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Effects of Acute and Chronic Administration of Caffeine on Schedule Dependent and Schedule Induced Behavior[1]

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WAYNER, M. J., F. B. JOLICOEUR, D. B. RONDEAU AND F. C. BARONE. *The effects of acute and chronic administration of caffeine on schedule dependent and schedule induced behavior.* PHARMAC. BIOCHEM. BEHAV. 5(3) 343–348, 1976. – The effects of caffeine (3.125, 6.25, 12.5, 25, 50, and 100 mg/kg) on lever pressing, schedule induced licking and water consumption induced by a fixed interval 1 min schedule were studied. Changes in these dependent variables were assessed when animals were reduced to 80% of their initial body weight by partial food deprivation and when body weights recovered after the animals were returned to conditions of ad lib feeding. Results indicate differential effects of the drug between animals at 80% body weight and when they are permitted to recover. Tolerance was examined for a single large dose only for the same dependent variables in animals at 80% body weight.

Caffeine Schedule induced polydipsia Adjunctive drinking Licking Drinking
Schedule dependent behaviors Lever presses

CAFFEINE is a widely abused drug in the sense that it is self-administered indiscriminately by many people. Some general pharmacological effects of caffeine seem to be well established [2,4]. Heart rate, muscle contraction, gastric secretion and respiration tend to be elevated with some tolerance developing. Caffeine also has a diuretic action due to an increased rate of sodium and chloride excretion. At the level of the central nervous system, caffeine stimulates the activity of the cortex and medulla and increases reflex excitability. On the cellular level, caffeine inhibits the enzyme cyclic nucleotide phosphodiesterase that converts 3′, 5′ adenosine monophosphate to 5′ adenosine monophosphate. This fact could account for the widespread physiological changes produced by the drug. Investigations on behavioral changes produced by caffeine have been relatively scarce in comparison with other centrally active agents and have been concentrated primarily on the enhancing effects of the drug on locomotor activity [1,6]. Few studies have dealt with the effects of caffeine on schedule dependent behaviors [3,5] and to this date the possible effects of the drug on schedule induced behavior have not been investigated.

The general purpose of this study was to investigate the effects of several doses of caffeine administered intraperitoneally on schedule dependent lever pressing and schedule induced hyperdipsia. Specifically, the effects of the drug were assessed in terms of lever pressing, schedule induced licking, and water consumed on a fixed interval 1 min generator schedule in rats partially food deprived to 80% body weight and for the same dependent variables in the same test chamber when body weight recovered following a return to ad lib feeding. Tolerance to the drug for a single dose for the same dependent variables when animals were at 80% body weight and for the same generator schedule was investigated. Results indicate differential effects between animals at 80% body weight and when they are permitted to recover. Some tolerance was observed.

EXPERIMENT 1

The purpose of Experiment 1 was to measure the effects of 6 doses of caffeine – 3.125, 6.25, 12.5, 25, 50, and 100 mg/kg – on lever pressing, schedule induced licking, and water consumption in a 1 hr test session when animals were at 80% body weight due to partial food deprivation. Animals were subjected to a fixed interval 1 min food reinforcement schedule in a standard test chamber. Doses of caffeine were selected on the basis of previously published data on locomotor activity [6].

METHOD

Animals

Six male hooded rats were selected from our colony and

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placed in individual living cages. Their body weights were 296, 300, 301, 311, 331, and 335 g.

Procedure

After a 10 day period of adaptation, animals were reduced to 80% of ad lib feeding body weights by gradually restricting daily rations of food. Water was continuously available. Water intakes and body weight were recorded daily. Following 3 days of training to lever press for 45 mg Noyes pellets on a continuous schedule of reinforcement, animals were tested daily for 1 hr on a fixed interval 1 min generator schedule. The test chamber consisted of a standard LVE 1469 medium size test cage and matching sound attenuating cubicle with a lever and pellet dispensing mechanism. A food cup, delivery mechanism, test lights and lever were mounted in the standard fashion on one wall as provided by the manufacturer. A glass insulated stainless steel ball point drinking spout attached to a graduated eudiometer tube was placed in the center of the adjacent wall of the test cage, 4.0 cm above the grid floor and protruded 1.5 cm into the cage. Total number of licks and presses were recorded and amount of water consumed in ml during the daily 1 hr session was measured.

