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Oral Caffeine Consumption by Rats: The Role of Flavor History, Concentration, Concurrent Food, and an Adenosine Agonist

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NEWLAND, M. C. AND K. BROWN. *Oral caffeine consumption by rats: The role of flavor history, concentration, concurrent food, and an adenosine agonist.* PHARMACOL BIOCHEM BEHAV 42(4) 651-659, 1992.—Some determinants of caffeine consumption by rats were examined using the two-bottle choice test. To describe the role of flavor history, groups of eight rats each received one of three fluids as their only source of fluid beginning at 29 days of age and continuing throughout the experiments. One group ("water") received tapwater, a second group ("caffeine") received 0.5 mg/ml caffeine in tapwater, and a third group ("quinine") received 0.01 mg/ml quinine in tapwater. Two-bottle choice tests began when rats were 40 days old. In the initial tests, caffeine rats drank more caffeinated water than water rats. Quinine rats were midway between these two groups. On a second block of tests, quinine and water rats' caffeine consumption increased so that the three groups were indistinguishable. When 0.5 mg/ml caffeine was available for 24 h, about one third of the total fluid consumption was of caffeinated water for all three groups. The presence of food greatly increased both caffeine and water consumption across a range of caffeine concentrations spanning 0.125–4.0 mg/ml. Increasing caffeine concentration generally increased consumption of plain water and decreased that of caffeinated water (but not total caffeine consumed) for water rats. Caffeine rats generally drank more caffeine than water rats, largely due to a tendency toward increased consumption of the 0.5-mg/ml concentration. Consumption of caffeinated water peaked at 0.5 mg/ml and showed graded decreases at higher and lower concentrations. Caffeine consumption showed dose-related increases with presession administration of *l*-phenylisopropyl adenosine. The series of experiments characterize some of the determinants of caffeine consumption in rats. Overall, a history of forced exposure to caffeine, the presence of food, caffeine concentration, and preadministration of an adenosine agonist all increase the consumption of caffeine. The present experiments also provide some guidelines as to what concentrations are consumed by rats and the maximum dose level likely to be achieved in tests of this kind. There is some evidence from the present experiments that caffeine consumption is related to caffeine's pharmacological properties, although the influence of flavor has not been eliminated.

Caffeine Quinine Two-bottle test *l*-Phenylisopropyl adenosine Rats Flavor history Prandial drinking

THE list of drugs that are self-administered by both human and nonhuman mammals includes stimulants, barbiturates, sedative/hypnotics, benzodiazepines, opiates, and nicotine (11,24). The correspondence among drugs that are self-administered by different species, coupled with the widespread consumption of caffeine by humans, suggests that caffeine should be self-administered by animals.

Considering caffeine's widespread consumption by humans, it is interesting that this drug is only a weak reinforcer in experimental settings in which conventional drugs of abuse are stronger (6,21,23,24,26,27). This apparent discrepancy suggests that a better understanding of the conditions under which caffeine is consumed by nonhuman species might shed some light not only on human caffeine consumption in particular but also on the conditions under which drug self-administration occurs in general. Both rats (3,11,37) and baboons (24) have been reported to self-administer caffeine when delivered intravenously. However, caffeine self-administration was more erratic and showed greater intersubject variability than seen with other stimulants like cocaine.

The dominant route of caffeine self-administration by humans is the oral one (4,21,22). Oral self-administration of other drugs is sensitive to food deprivation and the concurrent availability of food (8,31), an effect also seen with caffeine (28). Flavor, the conditions of exposure, and the manner by which the drug is introduced are also important determinants of the robustness of drug-maintained responding (31,35). Vitiello and Woods (40) reported a direct relationship between consumption history and amount of caffeine consumed in a choice test. Rats previously exposed to the higher concentra-

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tions of caffeine in their drinking water consumed more caffeine than those exposed to lower ones. The effects of history, which may be related to the type of drug, could act by acclimating the organism to an otherwise aversive flavor, exposing the animal to a reinforcing stimulus, or both.

Self-administration of psychomotor stimulants can be increased by some doses of drugs that antagonize their effects at the receptor (41,42). Caffeine is thought to exert many of its behavioral effects by blocking an adenosine receptor (10,12,19,20,38,39). Compounds such as *l*-phenylisopropyl adenosine (*l*-PIA) are agonists at this receptor, and therefore antagonize some of the behavioral effects of caffeine. It is not known how such drugs affect caffeine self-administration.

The present experiments were designed to examine the influence of some of these variables on caffeine consumption in rats using a two-bottle choice test. The roles of a) history of the consumption of a bitter solution, b) concentration of caffeine, c) concurrent availability of food, and d) preadministration of a putative adenosine agonist on the consumption of water containing caffeine were examined.

METHOD

Subjects

Subjects were 24 male Long-Evans-derived rats purchased as 21-day-old weanlings from Harlan-Sprague-Dawley. They were housed individually in stainless steel, hanging cages with corn cob bedding in a room with a 12 L : 12 D cycle (lights on at 6:00 a.m.).

Chronic Caffeine Consumption

When rats were 26 days old, they were randomly divided into three groups. The "caffeine" group received 0.5 mg/ml caffeine (anhydrous caffeine purchased from Sigma Chemical Co., St. Louis, MO) in their drinking water, the "quinine" group received 0.01 mg/ml quinine in their drinking water, and the "water" group received untainted tapwater. All rats had unlimited access to Purina Rat Chow and fluid. The concentration of quinine was based upon observations that taste thresholds for quinine are about 50 times lower than those seen for caffeine (2,18). Informal testing indicated that these two concentrations were about equally bitter to humans. These solutions constituted the only source of fluid for the groups apart from that presented during testing sessions. The quinine and caffeine concentrations reduced fluid intake for the first 24 h about equally. Rats exposed to quinine were used in assessing the development of caffeine consumption and in comparing caffeine and quinine preference. Since quinine history was indistinguishable from caffeine and water history on the latter tests, these rats were not used in subsequent tests.

