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Absorption and Subjective Effects of Caffeine from Coffee, Cola and Capsules

ANTHONY LIGUORI,* JOHN R. HUGHES*†‡ AND JACOB A. GRASS*

**Department of Psychiatry, †Department of Psychology and ‡Department of Family Practice, University of Vermont, Burlington, VT 05401*

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LIGUORI, A., J. R. HUGHES AND J. A. GRASS. *Absorption and subjective effects of caffeine from coffee, cola and capsules.* PHARMACOL BIOCHEM BEHAV **58**(3) 721–726, 1997.—Coffee is often perceived as producing greater pharmacological effects than cola. The present study compared the magnitude and rapidity of peak caffeine levels and subjective effects between coffee and cola. Thirteen users of both coffee and cola (mean daily caffeine consumption = 456 mg) ingested 400 mg caffeine via 12 oz unsweetened coffee, 24 oz sugar-free cola or 2 capsules in a random, double-blind, placebo-controlled, within-subjects design. Subjects provided a saliva sample and completed subjective effect scales 15 min before and 30, 60, 90, 120, 180 and 240 min after ingestion. Mean peak saliva caffeine levels did not differ between coffee (9.7 ± 1.2 μg/ml) and cola (9.8 ± 0.9 μg/ml) and appeared to be greater with these beverages than with the capsule (7.8 ± 0.6 μg/ml; p = NS). Saliva caffeine levels peaked at similar times for coffee (42 ± 5 min) and cola (39 ± 5 min) but later for capsule (67 ± 7 min; $p = 0.004$). There was no main effect of vehicle or interaction of vehicle and drug on magnitude of peak effect or time to peak increase on self-report scales. In summary, peak caffeine absorption, time to peak absorption, and subjective effects do not appear to be influenced by cola vs. coffee vehicle. Perceived differences in the effects of coffee vs. cola may be due to differences in dose, time of day, added sweetener, environmental setting or contingencies. © 1997 Elsevier Science Inc.

Absorption Caffeine Coffee Cola Subjective effects

MORE than 85% of american adults use caffeine every day (11). Several studies have associated caffeine use with increased self-report ratings of well-being, alertness, motivation to work, self-confidence, etc. (13). Although adults predominantly obtain caffeine from coffee, cola is also a commonly used source of caffeine (3). Many people believe that coffee produces more robust pharmacological effects than cola. One possible reason for this belief is the greater caffeine dose per serving in brewed coffee (102 mg/6 oz) than in cola (36 mg/12 oz; (4)).

With dose held constant, whether caffeine absorption and subjective effects differ between cola and coffee vehicle is unclear. Few studies have directly compared absorption of caffeine from coffee with that from cola, and none have concurrently compared subjective effects of these vehicles. In one study (21), peak increases in serum caffeine levels were comparable (3–3.5 μg/ml) following administration of 155–160 mg caffeine via coffee or cola, although the time to peak increase was shorter with coffee (30 min) than with cola (120 min). In contrast, another study (5) compared absorption of mean doses of 108 mg caffeine in coffee and 15 mg caffeine in cola and found comparable times to peak serum concentration with coffee (52 ± 22 min) and cola (38 ± 8 min). However, these studies used only three and four subjects, respectively, and did not report whether subjective effects differed between coffee and cola. In addition, neither study reported a statistical comparison of the peak levels or time to peak serum concentration with the two vehicles.

The purpose of the present study was to compare systematically the salivary caffeine concentrations and subjective effects of 400 mg caffeine from coffee vs. the same amount from cola at the commonly used volumes in the same group of subjects. A third caffeine vehicle, capsule, was included because our subjects had no prior history of subjective effects associated with caffeine from capsules. Thus, capsule served as a control vehicle. The 400-mg dose was chosen to increase the likelihood of both positive and dysphoric subjective effects of caffeine relative to placebo (13).

