Pharmacology Biochemistry & Behavior, Vol. 31, pp. 579–584. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Aversive Conditioning Properties of Caffeine in Rats

ELIZABETH S. STEIGERWALD, KENNETH W. RUSINIAK,[1]
DEBBIE L. ECKEL AND MICHAEL H. O'REGAN

Eastern Michigan University, Ypsilanti, MI 48197

Received 2 March 1988

STEIGERWALD, E. S., K. W. RUSINIAK, D. L. ECKEL AND M. H. O'REGAN. *Aversive conditioning properties of caffeine in rats.* PHARMACOL BIOCHEM BEHAV **31**(3) 579–584, 1988.—Four experiments tested the conditioning effects of caffeine. Flavor and place cues were paired with IP caffeine injections and followed by tests for cue preference. In Experiment 1A, saccharin was paired with 1.25, 5 or 20 mg/kg of caffeine. In Experiment 1B, caffeine was delivered 30 min before, 5 min before, or 30 min after saccharin. Dose- and time-dependent conditioned taste aversions were produced. In Experiment 2, a place and taste cue were paired simultaneously with 5 or 20 mg/kg of caffeine. Conditioned place and taste aversions developed at 20, but not at 5 mg/kg. In Experiment 3, a place cue alone was paired with 0, 5, or 20 mg/kg of caffeine; dose-dependent conditioned place aversions developed. In Experiment 4, place and taste cues were paired with control treatments: pH-buffered caffeine, purine or vehicle. Caffeine produced taste aversions whereas the purine and vehicle did not. These aversive conditioning effects of caffeine across a variety of situations, doses and temporal arrangements stand in contrast to results obtained with other psychoactive drugs, such as amphetamine and alcohol.

Caffeine Drug conditioning Stimulants Conditioned taste aversion Purine

PSYCHOACTIVE drugs may have both appetitive and aversive effects that depend on a variety of conditions, such as drug type, dose, timing, and stimuli available (4). For example, a high dose of ethyl alcohol may condition aversions for both flavor and place cues with which it has been paired, whereas a low dose may induce a preference for associated flavors with no apparent effect on place preference (15). In contrast, the stimulant amphetamine may condition an aversion and a preference simultaneously (10,25). Reicher and Holman (10) gave rats a 1.4 mg/kg dose of amphetamine paired simultaneously with a distinctive flavor and place cue. The rats developed an aversion for the flavor and a preference for the location that had been paired with the drug. Sherman, Roberts, Roskam and Holman (16) further demonstrated that amphetamine conditioning depended on temporal relationships. Amphetamine conditioned cue aversion and preference only when given within 2 hr of the stimulus presentation.

Caffeine is another widely used stimulant which produces many of the same behavioral and physiological effects as amphetamine. It enhances locomotor activity and may produce withdrawal responses (19,23). Caffeine can potentiate amphetamine-induced activity (1, 14, 21) and may also directly release catecholamines (2). In addition, caffeine and amphetamine produce substantial generalization when used as discriminative stimuli in drug discrimination studies (6,24). Thus, caffeine may activate many of the same neural mechanisms as amphetamine. The present study tested whether caffeine would produce conditioning effects similar to those of amphetamine. The experiments were based upon the paradigm employed by Holman and his collaborators in investigating the conditioning properties of a variety of drugs. Flavor and place cues were presented either alone or as a compound stimulus and paired with caffeine injections. After multiple pairings, animals were tested for cue preference. Experiment 1 examined the effects of caffeine paired with flavor cues alone. Experiment 2 tested the effects of caffeine paired with flavor and place cues presented as a compound stimulus. Experiment 3 tested the effects of caffeine paired with place cues alone. And Experiment 4 was directed at assessing whether nonspecific effects of caffeine treatment could support conditioning. Since caffeine is a behavioral stimulant with some similarities to amphetamine, it might be expected to produce a similar conditioning pattern: an aversion for taste, but a preference for place.

