion of an indwelling catheter into the medial antecubital vein of the arm, were stored on ice in pre-chilled Vacutainer® tubes. The first cigarette was lit 55 min after catheter insertion. Because only 5 min separated the end of the first and the lighting of the second high-nicotine cigarette, blood samples were collected 2 min after each cigarette was completed. Tubes were centrifuged under refrigeration and serum and plasma samples were decanted and stored at −90° C. Samples were shipped on dry ice to Dr. Neal Benowitz's laboratory (San Francisco General Hospital) for gas chromatographic assays of nicotine (Jacob et al. 1981) and Dr. Nancy Haley's laboratory (American Health Foundation, Valhalla, New York) for radioimmune assays of BE and cortisol.

Ten minutes before the first and again 2 min after completion of each cigarette, during blood withdrawal, subjects completed the Feeling State Questionnaire (FSQ) indicating their feelings at that time. The FSQ consists of 14 ten-point Likert scales (ranging from "0 = none", to "10 = extreme"). "Pleasant", "unpleasant", "sick", and "nauseated", are individual items that were analyzed in the present investigation. The FSQ includes ten other items pertaining to moods (e.g., "angry") and bodily symptoms (e.g., "hands sweating", "heart pounding"). Previous studies have shown this instrument to be a valid measure that correlates with experimental manipulations and other measures of mood (Gilbert and Hagen 1980; Gilbert and Spielberger 1987).

Results

Repeated measures analyses of variance on three dose levels (Nicotine-free/0.0 mg, Own/1.0 mg, and High/2.4 mg nicotine) and three times within sessions (baseline, post-cigarette 1, and post-cigarette 2) were performed. Degrees of freedom were corrected by the Geiser-Greenhouse method (Vasey and Thayer 1987). Follow-ups to significant interactions ($P<0.05$) included analyses of simple main effects for time and dose and paired comparisons using the Bonferroni correction for three means ($P=0.05/3=0.017$). In all cases we report only the results of post-hoc statistical contrasts for which simple effects analyses using the Geiser-Greenhouse correction were significant at the $P<0.05$ level or beyond.

Plasma nicotine concentrations were below the level of detectability of the assay procedure (1.0 ng/ml) for all subjects at baseline, suggesting that subjects had followed instructions not to smoke on the days of testing. As expected, the three different cigarettes elevated plasma nicotine concentrations in a dose-related fashion (Fig. 1C): Smoking nicotine-free cigarettes had no effect on plasma nicotine concentrations [$F(1.02, 11.25)=0.87$, $P>0.37$]; smoking one's own (1.0 mg FTC-estimated nicotine delivery) cigarette raised plasma nicotine concentrations above nicotine-free control levels, after one [$F(1,11)=105.2$, $P<0.001$] and two cigarettes [$F(1,11)=107.7$, $P<0.001$]. Smoking 2.4 mg nicotine cigarettes for 5 min elevated plasma nicotine concentrations above the own dose after one [$F(1,11)=29.92$, $P<0.001$] and two cigarettes [$F(1,11)=12.02$, $P<0.006$].

Preliminary analyses showed that within-cell variances were nonhomogeneous for both BE and cortisol. Thus, subsequent analyses were performed on log transformed data, after adding 10 to each score to correct for zero values. Mean plasma Log (BE + 10) was significantly higher after two 2.4 mg cigarettes that with the other two doses (Fig. 1A); own and nicotine-free cigarettes did not differ: High versus Free [$F(1,11)=8.85$, $P<0.013$]; High versus Own [$F(1,11)=11.83$, $P<0.006$]; Own versus Free [$F(1,11)=0.83$, $P>0.37$]. Smoking 1.0 mg or 0.0 mg cigarettes did not elevate plasma BE above presmoking baselines [$F(1.25, 13.71)=0.47$, $P>0.55$; $F(1.83, 20.12)=0.10$, $P>0.89$, respectively].

