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Effects of Food Deprivation on Caffeine Consumption in Male and Female Rats

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HEPPNER, C. C., E. D. KEMBLE AND W. M. COX. *Effects of food deprivation on caffeine consumption in male and female rats.* PHARMACOL BIOCHEM BEHAV **24**(6) 1555–1559, 1986.—The effect of food deprivation on caffeine consumption was investigated in male and female rats utilizing two-bottle preference tests. During ad lib food and water access, proportional consumption of six increasingly concentrated caffeine solutions (0.01–0.125%) steadily declined as concentration increased with no sex differences. Across concentrations, females tended to ingest more mg/kg caffeine than males. Food deprivation increased both proportional and mg/kg caffeine consumption in both sexes. When returned to ad lib food, proportional, but not mg/kg, caffeine consumption returned to pre-deprivation levels. Consumption of a quinine solution (0.02%), comparable to the caffeine in two-bottle preference, declined somewhat during food deprivation. These results indicate that caffeine preference and mg/kg consumption are increased by food deprivation and that this effect does not result from increased preference for bitter tastes *per se*. Rather, the results suggest that increased caffeine intake during food deprivation is due to a specific interaction between reduced body weight and the drug. The results also suggest that the deprivation effect is somewhat weaker in females than males, perhaps due to sex differences in reactivity to caffeine.

Caffeine Food deprivation Two-bottle preference Quinine Rats Sex differences

FOOD deprivation schedules that substantially reduce body weight greatly increase intravenous and/or oral self-administration of ethanol [15,16], metholhexital [10], phencyclidine [4], amphetamine [9], ketamine [9], etonitazene [7], and cocaine [6]. Thus, although nicotine, methadone and THC intake may be exceptions [17,18], food deprivation is clearly an important determinant of intake of many psychoactive drugs in both monkeys and rats which seems to enhance the reinforcing properties of these drugs [10].

Although food deprivation increases self-administration by both oral and intravenous routes, the time course for the appearance and disappearance of increased oral intake is considerably longer than that for intravenous self-administration [8]. Among the important differences between these two routes (e.g., speed of drug action, nature of consummatory responses) which might contribute to the differences in their time course, the presence of salient taste stimulation during oral intake is an obvious candidate. Recently, Zeller, Berridge, Grill and Ternes [21] found that prior forced consumption of a bitter morphine solution in rats produced an apparent increase in its palatability. This shift was presumably mediated by the reinforcing properties of the drug. If other drugs (e.g., [4, 6, 7, 9, 10, 15, 16]) are presumed to have reinforcing properties for hungry animals [10], then similar palatability shifts may accompany the more gradual increase in their oral intake. Presumably, such gradual shifts would reflect pairing of a drug's taste with its reinforcing properties. It should be noted, however, that Carroll [8] found no increase in cocaine or phencyclidine drinking in food deprived rats. It is possible, however, that the anesthetic properties of these drugs interfered with taste in some way.

The present experiments examined caffeine preference and mg/kg ingestion in a two-bottle, drug-water choice test over a range of concentrations. Subsequently, the effect of food deprivation on caffeine intake was assessed. Food deprivation effects on consumption of a quinine solution, comparable to the caffeine in two-bottle reactivity, were also included to explore the effect of food deprivation on intake of a bitter-tasting solution. Two-bottle testing procedures were used throughout the experiments to prevent liquid deprivation due to low intake of some concentrations and to permit detection of any shifts in preference for the solutions. Since female rats exhibit a greater preference than males for some (e.g., [19,20]) but not all (e.g., [14]) tastes, both male and female rats were tested in these experiments.

[1]Requests for reprints should be addressed to Ernest D. Kemble or W. Miles Cox. The authors would like to thank Dr. M. E. Carroll for her helpful comments on an earlier version of this report.

