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Caffeine and Cigarette Smoking: Behavioral, Cardiovascular, and Metabolic Interactions

CHRISTOPHER R. BROWN AND NEAL L. BENOWITZ[1]

Division of Clinical Pharmacology and Experimental Therapeutics, Medical Service
San Francisco General Hospital Medical Center, School of Medicine
University of California, San Francisco, San Francisco, CA 94110

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BROWN, C. R. AND N. L. BENOWITZ. *Caffeine and cigarette smoking: Behavioral, cardiovascular and metabolic interactions.* PHARMACOL BIOCHEM BEHAV **34**(3) 565–570, 1989.—Coffee drinking and cigarette smoking are strongly correlated behaviors which have been suggested to act synergistically to produce adverse health consequences, particularly coronary heart disease (CHD). We studied in smokers the influence of four days of multiple daily doses of coffee containing different doses or no caffeine on cigarette smoking behavior, nicotine intake from smoking, heart rate and blood pressure, circadian serum glucose, and urinary catecholamine excretion. We observed a tendency toward greater cigarette consumption during caffeine consumption, and a tendency toward higher plasma nicotine levels during low-dose caffeine compared with the no-caffeine condition; however, these effects were small. No caffeine effects on any other of the above parameters were observed. Previously published research has usually studied effects of single doses of caffeine, which does not account for development of tolerance to effects of caffeine. If caffeine does contribute to CHD risk, it is not likely to be related to caffeine effects on smoking behavior, nicotine intake, blood pressure, heart rate, glucose tolerance, or catecholamine release. Adverse effects of long-term caffeine consumption on lipids cannot be excluded.

Caffeine Cigarettes Nicotine Coffee Catecholamines Cardiovascular

COFFEE consumption and cigarette smoking are strongly correlated in several epidemiologic studies (6, 10, 18, 21, 34, 41, 43). However, experimental studies have failed to show caffeine dose-related increases in cigarette smoking (3, 19, 23, 24). The effects of caffeine on smoking have been examined over brief intervals (a few hours), and results may not be relevant to coffee and cigarette consumption over the course of a day. One objective of our study was to test the hypothesis that regular coffee drinking, that is, several cups per day, would, in relation to the dose of caffeine, increase cigarette smoking or nicotine intake from smoking.

Cigarette smoking is a well known risk factor for coronary heart disease (CHD). Recently, coffee consumption has been associated in a dose-dependent manner with an increased risk of myocardial infarction (16, 20, 22, 38). Possible mechanisms of caffeine-induced CHD include increased blood pressure (7, 8, 13, 21, 31, 40), elevated cholesterol (17, 37, 42), and glucose intolerance (4,5). These mechanisms have been suggested by studies of single doses of caffeine in previously caffeine abstinent volunteers or, in the case of elevated cholesterol, by epidemiologic data.

Because of the strong correlation between cigarette smoking and coffee drinking, the possibility of additive or synergistic effects of these behaviors in causing adverse cardiovascular events must be considered (7,8). Synergism between coffee consumption and cigarette smoking in elevating serum cholesterol has, in fact, been reported in one study (11). The second objective of our study was to examine the influence of caffeine, consumed throughout the day, on the cardiovascular and metabolic effects of cigarette smoking.

METHOD

Subjects

Nine healthy men, 25 to 61 years of age (mean 37.8 years), who were regular smokers and coffee drinkers, were admitted to the General Clinical Research Center at San Francisco General Hospital Medical Center for 18 days. Subjects were recruited from newspaper advertisements and were for the most part unemployed blue collar workers. Each subject had normal liver function tests and no history of liver disease. Written informed consent was

[1]Requests for reprints should be addressed to Neal L. Benowitz, MD, San Francisco General Hospital Medical Center, Building 30, Fifth Floor, San Francisco, CA 94110.

obtained from each subject. The study was approved by the University of California, San Francisco, Committee on Human Research.

