Effect of smoking on caffeine clearance*

The elimination of caffeine from saliva was compared in groups of healthy smokers (n = 13) and nonsmokers (n = 13). Mean caffeine t½ in smokers (3.5 hr) was shorter than that in the nonsmokers (6.0 hr). The body clearance of caffeine in the smokers (155 ± 16 ml · kg^{-1} · hr^{-1}) was greater than that in the nonsmokers (94 ± 18 ml · kg^{-1} · hr^{-1}) ($p < 0.05$). No significant difference was noted in the apparent volume of distribution in smokers (720 ± 67 ml · kg^{-1}) and nonsmokers (610 ± 80 ml · kg^{-1}). These differences probably reflect the induction of hepatic aryl hydrocarbon hydroxylase (AHH) activity in smokers. The increased clearance of caffeine by smokers may contribute to the higher consumption of coffee reported to occur in this group.

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Certain observations have led us to postulate a surprisingly close relationship in rats between aryl hydrocarbon hydroxylase activity (AHH) and the metabolism of caffeine[1]: (1) pretreatment with 3-methylcholanthrene markedly enhances the animal's capacity to eliminate caffeine, whereas phenobarbital has only a small effect[1]; (2) pretreatment with 3-methylcholanthrene increases the catalytic activity of hepatic microsomal preparations toward caffeine[22]; and (3) the differential effects of 7,8-benzoflavone and SKF-525A β-diethylaminoethyl 2,2-diphenylvalerate on basal and induced microsomal monooxygenase activities toward 3, 4-benzpyrene[31] and caffeine[22] are analogous.

Cigarette smoke, a complex mixture[16] containing a variety of polycyclic aromatic hydrocarbons, is known to induce AHH in certain human tissues.[7, 23, 28] To further explore the relationship between AHH and the disposition of caffeine, we studied the effect of cigarette smoking on caffeine clearance in healthy young adults. The results bear directly on the question of whether caffeine might serve as a probe to study the role of AHH and its inducibility in relation to individual susceptibility to chemical carcinogenesis.[10] Furthermore, since cigarette smoking and the consumption of caffeine are among the most common habits of our species, their interaction has significance quite apart from AHH.

Methods

Subjects. Our subjects were 13 smokers and 13 control nonsmokers chosen from laboratory and hospital personnel. Each group consisted of 9 females and 4 males with an average age of 26 (range 20 to 45). No subjects in the nonsmoking group had ever used tobacco regularly. Smoking subjects consumed at least 20 cigarettes a day for a minimum of two years. With the ex-

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Table I. *Comparison of pharmacokinetic data for caffeine as determined from saliva (S) or plasma (P)*

Subject	*kel* (hr^{-1})		*aVd* ($ml \cdot kg^{-1}$)		*Cl* ($ml \cdot kg^{-1} \cdot hr^{-1}$)	
	S	*P*	*S*	*P*	*S*	*P*
2	0.461	0.417	482	505	220	210
3	0.295	0.207	660	886	196	183
12	0.250	0.266	743	615	185	164
4	0.117	0.101	900	796	106	80
25	0.117	0.129	1,020	1,179	117	152
Mean ± SE	0.249 ± 0.057	0.224 ± 0.056	761 ± 93	796 ± 117	165 ± 23	158 ± 22

Caffeine, 5 mg/kg, was administered orally as caffeine citrate to the five subjects. Saliva and plasma were sampled simultaneously over a 24-hr period. The data were fitted to the first-order, one-compartment equation with use of log-linear least-square regression analysis.

ception of three women in each group who were taking oral contraceptives, none of the subjects took any medication regularly. The usual daily intake of caffeine, mostly as coffee, was found by questionnaire to approximate 320 mg in the smokers and 150 mg in the nonsmokers.