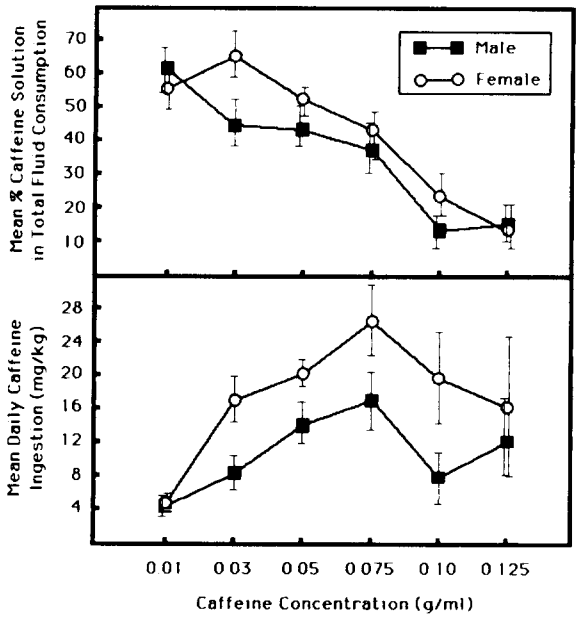

FIG. 1. Mean (±SEM) caffeine consumption as a percentage of total daily fluid intake for six caffeine concentrations in a g/ml (upper panel). Lower panel presents mean (±SEM) caffeine ingestion in mg/kg.

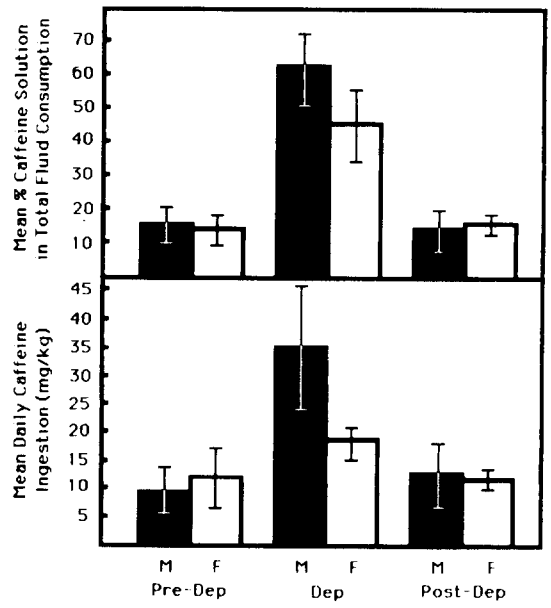

FIG. 2. Mean (±SEM) 0.10% caffeine consumption as a percent of total daily fluid intake prior to food deprivation (Pre-Dep), after 25% reduction in body weight (Dep), and after return to ad lib food (Post-Dep) by males (M) and females (F) is depicted in the upper panel. Lower panel presents mean (±SEM) caffeine ingestion in mg/kg.

EXPERIMENT 1A

Prior to studying food deprivation effects, it was important to examine levels of taste preference to various caffeine concentrations in nondeprived rats. Therefore, in the first experiment a wide range of caffeine solutions and water were presented in two-bottle preference tests.

METHOD

Subjects and Apparatus

Subjects were eight naive male (508–635 g) and eight naive female (334–415 g) rats supplied by the Holtzman Co. The rats were individually housed and tested in 23.0×38.0×23.0 cm cages adapted to hold two 100 ml graduated drinking cylinders. The animals had ad lib access to Purina Lab Chow throughout the experiment. The testing room was maintained at 20°C (±1.10°) with a 12 hr light/dark cycle.

Procedure

The rats were habituated to their cages and drinking tubes for seven days prior to testing. Both tubes were filled with tap water during this time. During the next 12 days the rats were given two days access to each of six increasingly concentrated caffeine solutions (0.01, 0.03, 0.05, 0.075, 0.10, and 0.125%, g/ml) in one tube and tap water in the second. All solutions were mixed in tap water and presented at room temperature. On each test day, fresh solutions were mixed and the position of the caffeine and water tubes reversed.