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Requests for reprints should be addressed to Anthony Liguori, Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: anthol@aol.com

METHODS

Subjects

Subjects were 13 adult volunteers recruited by advertisements or from prior studies in our laboratory. For inclusion in the study, subjects were required to (a) report having used caffeinated coffee and caffeinated soda in the prior 6 months; (b) report consumption of at least 400 mg of caffeine via any combination of coffee, tea and soda during a 2-day self-monitoring period (see below); (c) be willing to drink diet colas and "black" coffee with no added sweetener or creamer; (d) report no current psychiatric or alcohol or drug problem (except for nicotine dependence) and consume 1 or less alcoholic drink per weekday; (e) not be trying to stop or reduce caffeine or tobacco use and not be on a restricted-calorie (<2000 calories/day) diet; (f) not presently use prescription or over-the-counter psychoactive medications, antihistamines or oral contraceptives; (g) report no medical contraindications to caffeine use; (h) not be pregnant, planning to become pregnant or breast-feeding; (i) report no lactose intolerance; and (j) be between the ages of 18 and 60 years. Persons older than age 60 years were excluded because this population appears less sensitive to the subjective effects of caffeine (28).

The subjects' mean age was 43 (SD = 8). Eight subjects (62%) were men, and one (Subject 901) was a smoker. After giving informed consent, each subject kept a diary of his or her coffee, cola, and tea intake on the following Monday and Tuesday. During this introductory self-monitoring period, eight subjects drank both coffee and cola, four subjects drank coffee exclusively, and one drank coffee and tea but not cola. During these 2 days, subjects used a mean of 456 mg (SD = 153) caffeine daily, which is at approximately the 77th percentile for persons who drink caffeinated coffee [calculated from Table 6 of (26)]. The mean daily coffee intake for the group was 4.2 ± 1.6 6-oz cups, representing 92% of the group's caffeine intake. The eight subjects who used cola during the self-monitoring period drank an average of 1.3 ± 1.2 12-oz servings per day.

Subjects were told that the study would compare the effects of coffees, colas and capsules on mood and liking of these substances. They were also told that the coffees, colas and capsules could differ according to brand, strength, sweetener or caffeine content.

Beverages and Capsules

All caffeinated beverages and capsules had 200 mg of anhydrous caffeine added to each serving, and the commonly used serving volumes of coffee (6 oz) and cola (12 oz) were used. Two servings of any particular vehicle (coffee, cola or capsule) were consumed at the beginning of each session, so the cumulative dose was 400 mg. The coffees used were individual packets containing 2 g of instant decaffeinated coffee (Folgers). Lactose (50 mg) was added to each coffee to mask the bitter taste of the added caffeine. All coffees were made by steeping the packet in 6 oz of boiling water for 1 min. Subjects were not allowed to add any creamers or sweeteners to the coffees. The colas were 16-oz refrigerated bottles of caffeine-free diet cola (Diet Pepsi). Four ounces were removed from each bottle to simulate one 12-oz serving. The capsules were size 0, and placebo capsules contained approximately 400 mg lactose. Thus, two 6-oz servings of coffee, two 12-oz servings of cola or two capsules (with 8 oz of water) were consumed.

Before the study began, Triangle Taste Tests (1) were conducted in nine pilot subjects who sampled coffee and eight pilot subjects who sampled cola. These tests determined whether subjects could discriminate caffeinated from placebo beverages on the basis of taste. Each pilot subject was tested nine times. During each test, subjects sipped three beverages. Two of these beverages had 200 mg caffeine or 0 mg caffeine added, and the third beverage contained the converse dose. The subjects were asked to identify the different beverage. Six correct answers of nine tests were required for significant discrimination ($p < 0.05$, binomial test). One of nine subjects (11%) discriminated caffeinated from decaffeinated coffee, and zero of eight subjects discriminated caffeinated from non-caffeinated cola.

Setting

The laboratory contained only tables and chairs. When not ingesting beverage, providing saliva samples or completing forms, subjects were encouraged to read, write, and/or listen to portable radio or cassette players through headphones. Subject 901, a cigarette smoker, was allowed to smoke at leisure between test cycles. Between one and four subjects shared the laboratory space at any particular time. They were allowed to converse but were not permitted to discuss feelings or reactions to the coffees, colas or capsules. To help ensure compliance, one or more experimenters were within hearing distance of the subjects at all times.

Experimental Design

Sessions took place on Mondays, Wednesdays and Fridays of 2 weeks. During each session, the 4-h time course of absorption and subjective effects were measured for one of three vehicles (capsule, coffee or cola) at one of two caffeine doses (0 or 400 mg). The order of vehicle and dose presentation was random and double blind.