Procedure. Subjects were instructed to abstain from caffeine containing foods and beverages for 24 hours prior to and during the study. On the day of study, they were permitted their usual breakfast excluding caffeine. In the five subjects in whom both plasma and salivary caffeine concentrations were measured, caffeine (5 mg/kg) was administered orally as a solution of caffeine citrate (1 mg/ml). Subjects were instructed to rinse their mouths thoroughly immediately after ingestion of the caffeine. Salivary samples (5 ml mixed saliva) were collected in polyethylene vials at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 24 hr after ingestion and stored at 4° C until assay within two weeks. Blood samples (2 ml) were taken at the same time as saliva samples through an indwelling intravenous catheter which was flushed periodically with heparinized saline. The initial 0.5 ml of each blood collection was discarded. Plasma was separated and stored at 4° C for assay within two weeks. Only saliva was sampled in the other 21 subjects who were allowed to select 180 ml of coffee (n, 18), tea (n, 2) or cola (n, 1) as a source of the test dose of caffeine. An aliquot of the beverage was assayed for caffeine.

Assay procedure; kinetic and statistical analyses. Caffeine was measured by the radioimmunoassay procedure developed and supplied by Cook and colleagues[8] of Research Triangle Institute.

The caffeine concentration:time curves were analyzed by assumption of a first-order one-compartment model. The validity of this model was established when it was determined that mean caffeine clearance from plasma in the five subjects described subsequently in Table I was equivalent whether calculated by this model (158 ± 22 $ml \cdot kg^{-1} \cdot hr^{-1}$) or the method of area under the curve (159 ± 23 $ml \cdot kg^{-1} \cdot hr^{-1}$). The elimination rate constant, kel, was computed by least-square log-linear regression analysis of the descending portion of caffeine concentration as a function of time. The apparent volume of distribution (aVd) was calculated from the dose of caffeine administered divided by the extrapolated caffeine concentration at time 0 after subtraction of the actual 0-time value (a 24-hr abstinence from caffeine was usually sufficient to make this value negligible). The body clearance (Cl) was computed as the product of kel and aVd. Since caffeine is absorbed rapidly and completely, one-compartmental kinetic computations after oral and intravenous dosing are similar.[2] So also, the small differences in rate of absorption of caffeine from different beverages[19] should not affect our results. The unpaired Student's t test was used in statistical comparisons.

Comparison of the salivary and plasma modes of sampling. Simultaneous salivary and plasma caffeine decay curves were studied in five subjects. Except for a transiently high salivary:plasma concentration ratio in a few subjects during the first 1 to 1.5 hr, the salivary and plasma caffeine concentrations both decrease proportionally in a fashion consistent with first-order elimination. Typical results are

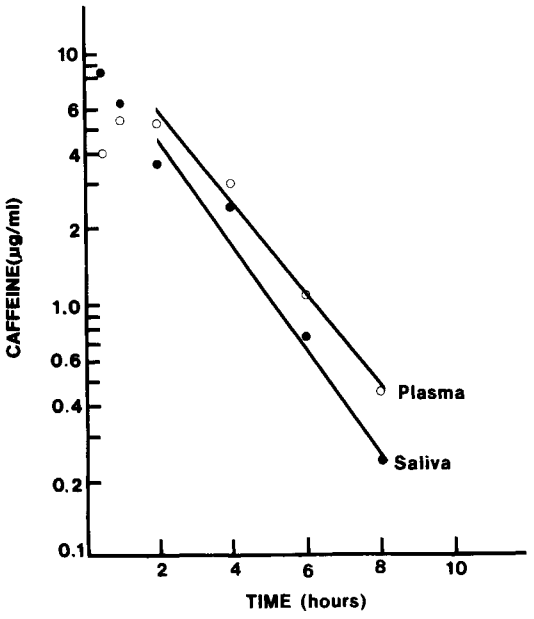

Fig. 1. Time-course of plasma and saliva caffeine concentrations after ingestion of caffeine (5 mg/kg) as caffeine citrate (5 mg/ml). The solid lines represent the least-squares regression line for the data points beginning from 2 hr postingestion.

presented in Fig. 1. The initially high salivary concentrations probably reflect residual caffeine in the mouth, and were ignored in computations. The salivary and plasma caffeine concentrations in each subject were subjected to linear least-squares regression analysis. The lowest correlation coefficient was 0.90, the mean correlation coefficient 0.96, and the y intercept 0.02. The salivary:plasma caffeine concentration ratio for the five subjects was 0.90 ± 0.17. Similar results have been reported by Cook and co-workers.[8] Values for kel, aVd, and Cl were computed separately from the salivary and plasma data of each subject (Table I). Agreement is generally good, and there is no significant difference between the mean value of any of the three parameters whether calculated from salivary or plasma data.