EXPERIMENT 1

To establish dose-response and time-response characteristics, caffeine injections were paired with saccharin in a common conditioned taste aversion paradigm.

METHOD

Subjects

The subjects were male albino Sprague-Dawley rats obtained from Harlan Sprague-Dawley, Indianapolis, IN. They weighed 290–320 g at the start of the experiment and were

[1]Requests for reprints should be addressed to Kenneth W. Rusiniak, Eastern Michigan University, Department of Psychology, Ypsilanti, MI 48197.

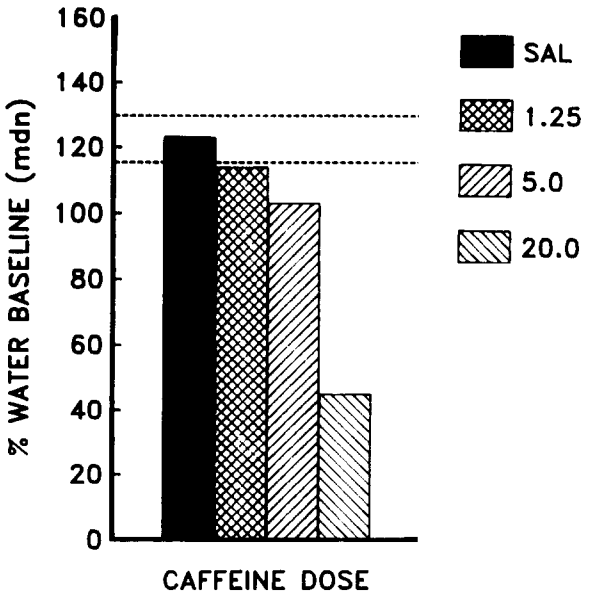

FIG. 1. Consumption of saccharin on test trials for Experiment 1A. Dashed lines indicate the range of consumption on the salt test. All scores are median percent of water baseline.

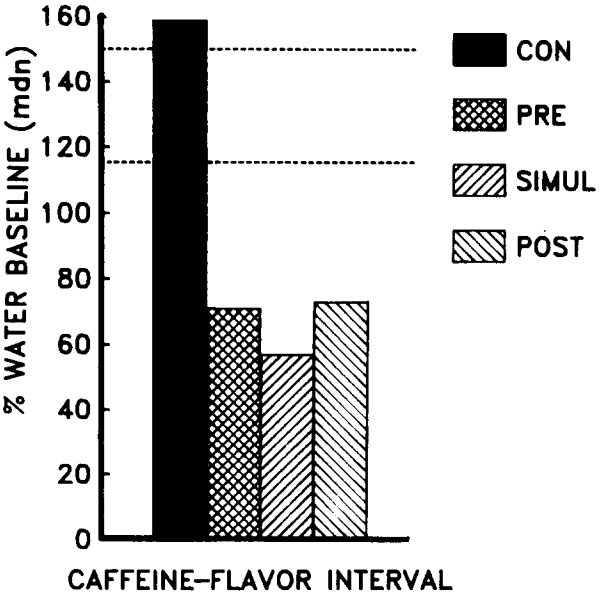

FIG. 2. Consumption of saccharin on test trials for Experiment 1B. Dashed lines indicate range of salt consumption.

housed in single cages in a colony room under constant illumination. They had free access to Purina Rat Chow; water intake was restricted as indicated below.

Procedure

Each day rats were handled and weighed. After one week, they were deprived of water and given 20 min access to tap water daily. After one week of adaptation to the drinking schedule, flavored fluids were substituted for tap water as indicated below; unflavored tap water was presented on all other days. On Days 1, 8 and 15, 0.2 M NaCl was given as a control flavor. On Days 3, 10 and 17, 0.1% saccharin water was presented in conjunction with caffeine treatments; IP caffeine injections were given on the first two saccharin trials (acquisition), but not on the last saccharin trial. Fluids were presented in a calibrated drinking tube to allow daily measurement of consumption.