Development of Caffeine Consumption

Two-bottle testing began when rats were 40 days old, after caffeine and quinine groups had been consuming tainted water for 14 days. Two water bottles were placed on the front of each home cage. One bottle contained 0.5 mg/ml caffeine and the other contained tapwater. The amount of fluid consumed from each bottle over 24 h was determined by weighing the bottles and converting the weight to milliliters (1 g = 1 ml fluid). During the first 2 days (block 1) of this test, the water group received the caffeine bottle on the side that customarily contained water and the water bottle was located where no bottle had been located previously. For the caffeine and quinine groups, the water bottle was located where their bottle (containing caffeine or quinine) had been located and the caffeine bottle was located where no bottle had previously been. Thus, for all groups a new fluid was located where the old fluid had been. For the quinine group, a new, nonbitter solution (tapwater) was located where the bitter quinine had been located. On the third and fourth days (block 2), the location of these bottles was reversed. To estimate leakage resulting from handling the bottles, full bottles were placed on empty cages for the same duration and then weighed. This estimate of leakage was subtracted from all measures.

Comparison of Caffeine and Quinine Preference

After the above tests, each rat was presented with a choice between tapwater and 0.5 mg/ml caffeine (as above) and a choice between tapwater and 0.01 mg/ml quinine. Consumption of each solution was determined by weighing the bottles after 24 h. The location of the bottles was reversed unpredictably so that each location of each solution was tested at least once.

Caffeine Preference at Different Concentrations With and Without Food

The water and caffeine groups were presented with two bottles for 4 h. One bottle contained tapwater and the other contained 0.1, 0.2, 0.5, 1.0, 2.0, or 4.0 mg/ml caffeine dissolved in tapwater. Tests were conducted 2 days/week and separated by at least 1 day. Each solution was evaluated at least once on each side of the cage. The test was conducted both with and without food present. Rats had been food and fluid deprived for 5 h before the test. Water and caffeine rats continued to drink tapwater and 0.5 mg/ml caffeine, respectively, when testing was not being conducted.

l-*PIA and Caffeine Preference*

An acute dose of 0.15 or 0.3 mg/kg *l*-PIA was administered IP to each rat 10 min before a 4-h test with food present in the home cage. The 4-h test was conducted as described in the previous section with no food present and a 4.0-mg/ml solution of caffeine. This concentration was chosen because the amount of caffeine consumed was such that either a decrease or an increase could be detected.

Data Analysis

Data analyses were conducted both graphically and with independent groups analysis of variance (ANOVA) followed by Newman-Keuls posthoc multiple comparisons. When an interaction was statistically significant, posthoc comparisons were conducted at all levels of the variables and only posthoc comparisons with a p value less than 0.05 are reported.

Experiments were conducted as within-subjects designs but the stringent requirements of repeated-measures analyses (sphericity and complete data on each subject) mitigated against using repeated-measures ANOVA. For example, some data points had to be omitted because they were extremely deviant, greater than 3 standard deviations removed from the mean for that condition and deviant from other replications for that subject. These data points contributed excessively to the F value. While these deviant data could represent a binge of caffeine consumption, it is more likely that they represent a data-entry error or leakage that sometimes occurred when a rat leaned against the water spout. Only one or two data points were omitted from any analysis but a repeated-measures ANOVA would preclude using any data from that

subject. It was decided, instead, to conduct an independent factorial design. This design loses some power by not comparing a subject against its control values and may gain in some power by increasing degrees of freedom. All decisions based upon p values are supported graphically.

RESULTS

Acquisition

Figure 1 shows the amount of caffeine and water consumed during the first two and the second two acquisition sessions.