After lever press rate and schedule induced hyperdipsia stabilized, a series of intraperitoneal injections was initiated. Injections were administered every other day, 40 min prior to the test session. First the animals received five 0.9% saline injections. Results on the last 3 days of saline injection constituted the predrug baseline condition. The following doses of caffeine were then administered: 3.125, 6.25, 12.5, 25, 50, and 100 mg/kg. The drug was dissolved in 0.9% saline. The order of administration of the 6 doses varied for each animal. Finally, three 0.9% saline injections were administered and constituted the postdrug baseline condition.

RESULTS

Data were analyzed by means of single factor ANOVAs having repeated measures. One analysis was carried out for each of the three dependent variables, total number of lever presses and licks and water consumed in ml during the 1 hr sessions. Eight levels of the factor were included in each analysis; predrug baseline, each of the 6 doses of caffeine, and post drug baseline. All main effects were significant: lever presses, $F(7,35) = 20.64$, $p<0.01$; licks, $F(7,35) = 5.23$, $p<0.01$; and water consumed, $F(7,35) = 31.39$, $p<0.01$. Post hoc Dunnett tests were then performed for each dependent variable. In each case the predrug baseline condition was considered as the control treatment for comparisons with all the drug doses and post drug baseline condition. These tests revealed that 100 mg/kg was the only dose of caffeine which differed significantly from control treatments ($p<0.05$). No difference was found between the pre- and postdrug baseline data. Therefore, the major effects of caffeine were to decrease lever pressing, licking, and consumption of water at the highest dose. The effects are illustrated in Fig. 1 where the mean number of presses (thin continuous line), mean number of licks (solid points connected by a solid line), and mean water consumed in ml (solid points connected by a broken line) for all animals are presented as a function of the predrug baseline data (mean of the last three precaffeine injections) and the 6 doses of caffeine administered. Mean numbers of pellets consumed during the 1 hr sessions are given in Table 1, Experiment 1. A one-way ANOVA was performed and no significant differences were found. Therefore, the decreases in drinking and licking cannot be attributed to a decrease in the number of pellets consumed. The fact that the pre- and postdrug baseline data did not differ indicates that there was no overall change in responding during the course of

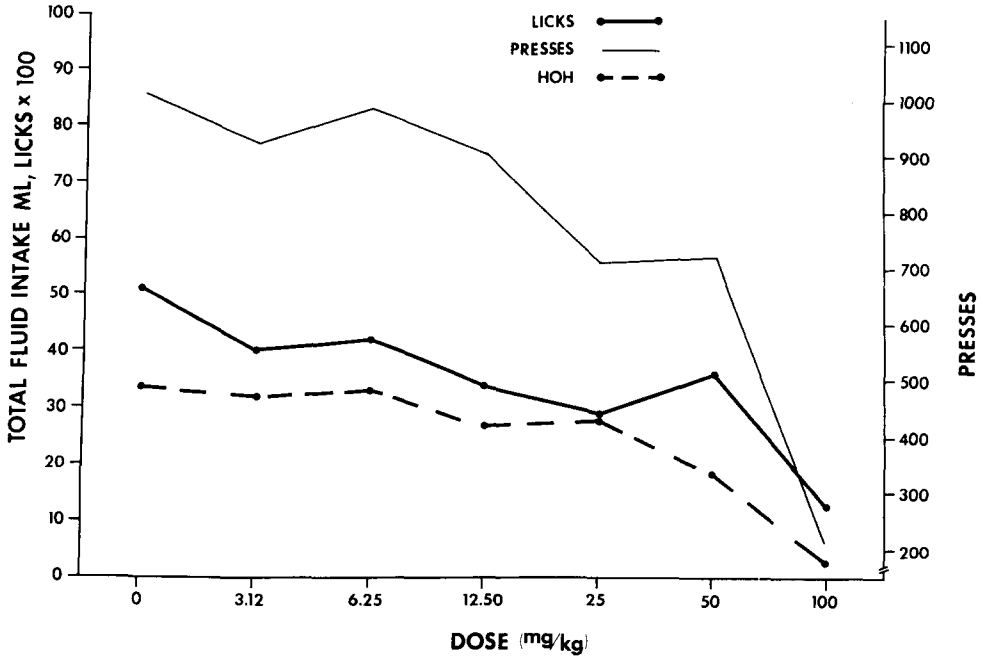

FIG. 1. Mean number of presses, licks and mean water consumed in ml for the 6 animals in Experiment 1 presented as a function of the predrug baseline data and the 6 doses of caffeine administered.

