Pharmacology Biochemistry & Behavior, Vol. 4, pp. 591–599.

Comparative Effects of Various Naturally Occurring Cannabinoids on Food, Sucrose and Water Consumption by Rats

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(Received 20 February 1976)

SOFIA, R. D. AND L. C. KNOBLOCH. *Comparative effects of various naturally occurring cannabinoids on food, sucrose and water consumption by rats.* PHARMAC. BIOCHEM. BEHAV. 4(5) 591–599, 1976. – The effects of intraperitoneally injected Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN) and cannabidiol (CBD) were compared to d-amphetamine sulfate (d-AMP) on food and water consumption and intake of two different concentrations of sucrose solutions. Three groups of rats were given the following dietary regimens within a 6-hr feed period day: 1 – water and dry food; 2 – water, dry food and five percent sucrose solution; 3 – water, dry food and 20% sucrose solution. Food and water consumption were dramatically reduced by each test drug at feeding periods immediately following and in some instances up to 4 days after dosing in all 3 groups. However, sucrose consumption was much less affected by each cannabinoid, indicating a preference for sweet calories, whereas d-AMP had an equal anorexic action on both food and sucrose consumption. These data suggest for the first time in rats that a preference for sweet calories occurs during an overall anorexic effect of THC, CBN and CBD.

Δ^9-Tetrahydrocannabinol Cannabidiol Cannabinol d-Amphetamine SO_4 Consummatory behavior

THE anorexigenic effect of Δ^9-tetrahydrocannabinol (THC) following a single dose to rats has been well documented [5, 6, 7, 10, 12, 13, 14]. In addition, several of these same investigators have shown inhibitory effects for THC on water intake. More recently [15], it has been shown that food intake is markedly reduced immediately after 2.5 and 5.0 mg/kg of THC and also that this effect persisted even during the feeding period 24 hours later. These data on food consumption by rats following THC administration differ from the effects reported in humans. A body of folklore as well as controlled clinical investigations concerning the effect of marihuana on human appetite for food [1, 2, 3, 8] reveal increases in food intake with a special desire for sweet foods. In addition, it has been observed that a 28% increase in appetite occurred in dogs which were required to smoke 4 marihuana cigarettes a day for 3 months [9].

The purpose of the present investigation was to determine the effects of THC, cannabidiol (CBD), cannabinol (CBN) and d-amphetamine (d-AMP) on total caloric intake by rats which had access to food and sucrose solutions as sources of calories as well as water for six hours each day.

METHOD

Animals and Training

The animals used were 60 male albino rats (Sprague-Dawley strain obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts 01887 U.S.A.) weighing 135–175 g at the start of the training. Each rat was housed individually in standard cages (wire mesh floor with three sides of solid stainless steel with a wire mesh front) in a laboratory environment consisting of controlled illumination with 12 hr of light (6 a.m. to 6 p.m.) alternating with 12 hr of dark (6 p.m. to 6 a.m.), temperature regulated at 22 to 24°C and relative humidity 40 to 60%.

The 60 rats were equally divided into 3 groups. Each rat received its designated diet of dry food and fluid for a 6-hr period each day (9 a.m. to 3 p.m.), thus being trained to consume its daily caloric intake within this time interval. The diet consisted of 35.0 g of dry food (3.04 Kcal per g) and 160 ml of water in one bottle for each animal. The other bottle contained 160 ml of water for Group 1, of 5% sucrose solution (3.87 Kcal per g or 0.194 Kcal per ml) for Group 2, and of 20% sucrose solution (0.774 Kcal per ml) for Group 3. Food consumption and water and sucrose intake were measured daily. Drug tests were begun after a baseline period of 40 days.

Drugs. All drug doses were administered intraperitoneally (IP) in a volume of 1.0 ml/kg of body weight. The vehicles were undiluted propylene glycol (PG) for THC, CBD and CBN, as described earlier [16] and distilled water for d-AMP (prepared as the sulfate salt). All control injections contained the same volume of the vehicle.

Procedure

After baseline data were collected drug effects were

evaluated on a weekly basis. Body weight measurements and drug injections were made on Wednesday of each week at 9 a.m., immediately before the food and fluid were presented. Six-hour food, sucrose and water intake were measured on the day of injection and daily to determine acute drug effects as well as any carry-over effects. Not until baseline consumption was once again achieved was the next drug injection given, which was no sooner than seven days after the previous one. The same dose of drug or vehicle being tested was administered to all rats in each group on a given injection day.

Various drug treatments were compared with respective vehicle controls or with other conditions for each animal. Therefore, the data were analyzed by the Student's t test for paired comparisons. Statistical significance was based on the standard error of the differences between the conditions which were compared. Additional comparisons were made between different groups, in some cases using the difference scores and standard errors of the difference scores for calculating the Student's t test for independent groups.

