PHARMACODYNAMICS AND DRUG ACTION

Relationship of electroencephalographic and cardiovascular changes to plasma nicotine levels in tobacco smokers

Objective: The effects of smoking one tobacco or placebo cigarette on the mean change in voltage of the electroencephalogram (EEG), arterial blood pressure, heart, and eye blink rates were correlated with the increase in plasma nicotine, exhaled carbon monoxide, and carboxyhemoglobin levels.
Methods: Twenty nonsmokers (age range, 19 to 42 years; mean age ± SE, 27.0 ± 1.9 years) and 65 regular tobacco smokers (age range, 20 to 48 years; mean age ± SE, 27.7 ± 0.8 years) were studied about 10 to 12 hours after overnight tobacco deprivation and immediately after inhaling air through a straw or after smoking one of their own brands of cigarettes, respectively.
Results: An increase of at least 10 ng/ml plasma nicotine was needed to obtain a statistically significant decrease in $alpha_1$ and an increase in beta EEG activity. An increase of at least 15 ng/ml plasma nicotine was needed to obtain a statistically significant decrease in delta EEG activity. The mean dominant alpha frequency, heart rate, systolic and diastolic blood pressure, exhaled carbon monoxide, and carboxyhemoglobin levels increased significantly with increasing plasma nicotine concentrations.
Conclusions: Measurement of plasma nicotine levels is especially important to quantify the relationship between tobacco smoking, mean EEG activity, and cardiovascular changes. Nicotine plasma concentrations greater than 10 μg/ml produce consistent and statistically significant changes in brain wave activity. Smaller increments in plasma nicotine produce less consistent EEG changes. (CLIN PHARMACOL THER 1994;55:370-7.)

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There have been many reports on the qualitative and quantitative electroencephalographic (EEG) effects of tobacco smoking in humans. In general, tobacco smoking decreases delta (1 to 4 Hz) and theta (4.5 to 7.5 Hz) activity, increases the dominant alpha (8-12 Hz) frequency, and increases activity in the $beta_1$ (12.5 to 17.5 Hz) and $beta_2$ (18 to 30 Hz) bands.[1-15] To date, there has been no study in which plasma levels of nicotine have been correlated with EEG effects. Two studies have reported cardiovascular effects that are correlated with plasma nicotine levels.[16,17] The purpose of this study was to describe the relationships of EEG and cardiovascular effects to plasma levels of nicotine in tobacco smokers who smoked their first cigarette of the morning in the laboratory after 10 to 12 hours of abstinence from tobacco products.

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METHODS

Subjects. All procedures involving experiments on human subjects were done in accord with the ethical standards of the Helsinki Declaration of 1975. Eighty-five healthy adult male Japanese volunteers gave informed consent to participate. Twenty were nonsmokers (age range, 19 to 42 years; mean age ± SE, 27.0 ± 1.9 years). Sixty-five were daily smokers (age range, 20 to 48 years; mean age ± SE, 27.7 ± 0.8 years). The tobacco smokers had all smoked cigarettes and inhaled tobacco smoke for many years. All smoked their own brands of commercial cigarettes of known nicotine (0.5 to 2.7 mg; mean ± SE, 0.9 ± 0.05 mg) and tar (6 to 26 mg; mean ± SE, 10 ± 0.6 mg) content. The subjects were asked to stop smoking about 11 PM the night before. They came to the laboratory at about 8:30 AM the next day and smoked one of their own cigarettes at about 9 to 10 AM after an approximately 10 to 12-hour period of abstinence. Each subject was allowed to eat a small breakfast and to drink fluids; however, subjects were asked to not drink any caffeine-containing beverages.

Scalp electrodes were applied to record monopolarly 16 channels of EEG by use of the 10-20 International System. Each subject lay in a bed in the EEG laboratory. Before sham or tobacco smoking, a 10 ml venous blood sample was drawn into a heparinized tube and labeled for nicotine and cotinine analyses. There was a 2-minute rest period during which the subject closed his eyes and attempted to relax for another 2 minutes. After all recordings were satisfactory, the subject was asked to either sham smoke a placebo cigarette or smoke one cigarette of his own brand. The nonsmokers inhaled air through the placebo cigarette to simulate smoke inhalation. Tobacco smokers were asked to smoke in comfort and inhale deeply but at their usual rates of smoking. Filter cigarettes were permitted as long as they were the subject's usual brand. The EEG recordings were repeated immediately thereafter, as were the postsmoking blood samples.

