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BRIEF COMMUNICATION

Caffeine Withdrawal Symptoms and Self-Administration Following Caffeine Deprivation

SUZANNE H. MITCHELL,*[1] HARRIET DE WIT* AND JAMES P. ZACNY*†

*Department of Psychiatry and †Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL

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MITCHELL, S. H., H. DE WIT AND J. P. ZACNY. *Caffeine withdrawal symptoms and self-administration following caffeine deprivation.* PHARMACOL BIOCHEM BEHAV 51(4) 941-945, 1995.—This study examined the effects of complete or partial caffeine deprivation on withdrawal symptomatology and self-administration of coffee in caffeine-dependent coffee drinkers. Nine habitual coffee drinkers abstained from dietary sources of caffeine for 33.5 h. Caffeine deprivation was manipulated by administering capsules containing 0%, 50%, or 100% of each subject's daily caffeine intake (complete, partial, and no deprivation conditions). Caffeine withdrawal symptomatology was measured using self-report questionnaires. Caffeine self-administration was measured using: i) the amount of coffee subjects earned on a series of concurrent random-ratio schedules that yielded coffee and money reinforcers; ii) the amount of earned coffee they consumed. Saliva samples revealed that subjects complied with the caffeine abstinence instructions. Caffeine withdrawal symptoms occurred reliably following complete caffeine deprivation, though not in the partial deprivation condition. Caffeine self-administration was not related to deprivation condition. We conclude that caffeine withdrawal symptomatology is not necessarily associated with increased caffeine consumption.

Caffeine deprivation Self-administration Withdrawal Caffeine Human Random-ratio schedules

MOST habitual caffeine users experience a specific pattern of physiological withdrawal symptoms within 24 h of complete caffeine deprivation [for review see (8)], even after low daily doses of caffeine. For example, Griffiths and colleagues reported that subjects whose daily caffeine intake was 100 mg (approximately one cup of coffee) experienced headache and fatigue when caffeine was omitted from their diets (12). Other withdrawal symptoms have been described, including decreased alertness and vigor, and increased irritability (7). Although caffeine withdrawal symptomatology following complete caffeine deprivation has been examined in a number of studies, no studies have examined partial caffeine deprivation.

Complete caffeine deprivation increases the frequency with which caffeinated coffee is chosen and is self-administered relative to decaffeinated coffee [e.g., (11), but also see (9,13)]. In studies measuring withdrawal symptoms together with self-administration, it has been noted that withdrawal symptoms usually accompany this increased self-administration [e.g., (14,15)]. As in research examining only the symptomatology of caffeine withdrawal, the effect of partial caffeine deprivation on the amount of caffeine self-administered by subjects has not been assessed.

The current study was designed to examine the effects of complete and partial caffeine deprivation on withdrawal symptomatology and on the amount of caffeine subjects self-administered. We assessed responding for caffeinated coffee in regular, habitual caffeine users (coffee drinkers) after 33.5 h of either complete caffeine deprivation (0% daily caffeine in-

[1] Requests for reprints should be addressed to Suzanne H. Mitchell, Department of Psychology, Conant Hall, University of New Hampshire, Durham, NH 03824.

take), partial deprivation (50%), or no deprivation (100%). Each deprivation condition was examined twice. Caffeine withdrawal symptomatology was measured using self-report questionnaires. Self-administration behavior was measured by i) the amount of caffeinated coffee earned by subjects responding on a computer task, and ii) the amount of earned coffee they consumed. It was anticipated that the number and severity of withdrawal symptoms, as well as the consumption of coffee, would be positively related to the degree of caffeine deprivation.

METHOD

Subjects

Five male and four female volunteers participated in the study, which was approved by the local institutional review board. Subjects were recruited from the local community via newspaper and bulletin board advertisements. Eligible candidates had to be between 21 and 35 years (actual mean age ± SE: 25.4 ± 1.5 years), smoke less than five cigarettes/day (actual mean smoking: 0.3 ± 0.2 cigarettes/day), and drink at least five 5-oz cups of caffeinated coffee daily (i.e., have a mean daily caffeine intake of at least 500 mg caffeine/day) (actual mean intake: 686.4 ± 47.7 mg/day). Each subject's approximate daily caffeine intake was calculated from his/her self-reported beverage consumption, using figures based on those provided by (23) and (4). All subjects reported that they usually consumed their daily amount of coffee before 1400 h, but half of the subjects had either caffeinated soda or hot chocolate after that time. Candidates fulfilling the selection criteria were screened to exclude any volunteers with a current medical problem, a history of any psychiatric disorder, or a current substance use disorder [DSM-III-R criteria (1)]. Subjects gave informed consent at the outset of the study and were paid for participating during a debriefing session, held after completion of the study.

