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Food and Nicotine Metabolism

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LEE, B. L., P. JACOB, III, M. E. JARVIK AND N. L. BENOWITZ. *Food and nicotine metabolism.* PHARMACOL BIOCHEM BEHAV **33**(3) 621–625, 1989.—To examine the plausibility of the hypothesis that smoking a cigarette after a meal is motivated by accelerated metabolism of nicotine, we studied the influence of a high-protein meal on the disposition of nicotine in seven healthy smokers. Indocyanine green clearance, an estimate of hepatic blood flow, increased 31%, 50 minutes after the test meal. Consuming the meal during a steady state infusion of nicotine resulted in a small (18%) but consistent decrease in blood levels of nicotine. Our data demonstrate that food accelerates the metabolism of nicotine, but the time course and magnitude of the decline in levels of nicotine suggest that altered disposition of nicotine is not the primary motivation for smoking after meals.

Smoking Nicotine Food Meals Metabolism Liver blood flow

EATING a meal increases the desire for a cigarette as well as the satisfaction derived from smoking a cigarette postprandially. Evidence for this phenomenon exists in several surveys (10,14) as well as in a recent laboratory study (12). Smokers tend to regulate the intake of nicotine, adjusting their smoking behavior to maintain a certain concentration of nicotine in the body (1,3). A possible explanation for smoking after a meal is that the meal reduces blood levels of nicotine.

Nicotine is metabolized rapidly with a nonrenal clearance of about 70% of liver blood flow (2). The clearance of drugs such as propranolol and lidocaine, which are highly extracted by the liver, is influenced by hepatic blood flow (7,15). It is expected, therefore, that clearance of nicotine is also affected by liver blood flow.

Liver blood flow increases approximately 40% within 30 minutes of eating a meal (5). Eating a meal, presumably by increasing hepatic blood flow, accelerates the metabolic clearance of propranolol and lidocaine (7,15). We hypothesized that meal-related increased hepatic blood flow might likewise increase the clearance of nicotine. If correct, smoking after a meal might be triggered by a decline in level of nicotine in the body. We studied the influence of a high-protein meal on the disposition of nicotine and indocyanine green in seven healthy smokers. Indocyanine green (ICG) is highly extracted by the liver and clearance of ICG is commonly used as an estimate of hepatic blood flow. Indocyanine green clearance was measured before and after the meal to assess the effect of the meal on hepatic blood flow (13).

METHOD

Subjects

Seven healthy male subjects, ranging in age from 32 to 61 years, who were regular smokers, participated in a 4-day study in the General Clinical Research Center at San Francisco General Hospital Medical Center. None had a history of liver disease and all had normal liver function tests. Written informed consent was obtained from each subject. The study was approved by the University of California, San Francisco, Committee on Human Research.

Experimental Design

The subjects were studied with an incomplete 3×3 Latin square on three separate days. Each subject received three treatments consisting of a nicotine infusion with a meal, a nicotine infusion while fasting, and a placebo infusion of saline with a meal. The subjects were blinded as to whether the infusion was nicotine or placebo. The nicotine infusion was given before the meal to achieve a steady state concentration, which is the most sensitive situation in which to detect a transient change in clearance due to a meal. After overnight abstinence from food and cigarette smoking and 1 hour of rest in the supine position, a

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TABLE 1

SUBJECT CHARACTERISTICS AND MEAL CONSUMPTION

Subject	Age (year)	Weight (kg)	Meal Consumption (g) Protein	Carbohydrate	Fat	Calories
RB	40	91	49.3	37.5	37.8	699.6
TH	43	78	43.4	36.2	32.1	612.2
FD	40	72	39.8	31.3	30.1	565.9
HM	61	68	36.3	28.3	27.0	506.4
WN	39	83	35.9	29.0	27.0	513.2
AR	40	75	43.5	34.2	33.5	621.6
WE	32	62	43.2	32.8	32.3	604.8

loading infusion of nicotine bitartrate, 2.5 μg nicotine base/kg/min, for 30 minutes was given intravenously. A continuous infusion of nicotine, 0.35 μg/kg/min, followed for the next 150 minutes. These doses were selected to achieve and maintain a steady state blood nicotine level of approximately 25 ng/ml, similar to that observed in habitual smokers. Three bolus doses of ICG, 0.5 mg/kg, were given through a separate intravenous catheter. ICG was injected 20 minutes before, 45 minutes, and 145 minutes after the beginning of nicotine infusion.