TABLE 1

MEAN ± S.E. NUMBER OF PELLETS CONSUMED DURING 1 HR SESSIONS ON INJECTION DAYS OF EXPERIMENTS 1 AND 2

Doses (mg/kg)	Experiment 1 (Reduced Weight)	Experiment 2 (Ad lib Weight)
3.125	58.1 ± 1.4	42.3 ± 12.5
6.25	58.9 ± 2.0	47.6 ± 5.9
12.5	58.5 ± 1.2	42.6 ± 8.0
25.0	57.8 ± 1.4	42.0 ± 4.3
50.0	57.3 ± 1.9	38.6 ± 10.3
100.0	47.8 ± 17.2	19.8 ± 10.3
Baseline 0.9% NaCl	58.7 ± 1.2	40.0 ± 10.2

TABLE 2

MEAN ± S.E. HOME CAGE WATER CONSUMPTION IN ML ON INJECTION DAYS OF EXPERIMENTS 1 AND 2

Doses (mg/kg)	Experiment 1 (Reduced Weight)	Experiment 2 (Ad lib Weight)
3.125	25.7 ± 2.6	36.5 ± 1.4
6.25	25.0 ± 4.7	39.7 ± 2.2
12.5	25.7 ± 2.6	39.5 ± 2.2
25.0	29.0 ± 5.3	38.8 ± 1.9
50.0	30.7 ± 6.8	44.7 ± 2.4
100.0	35.5 ± 5.7	45.5 ± 2.8
Baseline 0.9% NaCl	22.5 ± 2.1	40.8 ± 2.3

the experiment which could be attributed to the drug or other factors.

The mean home cage water consumption and standard errors for pre- and postsaline baselines and on caffeine injection days are included in Table 2, Experiment 1. A one way ANOVA with repeated measures revealed significant differences, $F(7,35) = 3.24$, $p<0.01$. A post hoc Dunnett test indicated that only the 2 highest doses, 50 and 100 mg/kg, produced significant increases in home cage intakes as compared to the predrug baseline data ($p<0.05$). Pre- and postdrug baseline intakes did not differ.

EXPERIMENT 2

The purpose of this experiment was to examine the effects of the same 6 doses of caffeine – 3.125, 6.25, 12.5, 25, 50, and 100 mg/kg – on the same dependent variables in the same animals utilized in Experiment 1 but after they had recovered body weight following a return to ad lib eating. The nature of adjunctive drinking under these conditions and the methods involved to produce it have been described elsewhere [7]. In essence, when animals recover predeprivation body weights under ad lib eating conditions, they are then returned to the identical test chamber for 1 hr test sessions every day. Therefore, the effects of the drug are assessed in relatively normal animals with a built-in predisposition to respond in certain ways. Thus, drug effects are not confounded by food deprivation. Results indicate a more complex effect of caffeine than resulted in Experiment 1.

METHOD

Animals

The same 6 animals after completion of Experiment 1 were utilized in this experiment.

Procedure

Following the termination of the first experiment animals were brought back to their ad lib feeding weight over a period of 6 days by gradually increasing their daily ration of food. At the end of this period body weights were 374, 362, 355, 396, 372, and 417 g. Animals were then tested again for 60 min daily test sessions at their free feeding weights. The experimental chamber, pellet delivery mechanism, drinking spout, and generator schedule were identical to that utilized in Experiment 1. When lever presses and schedule induced hyperdipsia had stabilized under these conditions over a period of 12 days, a new sequence of injections was initiated. Injection procedures were the same as those utilized in the first experiment; that is, animals received intraperitoneal injections every other day, 40 min before the daily test session. Again the last 3 of the 5 precaffeine 0.9% saline injections constituted the predrug baseline condition. Following the administration in a non-systematic order of the same 6 doses of caffeine, animals received three 0.9% saline injections which comprised the postdrug baseline condition.