Procedure

Orientation session. Before participating, each subject attended an orientation session. During this orientation, the experimental procedures were explained and subjects practiced the computer task to be used during the experimental sessions. At this time subjects filled out a survey form that required them to identify how they normally prepared their coffee (preferred brand, use of milk, etc.) and to describe the frequency and amounts of their usual daily beverage consumption (coffee, decaffeinated coffee, tea, soda, hot chocolate, water, etc.).

Experimental sessions. Subjects participated in six experimental sessions, spaced at least 48 h apart. During the course of the six experimental sessions, each subject received three doses of caffeine (0%, 50%, and 100% of his/her self-reported daily intake) on two occasions. The order of the three caffeine dose conditions was randomized within the first three sessions and within the second three sessions.

Subjects were instructed in the consent form to abstain from taking any drugs other than those provided by the experimenter for the 24 h preceding each session (the "presession day") and the 9.5 h on the morning before the experimental session. Thus, subjects were prohibited from ingesting any drugs for a total of 33.5 h. They were explicitly instructed that this prohibition extended to "everyday" drugs such as aspirin, caffeine, and alcohol in addition to prescription drugs and "recreational" drugs (e.g., marijuana, cocaine).

On the presession day subjects came to the laboratory at 0900 h for 5 min to take a capsule and to collect two additional capsules. They were instructed to take one of the additional capsules at 1500 h on the presession day and the other at 0800 h the day of the session. Subjects were required to call the laboratory each time they took a capsule. Capsules were individually prepared so that each capsule contained sufficient caffeine to provide a subject with either 0%, 25%, or 50% of his/her daily caffeine intake. A dextrose filler was used to ensure all capsules were filled equally, regardless of caffeine content. In this way subjects received either 0% (2 × 0%), 50% (2 × 25%) or 100% (2 × 50%) of their approximate daily caffeine intake on the presession day and 0%, 25%, or 50% on the morning of the session. Capsules were administered double-blind. Subjects were informed that the capsules could contain a placebo, stimulant, or tranquilizer and that the purpose of the study was to examine whether the substance contained in the capsule would affect the subjects' desire to consume coffee.

On the day of the session, subjects were instructed to eat breakfast after taking the capsule at 0800 h. Then they came to the laboratory at 0930 h. When they first arrived in the laboratory a saliva sample was collected for later caffeine analysis (2), by Labstat Incorporated, Canada, to verify that subjects had taken the capsules and abstained from other, dietary sources of caffeine. Subjects were told that the analysis of their saliva would reveal both that the capsules had been taken and that they had abstained from all other drug use, as required by the study.

Subjects then completed two Visual Analog Scales (VAS) to assess caffeine withdrawal symptomatology. One concerned the subjects' sensations over the preceding 24 h, and the other with subjects' current sensations. Both were paper and pencil questionnaires on which there were ten 100-mm lines. Each line was labeled with an adjective: "alert-energetic," "anxious," "headachy," "disorientated-inefficient," "irritable," "relaxed-content-calm," "restless-nervous-jittery," "sluggish," "stimulated" and "tired-sleepy." Subjects were instructed to draw a vertical mark on the line in the place that corresponded to the extent of the sensation in question, from "not at all" to "very much."

Then subjects performed a computer task (described below) that allowed them to earn points exchangeable for coffee or for money. This task took approximately 15 min. After completing the task, subjects prepared the amount of preferred brand coffee that they had earned using a drip coffeemaker, under the supervision of the experimenter. They received the prepared coffee and the money they had earned in the task at the same time. Afterwards, subjects remained in the laboratory for 2 h, during which time they could drink the coffee that they had earned. Any coffee remaining after the 2-h period ended was measured. Subjects were allowed to read, study, and/or watch TV during the 2 h. Water was available throughout this period but subjects were not permitted to eat.