EEG recordings and analysis. The experimental design used 16 scalp cortical recording sites from monopolar records linking A_1 to the left and A_2 to the right ear as reference leads per the 10-20 International System. EEG recordings were taken from scalp electrodes attached with electrode paste with use of a Nihon Kohden 17 channel EEG, model 4317 (Nihon Kohden Corp., Tokyo, Japan). The EEG data were recorded on paper on line and also on quarter-inch magnetic tape. A Sony tape recording system (NFR-3000, model DRF-39515, Tokyo, Japan) was used for recording all 16 channels of EEG data. An interface was provided by a Magatani unit which allowed 16 channel recording on an 8 channel Sony tape recorder. Subsequently, at the experimenter's convenience, the data were replayed from the tape recorder back through the EEG amplifiers into the Nihon Kohden ATAC power frequency spectral analyzer. Monopolar EEG recordings were taken from F_{p1}, F_{p2}, F_3, F_4, C_3, C_4, P_3, P_4, F_7, F_8, T_5, T_6, F_z, P_z, O_1, and O_2. The EEG amplifier band width was 1 to 30 Hz, with the 60 Hz filter on.

The topographic EEG data were analyzed on the basis of voltages grouped in a 6 × 6 grid representing the top of the head. The technique used was described by Ueno et al.[18] The total summated activity for all 16 channels of EEG data was computed for each frequency band: delta, 1.0 to 3.4 Hz; theta, 3.6 to 7.4 Hz; $alpha_1$, 7.6 to 10 Hz; $alpha_2$, 10.2 to 12.4 Hz; beta, 12.6 to 26 Hz. Dominant alpha frequency before and after smoking was calculated from the spectral analysis of Pz. Ten seconds of artifact-free typical records were analyzed before and immediately after tobacco or sham smoking.

Nicotine analysis. Venous blood samples were removed just before and after tobacco smoking. Each blood sample collected in a heparinized tube was placed on ice for subsequent centrifugation while the experiment was conducted. Plasma samples were removed and stored at −70° C. Plasma nicotine was subsequently measured by use of the HPLC method described by Hariharan et al.[19] This method has a sensitivity of 1 ng/ml nicotine and 5 ng/ml cotinine.

Cardiovascular parameters. Systolic and diastolic blood pressures were determined from the most accessible arm by use of an automatic blood pressure monitor (Life Scope 7, model OEC-7402, Nihon Kohden Corp.). Blood pressure was expressed in millimeters of mercury. Heart rate was calculated from lead II of the electrocardiogram. Eyelid blink rates were counted as EMG artifacts from F_{p1} or F_{p2} of the EEG. Both heart and eye blink rates were expressed as events per minute.

Carbon monoxide and carboxyhemoglobin. The exhaled air carbon monoxide level was measured by a Gastec carbon monoxide detector (Gastec Co., Kanagawa, Japan). The red blood cell carboxyhemoglobin was measured by use of an IL 282 CO-Oxymeter (Instrumentation Laboratory, Lexington, Mass.).

Data analysis. All data were analyzed by use of one-factor ANOVA (Scheffe's test) and linear regression analyses, with $p < 0.05$ considered to be statistically significant.

Table I. Change in mean total electroencephalographic activity per frequency band and the range of plasma nicotine concentrations

Concentration of plasma nicotine	*Delta (μV)*	*Theta (μV)*	*Alpha$_1$ (μV)*	*Alpha$_2$ (μV)*	*Beta (μV)*
Nonsmokers	−0.64 ± 0.10	−0.42 ± 0.09	−0.31 ± 0.13	0.87 ± 0.13	0.43 ± 0.05
0.1–4.9 ng/ml	−0.02 ± 0.09	0.42 ± 0.11*	0.42 ± 0.16	1.51 ± 0.13*	−0.18 ± 0.09
5.0–9.9 ng/ml	−0.42 ± 0.17	−0.44 ± 0.10	−0.86 ± 10.20	1.12 ± 0.11	0.09 ± 0.10
10.0–14.9 ng/ml	−0.90 ± 0.24	−1.14 ± 0.14*	−4.04 ± 0.28**	3.03 ± 0.21**	0.36 ± 0.21*
15.0–20.5 ng/ml	−3.37 ± 0.18**	−0.60 ± 0.10	−3.88 ± 0.40**	0.96 ± 0.23	0.84 ± 0.24**

*$p < 0.01$.
**$p < 0.001$.