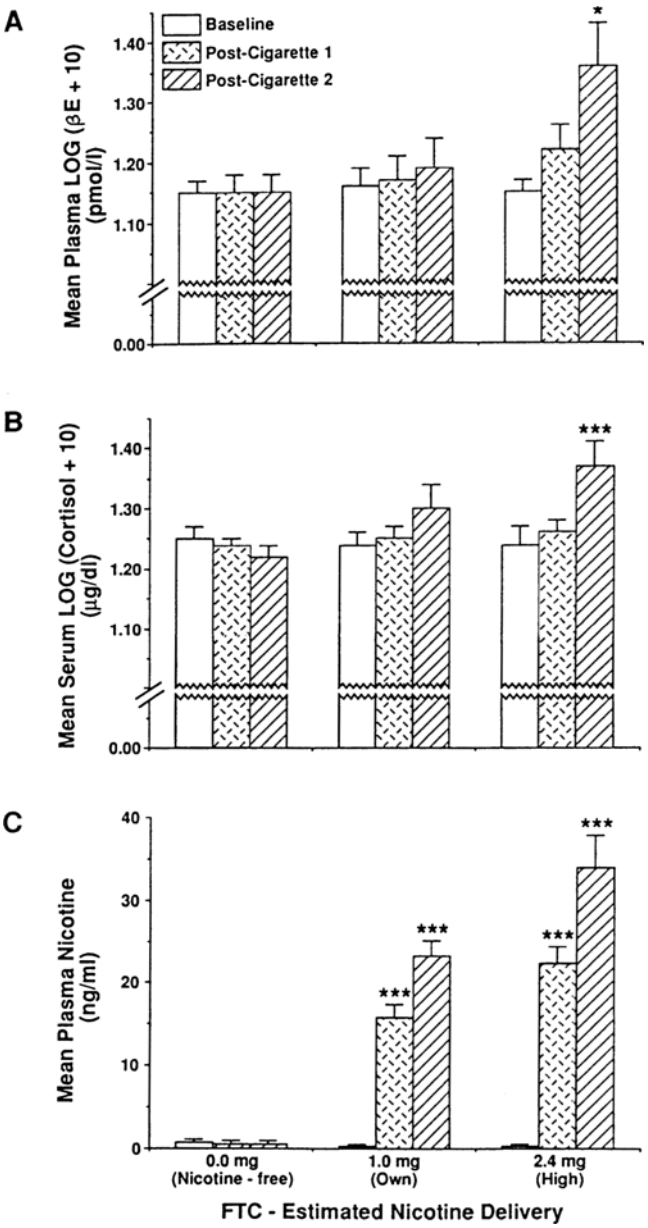

Fig. 1A–C. Effects of quasi-ad libitum smoking of cigarettes with different FTC-estimated nicotine deliveries on **A** plasma Log (BE + 10), **B** serum Log (cortisol + 10), and **C** plasma nicotine concentrations. *Vertical bars* represent +1 SEM ($N = 12$). *Asterisks* represent significance of differences from corresponding nicotine-free (0.0 mg) cigarette: * = $P < 0.017$; *** = $P < 0.001$. ($P < 0.017$ = minimally significant P-value for Bonferroni multiple comparisons)

For the most part, smoking-induced changes in serum cortisol mirrored those of BE (see Fig. 1B). After two 2.4 mg cigarettes serum cortisol was elevated significantly above the 0.0 mg, but not the 1.0 mg condition. Serum cortisol was marginally but not significantly higher after 1.0 mg than after 0.0 mg cigarettes using the Bonferroni multiple contrasts procedure {(critical value = 0.0167): High versus Free [$F(1,11) = 19.60$, $P < 0.001$], High versus Own [$F(1,11) = 2.81$, $P > 0.12$], Own versus Free [$F(1,11) = 6.78$, $P > 0.024$]}.