Caffeine dose and the interval between saccharin and caffeine injection were varied in two separate experiments. In Experiment 1A, the dose-response study, four groups of rats (n=7 each) received an IP injection 5 min before saccharin presentation; three groups received 1.25, 5 or 20 mg/kg of pure base caffeine (Anhydrous Caffeine, No. C-0750, Sigma Chemical Company, St. Louis, MO) dissolved in water. The concentration of caffeine injections was adjusted (0.094, 0.375, 1.5 mg/ml) to keep injection volume constant across groups at 13.3 ml/kg. A fourth group received an equivalent volume of isotonic saline.

Experiment 1B, the time-response study, followed the same design and procedure except that dose was held constant at 20 mg/kg and the flavor-drug injection interval was varied. Groups (n=6 each) received caffeine injections 30 min before, 5 min before or 30 min after the saccharin trials. A control group received isotonic saline injections 5 min before saccharin; they also received caffeine injections 28 hr later on a water trial. Test scores were expressed as a percent of water baseline taken 2 days before the first flavor trial.

RESULTS AND DISCUSSION

Figure 1 shows results of the dose-response curve obtained in Experiment 1A. Water baselines ranged from 12.2–14.2 ml and did not differ among groups. Rats showed a reliable saccharin aversion after the 20 mg/kg dose, but not at any other dose. The 20 mg/kg group drank less saccharin than all other groups (p's<0.05, Ranks Test), which did not differ among one another. Furthermore, saccharin consumption in the 20 mg/kg group was lower than that for the salt control flavor, indicating a flavor-specific taste aversion. Although the 5.0 mg/kg group did not differ statistically as a group, a few rats did reduce consumption, suggesting a threshold effect.

The time-response curve of Experiment 1B is shown in Fig. 2; similar results were obtained. Water baselines ranged from 12.0–14.3 ml and did not differ among groups. Rats given caffeine within 30 min of saccharin presentation reduced consumption on the test relative to both the control group (p's<0.05, Ranks Test) and the control flavor (p's<0.05, Signed Ranks Test). Although consumption tended to be higher when there was a 30-min interval between saccharin and caffeine injection, neither group was significantly different from the simultaneous condition.

These results indicate that caffeine has some aversive properties that will produce a conditioned taste aversion when delivered within 30 min of saccharin consumption. The aversive effects appear to have a threshold close to 5 mg/kg and are strong at 20 mg/kg.

EXPERIMENT 2

Both appetitive and aversive effects of amphetamine have been demonstrated when the drug is paired simultaneously

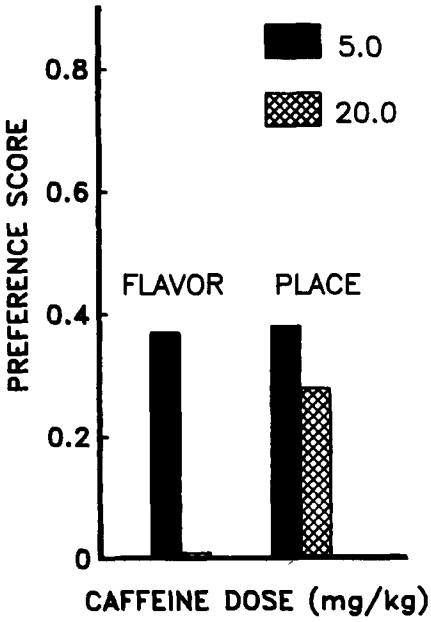

FIG. 3. Median preference scores for flavor and place cues in Experiment 2.

with place and flavor cues (10, 16, 25). Experiment 1 showed that caffeine, like amphetamine, would condition a flavor aversion. The present experiment tested whether caffeine, like amphetamine, would also condition a place preference. Following the methodology of Reicher and Holman (10), a distinctive taste and place were paired repeatedly with injections of caffeine and followed by preference tests for the taste and place cues. Both low and high doses of caffeine were tested since appetitive and aversive properties may be dose dependent.