RESULTS

EEG effects. In view of previous literature[1,3,11,13,15] indicating very important alpha EEG changes with tobacco smoking, the EEG measurements of all 85 subjects were analyzed with respect to give different conditions based on the differences in plasma nicotine before and after smoking (Table I). A decrease in delta EEG activity was statistically significant when an increase in plasma nicotine of 15 ng/ml or more was obtained. A decrease in alpha$_1$ and an increase in beta EEG activity were statistically significant when an increase in plasma nicotine of 10 ng/ml or more was obtained. Additional changes in the mean total EEG activity were noted with plasma nicotine concentrations that included theta and varying alpha$_2$ activity, as noted in Table I, but no clear linear relationship over increasing nicotine concentrations was noted. Nonsmokers who inhaled air to mimic smoking had EEG changes that were not statistically significant.

The relationship between the difference (Δ) in mean EEG activity of all 16 channels and plasma nicotine levels before and after smoking for each of 85 volunteers is shown in Fig. 1, *A* through *D*. Statistically significant correlations were observed between the change in delta ($p < 0.05$) and alpha$_1$ ($p < 0.01$), but not mean theta and alpha$_2$ activity and plasma nicotine level. Linear regression analyses between the difference in the mean EEG activity and plasma nicotine levels revealed the following: difference in mean delta activity and plasma nicotine, $y = -0.118x + 0.049$, in which y is the change in mean delta and x is the change in plasma nicotine level. The correlation coefficient was $r = 0.224$ ($p < 0.05$). The difference in mean alpha$_1$ activity and plasma nicotine was $y = -0.269x + 0.43$, in which y is the change in mean alpha$_1$ and x is the change in plasma nicotine level. The correlation coefficient was $r = 0.342$ ($p < 0.01$). The correlation coefficient of mean theta activity and plasma nicotine was $r = 0.126$ ($p > 0.1$, which is not significant with use of a two-tailed *t* test). The equation for alpha$_2$ activity and plasma nicotine was $y = 0.15x + 0.752$, in which y is the change in mean alpha$_2$ activity and x is the change in plasma nicotine. The correlation coefficient was $r = 0.164$ ($p \leq 0.1$, which is not significant with use of a two-tailed *t* test). The mean dominant alpha frequency at P_z before sham smoking was 9.70 Hz. After sham smoking, the nonsmokers showed no increase in their dominant alpha frequencies. The dominant alpha frequency before tobacco smoking was 9.70 to 10.25 Hz. After tobacco smoking the dominant alpha frequency range was 10 to 12 Hz. A statistically significant correlation exists between the increase in dominant alpha frequency and the increase in plasma nicotine levels (Fig. 2, *A*). A linear regression analysis between the change in dominant alpha frequency and the change in plasma nicotine level indicated that $y = 0.062x - 0.043$, in which y is the increase in dominant alpha frequency and x is the change in plasma nicotine level. The correlation coefficient was $r = 0.402$ ($p < 0.01$). The difference in mean beta activity and plasma nicotine was $y = 0.087x - 0.393$, in which y is the change in mean beta and x is the change in plasma nicotine. The correlation coefficient was $r = 0.253$ ($p < 0.05$; Fig. 2, *B*). A statistically insignificant ($p > 0.1$) correlation was obtained between the increase in eye blink rate and plasma nicotine levels ($r = 0.176$; Fig. 2, *C*) by use of the two-tailed Student *t* test. However, after smoking, the increase in eye blink rate and the increase in plasma nicotine (Δnicotine) were significantly correlated ($r = 0.265$; $p < 0.05$; data not shown).