Experimental Protocol

The study was conducted in four consecutive treatment blocks, each of four days duration. Each subject participated in all four blocks. The blocks consisted of placebo, low-, or high-dose caffeine while smoking cigarettes and high-dose caffeine when abstaining from tobacco. The sequences of treatment blocks were determined using 4×4 Latin squares. Subjects were told that the researchers were studying effects of coffee and cigarette smoking on body functions. They were told that they would be given coffee containing different amounts of caffeine, but would not be told how much caffeine.

Caffeine, 1 mg/kg (low dose) or 2 mg/kg (high dose) in decaffeinated instant coffee, was given to subjects every 2 hours from 8 a.m. through 6 p.m. (total 6 cups/day, daily caffeine dose 0, 6, or 12 mg/kg/day). Coffee was prepared by adding anhydrous caffeine or nothing (placebo) to decaffeinated instant coffee mixed with a constant volume of water. The decaffeinated coffee (Taster's Choice, Nestle Foods Corp., Purchase, NY) was assayed and found to contain 1.1 mg caffeine per envelope. Subjects were allowed a fixed amount of nondairy creamer and sugar if they desired. During each smoking block the subjects were allowed to smoke their own brand of cigarette freely. Compliance during tobacco abstinence was assured by measuring exhaled carbon monoxide every 4 hours, which should be <8 ppm when abstaining from smoking.

On the third or fourth day of each block, a circadian blood sampling study was performed. Blood was drawn via an indwelling catheter every 2 hours during the day and every 4 hours while asleep and assayed for nicotine, cotinine (the major metabolite of nicotine), caffeine, and glucose concentrations. Total urine output was collected daily for measurement of catecholamine concentrations.

Supine (for 5 minutes) blood pressure and heart rate were obtained daily at 7 and 11 a.m. and 7 and 11 p.m. The diet was a standard hospital diet consisting of 15% to 17% protein, 39% to 45% carbohydrate, and 40% to 46% fat with all caffeine-containing beverages and chocolate prohibited. To assess the effect of caffeine on carbohydrate metabolism in a controlled fashion, meals on the circadian study days in all study blocks were identical.

Blood was collected in tubes containing oxalic acid as an anticoagulant and frozen at -10°C until analysis. Concentrations of nicotine, cotinine, and caffeine were analyzed using gas chromatography with nitrogen-phosphorus detection and capillary column, modified from the assay of Jacob *et al.* (14). The internal standard for caffeine was 7-ethyltheophylline. Urinary catecholamines were extracted according to the methods of Higa *et al.* (12) and Anton and Sayre (1) and analyzed using HPLC separation with coulometric electrochemical detector. Glucose was analyzed on a YSI glucose analyzer (Yellow Springs International, Yellow Springs, OH).

Data Analysis

Tobacco consumption, physiologic and metabolic data from different treatment blocks were compared using repeated measures analysis of variance with Tukey post hoc tests. Because of nonlinear distribution, a log transformation of urine catecholamine values was performed prior to analysis. Area under the curve (AUC) computations were performed by using the trapezoidal method, using plasma or blood concentrations over 24 hours. Data from the third or fourth day of each treatment block were used for analysis. Comparison of cardiovascular measurements and urinary excretion of catecholamines on blood-drawing and no blood-drawing days revealed no significant difference, so all data presented are from the blood-drawing day.

TABLE 1

CHARACTERISTICS OF VOLUNTEER SUBJECTS (N = 9)

	Mean ± SD	Range
Age (year)	37.8 ± 9.7	25–61
Weight (kg)	73.0 ± 8.2	60.9–87.6
No. cigarettes/day	38.9 ± 7.4	30–50
FTC* tar (mg/cigarette)	18.1 ± 3.5	14–23
FTC nicotine (mg/cigarette)	1.1 ± 0.2	0.9–1.3
Plasma cotinine (random) (ng/ml)	498.1 ± 186.5	157.7–760.3
Coffee (cups/day)	5.6 ± 2.1	3–8
Cola (cans/day)	1.4 ± 1.3	0–4
Tea (cups/day)	0.3 ± 0.7	0–2

*FTC, U.S. Federal Trade Commission machine-determined yields.