RESULTS

Baseline Data

Table 1 reveals that mean food consumption for rats in Group 1, whose only source of calories was dry laboratory chow, was 18.2 g during the last 10 days of the baseline period. Moreover, food consumption was dramatically reduced when sucrose solutions were presented as alternate sources of calories. When a 5% sucrose solution was added to the diet (Group 2), food consumption decreased to a mean of 12.5 g, or 32.4% ($p<0.001$) when compared to Group 1 rats, thus accounting for 69.0% of their total caloric intake. Food consumption dropped an additional 31.3% to 8.6 g in those rats (Group 3) who were maintained on a 20% sucrose solution plus dry food. In these animals only 44.6% of their caloric intake was due to food. The rats in Groups 2 and 3 obtained most of their fluid from the sucrose solutions. However, data presented in the next to last row of Table 1 show close similarity among the three experimental groups in mean total caloric intake (55.5 to 59.9 Kcal). Hence, determination of drug effects on total caloric intake as well as source of calories can be effectively evaluated in these groups of animals.

TABLE 1

BASELINE* FOOD CONSUMPTION AND SUCROSE, WATER AND TOTAL CALORIC INTAKE FOR EACH EXPERIMENTAL GROUP DURING THEIR SIX-HOUR FEEDING PERIOD

Parameter	Group I† Water	Group II† 5% Sucrose	Group III† 20% Sucrose
Food Consumption			
g	18.2±0.47	12.5±0.29	8.6±0.43
(Kcal)	(55.5±1.43)	(38.1±0.88)	(26.7±1.31)
Sucrose Intake			
ml	—	88.8±7.74	42.9±3.34
(Kcal)	—	(17.2±1.49)	(33.2±2.55)
Water Intake			
ml	35.7±0.81	10.2±0.95	1.9±0.70
Total Caloric Intake			
(Kcal)	(55.5±1.43)	(55.3±2.19)	(59.9±4.08)
Total Fluid Intake			
ml	35.7±0.81	99.0±6.38	44.8±3.01

*These data represent mean (± SE) daily values per rat for the last ten days (Day 31 through Day 40) of the baseline period.
†N = 20 rats.

Drug Effects on Group 1 Rats

Table 2 shows that food consumption was significantly reduced ($p<0.001$) by all drug treatments immediately after dosing (Day 1), i.e., acute drug effect, when comparisons were made with the preceding day. Both THC and d-AMP produced potent anorexic action over the initial 6-hr feeding period and for both drugs this effect was significantly ($p<0.01$) greater following the high dose compared to the low dose, indicating a dose-response effect. These reductions in food consumption induced by the 2.5 and 5.0 mg/kg doses of THC and d-AMP amount to 35.9 and 44.2% and 28.5 and 43.1%, respectively. Since the only source of calories for Group 1 rats was food these reductions also reflect observations for total caloric intake. In addition, Table 2 reveals that 50.0 mg/kg doses of CBN and CBD produced a highly significant anorexic action during the first 6-hr feeding interval after IP dosing. For CBN, the mean decrease of 9.4 g approximated that produced by 5.0 mg/kg of THC, while CBD had a slightly greater effect.

TABLE 2

THE EFFECT OF ACUTE ADMINISTRATION OF THC, CBN, CBD AND d-AMP ON DAILY 6-HR FOOD INTAKE BY RATS IN EXPERIMENT GROUP 1

Drug and IP Dose, mg/kg	Change in Food Intake (Mean ± SE), in G				
	Acute Drug Effect (Day 1-Day 0)	Carry-Over Effect (Day 2-Day 0)	(Day 3-Day 0)	(Day 4-Day 0)	(Day 5-Day 0)
PG	−0.8 ± 0.21	0.2 ± 0.20	0.4 ± 0.39	0.1 ± 0.29	−0.3 ± 0.40
THC: 2.5	−6.4 ± 0.60‡	−3.2 ± 0.37†	−0.3 ± 0.22	—	—
5.0	−9.6 ± 0.81‡	−5.0 ± 0.38‡	−0.3 ± 0.19	—	—
CBN: 50.0	−9.4 ± 1.09‡	−8.5 ± 0.96‡	−5.3 ± 0.83‡	−3.3 ± 0.41†	−0.6 ± 0.28
CBD: 50.0	−10.8 ± 0.88‡	−5.6 ± 0.47‡	−3.8 ± 0.33†	−1.9 ± 0.44*	−0.5 ± 0.30
Saline	−0.6 ± 0.26	−0.2 ± 0.13	−0.4 ± 0.31	−0.3 ± 0.39	−0.1 ± 0.32
d-AMP: 2.5	−5.4 ± 0.40‡	−0.0 ± 0.21	—	—	—
5.0	−8.0 ± 0.61‡	−1.2 ± 0.13*	−0.1 ± 0.20	—	—

When compared with predrug food intake: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

TABLE 3

THE EFFECT OF ACUTE ADMINISTRATION OF THC, CBN, CBD AND d-AMP ON DAILY 6-HR WATER INTAKE BY RATS IN EXPERIMENTAL GROUP 1

Drug and IP Dose, mg/kg	Change in Water Intake (Mean ± SE), in ml			
	Acute Drug Effect (Day 1—Day 0)	(Day 2—Day 0)	Carry-Over Effect (Day 3—Day 0)	(Day 4—Day 0)
PG	−2.6 ± 3.4	−1.7 ± 2.0	1.8 ± 3.1	1.0 ± 2.6
THC: 2.5	5.3 ± 3.1†	−2.4 ± 2.4	—	—
5.0	−9.9 ± 3.5‡	−4.1 ± 2.2†	−2.1 ± 3.0	—
CBN: 50.0	−13.3 ± 2.8‡	−7.8 ± 3.6†	0.3 ± 2.1	—
CBD: 50.0	−8.3 ± 2.9‡	−4.8 ± 2.5†	−4.8 ± 3.1*	1.3 ± 4.1
Saline	−2.6 ± 3.0	−2.0 ± 2.9	2.8 ± 3.0	0.4 ± 3.0
d-AMP: 2.5	3.3 ± 1.4*	0.5 ± 2.6	—	—
5.0	−7.7 ± 3.9†	2.4 ± 1.0	0.1 ± 2.1	—