Table 1. Mean subjective ratings after quasi-ad libitum smoking of High (2.4 mg), Own (1.0 mg), or Nicotine-free (0.0 mg) cigarettes. P-values (in parentheses) represent significance of differences from nicotine-free control, one-tailed tests

	Cigarette 1			Cigarette 2		
	High	Own	Free	High	Own	Free
Pleasant	4.7 [a]	5.5 [a]	5.5	3.9 [a]	5.5 [a]	5.4
Unpleasant	3.2 (0.006)	1.3 (0.324)	1.0	3.9 (0.001)	1.4 (0.171)	0.8
Sick	3.0 (0.006)	1.1 (0.408)	0.7	3.8 (0.009)	0.8 (0.306)	1.4
Nausea	2.7 (0.007)	1.4 (0.082)	0.7	3.7 (0.001)	0.8 (0.550)	0.6
Malaise[b]	3.0 (0.004)	1.3 (0.191)	0.7	3.8 (0.001)	1.0 (0.872)	0.9

[a] Because of baseline differences, effects of smoking on the Pleasant dimension were evaluated using difference scores (see text)
[b] Malaise = (Unpleasant + Sick + Nausea)/3

The different cigarettes also affected FSQ-assessed subjective feelings differently. Subjects reported more malaise (nausea, sick, and unpleasant feelings) after both high-nicotine cigarettes than after nicotine-free cigarettes. In contrast, smoking one or two of their own cigarettes did not increase self-reported malaise (Table 1).

Because subjects reported stronger pleasant feelings on average at baseline on the high-nicotine than on the nicotine-free test day [$F(1,11) = 8.59$, $P < 0.014$], pleasant feelings were analyzed using a 2 (post-cigarette 1, post-cigarette 2) × 3 (doses) ANOVA on difference (baseline − post-smoking) scores. Pleasant feelings did not change significantly after smoking only one cigarette, regardless of nicotine content (all P's > 0.05). However, subjects felt less pleasant after two 2.4 mg cigarettes ($\overline{X} = -2.1$) than after two 1.0 mg ($\overline{X} = -0.25$) or two 0.0 mg cigarettes ($\overline{X} = -0.1$), [$F(1,11) = 7.97$, $P < 0.017$; $F(1,11) = 8.00$, $P < 0.016$ respectively].

Measures of subjective distress were also correlated with increases in blood BE and cortisol after two 2.4 mg, but not after two 1.0 mg cigarettes. Change in Log (BE + 10) correlated positively with changes in nausea ($r = 0.532$, $P < 0.038$), sickness ($r = 0.691$, $P < 0.006$), and malaise ($r = 0.555$, $P < 0.031$). Similarly, change in Log (cortisol + 10) correlated positively with changes in nausea ($r = 0.613$, $P < 0.017$), sickness ($r = 0.748$, $P < 0.003$), and malaise ($r = 0.704$, $P < 0.005$). However, 2 of 12 subjects did not report increased malaise in spite of increases in Log (BE + 10) of 0.10 units or more, and three subjects reported large increases in malaise (2.67+) without substantial increases in Log (BE + 10) (less than 0.10). Similarly, while all subjects exhibiting increases in Log (cortisol + 10) of 0.14 or more units reported malaise, three who changed less than 0.14 units also reported malaise. Changes in Log BE and in Log cortisol concentrations correlated relatively highly with each other

($r=0.674$, $P<0.008$), but not with changes in plasma nicotine ($r=0.134$, $P>0.33$; $r=-0.173$, $P>0.29$, respectively).

Discussion

Results of this experiment confirm that smoking two high-nicotine cigarettes within 15 min after several hours of smoking abstinence elevates blood BE and cortisol concentrations (Pomerleau et al. 1983; Seyler et al. 1984, 1986). Furthermore, after smoking high-nicotine cigarettes subjects reported significant increases in malaise, also confirming earlier reports (Seyler et al. 1984, 1986). Our finding that peripheral BE was not elevated significantly after smoking two 1.0 mg nicotine cigarettes at the more normal, 30-min pace characterizes the effects of smoking under more ecologically valid conditions.

An important implication of these results is that elevations in peripheral BE and cortisol resulting from rapid smoking of high-nicotine cigarettes may be associated with dysphoria and malaise, and may not be representative of normal smoking in low-stress situations. The hypothesis that BE mediates positive reinforcement effects implies a positive correlation between peripheral BE concentrations and measures of pleasantness. Contrary to this hypothesis, we found that smoking-induced increases in plasma BE concentrations correlated somewhat negatively (although not significantly) with changes in self-reported pleasantness, and correlated positively with malaise. Furthermore, the elevation of peripheral cortisol levels, a widely recognized marker of physiological and subjective stress (Selye 1976; Munck et al. 1984), supports this interpretation.