Cardiovascular effects. After sham smoking, the nonsmokers showed no increase in mean heart rate or systemic arterial blood pressure. The relationship between the difference in heart rate or blood pressure and nicotine levels before and after smoking for all 85

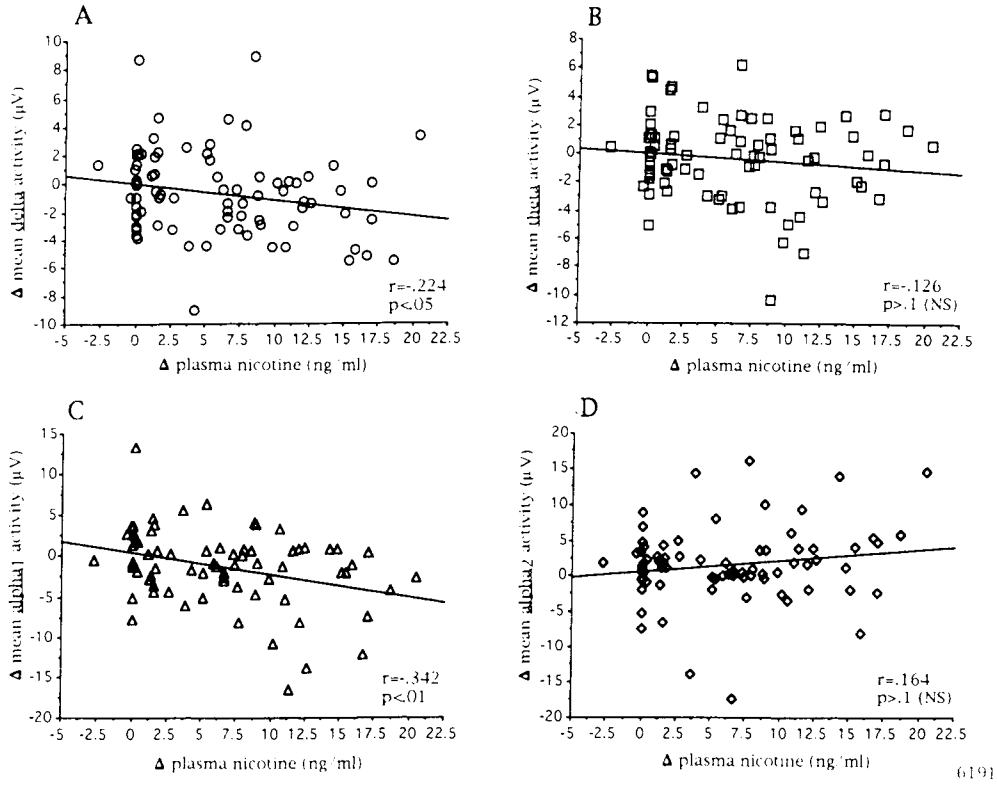

Fig. 1. Correlation between increase in plasma nicotine and mean total delta, theta, alpha$_1$, and alpha$_2$ electroencephalographic (EEG) activity. The Δ increase in plasma nicotine before and after smoking either a sham cigarette in the case of 20 nonsmokers or a personal choice tobacco cigarette for 65 tobacco smokers is shown on the *x*-axis in all four graphs **(A** through **D).** The after minus before change in mean EEG activity from 16 scalp electrodes separated into delta **(A),** theta **(B),** alpha$_1$ **(C),** and alpha$_2$ **(D)** bands are plotted on the *y*-axis. Although there is a great deal of variability among individual subjects, there are statistically significant trends with respect to increasing levels of plasma nicotine except for the change in alpha$_2$ activity. Each *point* represents an individual volunteer. There are from 75 to 79 points that in some cases overlap, for a total of 85 individual subjects. The *r* and *p* values are given in the lower right-hand corner for each correlation.

volunteers is shown in Figs. 2, *D* and Fig. 3, *A* and *B*. A statistically significant positive correlation exists between the increase in heart rate ($p < 0.001$), systolic blood pressure ($p < 0.01$), or diastolic ($p < 0.001$) blood pressure and the increase in plasma nicotine. Linear regression analyses of the increase in heart rate or blood pressure and the increase in plasma nicotine revealed that y = 0.829x + 2.79, in which y is the increase in heart rate and x is the increase in plasma nicotine level. The correlation coefficient was $r = 0.588$ ($p < 0.001$). The increase in systolic blood pressure and plasma nicotine level was y = 0.386x + 2.27, in which y is the increase in systolic blood pressure and x is the increase in plasma nicotine. The correlation coefficient was $r = 0.322$ ($p < 0.01$). The increase in diastolic blood pressure and the increase in plasma nicotine level was y = 0.386x + 1.41, in which y is the increase in diastolic blood pressure and x is the increase in plasma nicotine. The correlation coefficient was $r = 0.512$ ($p < 0.001$).