Pre-experiment Procedures

From bedtime on the Tuesday of the self-monitoring period through the conclusion of the study 17 days later, subjects were required to abstain from all caffeine-containing substances other than those provided by the experimenters. When the first experimental session began, each subject had abstained from caffeine for 5 days. Abstentium was verified by saliva sampling 3 days before and at the first experimental session. The 5-day prestudy abstention period allowed peak caffeine-withdrawal symptoms to subside before self-report questionnaires were administered (14).

Procedure for Each Session

Sessions lasted from 0800 to 1230. Subjects were permitted to eat "a light, low-calorie breakfast" between 0630 and 0700 on the mornings of test sessions but were not allowed to eat during test sessions. Subjects completed a test cycle at the beginning of each session. They then ingested the day's vehicle (coffee, cola or capsule). When subjects received beverages, they were instructed to ingest the liquid as quickly as possible within 5 min. Subjects completed test cycles 30, 60, 90, 120, 180 and 240 min after ingesting the vehicle.

Test Cycle Measures

Saliva caffeine. Subjects provided a 3-ml saliva sample by expectorating directly into a test tube. Subjects who had difficulty producing the required volume of saliva were allowed to chew on a "salivette" (Sarstedt, Germany) to stimulate salivation. Samples were frozen and saliva–caffeine concentrations were determined based on the method described by Brown et al. (6) and Jacob et al. (18), using gas chromatography with a structural analogue of caffeine as the internal standard (Lab-Stat, Kitchener, Ontario, Canada).

Paper-and-pencil questionnaires.

Profile of mood states (POMS). This 65-item questionnaire (22) produces scores of anger, anxiety, confusion, depression, fatigue, friendliness and vigor. Friendliness scale data are not reported because of the scale's limited validity (22).

Visual-analogue scales (VAS). Subjects completed the VASs by answering the questions: "Have you felt any drug effect?" "Do you feel high?" "Have you felt any good effects?" "Have you felt any bad effects?" "Do you like the drug?" and "Do you feel alert - energetic?" Subjects responded by drawing a line intersecting a 100-mm line that represented a spectrum marked with "not at all" at 0 mm and "extremely" at 100 mm. These scales have been shown to be sensitive to caffeine effects (25).

Behavior checklist. The behavior checklist consisted of 10 items that subjects rated on a 10-point scale from 0 ("not at all") through 5 ("moderate") to 9 ("very much"). The adjectives rated were anxious/tense/nervous, confident, dizzy/light-headed/faint, drowsy/sleepy, fatigued/tired, headache, jittery/tremulous, lazy/sluggish/slow moving, motivated to work, and well-being. The items on this checklist have been shown to be sensitive to caffeine effects (16).

Data Analysis

For each session, the magnitude of the peak effect and the area under the drug action curve (AUC) were computed for salivary caffeine levels and scores on the POMS, behavior checklist and VAS. AUC scores were computed by using the trapezoidal method. Peak effect and AUC scores for the six sessions were entered into 3 × 2 repeated measures analyses of variance (ANOVAs) that included a vehicle factor (coffee vs. cola vs. capsule) and a drug factor (caffeine vs. placebo). Significant drug × vehicle interactions were identified with the Student-Newman-Keuls method of pairwise multiple comparisons.

Time to peak increase from baseline for caffeine absorption and certain subjective effects was analyzed with a one-way repeated measures ANOVA that included three conditions (caffeinated coffee vs. caffeinated cola vs. caffeinated capsule). Time to peak increase was analyzed for a self-report measure if (a) there was a significant main effect of drug on the measure in the peak effect ANOVA and (b) at least two-thirds of subjects (9 or more) reported a peak effect in the same direction (e.g., increase in alertness score from baseline) with all three caffeinated vehicles.

RESULTS

Validation of Caffeine Abstinence

All saliva caffeine levels at 3 days prior and immediately prior to test sessions were below 1 μg/ml, which is consistent with levels reported following 24 h of caffeine abstention (19).