A high protein meal, consisting of eggs, bread, ham and milk (39.3 g protein, 31 g carbohydrate, and 29.7 g fat, Table 1), was selected since the protein content of the meal seems to be an important determinant of the increase in liver blood flow (5,17). The meal was consumed over a 10-minute period, which started 90 minutes after the beginning of the nicotine infusion. Caffeine-containing beverages and alcohol were prohibited during the hospital stay. The two other treatments—nicotine infusion while fasting and saline infusion with meal—were studied with a similar infusion and sampling schedule.

Venous blood samples for measurement of nicotine concentration were collected at 0, 40, 50, 60, 75, 90, 100, 115, 130, 145, 155, 165, and 180 minutes. Concentrations of nicotine were measured by gas-liquid chromatography (11), modified for use of a capillary column. Venous blood samples for measurement of ICG were drawn from an antecubital catheter opposite to the infusion catheter at 0, 1, 3, 5, 7, 9, 11, 13, 15, 17, and 20 minutes after each dose. Samples were centrifuged, and plasma ICG concentrations were determined the same afternoon by a spectrophotometric method (6). This method has been shown to give identical results to the more specific chromatographic method (20).

A subjective questionnaire consisting of 17 questions inquiring about nicotine-related effects and desire for a cigarette was administered every 30 minutes during the study period. The questions were rated on a scale of 0, not at all, to 9, extremely.

Data Analysis

Indocyanine green blood clearance was determined as an indicator of hepatic blood flow (hepatic arterial plus portal venous blood flow). The plasma concentration of ICG declined monoexponentially. The rate constant (K) of ICG elimination and the extrapolated zero-time concentration (C_{po}) were determined from the plasma ICG concentration-time curve. Plasma clearance of ICG was calculated as:

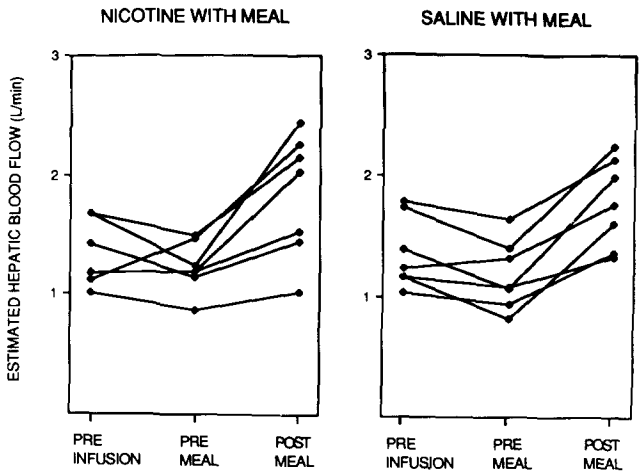

FIG. 1. Estimated hepatic blood flow before nicotine and saline infusions, and before and after the test meal for seven subjects. Preinfusion and premeal values were similar. The meal significantly increased hepatic blood flow in both study conditions. Two subjects had identical values for hepatic blood flow in preinfusion and premeal conditions, so only six lines connecting these treatments are apparent.

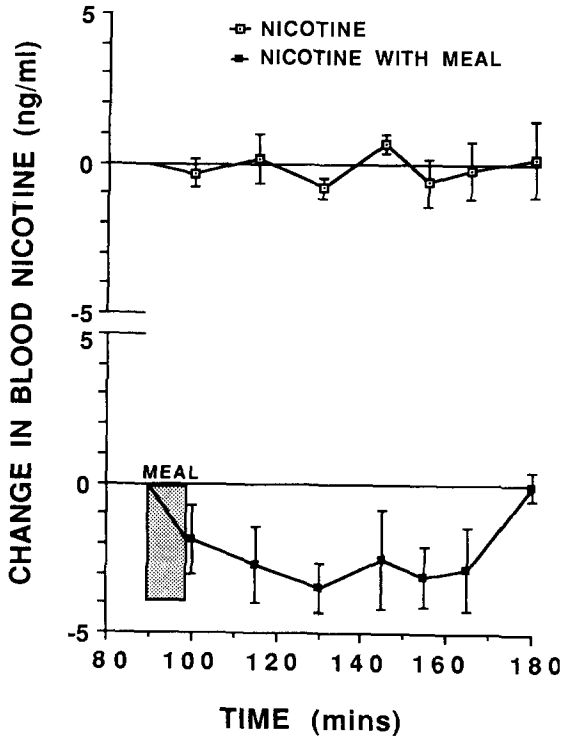

FIG. 2. Average change in blood concentrations of nicotine from baseline with and without a meal (N = 7). The baseline value (solid horizontal line) represents the average of five concentrations taken from 40 to 90 minutes; mean 21.4 ± 1.8 ng/ml and 23.0 ng/ml in the no meal and meal conditions, respectively.