Exhaled carbon monoxide, carboxyhemoglobin, and EEG changes after tobacco smoking. Relatively high positive correlations were found between the increase in exhaled carbon monoxide, carboxyhemoglobin, and the increase in plasma nicotine (Fig. 3, *C* and *D*). Linear regression analysis of the increase in exhaled carbon monoxide or carboxyhemoglobin and the increase in plasma nicotine revealed that y =

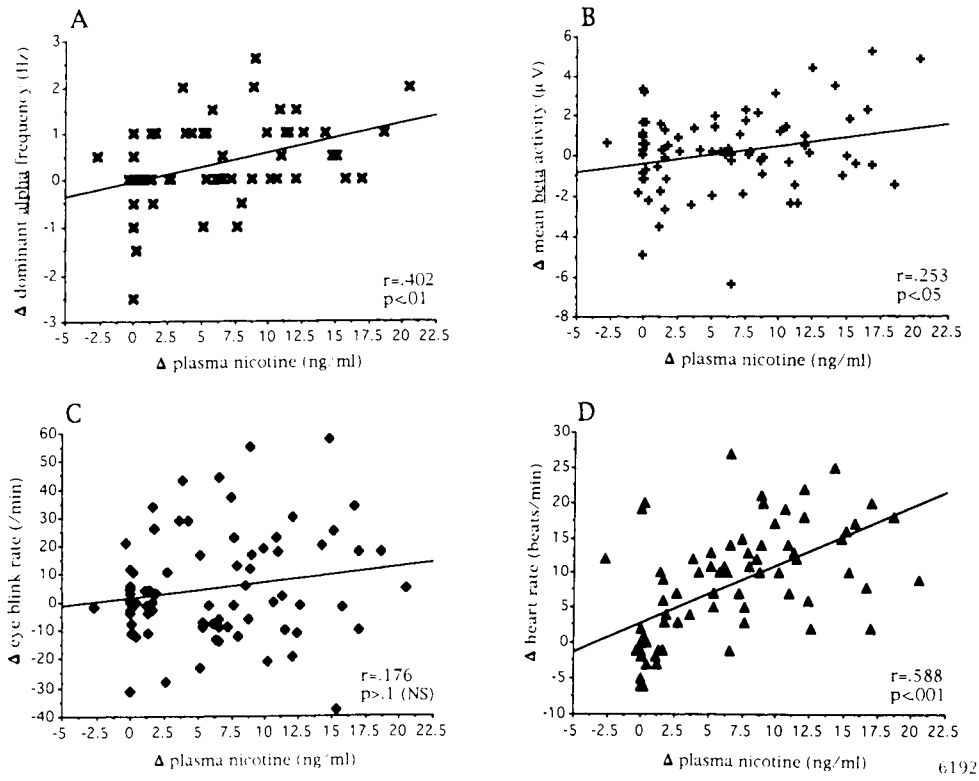

Fig. 2. Correlation between the increase in plasma nicotine, dominant EEG alpha frequency, beta activity, eye blink, and heart rate. Graphs **A** through **D** in this and the subsequent figure are similar to those in Fig. 1. There are significant correlations in mean dominant alpha and beta activity and in heart rate with increasing plasma nicotine levels. For the dominant alpha EEG analysis, the data of 51 subjects were used because of computer data recovery problems on the remaining subjects.

0.254x + 0.905, in which y is the increase in exhaled carbon dioxide and x is the increase in plasma nicotine. The correlation coefficient was $r = 0.571$ ($p < 0.001$). The increase in carboxyhemoglobin and the increase in plasma nicotine level was y = 0.59x + 0.216, in which y is the increase in carboxyhemoglobin and x is the increase in plasma nicotine level. The correlation coefficient was $r = 0.711$ ($p < 0.001$).

The change in delta, theta, $alpha_1$, $alpha_2$, and beta EEG activity did not correlate significantly with the change in exhaled carbon monoxide or carboxyhemoglobin after tobacco smoking ($p < 0.05$). The changes in heart rate and systolic and diastolic blood pressure did correlate significantly with the change in exhaled carbon monoxide and carboxyhemoglobin ($p < 0.001$).