Cigarette smoking and caffeine elimination. Individual values for kel, aVd, and Cl are presented in Table II for nonsmokers and in Table III for smokers. The mean caffeine t½ in smokers was 3.5 hr, while that in the nonsmokers was 6.0 hr. There was an increase in caffeine Cl from 94 ± 8 ml/kg/hr (nonsmokers) to 155 ± 16 ml/kg/hr (smokers) ($p < 0.05$). This difference reflected mainly an increase in kel (0.130 ± 0.013 to 0.230 ± 0.029 hr^{-1}; $p < 0.05$) in the smokers. The increase in aVd in smokers (610 ± 80 to 720 ± 67 ml/kg^{-1}) was not significant. The distributions of caffeine Cl values in the smokers and nonsmokers were similar (Fig. 2).

As noted above, caffeine consumption, especially as coffee, is higher in smokers than in nonsmokers. Despite this association, the correlation coefficient between coffee consumption and caffeine clearance is only 0.23, indicating that coffee consumption is not the major determinant of clearance in these subjects.

Discussion

A series of in vivo and in vitro experiments in rats in our laboratory,[1, 22] as well as a recent report by Welch, Hsu, and DeAngelis,[29] have indicated a close relationship between AHH and the capacity to metabolize and eliminate caffeine. The object of our investigation was to explore the situation in man by studying the effect of cigarette smoking on caffeine clearance. Caffeine clearance was found to be 55% higher in smokers than in nonsmokers ($p < 0.05$), but the extent to which this result can be taken as evidence for a relationship between AHH and caffeine metabolism in human beings depends on two assumptions: that metabolism is rate-limiting for caffeine clearance and that the predominant effect of cigarette smoking on xenobiotic metabolism is induction of AHH.

With reference to the first assumption, it is likely that the increased clearance of caffeine in smokers reflects increased metabolism because the disposition of caffeine is essentially one-compartmental with only a small fraction of an ingested dose excreted unchanged by adults.[9] The enhancement of drug metabolism in association with cigarette smoking has been invoked before to explain the increased clearance of theophylline[13, 14] and antipyrene,[12, 27] the increased biotransformation of pentazocine[15] and phenacetin,[17, 21] and the decreased actions of certain other drugs[3–5] in smokers. The decreased bioavailability of phenacetin in cigarette smokers has been ascribed more speci-

Table II. *Pharmacokinetic data for caffeine in nonsmoking, healthy subjects*

Subject	*t½ (hr)*	*kel* (hr^{-1})	*aVd* ($ml \cdot kg^{-1}$)	*Cl* ($ml \cdot kg^{-1} \cdot hr^{-1}$)
14	4.2	0.167	370	61
15	3.0	0.234	116	270
16	7.6	0.091	580	52
17	3.8	0.183	386	70
18	6.4	0.109	330	36
19	7.7	0.090	786	70
20	9.4	0.074	288	21
21	6.7	0.103	610	63
22	4.2	0.162	682	110
23	7.7	0.090	161	145
24	7.1	0.097	784	76
25	5.9	0.117	1,020	117
26	3.7	0.185	730	135
Mean ± SE	6.0	0.130 ± 0.013	610 ± 80	94 ± 18

Caffeine (0.7 to 2.2 mg/kg) was administered as 180 ml of coffee, tea, or cola drink except to those subjects described in Table I. Saliva was sampled 8 times over a 24-hr period and data were analyzed using log-linear least-square regression analysis.