RESULTS

Characteristics of the subjects including preadmission cigarette and caffeine consumption are shown in Table 1.

Plasma caffeine, nicotine, and cotinine levels throughout the day in different treatments are shown in Fig. 1. The peak caffeine concentrations were 1.2 ± 0.2, 2.9 ± 0.3, and 3.8 ± 0.3 μg/ml for low-dose, high-dose, and high-dose/tobacco abstinence blocks, respectively. The number of cigarettes smoked, grams of tobacco burned, the 24-hour AUC for carboxyhemoglobin, serum nicotine and serum cotinine values, and urinary excretion of nicotine and cotinine are displayed in Table 2. The subjects smoked a slightly greater number of cigarettes and consumed a slightly greater number of grams of tobacco (neither statistically significant) while drinking caffeinated compared with noncaffeinated coffee. Plasma nicotine AUC tended to be higher during low dose caffeine compared with no caffeine or high dose concentrations ($p = 0.09$). Other measures of intake of nicotine, including AUC cotinine and 24-hour urinary excretion of nicotine or cotinine, were similar while consuming different doses of caffeine or noncaffeinated coffee.

There were no significant differences between the average blood pressure or heart rate comparing treatment blocks (Table 3). The heart rate tended to be lower during smoking abstinence compared to other treatments, although the difference was not significant.

Dopamine excretion was significantly lower during the cigarette abstinence block ($p < 0.05$) compared with each of the treatment blocks with free smoking (Table 3). Epinephrine excretion was lower during the tobacco abstinence block but this reached statistical significance only for the comparison with the low-dose caffeine block. Norepinephrine levels also tended to be lower during tobacco abstinence but did not reach statistical significance. No differences were observed in catecholamine excretion comparing different caffeine treatment blocks when

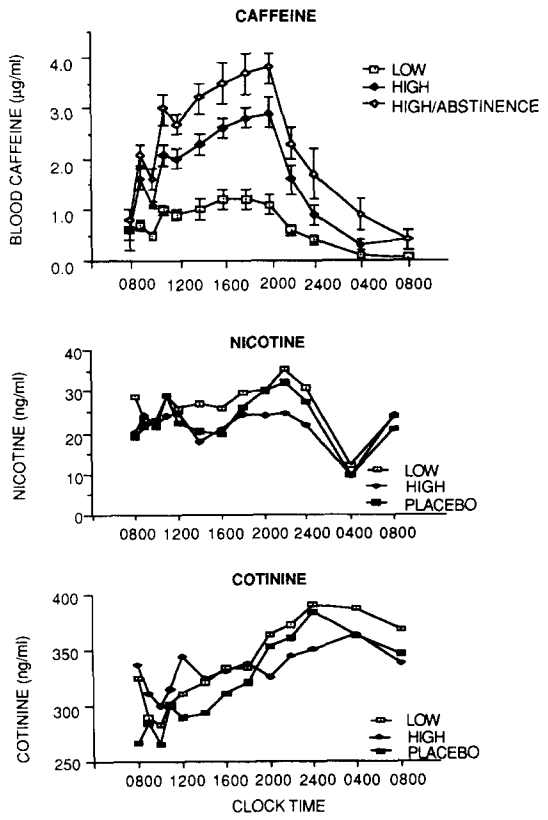

FIG. 1. Circadian plasma concentrations of caffeine, nicotine, and cotinine while consuming coffee every 2 hours from 8 a.m. to 6 p.m. Each cup of coffee contained 0 (placebo), 1 mg/kg (low dose), or 2 mg/kg (high dose) caffeine. Data represent mean of 9 subjects (±SEM).

subjects were smoking. Serum glucose-time curves for 24 hours (AUC) from the circadian study were similar for each of the treatment blocks.

DISCUSSION

Several aspects of the design of our study deserve comment. First, the total daily dose of caffeine given to our subjects was higher than typical caffeine consumption. In the United States, daily consumption averages 200 mg (9), whereas the doses for our subjects approximated 400 and 800 mg for low and high doses, respectively. We chose these doses to maximize the possibility of detecting effects of caffeine. However, even the 800 mg daily dose, which corresponds to 4–8 cups of strong coffee, is not an unusual level of consumption within the population.