When compared with predrug water intake: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

A highly significant reduction in 6-hr food consumption was observed on the postdrug day 24 hr following injection of 2.5 ($p<0.01$) or 5.0 mg/kg ($p<0.001$) of THC compared with the predrug day. This carry-over THC effect was again greater following the higher dose than the lower dose ($p<0.01$). In fact, this activity was approximately 50.0% of that observed on the drug day. By the second postdrug day the anorexigenic activity of THC was gone. Rats treated with CBN still had a mean reduction in food consumption of 8.5 g on the first postdrug day which did not differ significantly ($p<0.1$) from the acute drug effect. By the second postdrug day the anorexic action had been reduced by only 43.6%, by 64.9% (3.3 g) on postdrug Day 3 and finally back to baseline one day later. The course of anorexic activity caused by CBD was quite similar to CBN except that food consumption was reduced a mean of 5.6 g during the 6-hr feeding interval on the first postdrug day, which was 48.2% less than the acute effect. Similarly, the anorexic effect of CBD was gradually reduced until the fourth postdrug day, when no significant reduction was observed when compared with the predrug baseline data (Day 0). On the other hand, the principal carry-over effect 24 hr following d-AMP administration was an increase in food consumption after the higher dose of 5.0 mg/kg ($p<0.05$).

Neither vehicle produced a significant effect on food consumption in these rats on the dosing or any postdrug day.

Water intake by rats in Group 1 was significantly reduced by all cannabinoids and d-AMP (Table 3) during the 6-hr period after dosing. Unlike the effect on food intake, the high dose of both THC and d-AMP did not produce a greater decrease ($p<0.1$) than the low dose. The acute effect for 2.5 (−5.3 ml) and 5.0 mg/kg (−9.9 ml) of THC represents a drop in water intake of 17.3 and 28.5%, respectively, compared to predrug baseline data, whereas similar doses of d-AMP resulted in 10.0 and 22.3% reductions. Similarly, 50.0 mg/kg doses of CBN and CBD produced significant reductions in the amount of water taken in. The effects of CBN and CBD did not differ significantly from each other ($p<0.1$), but were strikingly similar to the activity of 5.0 mg/kg of THC.

Table 3 indicates that on the first postdrug day only those rats which were injected with the high dose of THC, CBN or CBD still were consuming a significantly lesser volume of water. For THC- and CBN-treated rats this effect was reversed during the 6-hr period water was available 48 hr after dosing, while dissipation of the carry-over activity of CBD occurred on the third postdrug day.

Finally, water consumption by these rats was unaltered during the course of the study by either the PG or saline vehicles.

Drug Effects on Group 2 Rats

Figure 1 reveals that THC caused a dose-dependent decrease in food consumption not only on the day of injection (Day 1), but also during the first 6-hr feeding period 24 hr after injection. The degree of inhibition of food intake for the 2.5 mg/kg dose was 26.8 and 21.8% on Days 1 and 2, respectively, while 5.0 mg/kg of THC caused 50.0 and 38.7% reductions at the same testing times. By the second postinjection day (Day 3), however, food intake had returned to the PG vehicle baseline level. On the other hand, total consumption of the 5% sucrose solution was significantly reduced only on Day 1 following either 2.5 (25.7%, $p<0.05$) or 5.0 mg/kg (44.6%, $p<0.001$) of THC, this too, occurring in a dose-related manner. The effect of THC on water intake by rats in Group 2 very closely paralleled the pattern of activity displayed on sucrose intake.

Two other naturally occurring cannabinoids, CBN and CBD, each produced a marked anorexic effect in Group 2 rats (Fig. 2). On the injection day (Day 1) and first postinjection day (Day 2) 50.0 mg/kg of CBN produced substantial reductions in food consumption of 46.7 and 69.6% respectively, with the Day 2 effect being significantly greater ($p<0.02$) than Day 1. However, the carry-over anorexic effect of CBN diminished gradually until Day 5 (fourth postinjection day) when food consumption returned to PG vehicle baseline control values. On the other hand, the acute inhibitory action of 50.0 mg/kg of CBD on food consumption (70.9%) was greater ($p<0.01$) than CBN. Similar to CBN, this effect of CBD was completely reversed by Day 5 following a nearly linear progression. Hence, comparison of the acute effects on food consumption, 50.0 mg/kg of CBN and 5.0 mg/kg of THC (Fig. 1) were nearly equally effective while 50.0 mg/kg of CBD produced a more pronounced ($p<0.02$) decrease than THC.