DISCUSSION

To our knowledge, the mathematic relationship of human EEG responses to blood levels of nicotine has never been reported before this study. Knott[8] found an increase in alpha activity during and after smoking. Norton et al.[14] reported a decrease in alpha activity, whereas higher amounts of nicotine caused slower wave delta and theta activity than lower doses. Norton et al.[14] suggested that these differences may be related to dose. However, these investigators did not measure plasma nicotine levels before and after smoking. In addition, their recording of alpha activity was not divided into $alpha_1$ and $alpha_2$ sub-bands. Domino and Matsuoka[11,15] observed that after tobacco smoking the topographic distribution of EEG frequencies showed a more diffuse increase in $alpha_2$ (10.25 to 12.5 Hz) and a decrease in $alpha_1$ (7.75 to 10 Hz) in most subjects in a dose-related fashion. Although many types of EEG changes after smoking were observed in the present study, there was an obvious decrease in $alpha_1$ activity after tobacco smoking in subjects that had mean increases in a plasma nicotine greater than 10 ng/ml. An increase in plasma nicotine levels led to

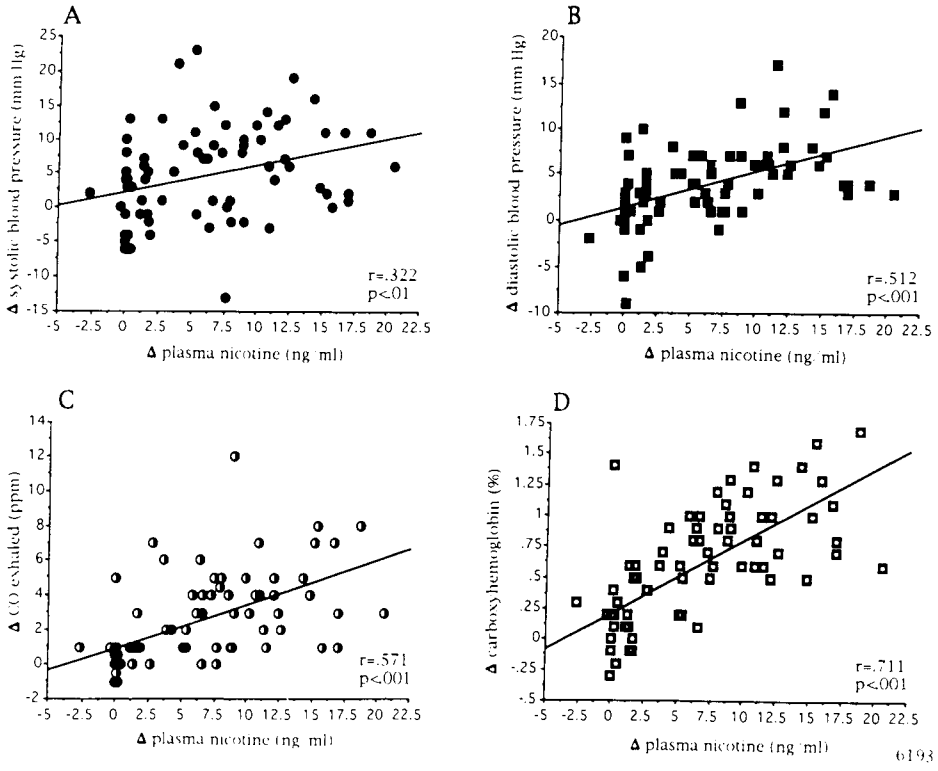

Fig. 3. Correlation between the increase in plasma nicotine, systolic and diastolic blood pressure, exhaled carbon monoxide, and carboxyhemoglobin. All four correlations are highly statistically significant as noted. The best positive correlation is between the increase in plasma nicotine and red blood cell carboxyhemoglobin (r = 0.711).