Computer task. The computer task used during each session was based on a software package known as Apple Picker (21). The task involved five trials, each trial requiring 100 responses. On every trial, subjects were exposed to two concurrent RR schedules of reinforcement and could apportion their responding between the two schedules, depending on their preferences. One schedule was associated with coffee, one with money. The probability of earning points from the coffee schedule varied systematically across trials: probabilities of 0.06, 0.13, 0.25, 0.50, and 0.75 (RR16, RR8, RR4,

RR2, and RR1.3) were given in ascending or descending order. The money schedule was always associated with a 0.25 probability of reinforcement (RR4). Each subject experienced either the ascending or descending order on the first three sessions and the other order on the second three sessions. Placards listing the probabilities were on display throughout the task.

Each reinforcement schedule was associated with an array of symbols on the computer screen: one schedule had 100 'X's and the other had 100 'O's. Subjects could earn a point on the RR schedule by pressing the mouse button when the cursor was over a symbol. Each point earned was exchangeable for 0.036 cups of coffee or $0.024. If subjects responded exclusively on the coffee schedule for all five trials (i.e., a total of 500 responses, earning approximately 169 points), the average number of cups of coffee that could be earned was 6.00 (169 points × 0.036 cups). If they responded exclusively on the money schedule for all trials (i.e., a total of 500 responses, earning approximately 125 points), the average amount of money that could be earned was $3.00 (125 points × $0.024).

Dependent Measures and Data Analysis

To verify that subjects had ingested their capsules and complied with deprivation instructions, the caffeine content of their saliva samples was examined using two-way within-subjects analysis of variance (ANOVA) with repeated measures on caffeine dose (0%, 50%, 100% of normal daily intake) and occasion (first or second occasion a dose was administered). Two-way within-subjects ANOVAs were also conducted on subjects' pretask caffeine withdrawal symptomatology measures to assess whether caffeine withdrawal symptoms differed across caffeine dose conditions.

Changes in caffeine self-administration were analyzed using two-way within-subjects ANOVAs on the number of cups of coffee earned during the computer task and the amount of coffee consumed during the 2 h after completing the task. Variations in responding for coffee as a function of the different probabilities of reinforcement on the coffee schedule (0.06, 0.13, 0.25, 0.50, and 0.75) were examined using a three-way ANOVA with repeated measures on caffeine dose, occasion, and probability.

RESULTS

Analysis of the subjects' saliva indicated that they took the capsules in accordance with the experimental instructions: the mean amount of caffeine in subjects' saliva was a direct function of the caffeine dose [0%: 196.1 ± 62.2 ng/ml; 50%: 2477.0 ± 325.4 ng/ml; 100%: 5926.1 ± 667.8 ng/ml; $F(2, 16) = 30.97, p < 0.001$].

Subjects exhibited more caffeine withdrawal symptoms when they were in the 0% caffeine condition than during the 50% and 100% caffeine conditions (Fig. 1). Subjects reported more headaches, $F(2, 16) = 7.05, p < 0.01$, over the 24 h before experimental sessions on which they were completely abstinent from caffeine compared to sessions on which some caffeine was received. There was also a significant effect of caffeine dose on feeling sluggish, $F(2, 16) = 4.93, p < 0.05$, and tired-sleepy, $F(2, 16) = 3.74, p < 0.05$, over the same period.

In addition, subjects reported some caffeine withdrawal symptoms immediately prior to performing the computer task. Subjects reported feeling more headachy before sessions of the 0% caffeine dose condition than before the 50% and 100% conditions, $F(2, 16) = 6.40, p < 0.01$. They also felt more sluggish and more tired-sleepy during the first, but not the second, occasion that the 0% condition was administered than during the other conditions [caffeine dose × occasion: $F(2, 16) = 7.88, p < 0.01$ and $F(2, 16) = 7.46, p < 0.01$, respectively].