However, some design limitations of the present study are noteworthy. First, these results characterize responses of young, physically fit, Caucasian males, and may not be characteristic of other populations. Second, the use of non-tobacco cigarettes may not be adequate as a control, since tobacco may contain constituents other than nicotine that could contribute to nausea. Third, although BE was not elevated by smoking own cigarettes, it is unclear whether this was due to the cigarettes' lower FTC-estimated nicotine deliveries (1.0 mg), or to the spacing of cigarettes at 30-min intervals. Given unlimited access to their own cigarettes, subjects might have smoked more than two during the test interval, thereby boosting plasma nicotine high enough to elevate peripheral BE concentrations. Further studies of the effects of smoking multiple, normal-nicotine cigarettes under ad libitum conditions are needed to evaluate this possibility.

Differing from the general pattern, two subjects showed increased plasma BE, and three showed increased serum cortisol after high-nicotine cigarettes, without malaise. These discrepancies could reflect true individual differences in responsivity to nicotine. However, it is also possible that temporal variations in patterns of smoking contributed to these differences. For example, large and/or rapid puffing during the first minutes of smoking could have produced malaise and associated neuromodulator release, and reduced puff frequency and size during the final mins of smoking. On the other hand, a moderate, steady rate of smoking throughout the entire 5-min interval could have produced tachyphylaxis to the malaise-inducing effects of nicotine, while producing the same levels of plasma nicotine. Therefore, to control for rate and volume of puff delivery, we repeated the experiment using a quantified smoke delivery system (QSDS).

Experiment 2

Materials and methods

Subjects. Twelve Caucasian males, aged 21–35, and weighing 160–180 pounds were recruited by local newspaper advertisements. One subject had participated previously in experiment 1. All had smoked from 2 to 26 years ($\bar{X}=11.2$ years), and were currently smokers of at least 15 per day of Camel Filer® or Marlboro® 85 mm cigarettes ($\bar{X}=21.5$/day, SD = 7.3).

Apparatus. The quantified smoke delivery system (QSDS; Gilbert et al. 1988) takes 2-s duration, 35 cc, sinusoidal-shaped puffs drawn at 30-s intervals by a 50-cc glass syringe. The cigarette is connected to the syringe by means of a 2.0 cm piece of Penrose® drain tubing and a three-way solenoid valve. The filter end of the cigarette is placed into one end of the drain tubing, while the other end of the tubing is connected to the valve. Operating the motor draws into the syringe a puff of smoke which is expelled over 2 s into the smoker's mouth. The smoker immediately inhales the smoke and holds it in his lungs until a signal light goes out, 5 s after inhalation.

Procedure. Subjects were tested under conditions similar to those of experiment 1, using the QSDS. Using the same counterbalanced orders as in experiment 1, testing was carried out with three different cigarettes: a high (2.6 mg FTC-estimated nicotine delivery) Kentucky Reference cigarette (1A4); a modal (1.3 mg FTC-estimated nicotine delivery) Kentucky Reference cigarette (1A3); and the nicotine-free (0.0 mg nicotine, tobacco-free, herbal (HoneyRose® control) cigarette. Cigarettes with slightly higher FTC-estimated deliveries than in experiment 1 were used to compensate for the somewhat lower nicotine deliveries typically achieved from a given cigarette with the QSDS, relative to ad libitum smoking. The term "high-nicotine" is used here because no commercial cigarette manufactured in the USA in 1988 had a FTC rating of more than 1.9 mg nicotine. The term "modal" is used here because the 1A3 Kentucky Reference cigarette, when smoked via the QSDS, approximates the 1.0 delivery of the most popular (modal) cigarette in the USA at the time of the study (Maxwell Consumers Report 1990). Blood samples and psychological measures were obtained at time periods similar to those of experiment 1. However, because the high-nicotine cigarettes required 18–19 puffs, delivered at 30-s intervals, to complete smoking to butt-length of 8 mm, they required 8.5–9 min to complete; in contrast, each high-nicotine cigarette in experiment 1 was smoked for only 5 min before the subject was required to stop smoking. Therefore, in order to preserve, as in experiment 1, a 5-min interval between the end of cigarette 1 and the beginning of cigarette 2, the interval between lightings of the two cigarettes was standardized at 14 min. The two 0.0 mg and 1.3 mg nicotine cigarettes were lit, as in experiment 1, at 30-min intervals.