RESULTS

The results of this experiment are summarized in Fig. 1. The upper panel presents mean caffeine consumption as a percentage of total fluid intake averaged for two days access to each concentration. A repeated measures analysis of variance was utilized to examine sex differences (between subjects) and changes in proportional caffeine consumption across concentrations (within subjects). It can be seen that there was a steady decrease in proportional consumption of the solution as the concentration of caffeine increased, $F(5,70)=18.80$, $p<0.001$. Analysis of variance also revealed no significant sex differences, $F(1,14)=2.06$, and no sex by concentration interaction, $F(5,70)=1.25$. At the lowest concentration (0.01%), 12 of 16 rats drank more than 50% caffeine solution, suggesting a mild preference for this solution (Sign Test, $x=4$, $0.05<p<0.10$). Caffeine was clearly rejected at the higher concentrations with 15 of 16 rats drinking less than 50% caffeine solution at 0.10% and all rats drinking less than 50% at 0.125%.

Mean daily caffeine ingestion (mg/kg) at each concentration is depicted in the lower panel of Fig. 1. Caffeine consumption increased as its concentration increased from 0.01 to 0.075% but declined at 0.10%, $F(5,70)=5.55$, $p<0.001$. Overall, female rats tended to consume more caffeine than males, $F(1,14)=4.23$, $0.05<p<0.10$, but with no suggestion of a sex by concentration interaction ($F<1.0$).

EXPERIMENT 1B

Experiment 1B assessed the effect of food deprivation on caffeine consumption. For this experiment, a caffeine concentration (0.10%) was chosen which was consumed in small but reliable quantities by most (15 of 16) rats in Experiment 1A.

METHOD

Subjects and Apparatus

The animals from Experiment 1A served in this experiment. The testing cages and drinking tubes used in Experiment 1B were the same as those in Experiment 1A.

Procedure

Following Experiment 1A, and 5 days prior to Experiment 1B, the animals were given access to Purina Lab Chow and ad lib access to tap water in both tubes. At this point, the animals were given two days access to 0.10% caffeine solution and water to assess possible changes in reactivity to this solution as a result of their experience with it in Experiment 1A. Next, food deprivation was initiated. The animals' body weights were reduced to 75% (±3%) of ad lib value by restricted feeding during a 12-day period. Both drinking tubes contained tap water during this time. The subjects then received two days access to 0.10% caffeine and tap water. Following 14 days of ad lib food access, the rats received a final two-day test of caffeine consumption.

RESULTS

Proportional 0.10% caffeine consumption prior to food deprivation (Pre-Dep) in this experiment (Male, mean=15.11%; Female, mean=13.09%) did not differ reliably from that in Experiment 1A (Male, mean=12.54%; Female, mean=23.84%, $F<1.0$) with neither a sex difference nor sex by replication interaction ($F's<1.0$). Similarly, there was no significant change in mean daily 0.10% caffeine ingestion (mg/kg) from Experiment 1A (Male, Mean=7.86 mg/kg; Female, mean=19.64 mg/kg) to Experiment 1B (Male, mean=9.80 mg/kg; Female, mean=12.65 mg/kg; $F<1.0$). Although female rats tended to consume more caffeine than males, there was no overall sex difference, $F(1,14)=1.76$, and no sex by replications interaction, $F(1,14)=2.62$. Water consumption during ad lib food access (mean=56.4 ml) sharply declined at reduced body weight (mean=22.4 ml, $p<0.05$). Although females drank somewhat less than males under both ad lib (Male, mean=59.1 ml; Female, mean=53.6 ml) and food deprived conditions (Male, mean=26.8 ml; Female, mean=18.1 ml), there was no significant sex difference under either feeding regimen ($ps>0.10$).