METHOD

Subjects

The subjects were 16 male albino Sprague-Dawley rats weighing 350–400 g, and housed as in Experiment 1. Rats were deprived of food and maintained at 85% of free-feeding weight and had unlimited access to water except during the training and test trials.

Apparatus

Rats were trained in a rectangular plywood shuttlebox (40 cm wide × 40 cm high × 80 cm long) with a grid floor, a transparent Plexiglas front, and hardware cloth ceiling. A wooden wall with a 12.5×10 cm door divided the shuttlebox into two compartments of equal size. Walls on one side of the chamber were painted flat grey, and the floor was covered with a green rubber carpet (pool turf). The walls on the other side were painted with black and white vertical stripes 2.5 cm wide, and the steel grid floor was left uncovered. The lights in the training room were dimmed, so that each side of the chamber was illuminated equally. Two drinking solutions were used. A sour solution consisted of 2.5 ml of 1 M HCl and 12.5 g sucrose dissolved in 235 ml water. The second solution consisted of 5 g NaCl and 12.5 g sucrose in 232.5 ml water. The solutions were presented in graduated drinking tubes placed in a hole on either end of the shuttlebox.

TABLE 1

MEAN ml CONSUMPTION OF FLAVORS ON CAFFEINE AND SALINE TRIALS DURING TRAINING

	Low Dose		High Dose	
Trial	Caffeine	Saline	Caffeine	Saline
1	5.5	4.2	6.0	6.3
2	4.3	8.0	2.1	7.0
3	4.1	7.2	0.6	8.2
4	5.4	6.8	0.8	10.4
5	6.7	8.5	1.2	13.8
6	7.3	10.8	0.6	15.3

Procedure

Rats were handled for 30 min each day for 13 days before the experiment. Food deprivation began one week prior to training; rats were fed approximately 2 pellets of Purina Lab Chow per day to maintain 85% of free-feeding weight. Two days prior to training, all rats received a sham saline injection and preexposure to 30 ml of a 5% (w/v) sucrose solution.

For the experimental training phase, rats were assigned randomly to one of two groups (n=8 each); one group received 20 mg/kg and the other 5 mg/kg of caffeine 5 min before exposure to the cues. Control and drug trials alternated daily for six trials each. On control days, each rat was injected with isotonic saline and placed in one side of the shuttlebox for 20 min with access to one of the flavored solutions. On drug days, each rat was injected with caffeine and placed in the opposite side of the chamber and given access to the other flavored solution. Box side and flavor solution were equally counterbalanced within each drug dose condition. Rats were fed 30 min after each training session.

Place and flavor preference tests were given 2 days after the last drug trial. On test 1, rats were injected with saline and then given access to both sides of the chamber for 20 min. All tests started on the control side of the chamber and no flavored solutions were available. The amount of time spent on each side was recorded by an observer. Immediately after the location test, rats were returned to the home cage and given a 20-min 2-bottle preference test between the two flavored solutions; volume consumed was recorded. A second test conducted the following day was identical, except that caffeine was injected 5 min beforehand. Preference scores were calculated for place and flavor cues using drug (B) and control (A) times and volumes (B/A+B).

RESULTS AND DISCUSSION

Figure 3 shows median preference scores for the first test trial. Median total consumption (A+B) for the low dose was 15.4 ml and 12.0 ml for the high dose. The 20 mg/kg group showed a significant aversion for both flavor and location cues associated with caffeine ($p<0.05$, Sign Test). In contrast, the 5 mg/kg group developed an aversion for the flavor ($p<0.05$), but not for the place cue. Virtually identical results occurred on the second test which was conducted after caffeine injection. For simplicity, data are not shown. Table 1

shows ml consumption during the training trials; these data support the test results. The high dose group showed differential consumption after two trials. The low dose group showed a small but consistent reduction in drinking on drug relative to saline trials. These results indicate that caffeine conditioning produces a dose-dependent aversion for both flavor and exteroceptive cues.