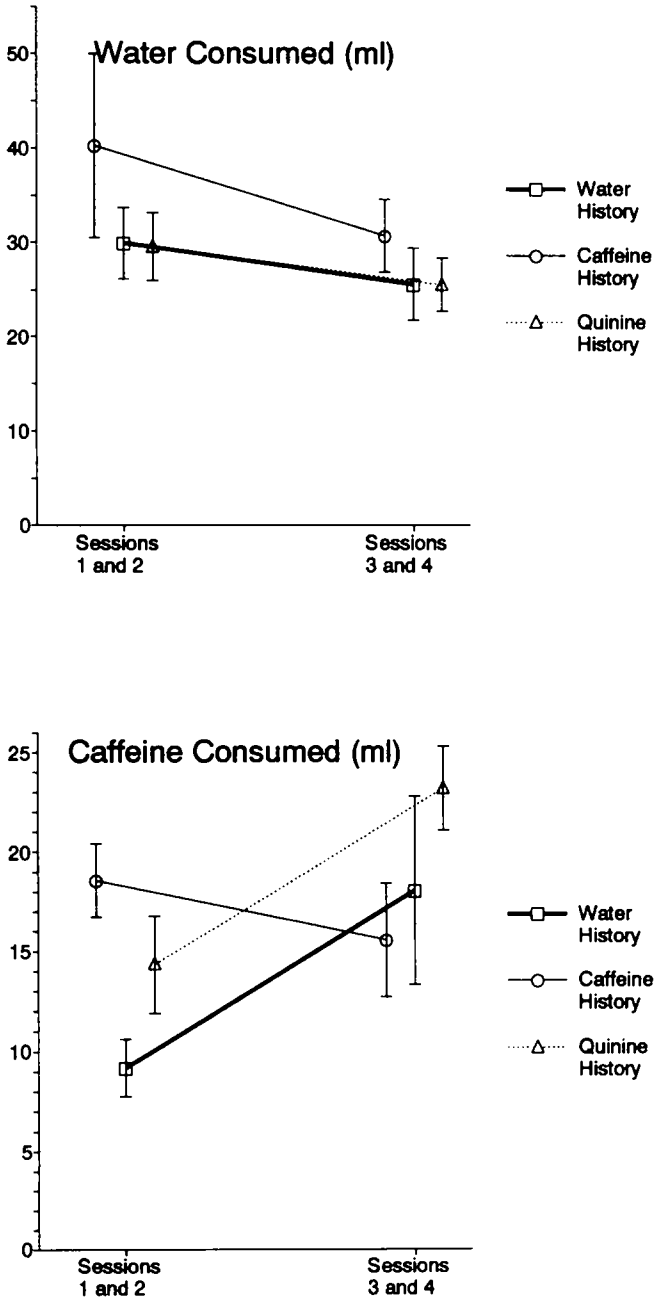

FIG. 1. Amount of tapwater (top) and caffeinated water (0.5 mg/ml, bottom) consumed by each of three groups of rats during the first two sessions of two-bottle choice testing. Error bars show ± 1 SEM.

Flavor history interacted with block number on the amount of caffeine consumed, $F(2, 35) = 3.0$, $p = 0.06$, but not on the amount of water consumed. There was also a main effect of home fluid, $F(2, 35) = 4.01$, $p = 0.03$. Posthoc comparisons revealed that water and caffeine rats were different from one another on the first session but neither group was distinguishable from quinine rats. The three groups were indistinguishable from one another during the second block because both water and quinine rats increased their caffeine consumption during the second block.

Quinine consumption was also assessed in these groups after caffeine consumption but the data are not shown in Fig. 1. Quinine rats consumed 6.5 ± 1.5 (mean ± one SEM) ml quinine on the first test and this decreased to 1.5 ± 0.3 ml on subsequent tests. Water and caffeine rats consumed 1.5 ± 0.3 and 1.7 ± 0.3 ml quinine, respectively, on all these tests. Since quinine consumption was so low, these tests were not continued.

Animals whose home-cage fluid contained caffeine appeared to consume about 33% more water than rats that had been consuming either water or quinine in their home cage (Fig. 1), but due to the great variability among caffeine-exposed rats (with no outliers) in consumption this difference was not statistically significant [$F(2, 39) = 2.2$, $p = 0.14$, for the main effect of home fluid]. The amount of water consumed in the second block was the same as that consumed during the first block for each group.

Relative Consumption Over 24 h

No systematic group differences appeared in the choice of fluids consumed (Fig. 2). Regardless of which fluid rats had in their home cage, the relative consumption of the different fluids was about the same. Approximately 30–40 ml consumption was of tapwater, 15–20 ml, or about one third of the total fluid consumed, was of caffeine, and very little was of quinine. No consistent position preference was observed so data from "left" and "right" conditions were combined in Fig. 2.

Caffeine Concentration and the Presence of Food

The role of caffeine concentration on caffeine and water consumption was assessed in 4-h sessions while the two fluids were concurrently available. These sessions were conducted both with and without food concurrently available. Since too little fluid was consumed under the "no-food" condition to produce reliable data, the analyses will emphasize the "food" conditions. Figure 3 shows the amount of water (top) and caffeine (middle) consumed at each concentration. The bottom panel shows the total caffeine in milligrams as estimated by multiplying the concentration by the amount consumed for each subject at each concentration.

No interaction appeared between home fluid and concentration on the amount of caffeine consumed with food present, $F(6, 207) = 1.5$, $p = 0.68$, but a main effect of both home fluid, $F(6, 207) = 5.98$, $p = 0.015$, and concentration, $F(6, 207) = 8.18$, $p < 0.0001$, appeared. Posthoc comparisons revealed that consumption at 4 mg/ml caffeine differed from that seen at all other concentrations. The main effect of home fluid indicates that rats that had 0.5 mg/ml caffeine as their home fluid consumed more caffeine than those that did not. Although an interaction did not reach statistical significance, visual inspection of the middle panel of Fig. 3 suggests an increasing trend in caffeine consumption for caffeine rats as the concentration in the test bottle approached 0.5 mg/ml.

The amount of water consumed increased with the concentration of caffeine present in the alternative bottle, $F(6, 206)$