RESULTS

The same statistical procedures as described in Experiment 1 were applied to the data of the present experiment. All main effects were significant: lever presses, $F(7,35) = 12.33$, $p<0.01$; licks, $F(7,35) = 7.01$, $p<0.01$; and water consumed, $F(7,35) = 9.04$, $p<0.01$. Post hoc Dunnett tests revealed that the 3.125 and 100 mg/kg doses of caffeine differed significantly from control treatments ($p<0.05$). No other dose related differences were found and the pre- and postdrug baseline conditions did not differ significantly from each other. Under the condition of the present experiment the effect of caffeine was twofold; it increased pressing and licking and water consumption at the smallest dose and it decreased the same behaviors at the highest dose. This is illustrated in Fig. 2 where the mean number of presses (thin continuous line), mean number of licks (solid points connected by a solid line), and mean water consumed in ml (solid points connected by a broken line) are presented as a function of the predrug baseline data (mean of the last three pre caffeine saline injections) and the 6 doses of caffeine. Mean numbers of pellets consumed during the 1 hr sessions are included in Table 1, Experiment 2. A one-way ANOVA revealed a significant main effect, $F(6,30) = 8.46$, $p<0.01$. Post hoc Dunnett tests indicated that 100 mg/kg of caffeine produced a significant decrease in the number of pellets consumed when compared to the predrug baseline condition. Therefore, one cannot conclude that the increases in licking and drinking produced by the highest dose of the drug are attributable to changes in the number of pellets consumed. However, the decreases in licking and drinking under these conditions are associated with a decrease in number of pellets consumed.

The mean home cage water consumption and standard errors for pre- and postsaline baselines and on caffeine injection days are included in Table 2, Experiment 2. A

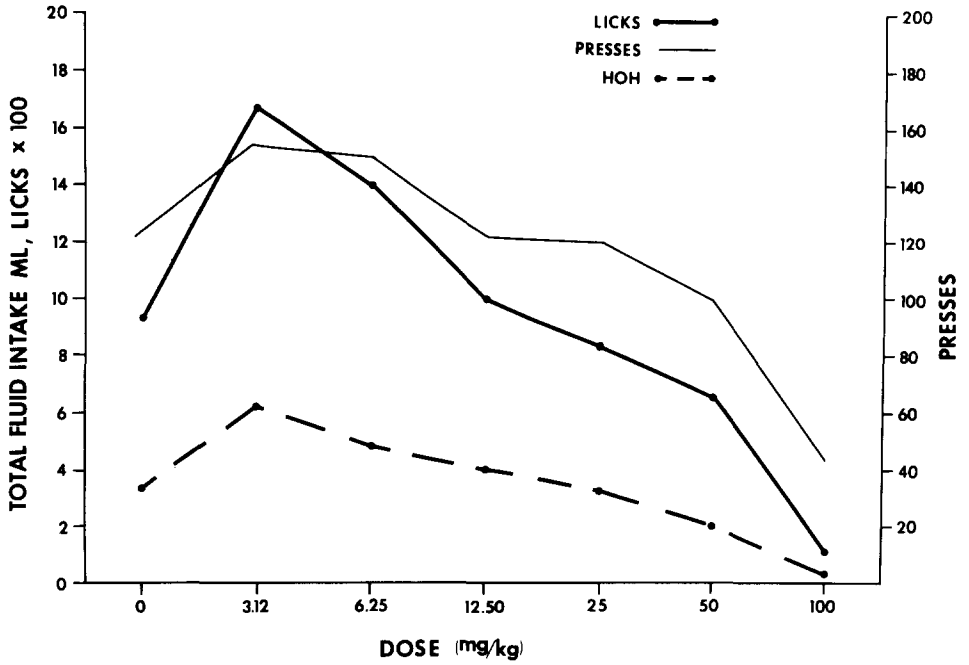

FIG. 2. Same as Fig. 1 except for Experiment 2.

one-way ANOVA with repeated measures revealed significant differences, $F(7,35) = 3.83$, $p<0.01$. A post hoc Tukey A test indicated increases in home cage water consumption on the two largest dose injection days, 50 and 100 mg/kg when compared to the smallest dose injection day, 3.125 mg/kg. No differences were observed between the baseline conditions and any doses of caffeine.