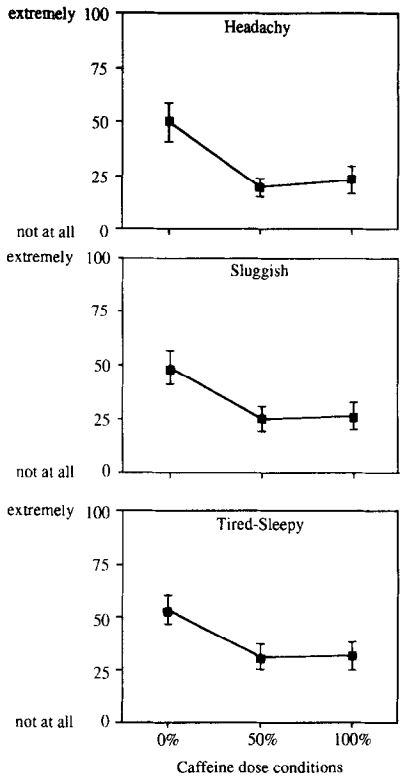

FIG. 1. Mean ratings of "headachy," "sluggish" and "tired-sleepy" for the 24 h prior to the task under the three caffeine dose conditions (in mm). Mean ratings were calculated from data obtained for all subjects at each replication. SEs are also shown.

There was a strong relationship between the probability of earning coffee and the amount of responding on the coffee schedule. As shown in Fig. 2, the higher the probability of earning coffee, the more responses were made, $F(4, 32) = 62.42, p < 0.0001$. However, this relationship between probability and responding was unaffected by the different caffeine dose conditions [caffeine dose × probability: $F(8, 64) = 0.81$, NS]. Further, total number of responses for coffee out of 500 during the computer task was unaffected by caffeine dose condition [0%: 179.1 ± 14.2 responses; 50%: 167.8 ± 14.1 responses; 100%: 183.6 ± 15.6 responses; $F(2, 16) = 1.14$, NS]. In addition, there was no relationship between caffeine dose condition and the amount of coffee subjects earned [0%: 3.7 ± 0.2 cups; 50%: 3.5 ± 0.2 cups; 100%: 3.9 ± 0.2 cups; $F(2, 16) = 2.40$, NS]. Moreover, the amount of the earned coffee subjects consumed during the 2-h posttask period was stable across caffeine dose conditions [0%: 3.3 ± 0.2 cups; 50%: 3.2 ± 0.2 cups; 100%: 3.4 ± 0.2 cups; $F(2, 16) = 1.26$, NS].

DISCUSSION

The current study was designed to examine the effects of complete and partial caffeine deprivation on both subjective withdrawal symptoms and self-administration of caffeinated

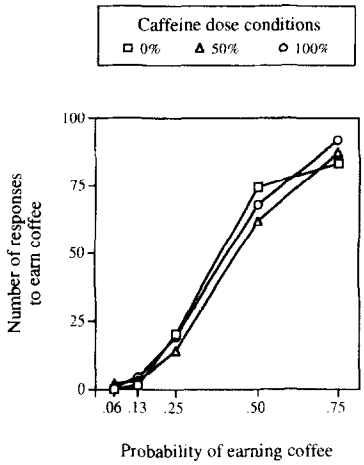

FIG. 2. Mean amounts of responding for coffee on the computer task as a function of the probability that responding would yield points exchangeable for coffee (0.06, 0.13, 0.25, 0.50, 0.75) under the three caffeine dose conditions. Means were calculated from data obtained for all subjects at each replication.

coffee. Complete caffeine deprivation was associated with the occurrence of a number of withdrawal symptoms. Subjects reported increased VAS ratings of "headachy," "sluggish," and "tired" 24 h and immediately before performing the computer task. Such effects of caffeine deprivation have been reported by other researchers [e.g., (14)]. Subjects experienced the most pronounced withdrawal symptoms during the complete deprivation conditions (0%), and far smaller effects during the partial and no deprivation conditions (50% or 100%). The occurrence of similar VAS scores for the partial and no deprivation conditions is somewhat surprising and suggests that doses of caffeine that are low relative to the amount consumed daily can be sufficient to prevent caffeine withdrawal symptoms. The fact that these VAS scores were greater than zero presumably reflects the normal state of our subjects. It is interesting to note that withdrawal symptoms were reported more reliably when subjects considered the deprivation period as a whole than when they considered only the moments immediately prior to the task. This result is compatible with the notion that withdrawal symptoms can vary in intensity during a period of deprivation, or that withdrawal symptoms can vary in intensity as a function of time of day. The role played by subjects' normal pattern of coffee intake on the extent and occurrence of these withdrawal symptoms is unclear.