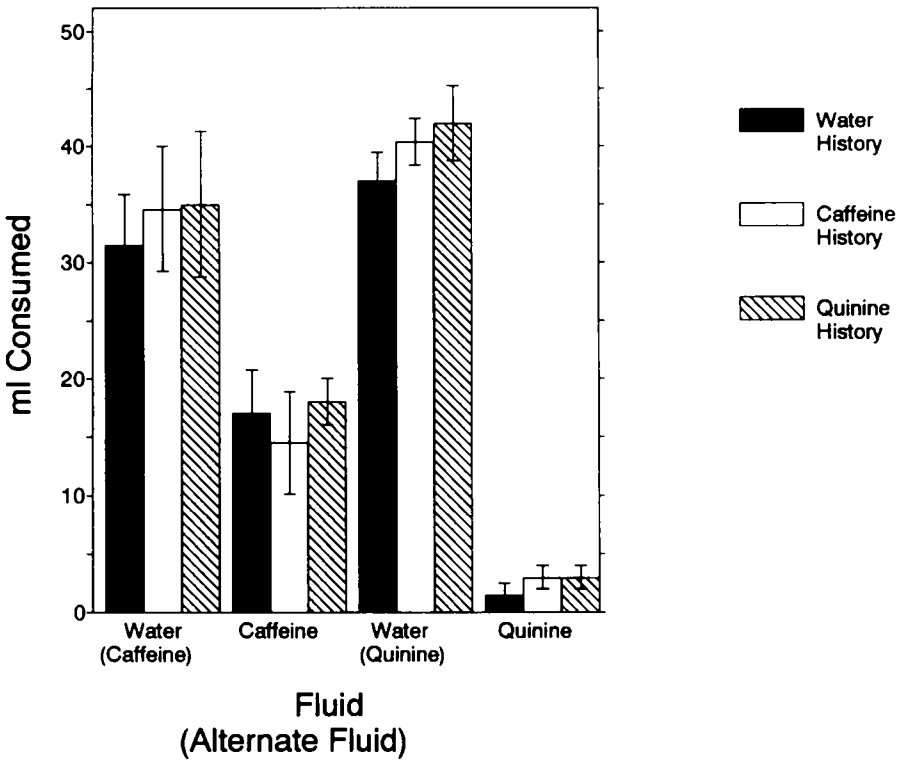

FIG. 2. Amount of water containing caffeine or quinine consumed during 24-h two-bottle choice testing. For comparison, the amount of tapwater consumed during caffeine tests and quinine tests are shown separately. Error bars show ± 1 SEM.

= 11.4, $p < 0.0001$, but water consumption was unrelated to the whether rats had water or caffeine as their home fluid.

An increase in the total fluid consumed can be inferred from the data presented in Fig. 3. Under control conditions, both groups consumed about 14 ml fluid and at the highest dose of caffeine about 19 ml was consumed, about a 36% increase. This increase was reliable [$F(6, 206) = 4.53$, $p = 0.0002$, for concentration] but did not interact with home fluid and no main effect of home fluid appeared.

The presence of food substantially affected the consumption of both fluids; very little fluid of any type was consumed when food was not concurrently available. Under the no-food condition, as under the food condition, caffeinated fluid consumption peaked at 0.5 mg/ml, the same concentration as present in their home cages, and this effect was statistically reliable for the no-food condition [main effect of concentration: $F(5, 244) = 5.6$, $p = 0.0093$] Posthoc comparisons showed that for caffeine animals caffeine consumption at 0.5 mg/ml was indistinguishable from that seen under the water (0 mg/ml) condition but different from that seen at other caffeine concentrations. The 4-mg/ml concentration was not evaluated with all rats under the no-food condition. For those on which it was tested, it appeared that none was consumed; fluid loss was indistinguishable from leakage.

Total caffeine intake increased with the concentration of caffeine up to 2 mg/ml and then leveled off at about 12 mg for both groups of rats [main effect of concentration: $F(6, 208) = 68.1$, $p < 0.0001$] and caffeine rats consumed more than water rats, $F(1, 208) = 5.4$, $p = 0.021$). Under the food condition, some caffeine was consumed at 4 mg/ml; this was enough so that about 14 mg caffeine, or 45 mg/kg, was consumed at both the 2- and 4-mg/ml concentrations.

Preadministration of l-PIA

Administering *l*-PIA 10 min before a test produced decreases in the amount of water consumed, $F(3, 40) = 7.96$, $p < 0.01$, and the higher dose increased the amount of caffeine consumed, $F(2, 40) = 6.36$, $p < 0.01$, so that at a dose of 0.3 mg/ml of *l*-PIA, less water, and about twice as much caffeine was consumed during this test than during control conditions (Fig. 4). Neither water nor caffeine consumption was related to the fluid in the home cage. At the higher dose of *l*-PIA, rats were sedated for the first hour or more of the test.

DISCUSSION

Acquisition

When first presented with the opportunity to consume either caffeine or tapwater, rats with no history of bitter-tasting fluid consumed relatively little caffeine or quinine while rats with a history of forced caffeine consumption consumed the drug readily. The proclivity to consume caffeine voluntarily may be due to a history of exposure to bitter-tasting solutions since quinine rats fell between the two groups on this measure.

After 3 days of availability, the three groups were indistinguishable from one another in their consumption of a concentration of caffeine high enough to have behavioral effects upon chronic exposure (16) and sufficiently bitter that it re-

