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Food and Water Intake, Meal Patterns and Activity of Obese and Lean Zucker Rats Following Chronic and Acute Treatment with Δ^9-Tetrahydrocannabinol[1,2]

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DREWNOWSKI, A. AND J. A. GRINKER. *Food and water intake, meal patterns and activity of obese and lean Zucker rats following chronic and acute treatment with Δ^9-tetrahydrocannabinol.* PHARMAC. BIOCHEM. BEHAV. **9**(5) 619–630, 1978.—A series of experiments investigated the effects of Δ^9-THC on food and water intakes and wheel-running activity of Zucker rats. Following chronic drug treatment (15 days), food and water intakes of all rats were suppressed, but intakes and body weights of the obese rats recovered more slowly than those of lean rats. Acute effects of the drug (24 hr) were examined using techniques of meal pattern analysis and were disscussed in relation to known patterns of anorectic drug action. The drug-induced anorexia was both delayed and of short duration, with no rebound eating observed for either solid or liquid diets. Both feeding rate and meal size were reduced, but meal frequency was transiently increased. The time of onset of the first meal remained unchanged. The time course of the suppression of feeding was paralleled by a suppression in running-wheel activity. These findings suggest that the drug-induced reduction in food and water intake may be the result of a decreased level of arousal.

Δ^9-THC Zucker rats Diet Meal patterns Activity

REPORTS that Δ^9-tetrahydrocannabinol (THC) both increases and decreases food intakes of laboratory rats [2] have led to suggestions that the dose-response curve to the drug is biphasic, with low doses stimulating [9,13] and high doses suppressing feeding [2]. In the present set of studies, we employed continuous data recording techniques and the analysis of meal patterns [5,10] to investigate the temporal profile and the mode of action of a range of doses of Δ^9-THC on food intake, and we compared our data with those reported for known anorectic agents [6,7].

Studies which established the "anorectic-like" effects of Δ^9-THC have employed rats chronically injected with large doses of the drug (up to 100 mg/kg/day) for periods of 5–30 days. Cumulative measures of food or water intakes were then obtained every 24 or 48 hr [3, 12, 20, 24, 25]. In contrast, studies showing increased food intakes following small doses of Δ^9-THC, employed acutely injected rats, with food and water intakes measured at 1 or 2 hr intervals for up to 6 hr following drug administration [9,13]. Furthermore, whereas chronic studies used rats that were fed ad lib, acute studies used rats that were maintained on 6–23 hr food or water deprivation schedules [14,25], or rats that had been acutely deprived for up to 24 hr prior to the experiment [3]. There is consequently a confounding between the degree of exposure to the drug (chronic or acute), the animals' nutritional state (ad lib or deprived), and the method of measurement of the food and water intakes (cumulative or periodic).

Each of these factors can critically influence the animals' daily food and water intakes. Chronic effects of Δ^9-THC need not parallel acute effects, since treated animals may develop tolerance [23,29], the drug may accumulate in tissue [22] or produce long-term toxicity [20]. Food deprivation may enhance the potency of anorectic drugs [6], so that testing the effects of Δ^9-THC following a deprivation period may result in an inaccurate assessment of drug action. Most critically, differences in the period of measurement may produce different estimates of intake if recovery from the effects of the drug is followed by compensatory behavior occurring within this period. Initial anorexia followed by rebound feeding, or initial enhancement of feeding followed by compen-

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[2]Parts of this research were presented at the Winter Conference on Brain Research 1975, 1977, and at the meeting of the Society for Neuroscience, 1976.

satory suppression might both have similar effects on cumulative intakes measured at 24 hr postinjection.

A detailed investigation of the effects of Δ^9-THC on food and water intakes of non-deprived animals under conditions of both chronic and acute drug administration is therefore needed. It is desirable to establish the temporal profile of action of Δ^9-THC in order to relate short-term effects of the drug to effects shown at the end of 24 hr. It is also desirable to specify the mode of drug action on the individual components of the feeding process; meal frequency and meal size [11,17], and to compare its effects to those of known anorectic agents.