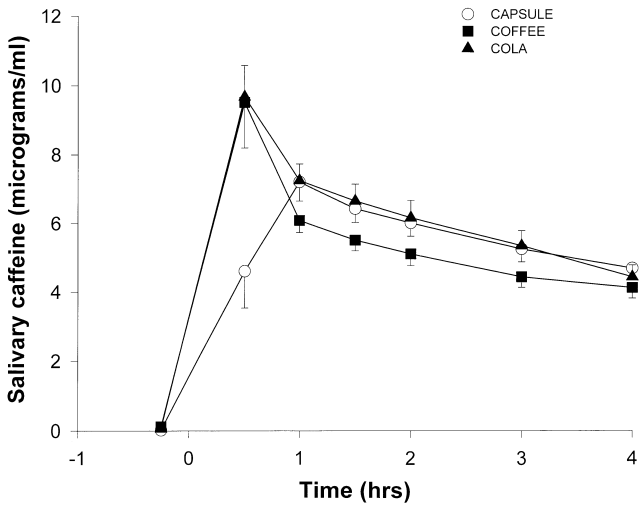

FIG. 1. Salivary caffeine levels (μg/ml) as a function of time before and after ingestion of caffeine in cola, coffee and capsules. Data are mean values for 13 subjects. Error bars show 1 SEM and are in a positive direction for cola and in a negative direction for capsule and coffee.

Caffeine Absorption

Peak increase. The mean peak increases in salivary caffeine with coffee (9.7 ± 1.2 μg/ml) and cola (9.8 ± 0.9 μg/ml) were similar (Fig. 1). Although the mean peak increase in salivary caffeine appeared lower with capsule (7.9 ± 0.6 μg/ml), there was no main effect of vehicle on peak increase in saliva caffeine level and no interaction between drug and vehicle. These negative results were due to large between-subject variability (Table 1). For example, the lowest peak increase in saliva caffeine level of the three vehicles was from capsule in six subjects (46%), from coffee in six subjects (46%) and from cola in one subject (8%).

Time to peak effect. Time to peak effect differed across vehicles [$F(2, 12) = 6.9$; $p = 0.004$]. Post hoc Student-New-

TABLE 1

PEAK INCREASES IN SALIVARY CAFFEINE CONCENTRATION (μg/ml) FOLLOWING 400 MG CAFFEINE ACROSS SUBJECTS AND VEHICLES

Subject	Coffee	Cola	Capsule
901	9.3	10.2	8.5
902	4.8	5.4	6.5
903	9.9	10.2	8.3
906	5.7	10.6	7.6
910	8.3	9.8	8.8
914	7.9	10.3	8.2
915	5.1	6.3	4.9
916	6.6	8.7	9.2
918	17.3	8.5	4.4
919	12.5	10.6	13.5
920	15.6	8.6	6.5
921	6.6	8.9	8.8
922	16.7	19.1	7.1
Mean (SE)	9.7 (1.2)	9.8 (0.9)	7.9 (0.6)

man-Keuls tests showed that time to peak effect was similar with coffee (mean ± SD = 42 ± 5 min) and cola (39 ± 5 min) but was longer with capsule (67 ± 7 min; $p < 0.05$). At the 30-min time point, peak caffeine absorption occurred in 9 subjects with coffee (69%), 10 subjects with cola (77%) and 2 subjects with capsule (15%). In contrast, at the 60-min time point, peak caffeine absorption occurred in 3 subjects with coffee (23%), 2 subjects with cola (15%) and 7 subjects with capsule (54%).

Area under the time action curve. There was a main effect of vehicle [$F(2, 12) = 10.6$; $p = 0.0003$] on AUC for saliva caffeine levels and an interaction between drug and vehicle [$F(2, 12) = 13.6$; $p < 0.0001$]. Post hoc Student-Newman-Keuls tests showed that the AUC with caffeinated cola was greater than that with caffeinated capsule, which was greater than that with caffeinated coffee (Fig. 1).

Subjective Effects

Peak effect. There were main effects of drug (caffeine > placebo) for behavior checklist items anxious/tense/nervous and jittery/tremulous, VAS items drug effect, high, good effect, bad effect, liking of drug and alert and the POMS tension-anxiety and vigor scales [$F(1, 12) \geq 5.9$; $p < 0.05$]. There were also main effects of drug (placebo > caffeine) for drowsy/sleepy and fatigued/tired on the behavior checklist [$F(1, 12) \geq 8.3$; $p < 0.01$]. There was no main effect of drug on ratings of confident, dizzy/light-headed/faint, headache, lazy/sluggish/slow-moving, motivated to work, well-being or the POMS depression-dejection, anger-hostility, fatigue or confusion-bewilderment scales. There was no main effect of vehicle or interaction of vehicle and drug on any of the 22 subjective items or scales.