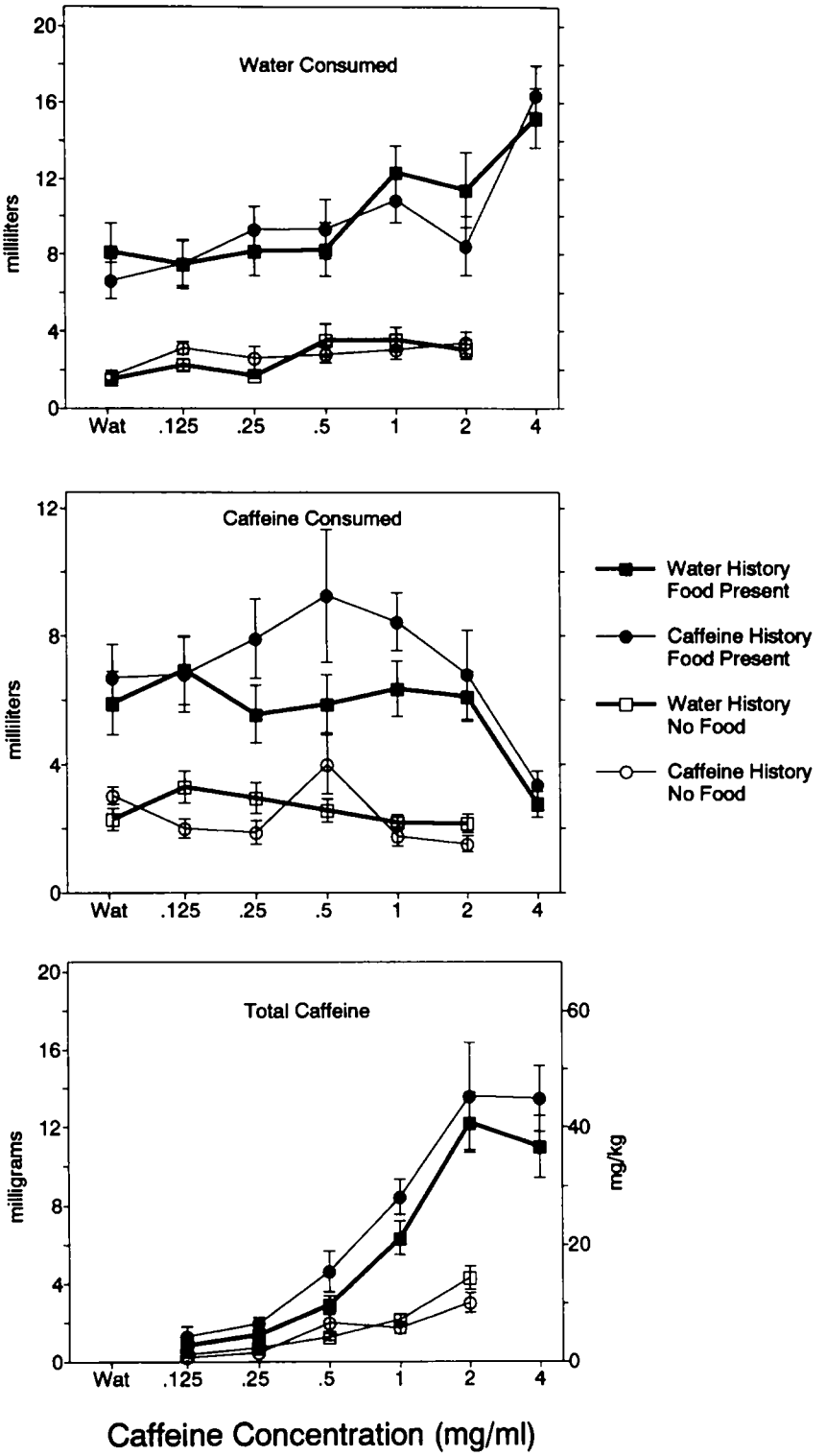

FIG. 3. Amount of water (top panel), caffeinated water (middle panel), and total caffeine intake (bottom panel) in 4-h, two-bottle choice tests in which the concentration of caffeine was varied. Filled and unfilled symbols represent data from sessions when food was and was not present, respectively, during the test session. Squares and circles represent, respectively, rats for which tapwater or 0.5 mg/ml caffeine was their home-cage fluid. Error bars show ± 1 SEM. A session at 4 mg/ml was not conducted with all rats under the no-food condition.

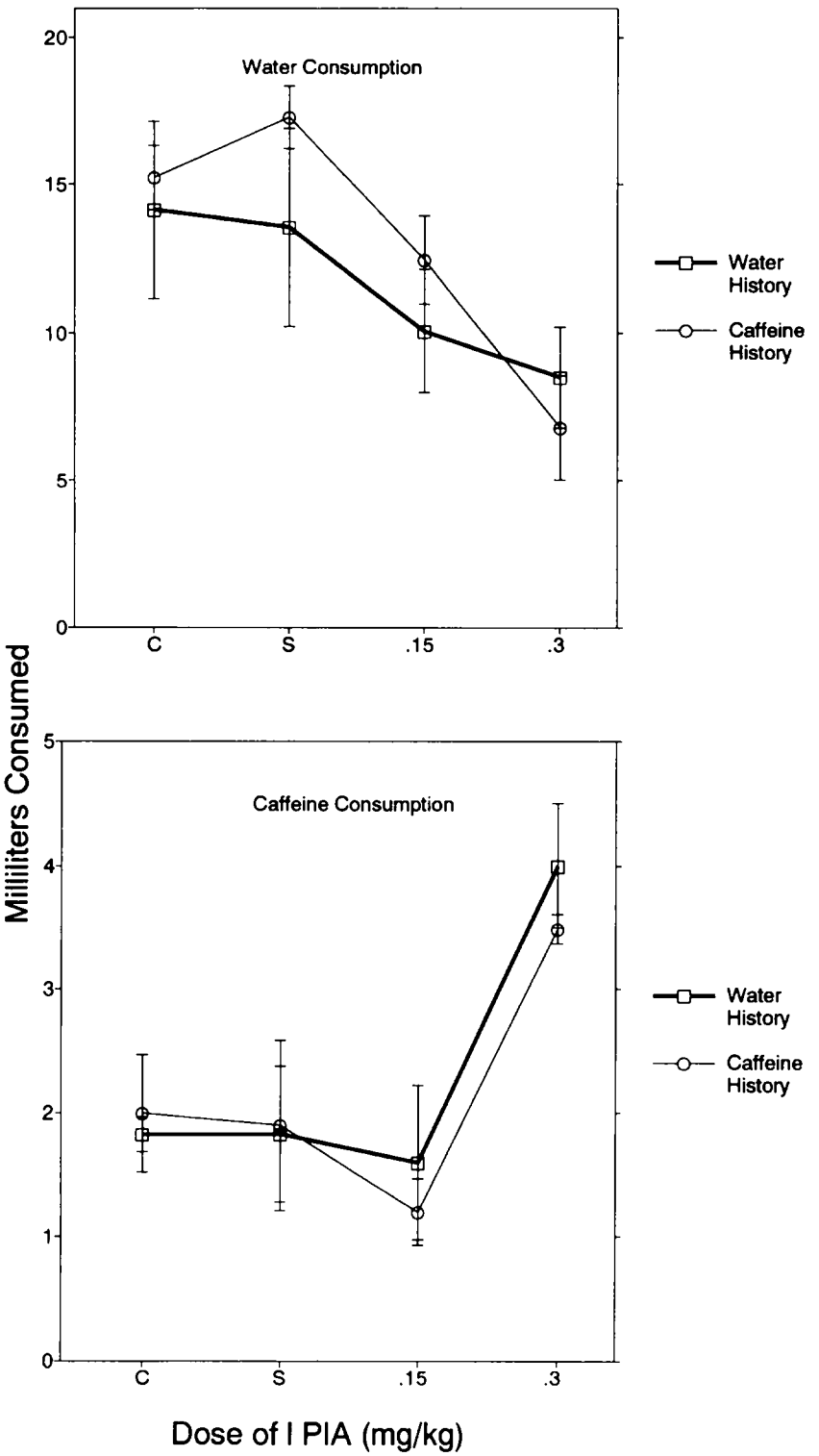

FIG. 4. Water and caffeine consumption from two-bottle tests when the session was preceded by *l*-PIA. C and S represent noninjected controls and vehicle injections, respectively.