Although several studies have shown that humans choose caffeine over placebo more frequently following complete caffeine deprivation compared to no deprivation [e.g., (11)], other studies have failed to observe this [e.g., (13)]. Hughes and colleagues suggest that the presence of withdrawal symptoms may be vital for self-administration to increase above baseline levels (15). In the current study, subjects did experience caffeine withdrawal symptoms after complete caffeine deprivation, but this was not associated with an increase in the amount of coffee self-administered. This suggests that coffee drinking in these subjects was under the control of factors other than the pharmacological effects of the caffeine contained in the coffee. The fact that subjects drank an average of 3.4 cups of coffee within 2 h after consuming an average of 343 mg of caffeine (in the 100% condition) also suggests that coffee drinking was independent of the caffeine content of the coffee.

One difference between this and the previous studies that may account for the different pattern of results that we observed was that our subjects were blind to the deprivation conditions and to the drug under investigation. It is possible that they did not associate the occurrence of headaches, etc., with caffeine deprivation. Such knowledge may be crucial to change caffeine consumption. In other caffeine self-administration studies, while subjects were blind to which capsule or which sachet of coffee contained caffeine, subjects were usually aware that the effects of caffeine were being investigated. For example, Griffiths and colleagues informed subjects that a variety of chemical compounds found in coffee, including caffeine and other substances, were being studied [(11) p. 130]. In other studies, subjects have been told that the caffeine content of the coffee that they are consuming may be varied [e.g., (9,10)] or subjects have been given different packets of coffee and told not to ingest caffeine from any other source [e.g., (13-15,22)]. Perhaps if our subjects had been informed that the experimenters were varying the amount of caffeine administered to them, and if they associated certain sensations (e.g., headache) with caffeine deprivation, then they would have self-administered more coffee whenever they experienced such caffeine withdrawal symptoms.

Although it is possible that the absence of differences in caffeine self-administration across the caffeine dose conditions was due to insensitivity of the task, three types of evidence argue against this. First, subjects responded differentially to the different probabilities of earning coffee: they responded less at low probabilities than at high probabilities. Second, other researchers have successfully used this task to measure changes in preference between different reinforcers, for example, highly preferred foods and less-preferred foods (25), and food or money and alcohol (31). Third, other workers have used this task to show that complete deprivation from another drug, nicotine, was associated with increased responding for that drug compared to no deprivation (5,24).

One important aspect of the experimental procedure used in our study was that subjects did not earn coffee directly while performing on the task, but rather they earned points that were exchanged for coffee after they had completed the task. This procedure makes the assumption that the value of points is related to the value of the commodity for which they are exchanged. This assumption is supported by the results of several studies in which the number of points earned changed as a function of a manipulation that altered the reinforcing value of the reinforcer but should not have altered the reinforcing value of the points per se. For example, using a task essentially the same as that used in our experiment, Epstein and colleagues found that subjects earned a larger number of points exchangeable for food while they were food deprived than when not deprived, and they earned a larger number of points exchangeable for cigarette puffs while they were smoking deprived than when not deprived (4). In addition, changing the value of a reinforcer has been associated with changes in the number of points earned in other studies in which points were exchanged for alcohol and money (3,26,27), cigarettes and money (19), coffee and money (20), money only (6,16), and food only (17,18,25,27).

In conclusion, the current experiment demonstrates that coffee drinking in habitual coffee drinkers is not increased by

a 33.5-h period of caffeine deprivation. This result indicates that, for caffeine, the presence of withdrawal symptoms is a more sensitive indicator of drug deprivation than subsequent drug consumption, and that withdrawal symptoms may occur while self-administration remains unaffected.