EXPERIMENT 3

The first experiment showed that, like amphetamine, caffeine would induce an aversion for flavored fluids. The second experiment showed that, unlike amphetamine, caffeine produced an aversion for both places and tastes simultaneously paired with caffeine. However, animals may have developed a place aversion rather than preference due to the second-order conditioning of a place cue with a conditioned aversive taste. Furthermore, flavor cues may have potentiated an illness-induced aversion for the exteroceptive cue (3, 12, 13). To eliminate these possibilities, the experiment was repeated with place cues alone.

METHOD

Subjects

The subjects used were 24 male albino Sprague-Dawley rats, weighing approximately 350 g.

Procedure

Materials and methods were identical to those in Experiment 2, except that no flavored solutions were present during training or testing. Groups (n=8 each) received 0, 5 or 20 mg/kg IP caffeine injections.

RESULTS AND DISCUSSION

Figure 4 shows the median preference score for each group. There was no preference for either side of the chamber with either the 0 mg/kg or the 5 mg/kg dose. Rats given the 20 mg/kg dose showed a significant aversion for the drug-associated side of the chamber ($p<0.05$, Signed Ranks). Further, it should be noted that rats in the 0 mg/kg group had no inherent preference for either side of the chamber. A comparison of these results with those of Experiment 2 also suggests little potentiation of place aversion by flavor. Thus, these place aversions cannot be attributed to second-order conditioning, potentiation, or inherent side preference.

EXPERIMENT 4

A final experiment tested whether the aversive conditioning effects of caffeine could be attributed to some factor besides the specific pharmacological action of caffeine. One possibility is that pH differences of caffeine simply irritated the peritoneum. Similarly, injection of any foreign organic compound may produce nonspecific toxic malaise regardless of the specific pharmacology, since it is well-known that a wide variety of compounds will produce conditioned taste aversions (5). Therefore, we compared IP buffered caffeine, buffered purine, which is the unmethylated base compound for caffeine, or simply the buffer vehicle as conditioning agents.

METHOD

Procedure

All experimental features were identical to those in Experiment 2 except as follows. Injections of caffeine solution were buffered to a pH of 5.5 with sodium benzoate and citric acid. The pH was monitored using a pH meter (Corning Model 10). Group CAF received 20 mg/kg buffered caffeine IP (n=7); Group PUR (n=11) received an equivalent dose of equimolar buffered purine; Group BNZ (n=4) received an equivalent dose of the benzoate-citric acid vehicle.

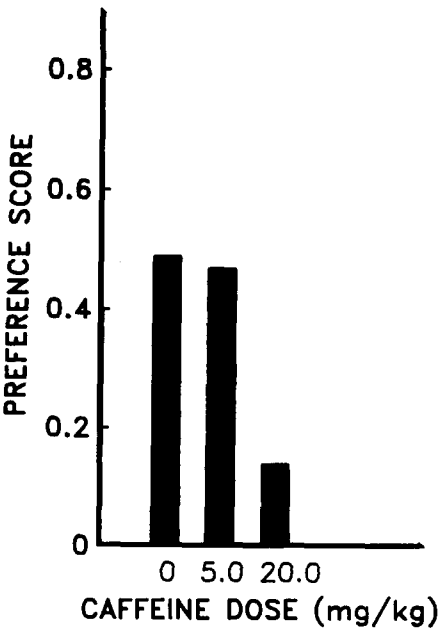

FIG. 4. Median preference scores for a place cue that had been paired with different caffeine doses in Experiment 3.