Second, we dosed our subjects with caffeine at regular intervals multiple times throughout the day to simulate regular coffee consumption. Most other studies of caffeine have examined effects of single doses. Robertson *et al.* (33) also studied repeated doses given at regular intervals throughout the day. Neither our study nor the Robertson study can exclude significant effects of caffeine dosed in an irregular manner, such as drinking coffee for only part of the day. The latter pattern, with the heaviest consumption in the morning and decreasing consumption throughout the day, may be a more common pattern among the general population.

Third, we have studied caffeine effects only after four days of regular consumption. We believe this should be adequate time to see cardiovascular and endocrine effects, if any, as these systems respond quickly to pharmacologic stimuli. However, the short-term design of our study makes it difficult to evaluate effects of caffeine on lipids, an important issue because of several recent studies linking coffee consumption to elevations in cholesterol (11, 17, 37, 42). Since the study was of a crossover design, caffeine abstinence symptoms may have been present in subjects switched from higher to lower dose levels. Such abstinence symptoms tend to be maximal at 24–48 hours after the dose reduction. For this reason, the fourth day of each block was chosen for data analysis.

Finally, our method of measuring blood nicotine and cotinine levels throughout the day allowed us to quantify intake of nicotine from cigarette smoking more precisely than other investigators who have simply counted cigarettes or measured puffing behavior.

Our results confirm previous findings regarding the cardiovascular effects of cigarette smoking and the lack of cardiovascular effects of chronic caffeine dosing (33), while adding new infor-

TABLE 2

QUANTIFICATION OF SMOKING AND NICOTINE INTAKE

	Caffeine Treatment			Treatment Error Variance
	No Caffeine	Low Dose	High Dose	
No. cigarettes/day	33.7 ± 7.2	37.2 ± 8.0	36.9 ± 8.2	177
Grams tobacco burned/day	23.3 ± 4.8	25.7 ± 5.5	25.3 ± 6.3	119
Plasma nicotine AUC* [(ng·hr)/(ml)]	538.9 ± 166.6	611.2 ± 176.5	493.0 ± 141.0	11365
Plasma cotinine AUC [(ng·hr)/(ml)]	8035.3 ± 3608.9	8460.7 ± 3440.9	8140.0 ± 4085.1	1493576
Carboxyhemoglobin AUC (%·hr)	225.9 ± 43.0	232.4 ± 45.6	218.0 ± 58.5	758
Urine nicotine (μg/24 hr)	1342 ± 609	1319 ± 594	1450 ± 734	244847
Urine cotinine (μg/24 hr)	2328 ± 877	2329 ± 970	2296 ± 1045	128122

*AUC, area under the plasma concentration curve from time 0 to 24 hours.

TABLE 3

MEAN BLOOD PRESSURE AND HEART RATE

	Cigarette Smoking			Cigarette Abstinence	Treatment Error
Caffeine Dose:	No Caffeine	Low	High	High	Variance
Systolic blood pressure (mmHg)	116.9 ± 9.8	118.3 ± 9.5	120.5 ± 8.2	118.5 ± 10.6	56
Diastolic blood pressure (mmHg)	67.4 ± 6.6	65.9 ± 4.3	64.9 ± 5.5	66.6 ± 4.7	31
Heart rate (bpm)	68.6 ± 13.9	68.5 ± 7.9	66.8 ± 8.5	61.4 ± 12.5	103
Urine catecholamines (μg/24 hr)					
Dopamine	101.9 ± 39.2*	93.7 ± 31.2*	86.8 ± 28.0*	66.2 ± 34.8	375
Epinephrine	2.6 ± 1.9	4.2 ± 3.3*	3.1 ± 1.8	2.2 ± 1.9	1.4
Norepinephrine	16.4 ± 9.4	17.3 ± 6.7	15.3 ± 7.0	12.1 ± 7.7	33
Plasma glucose AUC [(mg·hr)/(dl)]	2446 ± 201	2456 ± 246	2450 ± 210	2414 ± 187	7895