Time to Peak Increase. Seven items met our criteria for analysis of time to peak increase of subjective effect (jittery/tremulous, the POMS tension-anxiety scale, and VAS drug effect, high, good effect, bad effect and liking of drug scales). Time to peak increase was usually between 85 and 110 min and did not differ across caffeinated vehicles on any of these scales (range with coffee = 77–115 min, with cola = 83–98 min, with capsule = 93–130 min).

Area under the time action curve. All self-report items and scales that showed a significant main effect of drug on peak effect also showed a main effect of drug on AUC [$F(1, 12) \geq 6.1$; $p < 0.05$]. There were no significant main effects of vehicle or vehicle–drug interactions for any item or scale.

DISCUSSION

The focus of the present study was to compare absorption and subjective effects of caffeine between the more commonly used vehicles coffee and cola. Although other studies have focused on capsule as a vehicle for caffeine self-administration and subjective effects (9,15,27), capsule served as a control vehicle in the present study. We found no differences between coffee and cola vehicle in peak level of or time to peak increase in salivary caffeine. This finding replicates prior studies that found similar magnitudes of peak caffeine level from coffee and cola (21,29).

With both coffee and cola vehicles, absorption of 400 mg caffeine peaked at approximately 10 μg/ml saliva within 35–45 min of ingestion. In prior studies with coffee, approximate mean peak increases in blood caffeine levels were 1.6, 2.0 and 2.0 μg/ml with doses at or near 100 mg (5,24,30), 2.7 and 3.4 μg/ml with doses at or near 150 mg (21,31) and 3.9 and 4.0 μg/ml with doses at or near 200 mg (24,30). If caffeine absorption changes linearly as a function of dose (5) and if salivary caffeine levels are generally 70–80% of serum caffeine levels (23,32), then, based on these prior results, the peak salivary level following ingestion of 400 mg caffeine should be approximately 6 μg/ml. Mean peak levels with coffee (9.7 μg/ml), cola (9.8 μg/ml) and capsule (7.8 μg/ml) in the present study appeared higher than this. We doubt this was due to residual caffeine in saliva from the beverage because the saliva samples were collected 30 min after the beverage was ingested. We know of no obvious reasons for this apparent difference.

The mean times to peak saliva caffeine levels in the present study were similar with coffee (42 min) and cola (39 min) and comparable to those in a previous vehicle comparison in which mean peak plasma caffeine levels occurred after 52 min with mocha coffee and after 38 min with soft drink (5). The time-to-peak results with coffee in the present study also were consistent with those of several other studies that reported peak plasma caffeine levels within 30–45 min of coffee ingestion, regardless of whether the coffee was identified as brewed or instant (8,21,30,31). However, our results with cola differ from a previous study (21) that reported that peak plasma caffeine levels with cola were delayed until 120 min after ingestion.

There are several reasons one could hypothesize that caffeine would be absorbed more slowly from cola than from coffee. First, absorption of caffeine from cola could be delayed by the lower temperature of the beverage, which may reduce the rate of blood flow within the intestines (10). However, temperature has been reported not to influence caffeine absorption (2). Second, gastric emptying could be slowed by the phosphoric acid (17) present in colas. Third, absorption rate appears to increase with caffeine dose (5); consequently, the relatively smaller dose of caffeine in commercially available colas (36 mg/12 oz) vs. coffees (102 mg/6 oz) (4) may be associated with slower absorption. In the present study, we used the same dose in cola and coffee.

A fourth possible reason is that many colas, but not coffees, contain sugar, which would inhibit gastric emptying of caffeine (7) and delay absorption. In one of the two studies that directly compared coffee and cola (5), the influence of sugar is unknown because the investigators did not identify the type or amount of sweetener, if any, in either beverage. When the other study was published (1973), artificially sweetened cola was not commercially available; thus, one reason this study found delayed absorption with cola may have been that the investigators used a sugared cola (21). In contrast, we used a diet, sugar-free cola and did not find delayed absorption.

The subjective effects of caffeine were not influenced by vehicle. This negative result is consistent with results from our previous direct comparison of the subjective effects of cola and coffee in persons who regularly use both (20) and from a within-subjects comparison of the subjective effects of coffee and capsule (12). Thus, our results contradict conventional wisdom that coffee is "stimulating," whereas cola is merely a "thirst quencher"; i.e., any perceived differences in perceived effects of coffee vs. cola are not due to unique characteristics of the vehicles themselves. Rather, vehicle-based differences in stimulant effects may be due either to the higher serving dose of caffeine in coffee (102 mg/6 oz) than in cola (36 mg/12 oz) or by time of day, added sweetener, environmental settings or contingencies associated with use (e.g., morning coffee use vs. evening cola use).