duced fluid consumption upon initial forced exposure. The onset of caffeine consumption on day 3 in the water group may have resulted from animals' experience with the stimulus properties of caffeine acquired on the first 2 days, the relocation of the bottle containing caffeine to the other side, or both.

Being accustomed to bitter water may have predisposed caffeine and quinine rats to sample the caffeine solution, but it would not have supported its continued consumption. It appears that the maintenance of caffeine consumption in 24-h choice tests was not due solely to rats' flavor history. If rats were merely consuming the flavor they were accustomed to drinking, then quinine rats, which consumed some quinine on initial tests, would have continued to consume quinine. Instead, the amount of quinine consumed by these rats quickly declined to nearly zero even though the concentration of quinine was the same as that which they had been forced to drink previously.

When offered a choice, water rats consumed some caffeine but very little quinine, suggesting that the quinine solution was more bitter than the caffeine solution. The excessive bitterness of the quinine solution may have contributed to the small enhancement of caffeine consumption by quinine rats upon first exposure, but it precludes comparisons of the reinforcing properties of the two solutions with flavor held constant.

After consumption among the three groups appeared similar, about one third of the total fluid consumption in 24 h was of the 0.5-mg/ml caffeine solution regardless of flavor history. The fact that one third, and not one half, of fluid intake was of the caffeinated water is evidence that rats could distinguish the two fluids. Some fluid intake contained caffeine for all groups, very little was of quinine for any group, and quinine consumption declined after the first two-bottle test for the quinine group. All this suggests that consumption is not driven entirely by flavor history.

Concentration-Effect Functions

More caffeine was consumed by caffeine rats than by water rats during the 4-h tests used to determine the concentration-effect curves. This could represent tolerance to caffeine upon chronic exposure (17,29,33). Another mechanism is suggested by the inverted-U shaped curve describing the relationship between the ingestion of caffeinated water and concentration. The peak of this curve appeared at 0.5 mg/ml, the home-cage concentration. No such shape occurred for rats whose home-cage fluid was only water. This function strongly suggests that drug taking generalized from the familiar concentration to both higher and lower concentrations. The behavioral mechanism for this must be similar to that seen in cases of induction of responses along physically defined dimensions as in a study by Eckerman and colleagues (13) or along different stimulus dimensions [e.g., (7,43)].

Over a portion of the concentration-effect curve, caffeine and water may have been partially substitutable. With increasing caffeine concentration, the ingestion of caffeine declined and that of water increased. The powerful effect of the presence of food also points to substitutability between caffeine and water or at least that consumption of each fluid is influenced by some of the same variables. If the stimulus properties of caffeine had been entirely responsible for caffeine consumption, then one might expect food to be less important.

The importance of food suggests that caffeine consumption is, in part, prandial. The consumption of a fluid by rats is evoked by the consumption of food, a mechanism that is influential in the consumption of ethanol by rats (36). Prandial consumption of ethanol may be specific to the species studied but there is some evidence that with caffeine this is a more general phenomenon. In an unpublished master's thesis, Adcock (1) found that, on the average, 50% of caffeine consumption (range 30–90%) among young adults was associated with meals or snacks. The mechanism of prandial caffeine consumption is unknown at present, but the simplest hypothesis is that the caffeinated beverage or fluid is simply a source of fluid. The relationship between the availability of food and caffeine consumption may be more complex, however. The present experiments showed that caffeine consumption declined in rats that are not food deprived when food is unavailable. Heppner et al. (28) showed that under conditions of food deprivation caffeine consumption may increase.

With oral self-administration, flavor is important and the relative contribution of flavor can be difficult to disentangle from other stimulus properties of a drug. One approach to this problem might include a description of the amount of drug, not fluid, consumed and relating that to the response cost. Concentration is related to cost (5) and at low concentrations much fluid must be consumed to achieve an effect. In the present experiments, the dose of caffeine self-administered peaked at about 14 mg (about 30–50 mg/kg) and remained at that level at the highest two concentrations. An economic analysis (5) suggests that at concentrations below about 0.5 mg/ml the cost is too high to support self-administration and that at concentrations of 1 or 2 mg/ml a ceiling of body burden of caffeine is reached. This ceiling could be mediated, of course, by an interaction between the stimulus effects of caffeine and the flavor of the solution.

A comparison of the caffeine consumed during the 4-h tests used for establishing the concentration-effect relationships against the caffeine consumed during the 24-h tests displayed in Fig. 2 suggests a time course to caffeine preference. Over 24 h about one third of the fluid consumption was of the 0.5-mg/ml solution of caffeine. However, in the 4-h tests closer to one half of the fluid consumed was of caffeine. Such a time course could occur if subjects were consuming a large initial quantity of the drug and then tapering off the consumption over the course of hours, an effect that suggests that consumption is limited by a pharmacological effect of the drug.