RESULTS AND DISCUSSION

Figure 5 shows results from Test 1. The only significant preference change occurred for flavors paired with caffeine. Group CAF demonstrated a significant taste aversion ($p<0.05$). Neither purine nor the benzoate-citric acid vehicle produced any significant changes. In fact, purine injection tended to enhance flavor preferences. None of the groups developed a significant place aversion, nor did the groups differ among one another. Results from Test 2 added no information. As a whole, these results suggest that nonspecific properties of the caffeine treatments are not sufficient to produce strong aversive conditioning.

GENERAL DISCUSSION

Several experiments tested the motivational properties of caffeine using a conditioning paradigm which has proven useful in separating appetitive and aversive components of drugs. Given that caffeine is a stimulant, we were interested in whether our results would follow the same pattern as seen with amphetamine, another stimulant. Amphetamine has been shown to condition an aversion for flavors but a preference for place cues (10, 16, 25). There was no evidence for any appetitive effects of caffeine in any of the experiments reported here; caffeine either produced aversion or no effect upon both flavor and place cues. In addition, controls for peritoneal irritation and nonspecific toxicity indicated that little if any of the aversive conditioning could be attributed to factors other than the pharmacologic action of caffeine.

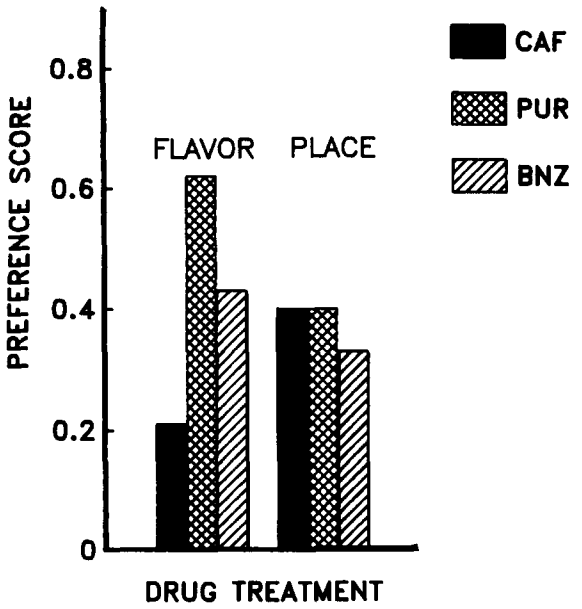

FIG. 5. Median preference scores from Experiment 4, comparing the conditioning effects of caffeine (CAF), purine (PUR), and the sodium-benzoate vehicle (BNZ). All test trials were conducted after saline treatment.

These results have implications for drug conditioning research. Flavor cue conditioning was a very sensitive index of caffeine effects, and indicated that the caffeine threshold was about 5 mg/kg when given as a bolus treatment to drug-naive subjects. In Experiment 1, rats that drank a mild saccharin flavor showed no significant aversion at 5.0 mg/kg. But in Experiment 2, rats that drank more intense, nutritive flavors, received repeated trials, and were given a two bottle test, demonstrated a significant aversion at 5 mg/kg. At 20 mg/kg strong averisons were produced across all experiments regardless of flavor, training and testing variations. These results demonstrate conditioned taste aversion at doses much lower than previously reported (22).

Place cue conditioning was less sensitive. The 5 mg/kg dose never produced any place aversion; the 20 mg/kg dose produced significant avoidance in Experiments 2 and 3, but not in Experiment 4, despite the similar training and testing conditions. This suggests that the place aversion conditioning threshold may be about 20 mg/kg, and that visceral irritation from unbuffered injections contributed to the development of the place aversions in Experiments 2 and 3. Interestingly, Lett (8) reported that lithium chloride, which produces gut-referred nausea, is more effective in producing flavor than place aversions, whereas gallamine, which has strong musculo-skeletal effects, has converse effects, producing stronger place than taste aversions. Possibly, conditioned flavor reactions may be more sensitive to interoceptive ingestional metabolic effects of drugs whereas conditioned place aversions are more sensitive to exteroceptive, musculo-skeletal and somatosensory drug action. In any case, the present experiments as a whole demonstrated aversive effects of caffeine across a variety of doses and experimental arrangements. Either caffeine produces uniform aversive effects, or the doses and temporal arrangements employed were not sufficient to demonstrate appetitive features.