significant decreases in delta and alpha$_1$ activity and an increase in beta activity in the present study. Benowitz et al.[20] reported that 10 healthy men from the San Francisco area who smoked their usual brands of cigarettes after an overnight abstinence from tobacco use and had a morning presmoking mean ± SE plasma nicotine level of 2.7 ± 1.7 ng/ml and a postsmoking mean increment of 14.3 ng/ml. A similar plasma increment was obtained for smokeless tobacco. This finding is remarkably similar to the 10 to 15 ng/ml increment obtained in the present study for an obvious EEG change. How wonderfully curious that San Francisco male tobacco users should achieve plasma nicotine levels that male tobacco smokers from Kitakyushu require for clear-cut brain wave changes. A 15 ng/ml increment in plasma nicotine seems to be rather high for the average Japanese male tobacco smoker (Domino EF, Kadoya C, Matsuoka S. Unpublished observations, June 1993). More subtle EEG changes occur at much lower increments of plasma nicotine because of the significant correlations obtained in the present study (see Table I). Golding[7] reported a shift to a higher dominant alpha frequency after tobacco smoking. The present data are similar and suggest that an increase of 10 ng/ml in plasma nicotine level leads to a shift to an approximately 0.6 Hz higher dominant frequency. Golding and Mangan[21,22] reported that smoking was associated with EEG stimulation (as measured by a decrease in alpha amplitude) under conditions of sensory isolation and EEG sedation (as measured by an increase in alpha amplitude) during stress. Wesnes and Warburton[23] observed that tobacco cigarette smoking increased speed and accuracy in a concentration-demanding rapid-processing task. The present experiments were done with the eyes closed and relatively low levels of arousal. The observed decreases in delta and alpha$_1$ activity, and increases in beta activity and dominant alpha frequency are consistent with nicotine induced cerebral stimulation.

Inasmuch as increased arousal tends to increase the eye blinking rate, a positive correlation was predicted with increasing plasma nicotine levels. The present data showed a positive trend, but this was not statisti-

cally significant by means of a two-tailed *t* test. As expected, cigarette smoking, as compared with sham smoking, significantly elevated heart rate, systolic blood pressure, and diastolic blood pressure. Hopkins et al.[16] and Hasenfratz et al.[17] concluded that the heart rate increase correlates closely with plasma nicotine. The data of the present study are in complete agreement. Birbaumer et al.[24] failed to show any differences in cardiovascular responses between cigarettes that contained different levels of nicotine. It is possible that this may be the result of a failure to measure plasma nicotine, which is the critical independent variable.

The observed highly significant ($p < 0.001$) positive correlations between the increase in exhaled carbon monoxide and carboxyhemoglobin and the increase in plasma nicotine levels are to be expected. Perhaps this explains why there were also significant correlations with heart rate and blood pressure when the variance was much less than with the EEG measures, which were not significantly correlated with either exhaled carbon monoxide or carboxyhemoglobin. The positive correlation between the increase in the dominant alpha frequency and the increase in exhaled carbon monoxide after smoking may be expected because the latter correlates significantly with the increase in plasma nicotine levels. Hasenfratz et al.[17] reported that female tobacco smokers after smoking two cigarettes, which took about 10 minutes, could be separated into high and low plasma nicotine groups. The change in plasma nicotine was very different for both groups, but the change in exhaled carbon monoxide was similar. In the present study, the change in plasma nicotine correlated positively with the change in exhaled carbon monoxide and carboxyhemoglobin shortly after smoking. If the EEG changes were primarily caused by the change in plasma nicotine (and therefore brain nicotine), one would expect more significant correlations with plasma nicotine than carbon monoxide or carboxyhemoglobin because the half-life of nicotine is much shorter than that of carbon monoxide or carboxyhemoglobin. It is clear that individual tobacco smokers vary markedly in the way and how often they inhale while smoking. Even with an attempt to standardize smoking techniques, it is obvious that it did not succeed for the individual variability in all three parameters was considerable.

The present research has several obvious weaknesses. First, although each smoker stated that he had stopped smoking overnight for a 10- to 12-hour period of abstinence, some of the presmoking levels of plasma nicotine and the carbon monoxide levels were higher than those that would be expected in an abstinent person. One tobacco smoker even had a higher prenicotine than postnicotine plasma level, suggesting a mislabeling of blood samples. However, none of the data from any subject were deleted from the present analysis. Second, a reference montage was used for 16 channels of monopolar EEG recordings. Yet we chose to calculate mean EEG voltage difference (after and before) to obtain a single value for each frequency band as a measure of total brain electrical activity. Obviously, a detailed topographic analysis of the data needs to be done to identify discrete regional brain differences. This will be the subject of a future report. Third, the selection of the EEG segments to be analyzed was based on discarding obvious EEG recording artifacts, including eye blinks, electrode wire sway, and motor movements, and is subject to subjective bias.

Considering all of the individual variability observed, as well as weaknesses in the study design, it is remarkable that a number of variables were found to correlate significantly with the increase in plasma nicotine levels, as would be predicted from previous literature on tobacco smoking.

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