The amount of caffeine consumed at the higher concentrations and at some of the lower concentrations was probably behaviorally active. During a 4-h test, rats consumed enough caffeine at 0.5 mg/ml to receive a dose of 10–20 mg/kg and at 2 mg/ml they consumed 35–45 mg/kg. Rats can discriminate 10 mg/kg caffeine injected IP from saline (30,34), but the discriminative stimulus properties of oral caffeine in rodents are unknown. Some recent reports using humans show that humans can discriminate 100 and 178 mg orally delivered caffeine (25) or 300 mg (9) from a placebo. Assuming a 70-kg human, 100 mg represents a dosage of about 1.4 mg/kg. In other studies, Elsner et al. (14) demonstrated effects of 5 mg/kg caffeine administered PO on some measures of a spatial alternation and visual discrimination and Carroll et al. (6) provided evidence of a withdrawal syndrome in rhesus monkeys after daily doses of 36 mg/kg/day caffeine mixed with food pellets.

Effect of an Adenosine Agonist

The presence of a caffeine withdrawal syndrome in humans suggests that caffeine consumption might be maintained in

part by the avoidance of a withdrawal syndrome (21,27). Withdrawal syndromes can be precipitated by drugs that act in opposition to the self-administered drug (15). Caffeine is thought to be an antagonist at an adenosine receptor and *l*-PIA is thought to be an agonist at this receptor. In the present studies, *l*-PIA decreased water consumption but increased the consumption of 4.0 mg/ml caffeine (Fig. 4). The amount consumed was about 14–16 mg caffeine, approximately the same amount or slightly more than what was consumed at this concentration during the 4-h tests. Although the sessions following *l*-PIA lasted nominally for 4 h, rats were observed to be sedated for about 1–1.5 h, so if this time is excluded then the rate of caffeine consumption may have shown an increase.

The increased consumption of caffeinated fluid after *l*-PIA is consistent with observations that *l*-PIA acts in opposition to caffeine at the receptor level and also suggests that pharmacological properties of caffeine are partly responsible for its consumption. This is also consistent, in general, with other observations of agonist/antagonist relationships influencing drug self-administration (42). Some caution is due since other factors, like the possibility that *l*-PIA altered sensitivity to a bitter fluid, cannot be eliminated.

Consumption of Caffeinated Fluids vs. Caffeine as a Reinforcer

The present experiments do not permit an unequivocal assessment of the strength of caffeine as a reinforcing drug, and they were not designed to. Two limitations of two-bottle tests are plain. The test is not well suited to characterizing the reinforcing efficacy of a drug since it does not permit manipulation of the response requirement (24,32). Moreover, with oral self-administration the relevant stimuli are difficult to isolate because at least two stimulus dimensions covary: the constellation of discriminative stimuli evoked by caffeine and the flavor of caffeinated water.

Instead, the present set of experiments characterize the conditions under which caffeine is consumed by rats. As the above discussion implies, consumed caffeine shares properties with reinforcing drugs. These shared properties could point to reinforcing properties of caffeine or to properties of other drugs that modulate their reinforcing properties.

The present experiments show that a history of forced exposure to caffeine facilitates the acquisition of caffeine and that this is due partly to a history of exposure to a bitter fluid. Such a history is irrelevant to the maintenance of caffeine consumption. In addition, the presence of food, caffeine concentration, and preadministration of an adenosine agonist all increase caffeine consumption. The present experiments also provide guidelines as to what concentrations are consumed by rats and the maximum dose likely to be achieved in tests of this kind. There is some evidence that caffeine consumption is related to caffeine's pharmacological properties, although the influence of flavor has not been eliminated.

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REFERENCES

1. Adcock, R. J. Normative caffeine use in adults: Self-report of consumption and related events. Unpublished master's thesis. Auburn, AL: Auburn University; 1991.
2. Amerine, M. A.; Pangborn, R. M.; Roessler, E. B. Principles of sensory evaluation of food. New York: Academic Press; 1965.
3. Atkinson, J.; Enslen, M. Self-administration of caffeine by the rat. Arziemittelforsch 26:2059–2061; 1976.
4. Barone, J. J.; Roberts, H. Human consumption of caffeine. In: Dews, P. B., ed. Caffeine. New York: Springer-Verlag; 1984:59–76.
5. Bickel, W. K.; DeGrandpre, R. J.; Higgins, S. T.; Hughes, J. R. Behavioral economics of drug self-administration: I. Functional equivalence of response requirement and drug dose. Life Sci. 47: 1505–1510; 1990.
6. Carroll, M. E.; Hagen, E. W.; Asencio, M.; Brauer, L. H. Behavioral dependence on caffeine and phencyclidine in rhesus monkeys: Interactive effects. Pharmacol. Biochem. Behav. 31:927–932; 1989.
7. Carroll, M. E.; Meisch, R. A. Concurrent etonitazene and water intake in rats: Role of taste, olfaction and auditory stimuli. Psychopharmacology (Berl.) 64:1–7; 1979.
8. Carroll, M. E.; Meisch, R. A. Increased drug-reinforced behavior due to food deprivation. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Advances in behavioral pharmacology. New York: Academic Press; 1984:48–88.
9. Chait, L. D.; Johanson, C. E. Discriminative stimulus effects of caffeine and benzphetamine in amphetamine-trained volunteers. Psychopharmacology (Berl.) 96:302–308; 1988.
10. Coffin, V. L.; Spealman, R. D. Modulation of the behavioral effects of chlordiazepoxide by methylxanthines and analogs of adenosine in squirrel monkeys. J. Pharmacol. Exp. Ther. 235: 724–728; 1985.
11. Collins, R. J.; Weeks, J. R.; Cooper, M. M.; Good, P. I.; Russell, R. R. Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacology (Berl.) 82:6–13; 1984.
12. Daly, J. W.; Bruns, R. F.; Snyder, S. H. Adenosine receptors in the central nervous system: Relationship to the central actions of methylxanthines. Life Sci. 28:2083–2097; 1981.
13. Eckerman, D. A.; Hienz, R. D.; Stern, S.; Kowlowitz, V. Shaping the location of pigeon's peck: Effect of rate and size of shaping steps. J. Exp. Anal. Behav. 33:299–310; 1980.
14. Elsner, J.; Alder, S.; Zbinden, G. Interaction between ethanol and caffeine in operant behavior of rats. Psychopharmacology (Berl.) 96:194–205; 1988.
15. Emmett-Oglesby, M. W.; Mathis, D. A.; Moon, R. T. Y.; Lal, H. Animal models of drug withdrawal symptoms. Psychopharmacology (Berl.) 101:292–309; 1990.
16. File, S. E.; Baldwin, H. A.; Johnston, A. L.; Wilks, L. J. Behavioral effects of acute and chronic administration of caffeine in the rat. Pharmacol. Biochem. Behav. 30:809–815; 1988.
17. Finn, I. B.; Holtzman, S. G. Tolerance to caffeine-induced stimulation of locomotor activity in rats. J. Pharmacol. Exp. Ther. 231:542–546; 1986.
18. Frank, M. Response patterns of rat glossopharyngeal taste neurons. In: Denton, D. A.; Cughlan, J. P., eds. Olfaction and taste. New York: Academic Press; 1975:59–64.
19. Glowa, J. R. Some effects of d-amphetamine, caffeine, nicotine, and cocaine on schedule-controlled responding of the mouse. Neuropharmacology. 25:1127–1135; 1986.
20. Goldberg, S. R.; Prada, J. A.; Katz, J. L. Stereoselective behavioral effects of *N*6-phenylisopropyl-adenosine and antagonism by caffeine. Psychopharmacology (Berl.) 87:272–277; 1985.
21. 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.