Results

Statistical procedures, including Geiser-Greenhouse corrections for repeated-measures factors, were the same as in experiment 1, except that individual paired-

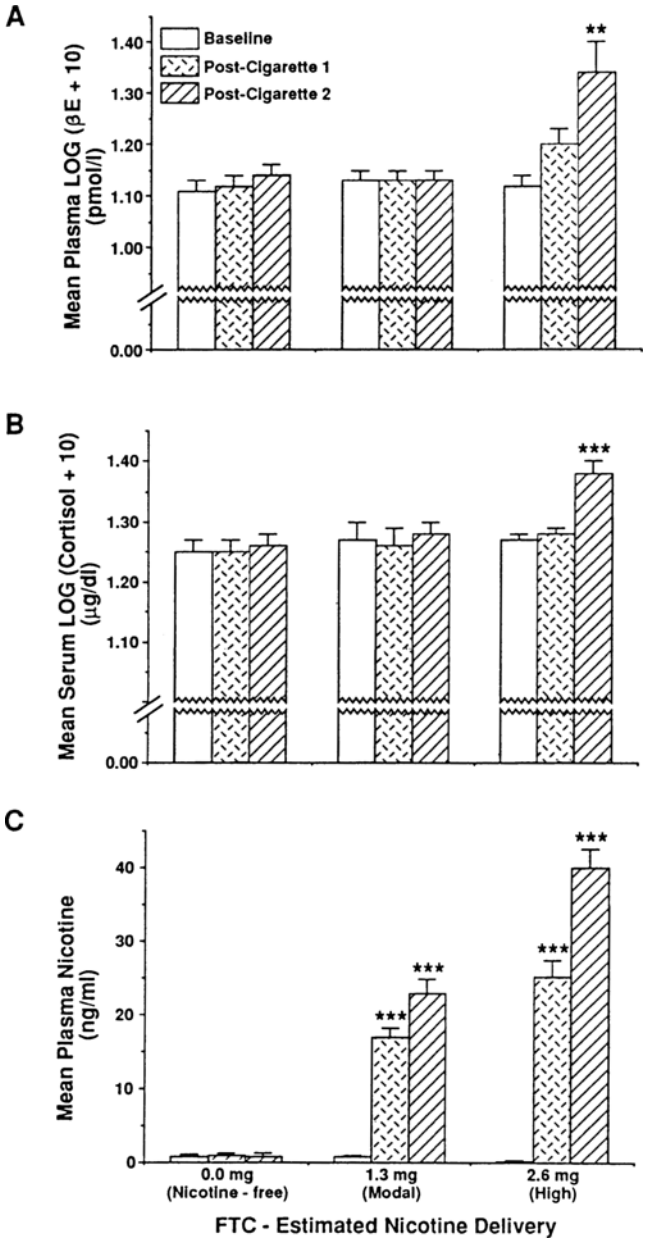

Fig. 2A–C. Effects of QSDS smoking of cigarettes with different FTC-estimated nicotine deliveries on **A** plasma Log (BE + 10), **B** serum Log (cortisol + 10), and **C** plasma nicotine concentrations. *Vertical bars* represent + 1 SEM ($N = 12$). *Asterisks* represent significance of differences from corresponding nicotine-free (0.0 mg) cigarette: ** = $P < 0.005$; *** = $P < 0.001$. ($P < 0.017$ = minimally significant P-value for Bonferroni multiple comparisons)

comparisons were planned based on results of experiment 2.

As expected, a dose-response relationship between nicotine delivery and plasma nicotine concentrations was found (Fig. 2C). Smoking 0.0 mg cigarettes had no effect on plasma nicotine concentrations [$F(1.37, 15.02) = 1.16$, $P > 0.32$]; smoking a 1.3 mg nicotine cigarette via the QSDS raised plasma nicotine above nicotine-free control levels after one [$F(1,11) = 151.2$, $P < 0.001$] and two cigarettes [$F(1,11) = 115.6$, $P < 0.001$]. Smoking a 2.6 mg cigarette elevated plasma nicotine significantly above the 1.3 mg dose after one [$F(1,11) = 31.34$, $P < 0.001$] and after two cigarettes [$F(1,11) = 54.76$, $P < 0.001$].