EXPERIMENT 3

Since the highest dose of caffeine seemed to be most effective when it was injected prior to the other doses in some of the animals of the previous experiments, the following experiment on behavioral tolerance to the effects of caffeine was carried out. Specifically, the highest dose of caffeine was administered every other day for a total of 8 administrations in 4 different animals under the conditions of Experiment 1. Results indicate decreasing effects with repeated administration of the drug.

METHOD

Animals

Four male hooded rats, 300–340 g in weight, were selected from our colony and placed in individual living cages.

Procedure

The test chamber, food deprivation procedure, training of the animals, and generator schedule were the same as described in the first experiment in this study. After animals had developed stable lever pressing rates and schedule induced polydipsia, they received intraperitoneal injections every other day, 40 min before the daily session. The following sequence of injections was given: five 0.9% saline injections; 8 administrations of a 100 mg/kg dose of caffeine; and three 0.9% saline injections. Results on the last 3 precaffeine saline days and on the three postcaffeine saline days constituted the pre- and postdrug saline baseline conditions.

RESULTS

Single factor ANOVAs having repeated measures were carried out on the data collected on each of the three dependent variables, lever pressing, schedule induced licking and water consumption in ml during the 1 hr sessions. Each analysis contained 10 levels of the factor: the predrug baseline condition, the 8 consecutive administrations of 100 mg/kg of caffeine and the postdrug baseline condition. All main effects were significant: lever pressing, $F(9,27) = 9.37$, $p<0.01$; licks, $F(9,27) = 8.89$, $p<0.01$; and water consumed, $F(9,27) = 9.40$, $p<0.01$. Individual comparisons between the predrug baseline condition and each of the other treatments were then performed for each dependent variable by means of Dunnett's Tests. Lever pressing for the first, second, third, fourth, and fifth injections of caffeine was significantly depressed compared to the predrug baseline. The remainder of the injections did not differ significantly. For licking, only the first administration of the drug produced a significant decrease. Water consumption was significantly depressed by the first, second, third and fifth injections of the drug. The other injections, including the fourth, did not produce any significant differences. For all dependent variables, differences between the pre- and postdrug baseline conditions were not significant. These findings indicate that behavioral tolerance to 100 mg/kg of caffeine had developed after one administration for licking and after 5 injections for lever pressing and water consumption. These effects are illustrated in Fig. 3 where mean total number of lever presses (thin continuous line), mean total licks (solid points connected by a solid line) and mean amount of water

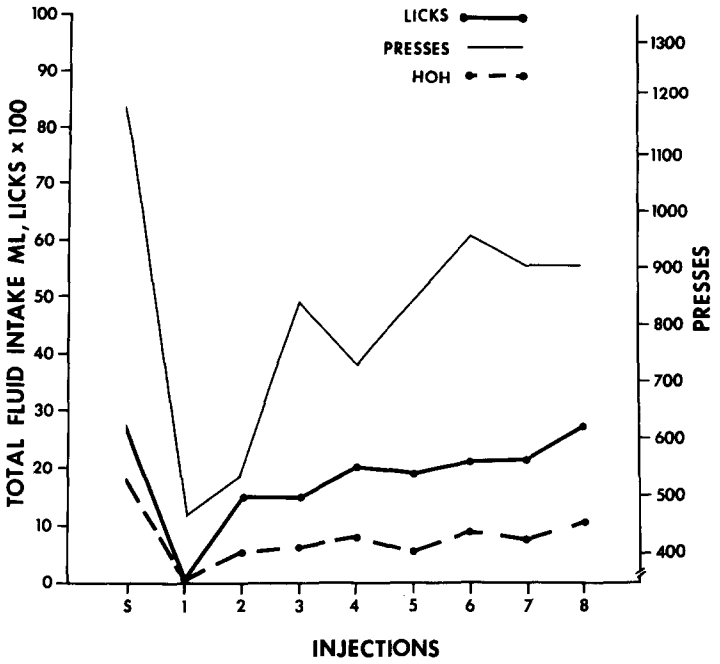

FIG. 3. Mean number of presses, licks and mean water consumed in ml for the 4 animals in Experiment 3 presented as a function of the predrug baseline data and the 8 injections of 100 mg/kg caffeine administered every other day.

consumed in ml (solid points connected by a broken line) are presented as a function of successive injection days.