Table III. *Pharmacokinetic data for caffeine in smoking, healthy subjects*

Subject	*t½ (hr)*	*kel* (hr^{-1})	*aVd* ($ml \cdot kg^{-1}$)	*Cl* ($ml \cdot kg^{-1} \cdot hr^{-1}$)
1	3.0	0.228	700	159
2	1.5	0.461	482	220
3	2.3	0.295	660	196
4	5.9	0.117	900	106
5	4.4	0.157	440	69
6	5.9	0.117	966	113
7	3.8	0.181	121	218
8	4.3	0.162	854	138
9	1.6	0.420	638	268
10	4.1	0.170	483	82
11	4.0	0.172	954	164
12	2.6	0.250	743	185
13	2.6	0.263	400	105
Mean ± SE	3.5	0.230 ± 0.029	720 ± 67	155 ± 16

Caffeine (0.7 to 1.9 mg/kg) was administered as 180 ml of coffee, tea, or cola drink except to those subjects described in Table I. Saliva was sampled 8 times over a 24-hr period and data were analyzed using a log-linear least-square regression analysis.

fically to induction of drug-metabolizing enzymes in the intestine.[17]

With reference to the second assumption, two recent observations are pertinent: firstly, caffeine elimination is remarkably slow in patients with liver failure,[24] indicating that this organ is probably of major importance in caffeine's biotransformation and, secondly, Pelkonen and colleagues[23] have found that AHH activity in liver biopsy specimens from smokers is increased relative to that of nonsmokers. These observations are consistent with the hypothesis that smokers clear caffeine more rapidly than nonsmokers predominantly because of induction of hepatic AHH. Since AHH is also present in human lung,[33] skin,[18] and lymphocytes[6, 32] and has been shown to be induced by cigarette smoking in pulmonary alveolar macrophage[7] and placenta,[28] it is interesting to speculate that organs other than liver might contribute to the metabolism of caffeine. Indeed, the contribution of extrahepatic metabolism may be accentuated in smokers since extrahepatic AHH in mouse[25] and rat[26, 30] is more inducible than that of liver. Finally, we cannot exclude the possibility that a complex mixture such as cigarette

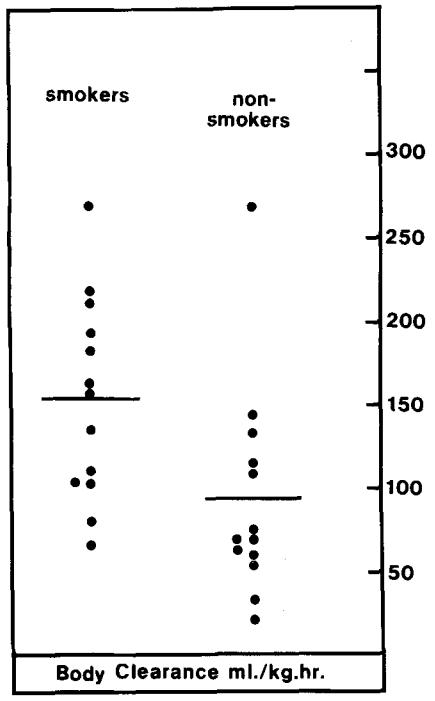

Fig. 2. Body clearance of caffeine in smokers and nonsmokers. Mean clearance values are indicated by the horizontal lines.

smoke[4] induces monoxygenase activities in addition to AHH and that such forms contribute to the increased clearance of caffeine in smokers.

One confounding factor in studies of cigarette smoking in man is that smokers consume more coffee than nonsmokers. We found a positive correlation between coffee consumption and caffeine clearance, but it was not statistically significant. It is intriguing to speculate that the smoker consumes more coffee than the nonsmoker in part to compensate for increased caffeine clearance. However, since caffeine itself can induce mixed-function oxidase activity toward certain substrates in animals,[20] and the same could apply to other components of coffee, the causal relationship between consumption and clearance remains to be clarified. Such considerations would seem to merit attention in the design and interpretation of epidemiologic and behavioral studies dealing with smoking or coffee consumption.

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