There is some evidence that caffeine may have appetitive properties. Vitiello and Woods (17) gave rats forced continuous exposure to caffeine mixed in mocha flavoring for 14 days followed by a choice among water, mocha and caffeine. Rats that consumed 50 mg/kg or more per day demonstrated a modest preference for caffeine over water and an aversion for the mocha component. Our results replicate the aversion, but not the preference. It is possible that forced exposure to small self-administered doses of caffeine minimizes the aversive and maximizes the appetitive components. The present experimental conditions may have enhanced aversive and minimized appetitive components.

Caffeine and amphetamine are both stimulants with some common behavioral and physiological effects. Both increase motor activity, produce sympathetic arousal, and suppress appetite (9, 11, 18). Caffeine pretreatment may either enhance or inhibit many of the effects of amphetamine (1, 14, 21). And drug discrimination studies indicate substantial generalization between the two drugs (6,24). However, there are important differences and asymmetries as well. For although caffeine pretreatment affects amphetamine-induced reactions, amphetamine pretreatment does not affect caffeine-induced reactions (20). And the drug discrimination studies report substantial, but far from complete, generalization (6,24). In addition, informal observations of caffeine-treated rats in the present study also suggest that stereotypical behavior patterns are different. The caffeine-treated rats rarely demonstrated the well-reported amphetamine-induced sniffing, gnawing and grooming; instead, they demonstrated piloerection, walking on their toes with arched backs and heightened activity typical of disgust reactions. In contrast to amphetamine, which is thought to directly activate catecholamine systems (11), caffeine may have a variety of actions. Caffeine may alter cyclic-AMP metabolism via its phosphodiesterase inhibitor action (7), thereby producing abnormal visceral autonomic activity to produce aversive effects. Caffeine may also enhance turnover in a variety of catecholamine and dopamine systems; dopaminergic drugs such as apomorphine and amphetamine are well-known aversive conditioning agents. Finally, caffeine is a potent adenosine receptor blocker (7); the behavioral role of adenosine receptors in conditioning processes is not clear at this time.

ACKNOWLEDGEMENTS

This research was supported by EMU graduate school research fund awards to K.W.R. and Merlyn C. Minick of EMU. E.S.S., D.L.E. and M.H.O. are presently at Wayne State University in the departments of Psychology, Industrial Toxicology and Physiology, respectively. We thank C. Rickelman for typing the manuscript and Merlyn Minick and Sylvia Von Kluge for helpful suggestions.

REFERENCES

1. Anden, N. E.; Jackson, D. M. Locomotor activity stimulation in rats produced by dopamine in the nucleus accumbens: Potentiation by caffeine. J. Pharm. Pharmacol. 27:666–670; 1975.

2. Berkowitz, B. A.; Tarver, J. H.; Spector, S. Release of norepinephrine in the central nervous system by theophylline and caffeine. Eur. J. Pharmacol. 10:64–71; 1970.