Table 2. Mean subjective ratings after QSDS smoking of High (2.6 mg), Modal (1.3 mg), or Nicotine-free (0.0 mg) cigarettes. P-values (in parentheses) represent significance of differences from nicotine-free control, one-tailed tests

	Cigarette 1			Cigarette 2		
	High	Own	Free	High	Own	Free
Pleasant	3.4 (0.046)	4.7 (0.820)	4.6	4.2 (0.633)	4.2 (0.658)	4.0
Unpleasant	1.8 (0.286)	1.5 (0.368)	1.2	2.2 (0.039)	1.4 (0.504)	1.2
Sick	1.6 (0.034)	1.3 (0.402)	0.8	1.8 (0.119)	1.3 (0.111)	0.8
Nausea	1.4 (0.236)	1.2 (0.674)	0.9	1.8 (0.046)	1.6 (0.456)	0.6
Malaise[a]	1.6 (0.111)	1.4 (0.442)	0.9	1.9 (0.038)	1.3 (0.101)	0.9

[a] Malaise = (Unpleasant + Sick + Nausea)/3

In addition, smoking 2.6 mg cigarettes elevated plasma BE concentrations significantly (Fig. 2A). Log (BE + 10) concentration was higher after QSDS smoking of two 2.6 mg cigarettes than in the other two dose conditions, while the modal and nicotine-free control cigarettes did not differ: High versus. Free [$F(1,11) = 12.36$, $P < 0.005$]; High versus Modal [$F(1,11) = 11.25$, $P < 0.007$]; Modal versus Free [$F(1,11) = 0.45$, $P > 0.52$]. As expected, smoking one or two nicotine-free or modal cigarettes did not elevate BE levels above baseline [$F(1.46, 16.01) = 2.00$, $P > 0.17$; $F(1.39, 15.26) = 0.07$, $P > 0.88$, respectively].

The pattern of changes in serum cortisol concentration with QSDS smoking was similar to that for BE (Fig. 2B). Smoking two high-nicotine cigarettes raised serum cortisol above the nicotine-free and modal conditions, which did not differ from each other: High versus Free [$F(1,11) = 22.20$, $P < 0.002$; High versus Modal [$F(1,11) = 24.16$, $P < 0.001$); Modal versus Free [$F(1,11) = 0.42$, $P > 0.54$].

Cigarettes with different nicotine deliveries also produced different subjective effects, but to a smaller degree than in experiment 1. Subjects typically reported more malaise (nausea, sick, and unpleasant feelings) after 2.6 mg than after 0.0 mg cigarettes (Table 2). In contrast, smoking 1.3 mg cigarettes did not reliably increase negative affect. Pleasant feelings decreased after the smoking of one high-nicotine [$F(1,11) = 5.04$, $P < 0.047$], but not after smoking a modal cigarette [$F(1,11) = 0.05$, $P > 0.82$].

In contrast to experiment 1, change in malaise did not correlate significantly with baseline-to-post-smoking changes in Log BE or Log cortisol concentrations in either the High or Modal conditions (all Ps > 0.05). However, as in experiment 1, all subjects exhibiting changes in Log (cortisol + 10) of 0.14 or more units exhibited increased malaise. Six of the seven subjects exhibiting

increases in Log (BE + 10) of 0.14 or more units reported increased malaise. Thus, while most smokers experienced malaise after smoking high-nicotine cigarettes, only a portion of these individuals showed increased blood neuromodulator concentrations. As in experiment 1, changes in Log BE and in Log cortisol concentrations after two 2.6 mg cigarettes were relatively highly correlated ($r = 0.558$, $P < 0.030$).