22. 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.
23. Griffiths, R. R.; Bigelow, G. E.; Liebson, I. A.; O'Keeffe, M.; O'Leary, R. N. Human coffee drinking: Manipulation of concentration and caffeine dose. J. Exp. Anal. Behav. 45:133-148; 1986.
24. Griffiths, R. R.; Brady, J. V.; Bradford, L. D. Predicting the abuse liability of drugs with animal drug self-administration procedures. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology. vol. 2. New York: Academic Press; 1979: 164-208.
25. Griffiths, R. R.; Evans, S. M.; Heishman, S. J.; Preston, K. L.; Sanneru, W. B.; Woodson, P. P. Low-dose caffeine discrimination in humans. J. Pharmacol. Exp. Ther. 252:970-978; 1990.
26. Griffiths, R. R.; Woodson, P. P. Reinforcing effects of caffeine in humans. J. Pharmacol. Exp. Ther. 246:21-29; 1988.
27. Griffiths, R. R.; Woodson, P. P. Caffeine physical dependence: A review of human and laboratory animal studies. Psychopharmacology (Berl.) 94:437-451; 1988.
28. Heppner, C. C.; Kemble, E. D.; Cox, W. M. Effects of food deprivation on caffeine consumption in male and female rats. Pharmacol. Biochem. Behav. 24:1555-1559; 1986.
29. Holtzman, S. G. Complete, reversible, drug-specific tolerance to stimulation of locomotor activity by caffeine. Life Sci. 33:779-787; 1983.
30. Holtzman, S. G. Discriminative stimulus properties of caffeine in the rat: Noradrenergic mediation. J. Pharmacol. Exp. Ther. 239:706-714; 1986.
31. Meisch, R. A. Ethanol self-administration: Infrahuman studies. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology. New York: Academic Press; 1977:36-85.
32. Meisch, R. A.; George, F. R.; Lemaire, G. A. Orally delivered cocaine as a reinforcer. Pharmacol. Biochem. Behav. 35:245-249; 1990.
33. Meliska, C. J.; Landrum, R. E.; Landurm, T. A. Tolerance and sensitization to chronic and subchronic oral caffeine: Effects on wheelrunning in rats. Pharmacol. Biochem. Behav. 35:477-479; 1990.
34. Modrow, H. E.; Holloway, F. A.; Carney, J. M. Caffeine discrimination in the rat. Pharmacol. Biochem. Behav. 14:683-688; 1981.
35. Samson, H. H. Initiation of ethanol-maintained behavior: A comparison of animal models and their implication to human drinking. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Advances in behavioral pharmacology: Neurobehavioral pharmacology. Hillsdale, NJ: Lawrence Erlbaum; 1987:221-248.
36. Samson, H. H.; Pfeffer, A. O.; Tolliver, G. A. Oral ethanol self-administration in rats: Models of alcohol-seeking behavior. Alcohol. Clin. Exp. Res. 12:591-598; 1988.
37. Schulte-Daxbroek, G.; Opitz, K. Increased caffeine consumption following chronic nicotine treatment in rats. IRCS Med. Sci. 9: 1062; 1981.
38. Snyder, S. H. Adenosine as a mediator of the behavioral effects of xanthines. In: Dews, P. B., ed. Caffeine: Perspectives from recent research. New York: Springer-Verlag; 1984:129-141.
39. Snyder, S. H. Adenosine as a neuromodulator. Annu. Rev. Neurosci. 8:103-124; 1985.
40. Vitiello, M. V.; Woods, S. C. Caffeine: Preferential consumption by rats. Pharmacol. Biochem. Behav. 3:147-149; 1975.
41. Wilson, M. C.; Schuster, C. R. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacologia 31:291-304; 1973.
42. Woolverton, W. L. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol. Biochem. Behav. 24:531-535; 1986.
43. Young, A. M.; Woods, J. H. Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. J. Pharmacol. Exp. Ther. 218:720-727; 1981.