The major findings of Experiment 1B are summarized in Fig. 2. Food deprivation sharply increased the proportional caffeine consumption (upper panel, Fig. 2) of both males and females, $F(1,14)=19.22$, $p<0.001$, with no reliable sex differences, $F(1,14)=1.59$, and no sex by deprivation interaction ($F<1.0$). Proportional consumption returned to Pre-Dep levels after 14 days ad lib access to food (Post-Dep) with no replication effect, sex difference, or sex by replication interaction (all $F's<1.0$).

Daily mg/kg caffeine ingestion (lower panel, Fig. 2) revealed a similar pattern of results. Food deprivation increased daily caffeine intake, $F(1,14)=7.60$, $p<0.05$. Although there was no overall sex difference ($F<1.0$), inspection of Fig. 2 suggests that male rats increased caffeine intake more dramatically than females during food deprivation. There was a more than threefold increase (9.80 to 35.15 mg/kg) in caffeine consumption by males but a more modest increase among females (12.64 to 18.31 mg/kg). Analysis of variance failed to reveal a significant sex by deprivation interaction, however, $F(1,14)=3.05$, $p>0.10$. After returning to ad lib food, the Post-Dep caffeine consumption of males (mean=13.02 mg/kg) increased somewhat over Pre-Dep levels (mean=9.80 mg/kg) while the Post-Dep intake of females (mean=12.06 mg/kg) declined from Pre-Dep levels (mean=12.65 mg/kg). Analysis of variance revealed a marginally significant sex by replications interaction, $F(1,14)=3.18$, $0.05<p<0.10$.

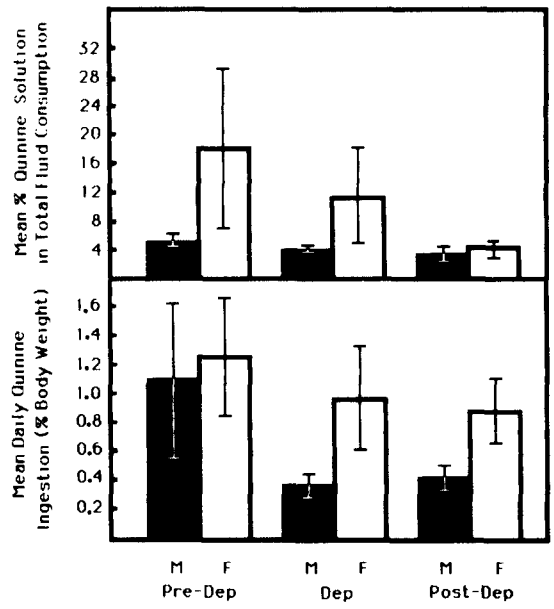

FIG. 3. Mean (±SEM) consumption of 0.02% quinine solution as a percent of total daily fluid intake prior to food deprivation (Pre-Dep), after a 25% reduction in weight (Dep), and following return to ad lib food (Post-Dep) by males (M) and females (F) in upper panel. Lower panel depicts quinine solution consumption as a percent of body weight.

EXPERIMENT 2

The results of Experiment 1B clearly revealed a substantial increase in proportional and mg/kg caffeine consumption during food deprivation. These results were consistent with previous reports of increased consumption (e.g., [7–9]) of various other psychoactive drugs during food deprivation. It remains unclear, however, what role the taste properties of caffeine may have played in the increased preferences for it. Thus, in Experiment 2 the effect of food deprivation on two-bottle consumption of a quinine solution was examined. A quinine concentration was selected which previous research [12] had shown to be rejected at levels similar to that of 0.10% caffeine solution in Experiment 1.

METHOD

Subjects and Apparatus

Subjects were eight naive male (385–457 g) and eight naive female (237–289 g) Holtzman rats, housed and tested in the same cages as those used in Experiment 1.

Procedure

The procedure closely followed that of Experiment 1B. The subjects were habituated to the cages and drinking tubes

(both containing water) for four days followed by two days of two-bottle preference testing with to a 0.02% (g/ml) quinine sulfate solution and water. Body weights were then reduced to 75% (±3%) of ad lib value by restricted food access for 10 days. The rats were weighed daily during this time. The subjects then received two further days of access to the quinine solution and tap water. The rats were then returned to ad lib food and water access for 10 days before receiving a final two-day test with the quinine solution and water.