Consumption of a five percent sucrose solution was also significantly inhibited (38.8%, $p<0.001$) during the first

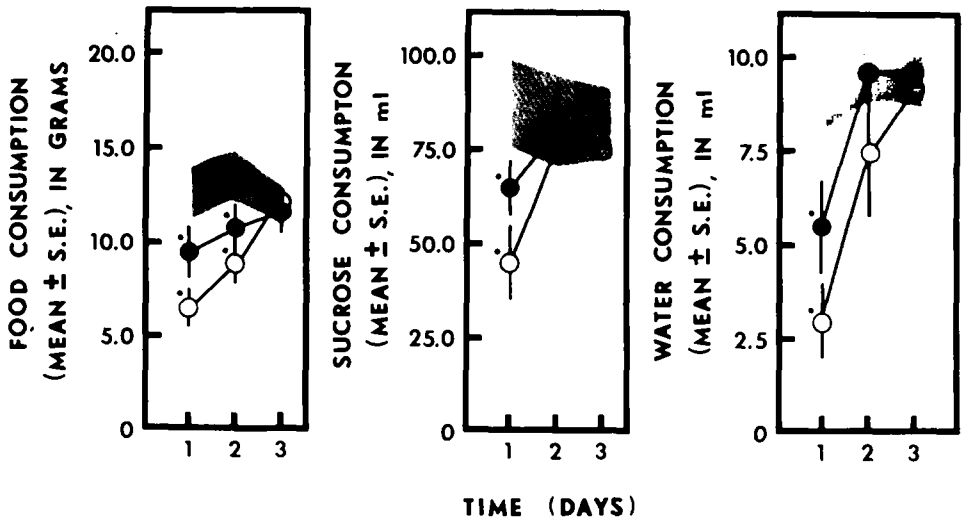

FIG. 1. The acute and carry-over effects of a single IP injection of 2.5 (●- —●) and 5.0 mg/kg (○ - —○) of THC on food, 5% sucrose and water consumption by rats. Shaded area in this and all subsequent figures represents the PG-vehicle control response. *$p \leq 0.05$ when compared with PG-vehicle response in this and subsequent figures.

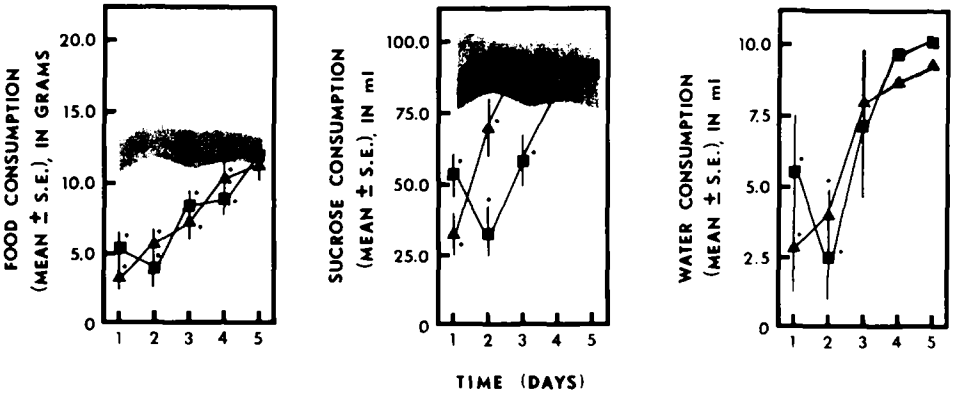

FIG. 2. The acute and carry-over effects of single IP injections of CBN (■- — ■), 50.0 mg/kg and CBD (▲-—▲), 50.0 mg/kg on food, 5% sucrose and water consumption by rats.

6-hr feeding period following CBN (Fig. 2). Similar to its effect on food consumption on the first carry-over day, sucrose intake was further reduced to a level of 64.5% less than PG vehicle baseline. On Day 3, sucrose consumption was still reduced by 31.7%, but returned to baseline by Day 4, one day prior to food consumption. On the other hand, the more pronounced inhibitory effect (64.4%, $p<0.001$) on sucrose intake caused by 50.0 mg/kg of CBD during the acute drug feeding period was markedly attenuated 24 hr later and did not differ statistically ($p<0.1$) from baseline by the second 24-hr postdrug period, i.e., Day 3. Finally, Fig. 2 reveals that both CBN and CBD caused significant inhibition of water intake (Day 1) in these same rats which persisted only through the first 6-hr feeding period after IP injection of either drug (Day 2). Although there were striking differences between the degree of inhibition for each drug on both test days, they were not statistically unsimilar due to the large S.E.