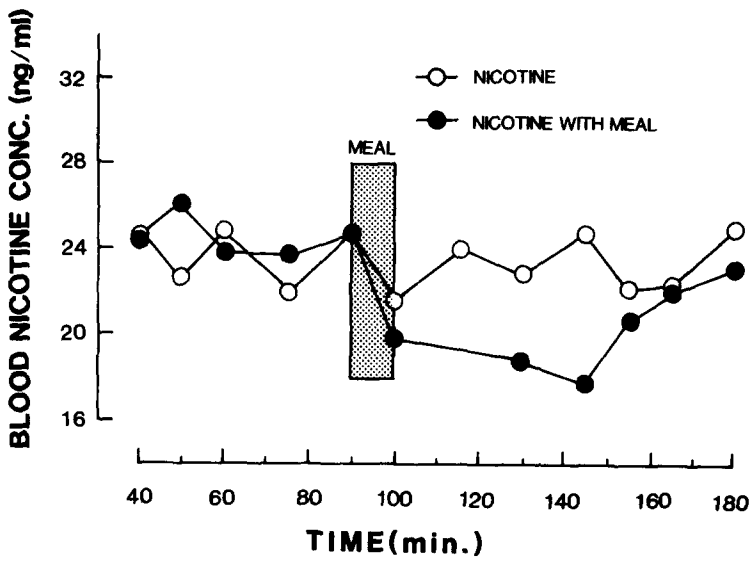

FIG. 3. Blood nicotine concentrations for one subject with and without a meal.

$$Clp = \frac{KD}{C_{po}}, \text{ where D is the dose administered.}$$

Blood clearance was then computed as:

$$Cl_{ii} = \frac{Clp}{(1 - Hct)}, \text{ where Hct is the venous blood hematocrit.}$$

Effects of the infusions and the meal on ICG clearance data were analyzed by repeated measures analysis of variance.

The concentrations of nicotine during the 50 minutes prior to the meal (40-, 50-, 60-, 75-, and 90-minute samples) were averaged to compute a premeal baseline value for both nicotine infusion groups. The subsequent change in blood concentration of nicotine values from 90 to 180 minutes were calculated as a difference from the baseline. The area under the change in blood nicotine concentration-time curve (AUC) from 90 to 180 minutes was then computed using the trapezoidal method. These particular post meal times were selected as times when maximal changes in hepatic blood flow were expected (5,21). The AUC with and without a meal were compared for difference from zero by unpaired *t*- and compared to one another by paired *t*-tests.

RESULTS

On average, blood clearance of ICG increased by 32% and 29% after the test meal in the nicotine and saline conditions, respectively (Fig. 1). Infusion of nicotine without the test meal did not affect the clearance of ICG.

An average premeal nicotine concentration of 23.0 ng/ml was achieved in the seven subjects in the nicotine with a meal group, and 21.4 ng/ml in the nicotine without a meal group. The difference between mean values was not significant. Figure 2 shows the change in blood nicotine concentrations from baseline at steady state following a meal or without a meal. In the absence of a meal, the concentration of nicotine remained fairly constant for the duration of the study. Following the meal, the level of nicotine consistently declined. The average maximal decline was 18.3% (range 7–30%). The median time of maximal decline was 45 minutes after the test meal. The area under the change in blood nicotine concentration-time curve (compared with steady state) from 90 to 180 minutes was not significantly different from zero without a meal. The AUC following the meal was significantly different from zero and greater than the no-meal condition ($p<0.05$). In one subject, the blood nicotine concentration decreased 30%, from 25 ng/ml before the meal to 17.5 ng/ml 45 minutes after the meal (Fig. 3).