The mean home cage water consumption and standard errors for pre- and postsaline baselines and on the eight 100 mg/kg caffeine injections days are included in Table 3. A one-way ANOVA with repeated measures revealed significant differences, $F(9,27) = 7.78$, $p<0.01$. A post hoc Dunnett test indicated that mean home cage water intakes were significantly increased over the predrug baseline following the first, fifth, sixth, and seventh administration of 100 mg/kg caffeine.

TABLE 3

MEAN ± S.E. HOME CAGE WATER CONSUMPTION IN ML ON INJECTION DAYS OF EXPERIMENT 3

Injections	Water Consumption
1	27.0 ± 2.0
2	21.3 ± 0.7
3	22.8 ± 4.5
4	21.3 ± 2.3
5	34.3 ± 2.7
6	29.3 ± 1.1
7	27.5 ± 2.1
8	22.5 ± 1.7
Baseline 0.9% NaCl	17.5 ± 1.4

DISCUSSION

The data on schedule dependent lever pressing and schedule induced licking and drinking when animals are at 80% body weight and on a food reinforcement schedule are affected little by caffeine except for a relatively high dose of 100 mg/kg. Such a high dose is equivalent to approximately 100 cups of coffee per day for the average person and represents an excessive dose. It is interesting that these differences in lever presses, licks and drinking were not associated with significant decreases in number of pellets consumed. The highest doses also produced increased drinking in the home cage, as illustrated in Table 2, which can probably be attributed to the diuretic effect of caffeine and reduced body fluids.

The effects of caffeine on lever presses, licks and water intakes when body weight recovers due to ad lib eating are different. It appears as if lever pressing, licking and drinking are more sensitive to caffeine under these conditions. All three measures were enhanced at the smallest dose of 3.125 mg/kg which is equivalent to 3 cups of coffee under normal conditions. Although the moderate doses seem to have no significant effects as compared to the baseline, the largest dose again reduced significantly lever presses, licks and water intakes. The increases in licks and water intakes which occur with the small dose of 3.125 mg/kg were not associated with a change in the number of pellets consumed; whereas the decreases which occurred with the largest dose of 100 mg/kg might be attributed to a significant decrease in the number of pellets eaten. The increases which occur at 3.125 mg/kg and the decreases at 100 mg/kg are not only reliable but represent significant changes which were also associated with decreases and increases in home cage water intakes as suggested by the results in Table 2. However, the only significant differences in home cage water intakes occur when the intakes at the two highest doses are compared with the lowest dose.

The tolerance effects of caffeine on schedule dependent

and schedule induced behaviors also appear to be different. All three measures were drastically decreased by the initial administration of the high dose of caffeine. This effect is similar and confirms the data obtained in the other two experiments. Tolerance as measured by schedule dependent lever pressing required 5 daily administrations before little or no effect of the drug was observed. Schedule induced licking was depressed significantly only following the first administration of caffeine. Drinking in terms of water consumption recovered after the third injection and no significant depression in intake occurred following the fourth administration. The decrease following the fifth administration is difficult to explain. Water consumption seems to vary somewhat independently of licking under these conditions. However, the differences between tolerance to caffeine as measured by lever presses and licks are obvious. Also, tolerance appears to develop readily to what seems to be a large dose of caffeine. The home cage intakes following successive daily administrations of this large dose of caffeine as indicated in Table 3 are difficult to interpret. The significant elevation following the first administration confirmed the observation in Experiment 1 but then significant increases do not occur again until the fifth, sixth and seventh administration. If increased home cage intakes are associated with increased urine volume due to the diuretic effect of caffeine then the possible interaction between drinking and a diuresis is impossible to determine without urine volume data.

These results confirm the conclusions of a previous study [8] and demonstrate that certain drugs have different effects when measured by schedule dependent and schedule induced behavior and when these behaviors are elicited at different body weights.

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