As can be seen from data presented in Fig. 3, d-AMP, like THC (Figure 1), caused a significant reduction in food intake by Group 2 rats during the acute drug feeding period (Day 1), which was clearly dose-related, since 5.0 mg/kg produced a reliably ($p<0.02$) greater effect (43.4%) than the 2.5 mg/kg dose (21.0%). In addition, this acute effect of both doses of d-AMP was approximately the same as produced by THC. The effect of d-AMP on food consumption was completely reversed by the next day, similar to THC. However, those rats which received the high dose of d-AMP ate slightly but not significantly more food (average of 14.0 g) than the PG baseline control the first 6-hr feeding period after dosing indicating a trend towards a compensatory increase in food consumption after acute anorexia. Similarly, 5.0 mg/kg of d-AMP caused a pronounced decrease (65.9%, $p<0.001$) in sucrose solution consumption immediately following dosing but during the next test period 24 hr after dosing these animals tended (but not significantly) to compensate by taking in more sucrose, i.e., mean increase of 20 ml or 22.8% over the mean control value. Rats did significantly ($p<0.05$) consume less sucrose solution only during the acute 6-hr feeding period following the 2.5 mg/kg dose of d-AMP. Likewise, water consumption was reduced by d-AMP only

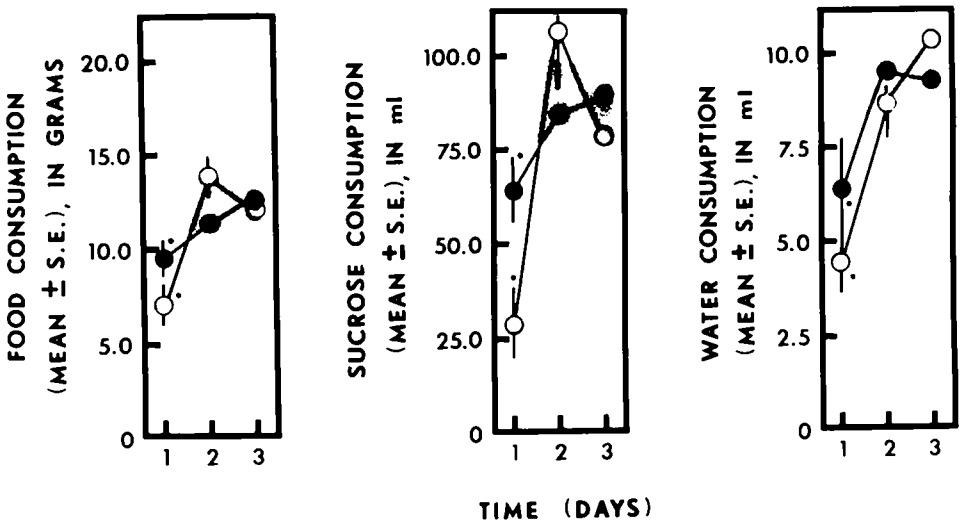

FIG. 3. The acute and carry-over effects of a single IP injection of 2.5 (●- —●) and 5.0 mg/kg (○— —○) of d-AMP on food, 5% sucrose and water consumption by rats.

during the first feeding interval, but not in a significant dose-dependent way.

Table 4 summarizes the results of experiments with each drug in Group 2 rats by presenting the percentage of total caloric intake due to food during the drug effect. Hence, caloric intake from the 5% sucrose solution source can be obtained by subtracting from 100 the value in Table 4. The predrug column reveals that approximately 70% of the total caloric intake by these rats was from food. These data suggest that the acute anorexic effect of THC (2.5 and 5.0 mg/kg) was the same on both food and sucrose consumption since the Day 1 percentage did not differ from predrug. However, carry-over anorexia caused by the high dose of THC was mainly in food consumption since a lesser percentage (64.5) of the total calories was from food, indicating a preference for sucrose. By Day 3 when the anorexic effect (Fig. 1) was reversed, the ratio of food: total calories was back to predrug levels. Similarly, the other cannabinoids tested, namely CBN and CBD, resulted in an alteration of this ratio in the direction of sucrose preference with significant changes on Day 1 for the former and Days 2 and 3 for the latter. On the other hand, each dose of d-AMP produced nearly equal reductions in both food and sucrose consumption resulting in similar ratios of food: total calories throughout the time of significant anorexia. Hence, these data reveal a different pattern of anorexic action between the cannabinoids THC, CBN and CBD and d-AMP in rats whose sources of calories were normal laboratory chow (dry food) and a 5% sucrose solution.

Drug Effects on Group 3 Rats

Figure 4 graphically depicts the effects of 2.5 and 5.0 mg/kg of THC in rats who have been trained to consume food, a 20% sucrose solution and water during a 6-hr interval as their daily dietary regimen. Clearly, food consumption is reduced in a dose-related way, i.e., 43.6 and 72.9% for the low and high doses, respectively, during the

TABLE 4

PERCENTAGE OF TOTAL CALORIC INTAKE DUE TO FOOD FOLLOWING ADMINISTRATION OF ACUTE ANOREXIC DOSES OF THC, CBN, CBD AND d-AMP IN RATS (GROUP 2) WHOSE SOURCE OF CALORIES WAS FOOD AND A 5% SUCROSE SOLUTION

Drug and IP Dose, mg/kg	Percentage of total caloric intake due to food*					
	Acute Drug Effect			Carry-Over Effect		
	Pre-Drug	Day 1	Day 2	Day 3	Day 4	Day 5
PG	70.2	72.7	72.8	71.6	72.1	70.9
THC: 2.5	71.1	70.0	67.4	68.1	—	—
5.0	71.4	69.4	64.5†	71.6	—	—
CBN: 50.0	68.9	61.0†	64.7	68.4	67.8	67.5
CBD: 50.0	67.7	63.1	56.4‡	52.5‡	63.9	76.0
Saline	68.2	69.9	68.8	69.0	68.8	69.4
d-AMP: 2.5	67.4	68.9	70.4	—	—	—
5.0	69.2	72.6	70.9	71.8	—	—

*Obtained from the ratio food calories: total calories x 100. When compared to each respective predrug value: †$p<0.05$; ‡$p<0.001$.