Responses to three questions showed significant treatment effects: 1) How strong is the infusion? 2) How satisfied are you? 3) How hungry do you feel? All subjects stated that the nicotine infusion felt stronger (more like smoking a cigarette) at the beginning of the infusion; the subjective effect of nicotine disappeared as the infusion progressed ($p<0.05$). During infusion of saline, the subjects were less satisfied before the meal than after the meal: satisfaction increased from 1 to 5 ($p<0.05$). Before the meal, subjects were less hungry while receiving the nicotine infusion. Following the meal, hunger was satisfied equally whether receiving nicotine or saline infusion. Ratings of desire to smoke a cigarette were similar in the fasting and meal conditions.

DISCUSSION

Our data confirm other reports that food increases hepatic blood flow and increases the clearance of rapidly metabolized drugs. Feeley and others examined the effect of eating a steak meal on concentrations of propranolol in the blood (9). Propranolol concentration decreased by 35% 30 minutes following the meal. More recently, Olanoff compared the disposition of intravenous and oral propranolol after a high protein meal versus fasting (16). Liver blood flow increased by 34% 60 minutes following the test meal. Systemic clearance of propranolol increased 38% after the meal, with no change in half-life or apparent volume of distribution. Elvin studied the effect of a high protein meal on the hepatic clearance of intravenous lidocaine (7). Following the meal, the clearance of lidocaine increased 16% from 1245 to 1477 ml/min. The meal had no effect on the serum protein binding of lidocaine.

Nicotine is eliminated in humans primarily by hepatic metabolism. Based on its nonrenal clearance, we estimate that its hepatic extraction ratio is high, about 70% (2). Its hepatic elimination is expected, therefore, to be influenced by liver blood flow. Nicotine concentrations indeed decreased after the meal, although the magnitude of the decline varied considerably within the seven subjects. That nicotine levels did not decrease very much in some subjects after the meal, despite a substantial increase in liver blood flow, is probably due to the long half-life (2 hours) of nicotine. A 30% change in clearance would be expected to result in a less than 30% change in nicotine concentration in the 80 minutes following a meal.

That the nicotine infusion felt stronger at the beginning of the infusion and less toward the end is consistent with the development of tolerance (2,18). All subjects were less hungry while receiving nicotine infusion compared to saline infusion, consistent with the idea that nicotine suppresses appetite. In a recent unpublished study in one of our laboratories (M.E.J.), when smokers were deprived of cigarettes, their craving for smoking was increased markedly by interposition of a satisfying meal. Possibly, failure to find that a meal increases the desire to smoke in the present study reflects the artificiality of the experimental environment; that is, subjects with catheters in their veins, lying in a bed, having repeated blood samples withdrawn, eating a meal in 10 minutes, etc.

When a smoker chooses to smoke his next cigarette is related to the time since the last cigarette, consistent with the idea that the smoker is attempting to replace nicotine as the body eliminates it (19). Smoking appears also to be prompted by environmental cues that are independent of the time since the last cigarette. For example, triggers of smoking after a meal might include a conditioned response to the end of a meal, release of gastrointestinal hormones which influence the desire to smoke, an association of meals, drinking coffee or alcohol and the desire to smoke (4,8), a desire for the stimulant action of nicotine to antagonize the sedating effect of a meal, or a decline in nicotine levels, as we have discussed previously.

Although our data show an effect of a meal on nicotine kinetics, the relevance of this effect as a determinant of smoking behavior is questionable. For most subjects, the magnitude of decline is small, averaging 18%. Whether a smoker can discriminate an 18% change in level of nicotine has not been tested experimentally, but considering the high level of tolerance to nicotine which develops and the variability in nicotine concentrations in an individual within the day and from day to day, we doubt it. Jarvik *et al.* (12) found that the craving for a cigarette increased markedly immediately following the meal. This is consistent with the behavior of smokers, i.e., lighting up at the end of a meal, which can be readily observed. However, in this study the decline in nicotine blood levels occurred gradually over approximately a 45-minute period, consistent with the 2-hour half-life of nicotine. We consider it unlikely that, for most people, a small, gradual decline in nicotine levels could explain why a cigarette is smoked immediately following a meal. However, one subject (shown in Fig. 3) experienced sharp and substantial declines in blood nicotine levels after the meal. Possibly, this subject is a more rapid metabolizer of nicotine with an intrinsically shorter half-life. Data from this subject do raise the possibility that in some people smoking after a meal may be motivated, at least in part, by pharmacokinetic factors.

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