Discussion

Results from this study using a more controlled dosing procedure confirm that BE is elevated after smoking high-nicotine cigarettes, but not after smoking more normal nicotine delivery cigarettes. However, in contrast to experiment 1, measures of malaise were less consistently elevated, and correlations between malaise and BE levels were smaller than with the quasi-ad libitum procedure, even though mean plasma nicotine and BE concentrations were quite similar after smoking high-nicotine cigarettes in both experiments. This finding leaves open the possibility that BE can be elevated without malaise. However, the discrepancy between the two studies may have occurred because the same plasma nicotine levels achieved by 5 min of quasi-ad libitum smoking in experiment 1 were achieved after 8.5–9 min of QSDS smoking. The less rapid smoking in experiment 2 may have produced a partial tachyphylaxis in the subjective response of malaise. Furthermore, since affective state was not measured until 10.5–11 min after the start of smoking in experiment 2, compared to 7 min in experiment 1, subjects may have recovered from the aversive effects of ingesting a high dose of nicotine by the time affective state was measured. In some clinical cases nausea and other indicators of malaise due to nicotine poisoning subside relatively rapidly, even though plasma nicotine concentrations remain extremely high (Benowitz et al. 1987).

While we found no evidence of plasma BE elevation 2 min after either the first or second modal cigarettes in both studies, it is conceivable that BE might have become elevated at a later time. Nevertheless, it is noteworthy that smoking high-nicotine cigarettes elevated plasma BE by 2 min after the end of smoking in both experiments. Furthermore, while the plasma nicotine loadings achieved with two modal cigarettes were approximately the same as after one high-nicotine cigarette, BE was not elevated by modal smoking in either experiment, supporting the interpretation that while *rapid* ingestion of nicotine may elevate BE, slower, more ecologically typical ingestion rates do not.

General discussion

Although numerous studies report that stress increases peripheral pituitary and adrenal hormone levels in humans and animals (Selye 1976; Akil et al. 1980), we are not aware of evidence that peripheral BE elevation is associated with positive hedonic states, except in the case of long-distance running ("runner's high", Wildmann et al. 1986), which clearly involves a physiological stress component. However, while BE may not increase reliably after one or two modal-nicotine cigarettes, it may after several cigarettes have been smoked over the course of a day. Also, in combination with psychological stress, smoking may enhance the likelihood of BE release, since smoking and stress may produce additive or synergistic effects endocrinologically. Additive effects of stress and nicotine have been reported for peripheral cortisol in humans (Pomerleau and Pomerleau 1990), and for peripheral corticosterone, epinephrine, and glucose in an animal model (Morse 1989). Stress-dependent effects of nicotine are also reported for EEG activity (Golding and Mangan 1982; Gilbert et al. 1989). Additionally, while smoking-induced elevation of plasma BE often occurs in conjunction with malaise, our results also support the view that some individuals may achieve plasma neuromodulator increases without reporting subjective distress. The conditions that promote smoking-induced release of BE without malaise require further study (Pomerleau and Rosecrans 1989).

The relationship of peripheral to central measures of neuromodulator concentrations is unclear. Many studies (e.g., see Post et al. 1982) suggest that central and peripheral levels of neuromodulators, including BE, can vary independently. However, peripherally-administered BE has been found to elevate BE levels in CSF in humans (Gerner et al. 1982), and diurnal covariation in human CSF and plasma BE has been reported (Barreca et al. 1986). The relevance of peripheral neuromodulator levels to their putative reinforcing effects remains to be determined.

Finally, it is noteworthy that quasi-ad libitum smoking of 1.0 mg nicotine cigarettes (experiment 1) marginally elevated serum cortisol levels. Along with unpublish ed results from this laboratory and the findings of others (Pomerleau and Pomerleau 1990), this suggests that in certain individuals and conditions, normal smoking may produce modest elevations of cortisol independent of stress and of increased peripheral BE. Individual differences in constitution and/or physiological dependence are likely to contribute to variations in physiological response to nicotine (Masson and Gilbert 1990). Individual differences in response to nicotine may also occur as a function of gender and race. Thus, future studies should systematically assess gender and racial differences. There are a number of similarities between the effects of cigarettes smoking and cortisol, and it has been suggested that cortisol may mediate some of nicotine's reinforcing effects (Gilbert 1979). For example, exogenous administration of cortisol, like nicotine, has been found to improve cognitive performance, alter electrocortical activity, and result in enhanced mood in certain circumstances (Born et al. 1988; Gilbert and Welser 1989).

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