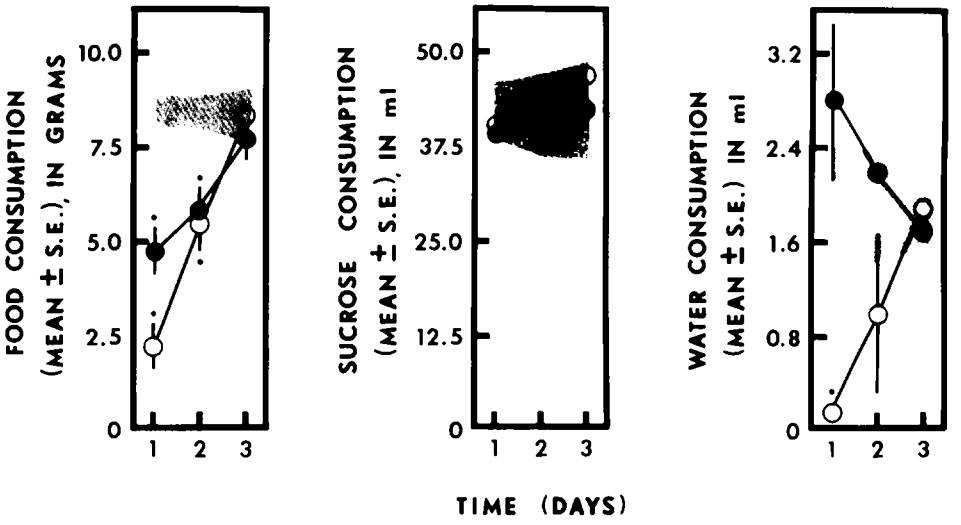

FIG. 4. The acute and carry-over effects of a single IP injection of 2.5 (•——•) and 5.0 mg/kg (○——○) of THC on food, 20% sucrose and water consumption by rats.

first feeding interval after dosing. Although on Day 2 a carry-over anorexic action persisted for both doses of THC, the degree of inhibition of food intake was approximately the same (33%) for each dose. By Day 3 the effect on food consumption was no longer visible, similar to what was observed in rats in Group 1 (Table 3) and Group 2 (Fig. 1). However, for these rats neither dose of THC inhibited consumption of a 20% sucrose solution at any feeding interval indicating that the drug produces a marked preference for this source of calories. In these same animals, water intake was inhibited only immediately following the 5.0 mg/kg dose of THC.

Fifty mg/kg of CBN caused a marked and sustained inhibition of food consumption in Group 3 rats (Fig. 5). For instance, the acute effect (Day 1) was 91.1% inhibition, while on Days 2, 3 and 4 the activity decreased to 79.7, 43.6 and 38.3%, respectively. By Day 5 this effect was gone. Similarly, 50.0 mg/kg of CBD caused a pronounced reduction of food intake which decreased in a linear fashion until complete abolition of the effect occurred by Day 5. For each testing interval, except Day 3, the effect produced by CBD was significantly less ($p<0.02$) than CBN. On the other hand, Fig. 5 reveals that each of these substances had a different effect on intake of a 20% sucrose solution when compared to food consumption. Acutely, both CBN and CBD caused substantial (67.1 and 55.3%, respectively) but statistically similar reductions. However, unlike food consumption by Day 2 for CBD and Day 3 for CBN consumption of the sucrose solution had returned to PG vehicle baseline levels. Water consumption by these same rats was unaffected by 50.0 mg/kg of CBD, but completely inhibited by CBN on Days 1 and 2, still significantly reduced ($p<0.02$) on Day 3 and back to baseline by Day 4.

The anorexic effect of d-AMP in Group 3 rats is illustrated in Fig. 6. Both food and sucrose consumption were inhibited during the initial 6-hr feeding period just following IP administration of 2.5 or 5.0 mg/kg doses. Moreover, these responses were significantly greater following the high dose compared to the low dose, i.e., $p<0.001$ for food and $p<0.05$ for consumption of the 20% sucrose solution. Similarly, for each dose of d-AMP the anorexic action was completely reversed by the first

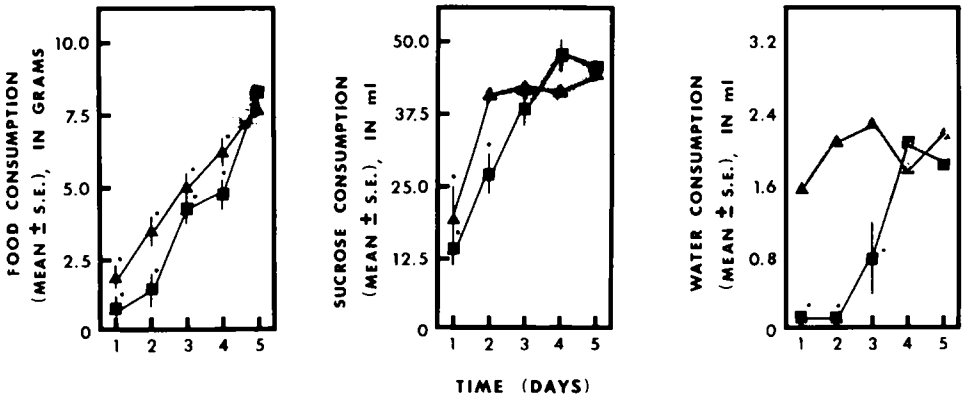

FIG. 5. The acute and carry-over effects of single IP injections of CBN (■——■), 50.0 mg/kg and CBD (▲——▲), 50.0 mg/kg on food, 20% sucrose and water consumption by rats.