RESULTS

Preliminary analysis compared proportional 0.10% caffeine consumption (mean=18.2%) by rats in Experiment 1B to 0.02% quinine consumption (mean=11.0%) under ad lib (Pre-Dep) food conditions. Mean proportional consumption for two days access was employed for these comparisons. Analysis of variance indicated no significant difference in consumption of the two solutions, $F(1,28)=1.10$, and no sex differences, $F(1,28)=2.73$, or sex by drug interaction, $F(1,28)=1.00$.

The major results of this experiment are summarized in Fig. 3. Quinine consumption as a percentage of total fluid intake (upper panel, Fig. 3) remained at low levels throughout this experiment with no suggestion of increased intake due to food deprivation ($F<1.0$). There was no sex difference, $F(1,14)=1.46$, and no sex by deprivation interaction ($F<1.0$).

Quinine solution consumption expressed as a percentage of body weight is summarized in the lower panel of Fig. 3. It can be seen that food deprivation tended to reduce quinine consumption relative to Pre-Dep levels, $F(1,14)=3.17$, $0.05<p<0.10$, with no suggestion of a sex difference or sex by deprivation interaction ($F's<1.0$). Although Post-Dep consumption tended to be lower than Pre-Dep, analysis of variance failed to reveal a significant replications effect, $F(1,14)=2.57$. There was no sex difference or sex by replications interaction ($F's<1.0$).

GENERAL DISCUSSION

Food deprivation clearly increased both proportional and mg/kg intake of caffeine solution in these experiments. This finding is thus consistent with other reports of increased self-administration of a wide range of pharmacological agents following food deprivation (e.g., [3, 4, 7, 8, 10, 15]). Taken together, these findings argue persuasively that food deprivation is a potent determinant of drug intake which is effective with a considerable range of drugs [8]. The fact that both two-bottle preference and daily caffeine ingestion were increased by food deprivation also suggests that increased self-administration was accompanied by increased palatability of the solution. Since consumption of a quinine solution, which was comparable to the caffeine solution in two-bottle reactivity, was not increased by food deprivation, it also seems clear that increased caffeine consumption did not result from a simple deprivation—induced increase in the palatability of bitter solutions. In this connection, it is interesting to note that quinine consumption is temporarily elevated following extended oral intake of phencyclidine analogs during food deprivation [4]. Since the phencyclidine analogs and quinine solution were similar in bitterness (Carroll, personal communication), it seems possible that elevated quinine intake resulted from generalized reinforcing properties of its taste originally acquired by the pairing of the taste and reinforcing properties of phencyclidine. This explanation is generally consistent with the gradual decline in quinine intake reported by Carroll [4]. Since the rats in Experiment 2 had no prior exposure to psychoactive bitter-tasting solutions, food deprivation would not be expected to increase quinine consumption. Although the present experiments do not directly demonstrate conditioned reinforcing properties of taste, they are consistent with such an explanation.

Although food deprivation clearly increased both caffeine preference and consumption of females in Experiment 1B, their intake was somewhat elevated in Experiment 1A and they diverged from males in post-deprivation caffeine consumption. Since the sexes also differed substantially in body weight, direct comparisons are difficult. Others, however, have reported apparent sex differences in responsiveness to other drugs (e.g., [2,11]). Alternatively, it might be suggested that the differing reactivity of males and females to some tastes (e.g., [19,20]) extends to caffeine and thus accounts for the present data. If so, however, it is difficult to understand why there was no difference in proportional intake. Finally, sex differences in a variety of other nonreproductive behaviors such as responsiveness to food deprivation or aversive stimulation (see, [1] for review) may have contributed to the present results in some way. In any case, the present data also argue for a careful consideration of possible sex differences in deprivation-induced drug intake.

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