Our experimental design had several assets, including a completely within-subjects design, subjects familiar with both coffee and cola as caffeine vehicles, an unfamiliar caffeine vehicle (capsule) as a control and validation of abstention from out-of-laboratory caffeine. Also, the self-reports of our subjects likely were not confounded by caffeine withdrawal because the subjects had abstained from caffeine for 5 days before beginning test sessions (13).

Our design could have been improved in several respects. First, more data collection time points within the 4-h test sessions, particularly during the first hour, would have provided more precise information about peak saliva caffeine levels and time to peak levels. Second, gathering data with sweetened colas and coffees would have enabled us to draw more definitive conclusions regarding our hypothesis that the presence of sugar in cola accounted for the difference in results between our study and those of a prior study (21). Third, to use generalizable servings with each vehicle, the volumes of the vehicles differed (i.e., 12 oz for coffee, 24 oz for cola and 2 pills with 8 oz of water). Given that the typical stomach volume is 34 oz, the differences in volume across vehicles may have influenced absorption, although direct testing would be needed to confirm this notion. Fourth, more stringent controls over presession food intake would probably have minimized the intersubject variability of caffeine absorption levels. Such controls could have included an identical in-laboratory breakfast across subjects or a presession fast of longer than 60 min. Finally, the subjective effects of caffeine are different at high (>200 mg) vs. low (<200 mg) doses (13). Whether vehicle would have influenced absorption and subjective effects of caffeine doses below 400 mg was not evaluated in the present study.

In summary, the magnitude of peak caffeine absorption and time to peak absorption do not appear to be influenced by cola vs. coffee vehicle, and, concurrently, subjective effects of caffeine were similar across cola and coffee vehicle. Perceived differences between the stimulant effects of cola and coffee are likely related to serving dose, time of day, added sweetener, environmental setting or environmental contingencies.