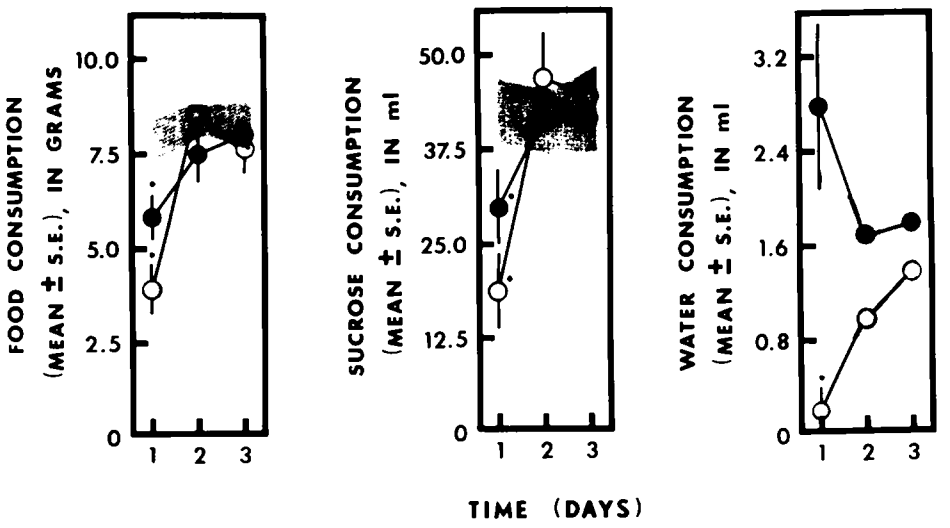

FIG. 6. The acute and carry-over effects of a single IP injection of 2.5 (•·——•) and 5.0 mg/kg (○— - -○) of d-AMP on food, 20% sucrose and water consumption by rats.

postdrug day. Moreover, water intake was significantly inhibited (86.7%, $p<0.02$) acutely and only by the high dose of d-AMP.

Finally, Table 5 reveals that the percentage of total caloric intake due to food consumption by Group 3 rats was approximately 40% compared to 70% in Group 2 rats (Table 4). Hence, these rats derived 60% of their total calories from sucrose (20% solution) or twice as much as those rats in Group 2 did (30%) from their 5% sucrose solution source. The data listed in Table 5 show that each of the cannabinoids during their course of induced anorexia strikingly altered percentage of total caloric intake due to food consumption. The most pronounced reduction in caloric intake induced by 2.5 and 5.0 mg/kg of THC was on food consumption. Similar to overall anorexia this effect was dose-related on Day 1, i.e., 31.6 and 18.3% for the low and high doses, respectively. For the 5.0 mg/kg dose this preference for sucrose persisted throughout Day 3, the time when caloric intake returned to baseline. However, the effect of the 2.5 mg/kg dose occurred only on the day of dosing. Fifty mg/kg of CBN initially altered the ratio to exactly the same extent as 5.0 mg/kg of THC, but its effect was of much longer duration, i.e., Day 4. On the other hand, 50.0 mg/kg of CBD was approximately as effective in reducing the percentage of total caloric intake due to food as 2.5 mg/kg, however, its effect significantly persisted for 2 days (Day 3) after dosing. Contrary to these findings with the cannabinoids, d-AMP, like in Group 2 rats (Table 4), produced a general anorexic action in which food and sucrose consumption were equally inhibited, resulting in ratios of food calories: total calories which did not change throughout the course of the study.

DISCUSSION

In the present investigation the general anorexic activity and inhibitory effect on water consumption produced by 2.5 and 5.0 mg/kg of THC in rats with food as their only

TABLE 5

PERCENTAGE OF TOTAL CALORIC INTAKE DUE TO FOOD FOLLOWING ADMINISTRATION OF ACUTE ANOREXIC DOSES OF THC, CBN, CBD AND d-AMP IN RATS (GROUP 3) WHOSE SOURCE OF CALORIES WAS FOOD AND A 20% SUCROSE SOLUTION

Drug and IP Dose, mg/kg	Percentage of total caloric intake due to food*					
	Acute Drug Effect			Carry-Over Effect		
	Pre-Drug	Day 1	Day 2	Day 3	Day 4	Day 5
PG	42.4	43.7	43.1	42.4	43.0	42.6
THC: 2.5	41.4	31.6†	36.5	42.9	—	—
5.0	40.4	18.3‡	31.8†	40.9	—	—
CBN: 50.0	40.4	18.5‡	16.4‡	30.6‡	28.6‡	42.0
CBD: 50.0	42.0	28.4‡	26.1‡	31.7‡	37.4	40.5
Saline	42.2	44.5	42.8	43.0	41.6	42.5
d-AMP: 2.5	40.0	41.4	41.5	43.1	—	—
5.0	40.1	44.9	41.2	40.2	—	—