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (3rd ed., revised). Washington: American Psychiatric Association; 1987.
2. 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.
3. Chutuape, M. D.; Mitchell, S. H.; de Wit, H. Ethanol preloads increase ethanol preference under concurrent random-ratio schedules in social drinkers. Exp. Clin. Psychopharmacol. 2:310–318; 1994.
4. Consumer Reports. "Gourmet" coffee: The hunt for great flavor. January 1991, p. 33–35.
5. Epstein, L. H.; Bulik, C. M.; Perkins, K. A.; Caggiula, A. R.; Rodefer, J. Behavioral economic analysis of smoking: Money and food as alternatives. Pharmacol. Biochem. Behav. 38:715–721; 1991.
6. Flora, S. R.; Pavlik, W. B. Human self-control and the density of reinforcement. J. Exp. Anal. Behav. 57:201–208; 1992.
7. Goldstein, A.; Kaizer, S.; Whitby, O. Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to caffeine. Clin. Pharmacol. Ther. 10: 489–497; 1969.
8. Griffiths, R. R.; Woodson, P. P. Caffeine physical dependence: A review of human and laboratory animal studies. Psychopharmacology (Berlin) 94:437–451; 1988.
9. Griffiths, R. R.; Bigelow, G. E.; Liebson, I. A. Human coffee drinking: Reinforcing and physical dependence producing effects of caffeine. J. Pharmacol. Exp. Ther. 239:416–425; 1986.
10. Griffiths, R. R.; Bigelow, G. E.; Liebson, I. A.; O'Keeffe, M.; O'Leary, D.; Russ, N. Human coffee drinking: Manipulation of concentration and caffeine dose. J. Exp. Anal. Behav. 45:133–148; 1986.
11. 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.
12. Griffiths, R. R.; Evans, S. M.; Heishman, S. J.; Preston, K. L.; Sannerud, C. A.; Wolf, B.; Woodson, P. P. Low-dose caffeine physical dependence in humans. J. Pharmacol. Exp. Ther. 255: 1123–1132; 1990.
13. 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.
14. Hughes, J. R.; Hunt, W. K.; Higgins, S. T.; Bickel, W. K.; Fenwick, J. W.; Pepper, S. L. Effect of dose on the ability of caffeine to serve as a reinforcer in humans. Behav. Pharmacol. 3: 211–218; 1992.
15. Hughes, J. R.; Oliveto, A. H.; Bickel, W. K.; Higgins, S. T.; Badger, G. J. Caffeine self-administration and withdrawal: Incidence, individual differences and interrelationships. Drug Alcohol Depend. 32:239–246; 1993.
16. Hyten, C.; Madden, G. J.; Field, D. P. Exchange delays and impulsive choice in adult humans. J. Exp. Anal. Behav. 62:225–233; 1994.
17. Lappalainen, R.; Epstein, L. H. A behavioral economics analysis of food choice in humans. Appetite 14:81–93; 1990.
18. Logue, A.; Pena-Correal, T. E.; Rodriguez, M. L.; Kabela, E. Self-control in adult humans: Variation in positive reinforcer amount and delay. J. Exp. Anal. Behav. 46:159–173; 1986.
19. Mitchell, S. H.; de Wit, H.; Zacny, J. P. Effects of varying the "openness" of an economy on responding for cigarettes. Behav. Pharmacol. 5:159–166; 1994.
20. Mitchell, S. H.; Laurent, C. L.; de Wit, H.; Zacny, J. P. Effects of price, "openness" of the economy and magnitude of the alternative reinforcer on responding for caffeinated coffee. Hum. Psychopharmacol. 10:39–46; 1995.
21. Norman, W. D.; Jongerius, J. L. Apple Picker: Computer software for studying human responding on concurrent and multiple schedules. Behav. Res. Methods Instrum. Comput. 17:222–225; 1985.
22. Oliveto, A. H.; Bickel, W. K.; Hughes, J. R.; Shea, P. J.; Higgins, S. T.; Fenwick, J. W. Caffeine drug discrimination in humans: Acquisition, specificity and correlation with self-reports. J. Pharmacol. Exp. Ther. 261:885–894; 1992.
23. Pennington, J. A. T.; Church, N. H. Bowes and Church's food values of portions commonly used, 14th edition. Philadelphia: Lippincott; 1985.
24. Perkins, K. A.; Epstein, L. H.; Grobe, J.; Fonte, C. Tobacco abstinence, smoking cues, and the reinforcing value of smoking. Pharmacol. Biochem. Behav. 47:107–112; 1994.
25. Smith, J. A.; Epstein, L. H. Behavioral economic analysis of food choice in obese children. Appetite 17:91–95; 1991.
26. Vuchinich, R. E.; Tucker, J. A.; Rudd, E. J. Preference for alcohol consumption as a function of amount and delay of alternative reward. J. Abnormal Psychol. 96:259–263; 1987.
27. Zacny, J. P.; Divane, W. T.; de Wit, H. Assessment of magnitude and availability of a nondrug reinforcer on preference for a drug reinforcer. Hum. Psychopharmacol. 7:281–286; 1992.