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REFERENCES

1. Amerine, R. R.; Pangborn, R. M.; Roessler, E. G.: Principles of sensory evaluation of food. New York: Academic Press; 1965.
2. Arnaud, M. J.: The pharmacology of caffeine. Prog. Drug Res. 31:273–313; 1987.
3. Barone, J. J.; Roberts, H. R.: Human consumption of caffeine. In: Dews, P. B. ed. Caffeine: Perspectives from recent research. New York: Springer-Verlag; 1984:59–71.
4. Barone, J. J.; Roberts, H. R.: Caffeine consumption. Food Chem. Toxicol. 34:119–129; 1996.
5. Bonati, M.; Latini, R.; Galletti, F.; Young, J. F.; Tognoni, G.; Garattini, S.: Caffeine disposition after oral doses. Clin. Pharmacol. Ther. 32:98–106; 1982.
6. Brown, C. R.; Jacob, P.; Wilson, M.; Benowitz, N. L.: Changes in rate and pattern of caffeine metabolism after cigarette abstinence. Clin. Pharmacol. Ther. 43:488–491; 1988.
7. Chvasta, T. E.; Cooke, A. R.: Emptying and absorption of caffeine from the human stomach. Gastroenterology 61:838–843; 1971.
8. Dobmeyer, D. J.; Stine, R. A.; Leier, C. V.; Greenberg, R.; Schaal, S. F.: The arrhythmogenic effects of caffeine in human beings. N. Engl. J. Med. 308:814–816; 1983.
9. Evans, S. M.; Critchfield, T. S.; Griffiths, R. R.: Caffeine reinforcement demonstrated in a majority of moderate caffeine users. Behav. Pharmacol. 5:231–238; 1994.
10. Gilbert, R. M.: Caffeine as a drug of abuse. In: Gibbins, R. J.; Israel, Y.; Kalant, H.; Popham, R. E.; Schmidt, W.; Smart, R. G., eds. Research advances in alcohol and drug problems. New York: Wiley; 1976:49–176.
11. Gilbert, R. M.: Caffeine consumption. In: Spiller, G. A., ed. The methylxanthine beverages and foods: Chemistry, consumption, and health effects. New York: Alan R. Liss; 1984:185–213.
12. Griffiths, R. R.; Bigelow, G. E.; Liebson, I. A.: Reinforcing effects of caffeine in coffee and capsules. J. Exp. Anal. Behav. 52:127–140; 1989.
13. Griffiths, R. R.; Mumford, G. K.: Caffeine–A drug of abuse? In: Bloom, F. E.; Kupfer, D. J. eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995:1699–1713.
14. Griffiths, R. R.; Woodson, P. P.: Caffeine physical dependence: A review of human and laboratory animal studies. Psychopharmacology 94:437–451; 1988.
15. Griffiths, R. R.; Woodson, P. P.: Reinforcing effects of caffeine in humans. J. Pharmacol. Exp. Ther. 246:21–29; 1988.
16. Hughes, J. R.; Higgins, S. T.; Bickel, W. K.; Hunt, W. K.; Fenwick, J. W.; Gulliver, S. B.; Mireault, G. C.: Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. Arch. Gen. Psychiatry 48:611–617; 1991.
17. Hunt, J. N.; Knox, M. T.: The slowing of gastric emptying by nine acids. J. Physiol. 201:161–179; 1969.
18. Jacob, P.; Wilson, M.; Benowitz, N. L.: Nicotine and cotinine determinations in biological fluids: An improved gas chromatographic method. J. Chromatogr. 222:61–70; 1981.
19. Jacobson, A. F.; Cerqueira, M. D.; Raisys, V.; Shattuc, S.: Serum caffeine levels after 24 hours of caffeine abstention: Observations on clinical patients undergoing myocardial perfusion imaging with dipyridamole or adenosine. Eur. J. Nucleic Med. 21:23–26; 1994.
20. Liguori, A.; Hughes, J. R.: Caffeine self-administration in humans: 2. A within-subjects comparison of coffee and cola. Exp. Clin. Psychopharmacology, in press.
21. Marks, V.; Kelly, J. F.: Absorption of caffeine from tea, coffee, and coca cola. Lancet 1:827; 1973.
22. McNair, D. M.; Lorr, M.; Droppelman, L. F.: Profile of mood states [manual]. San Diego, CA: Educational and Industrial Testing Service; 1971.
23. Newton, R.; Broughton, L. J.; Lind, M. J.; Morrison, P. J.; Rogers, H. J.; Bradbrook, I. D.: Plasma and salivary pharmacokinetics of caffeine in man. Eur. J. Clin. Pharmacol. 21:45–52; 1981.
24. Piters, K. M.; Colombo, A.; Olson, H. G.; Butman, S. M.: Effect of coffee on exercise-induced angina pectoris due to coronary artery disease in habitual coffee drinkers. Am. J. Cardiol. 55:277–280; 1985.
25. Rush, C. R.; Sullivan, J. T.; Griffiths, R. R.: Intravenous caffeine in stimulant drug abusers: Subjective reports and physiological effects. J. Pharmacol. Exp. Ther. 273:351–358; 1995.
26. Schreiber, G. B.; Maffeo, C. E.; Robins, M.; Masters, M. N.; Bond, A. P.: Measurement of coffee and caffeine intake: Implications for epidemiologic research. Prev. Med. 17:280–294; 1988.
27. Silverman, K.; Mumford, G. K.; Griffiths, R. R.: Enhancing caffeine reinforcement by behavioral requirements following drug ingestion. Psychopharmacology 114:424–432; 1994.

28. Swift, C. G.; Tiplady, B.: The effects of age on the response to caffeine. Psychopharmacology 94:29–31; 1988.
29. Van der Merwe, P. J.; Muller, F. R.; Muller, F. O.: Caffeine in sport. Urinary excretion of caffeine in healthy volunteers after intake of common caffeine-containing beverages. S. Afr. Med. J. 74:163–164; 1988.
30. Van Deventer, G.; Kamemoto, E.; Kuznicki, J. T.; Heckert, D. C.; Schulte, M. C.: Lower esophageal sphincter pressure, acid secretion, and blood gastrin after coffee consumption. Dig. Dis. Sci. 37:558–569; 1992.
31. Whitsett, T. L.; Manion, C. V.; Christensen, H. D.: Cardiovascular effects of coffee and caffeine. Am. J. Cardiol. 53:918–922; 1984.
32. Zylber-Katz, E.; Granit, L.; Levy, M.: Relationship between caffeine concentrations in plasma and saliva. Clin. Pharmacol. Ther. 36:133–137; 1984.