*Obtained from the ratio food calories: total calories x 100.
When compared to each respective predrug value: †$p<0.05$; ‡$p<0.02$; §$p<0.001$.

source of calories (Group 1) has been confirmed. In addition, the cannabinoids CBN and CBD were also shown to possess good anorexigenic activity at 50.0 mg/kg in comparison with 2.5 and 5.0 mg/kg of the standard agent d-AMP. However, unlike d-AMP, this anorexic effect of the cannabinoids occurred at doses which have been shown to produce little or no change in spontaneous locomotor activity [7,11]. In addition, each of these test substances resulted in somewhat different time course effects on food consumption. The anorexic effect of each dose of THC was prolonged lasting more than 24 hours into the first 6-hr feeding interval after dosing. Similarly, the duration of action of CBN and CBD in Group 1 rats was even greater lasting up to 3 days after dosing. One plausible explanation for this difference in duration of action may be due to the fact that the absorption, distribution, metabolic and/or excretion characteristics of CBN and CBD differ markedly from THC. Contrary to this, animals given the high dose of d-AMP showed a significant increase in food consumption on the first postdrug day following the initial anorexic action. However, rats injected with the 2.5 mg/kg dose did not display this phenomenon of compensatory food intake shown for d-AMP [15,17]. Hence, these data for THC and other constituents of marihuana on appetite in rats whose only source of calories was dry laboratory food differ from the reports of appetite stimulation with a preference for sweets reported for humans following oral consumption of THC [8] or marihuana smoking [1, 2, 3].

In order to test for the effect of these drugs on preference for sweet calories two different groups of rats had available either a five (Group 2) or 20% (Group 3) sucrose solution along with dry laboratory food as their source of calories each daily 6-hr feeding period. Table 1 clearly indicates that rats are excellent caloric meters [4]. Although mean total caloric intake (Table 1) did not differ significantly among the 3 groups of rats, there was clear evidence for highly significant reduction ($p<0.001$) in dry food consumption as the concentration of available sucrose solution increased. For instance, the percentage of the total caloric intake due to food decreased from 100% in Group 1 to 70% for animals in Group 2 to 40% in Group 3 rats.

Figures 1–3 clearly illustrate that all test substances produce significant reductions in both food and intake of a 5% sucrose solution during the 6-hr feeding interval immediately following drug injection (Day 1). However, for THC (Fig. 1) the carry-over inhibitory effect observed on food consumption was not paralleled by decreased sucrose consumption since the latter returned to PG vehicle baseline one day earlier. A similar pattern of action existed in rats dosed with CBN or CBD (Fig. 2). Hence, even during the anorexia produced by each of these cannabinoids a preference for sweet calories seemed to prevail. On the other hand, the anorexia produced by d-AMP (Fig. 3) for both food and sucrose consumption returned to control level at the same time. Table 4 more clearly depicts these findings showing that during acute anorexia as well as at various postdrug intervals the ratio of food calories: total calories was reduced by the cannabinoids but unchanged by d-AMP.

The preference for sweet calories by rats dosed with the cannabinoids was more pronounced and further verified in those animals who had a more concentrated (20%) sucrose solution available to them along with dry laboratory food (Group 3). Figure 4 reveals that sucrose consumption was unaffected by 2.5 or 5.0 mg/kg of THC at any time interval after dosing even though food consumption was dramatically reduced. CBN and CBD (Fig. 5) had a prolonged inhibitory effect on food consumption in these animals, but consumption of the 20% sucrose solution returned to baseline by Day 2 in CBD-treated rats and by Day 3 after CBN, similar to the pattern observed in Group 2 rats (Fig. 2). Contrary to this, both food and sucrose consumption after d-AMP administration returned to baseline at the same time, *i.e.*, by Day 2 (Fig. 6). Finally, these data can be better appreciated when the percentage of total caloric intake due to food is calculated (Table 5). All the cannabinoids drastically reduced this ratio which persisted up to 3 days (Day 4) after IP dosing in the case of CBN indicating a preference for sweet calories. On the other hand, this preference during anorexia was unnoticed in rats dosed with d-AMP.

The results of these experiments in rats whose total caloric intake is divided among dry laboratory food and two different concentrations of sucrose solutions revealed for the first time that THC as well as CBN and CBD produce a preference for sweet calories, similar to what has been observed in man following oral THC ingestion or marihuana smoking. However, unlike man, total appetite was not stimulated since caloric intake due to food consumption at the same time was still reduced.

ACKNOWLEDGEMENTS

The THC, CBN and CBD were generously supplied through the courtesy of Monique Braude Ph.D., of the Biomedical Research Branch, Division of Research, National Institute of Drug Abuse. The authors also gratefully acknowledge Smith Kline & French Laboratories, Philadelphia, Pennsylvania for their generous supply of d-AMP.

A preliminary report of this work was presented at the Sixth International Congress on Pharmacology, Helsinki, Finland, July 20–25, 1975.

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