*$p<0.05$ versus high dose abstinence.

mation regarding the possible interaction of caffeine and nicotine. We have shown that caffeine in repeated doses simulating coffee consumption throughout the day has a small effect, if any, on nicotine consumption, and no influence on the cardiovascular and metabolic changes caused by cigarette smoking. Independent of caffeine intake, cigarette smokers tended to have higher heart rates and catecholamine excretion when smoking than when abstaining from cigarettes, which are consistent with known effects of cigarette smoking (2). Caffeine levels were significantly higher during smoking abstinence than when smoking, consistent with the action of cigarette smoking to accelerate the metabolism of caffeine, as has been shown in other studies (25,29). With our repeated dosing regimen in smokers, caffeine had no effects at any dose on circadian heart rate, blood pressure, glucose, or daily catecholamine excretion.

We know of no prior studies that have systematically evaluated the interaction of cigarette smoking and coffee drinking in a manner similar to that done in our study. We simultaneously examined the behavioral, pharmacodynamic, and pharmacokinetic interaction of these two behaviors. Although many epidemiologic studies have shown a strong correlation between coffee consumption and cigarette smoking, short-term experimental studies have failed to demonstrate direct pharmacologic causation (3, 19, 23, 24, 26–28). One investigator showed an effect of coffee with or without caffeine to increase cigarette smoking (23,24). All have been short-term, single dose-of-caffeine studies, usually in caffeine-abstinent individuals. The results of our more realistic repeated-dose study indicate that while consuming caffeine, subjects tended to smoke more cigarettes and during low-dose caffeine tended to have higher plasma nicotine levels compared with the no-caffeine treatment. Because of the small number of subjects in our study, we cannot discount a significant caffeine effect. However, even if significant, the magnitude of the caffeine effect (10% for cigarette consumption, 13% for AUC nicotine) appears to be small.

The pharmacodynamic interaction between cigarette smoking and coffee consumption has been studied by Freestone *et al.* (7,8) and Heyden *et al.* (11). Freestone *et al.* (7) showed in hypertensive subjects a synergistic effect of caffeine and smoking to raise blood pressure, an effect which was greater and lasted longer than the effect of caffeine or smoking alone. This was a single-dose study with frequent measures of blood pressure. We measured blood pressure only at four-hour intervals, so we cannot exclude a transient increase in blood pressure following individual cups of coffee throughout the day. However, our finding that caffeine had no effect on blood pressure measured at regular intervals throughout the day suggests that if there is a caffeine-smoking interaction, it does not have much impact on average circadian blood pressure, which is believed to be most important in predicting cardiovascular complications of hypertension (30).

Single doses of caffeine have been shown to increase plasma catecholamines (32, 35, 36) and glucose (4, 15, 39). Heart rate has been shown to either increase or decrease after single doses of caffeine (5, 32, 35). Our study shows that after four days of multiple daily doses, caffeine has no effect on urine catecholamine excretion, circadian plasma glucose concentrations, heart rate or blood pressure. Our findings suggest that tolerance had developed with regular dosing, consistent with observations of others (13, 33, 36). We cannot exclude the possibility that caffeine taken intermittently or in higher doses does produce persistent cardiovascular effects.

Coffee consumption has been implicated as an independent risk factor for coronary heart disease. Possible mechanisms include increased blood pressure (7, 8, 13, 21, 31, 40), glucose intolerance (4,5), and elevated cholesterol (17, 37, 42). Our data showing a lack of effect of caffeine on blood pressure, heart rate, glucose tolerance, and catecholamines raise questions as to the importance of the first two mechanisms. Long-term effects of caffeine on lipids cannot be excluded. In that caffeine intake had a small, if any, effect on nicotine and no effect on carbon monoxide exposure from cigarette smoking or on the cardiovascular and metabolic consequences of cigarette smoking, we find no evidence of an interaction (as opposed to additive effects) between cigarette smoking and caffeine that contributes to increased CHD risk.

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