3. Best, M. R.; Brown, E. R.; Sowell, M. K. Taste-mediated potentiation of noningestional stimuli in rats. Learn. Motiv. 15:244–258; 1984.
4. Eikelboom, R.; Stewart, J. Conditioning of drug-induced physiological responses. Psychol. Rev. 89:507–528; 1982.
5. Gamzu, E. The multifaceted nature of taste-aversion-inducing agents. Is there a single common factor. In: Barker, L. M.; Best, M. R.; Domjan, M., eds. Learning mechanisms in food selection. Waco, TX: Baylor University Press; 1977:477–509.
6. Holloway, F. A.; Michaelis, R. C.; Huerta, P. L. Caffeine-phenylalanine combinations mimic the amphetamine discriminative cue. Life Sci. 36:723–730; 1985.
7. Katz, J. L.; Goldberg, S. R. Psychomotor stimulant effects of caffeine alone and in combination with an adenosine analogue in the squirrel monkey. J. Pharmacol. Exp. Ther. 242:179–187; 1987.
8. Lett, B. T. The painlike effect of gallamine and naloxone differs from sickness induced by lithium chloride. Behav. Neurosci. 99:145–150; 1985.
9. Rall, T. W. Central nervous system stimulants, the xanthines. In: Goodman-Gilman, A.; Goodman, L. S.; Gilman, A., eds. The pharmacological basis of therapeutics. New York: MacMillan; 1980:592–607.
10. Reicher, M. A.; Holman, E. W. Location preference and flavor aversion reinforced by amphetamine in rats. Anim. Learn. Behav. 5:343–346; 1977.
11. Robinson, T.; Becker, J. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11:157–198; 1986.
12. Rusiniak, K. W.; Hankins, W. G.; Garcia, J.; Brett, L. P. Flavor-illness aversions: Potentiation of odor by taste in rats. Behav. Neural. Biol. 17:1–17; 1979.
13. Rusiniak, K. W.; Palmerino, C. C.; Forthman, D. L.; Rice, A. G.; Garcia, J. Flavor-illness aversions: Potentiation of odor by taste with toxin but not shock. J. Comp. Physiol. Psychol. 96:527–539; 1982.
14. Schechter, M. D. Caffeine potentiation of amphetamine: Implications for hyperkinesis therapy. Pharmacol. Biochem. Behav. 6:359–361; 1977.
15. Sherman, J. E.; Hickis, C. F.; Rice, A. G.; Rusiniak, K. W.; Garcia, J. Preferences and aversions for stimuli paired with ethanol in hungry rats. Anim. Learn. Behav. 11:101–106; 1983.
16. Sherman, J. E.; Roberts, T.; Roskam, S. E.; Holman, E. W. Temporal properties of the rewarding and aversive effects of amphetamine in rats. Pharmacol. Biochem. Behav. 13:597–599; 1980.
17. Vitiello, M.; Woods, S. C. Caffeine: Preferential consumption by rats. Pharmacol. Biochem. Behav. 3:147–149; 1977.
18. Weiner, N. Norepinephrine, epinephrine and the sympathomimetic amines. In: Goodman-Gilman, A.; Goodman, L. S.; Gilman, A., eds. The pharmacological basis of therapeutics. New York: McMillan; 1980:138–175.
19. White, B. C.; Lincoln, C. A.; Pearce, N. W.; Reed, R.; Vida, C. Anxiety and muscle tension as consequences of caffeine withdrawal. Science 209:1547–1548; 1980.
20. White, B. C.; Haswell, K. L.; Kassab, C. D.; Harkins, D., Jr.; Crumbie, P. M. Caffeine reduces amphetamine-induced activity in asymmetrical interaction. Pharmacol. Biochem. Behav. 20:387–389; 1984.
21. White, B. C.; Keller, G. E., III. Caffeine pretreatment: Enhancement and attenuation of d-amphetamine-induced activity. Pharmacol. Biochem. Behav. 20:383–386; 1984.
22. White, B. C.; Mason, F. D. Caffeine-induced taste aversion and mimetic responses. Pharmacol. Biochem. Behav. 23:515–518; 1985.
23. White, B. C.; Simpson, C. C.; Adams, J. E.; Harkins, D., Jr. Monoamine synthesis and caffeine-induced locomotor activity. Neuropharmacology 17:511–513; 1978.
24. Winter, J. C. Caffeine-induced stimulus control. Pharmacol. Biochem. Behav. 15:157–159; 1981.
25. Wise, R. A.; Yoekel, R. A.; DeWitt, H. Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science 191:1273–1274; 1976.