The two principal modes of anorectic action are exemplified by d-amphetamine, which has been reported to delay the onset of feeding and to reduce meal frequency, and by fenfluramine, which has been reported to reduce meal size but not meal number [6,7]. Consequently, d-amphetamine is thought to act by suppressing appetite, while fenfluramine is thought to act by enhancing satiety [7]. Since Δ^9-THC has been reported to reduce the rats' food intakes [2], it is desirable to examine whether its mode of action is mediated primarily by changes in appetite or by changes in satiety.

Two further factors may be relevant to the effects of Δ^9-THC on consummatory behavior: the palatability of the diet and the reported tranquilizing effect of the drug [12]. The animals in the present study are therefore maintained on either lab chow or a palatable diet of sweetened condensed milk, and the method of on-line data recording is extended to include continuous monitoring of the rats' concomitant running-wheel activity. Furthermore, since obese and lean animals may differ in their response to anorectic agents [8], the effects of Δ^9-THC are studied using genetically obese Zucker rats and their lean littermates, which differ in their daily food intake [4] and have been reported to differ in the circadian distribution of their feeding behavior [5].

In the first experiment we examine the effects of a single dose (4 mg/kg) of Δ^9-THC on lab chow and water intakes during chronic treatment and recovery periods. This dose of the drug has been shown by previous investigators to affect food [20] or water intakes [24] or both [1]. In the second experiment we examine the acute effects of the same dose of Δ^9-THC on intakes monitored continuously for 24 hr postinjection. In the third experiment, we examine the effect of a range of doses of Δ^9-THC on meal parameters of rats maintained on a sweetened condensed milk diet. Finally, we examine spontaneous running-wheel activity following acute drug administration.

EXPERIMENT 1

The present experiment was designed to investigate whether 4 mg/kg of Δ^9-THC suppresses or enhances the rats' food and water intakes and whether equivalent effects are obtained for Zucker obese and lean rats. Food intakes and body weights were monitored daily during a 15-day drug treatment period, and during a 15-day recovery period when only vehicle injections were given. The rats were always injected with the drug at the beginning of each 12-hr dark cycle so that the drug might have its maximum effect during the time of maximal nocturnal feeding.

METHOD

Animals

Fifteen genetically obese (fa/fa) male Zucker rats and 15 lean (Fa/–) littermates were purchased from the Harriet G. Bird Memorial Laboratory, Stow, MA. All animals were approximately 5 months old at the start of the experiment, which began 1 week after their arrival in the laboratory. They were housed in individual hanging wire-mesh cages in a temperature-controlled room with a 12-hr light/dark cycle, with lights on between 6 a.m. and 6 p.m.

Drugs

Delta-9-THC was injected intraperitoneally (IP) in a volume of 1.0 ml/kg of body weight. The vehicle for injection was 10% polyethylene glycol-1% polysorbate 80 (Tween-80)-0.9% saline [25]. Fresh batches of the injection solution were made daily. All control injections contained equivalent volumes of the vehicle solution.

Procedure

The animals were given ad lib access to Purina Lab Chow and water, and their food and water intakes were measured daily at 6 p.m. Food left in the cage and spilled under the cage was weighed to the nearest 0.1 g. Water intakes were read directly from 100 cc graduated cylinders. The obese and lean animals were each divided into experimental and control groups, matched according to their body weights. An experimental obese Zucker was thus matched with a control obese Zucker of approximately similar weight, and an experimental lean Zucker was matched with a control lean Zucker of approximately similar body weight. Following 10 days of baseline period during which no injections were given, the two experimental groups (obese: n=8; lean: n=8) received daily drug injections for a period of 15 days, whereas the two control groups (obese: n=7; lean: n=7) received only the vehicle. All groups received the vehicle only during the subsequent 15-day recovery period. All injections were given between 5:30 and 6:00 p.m., immediately prior to the dark period. The data were submitted to a factorial analysis of variance for mixed designs and repeated measures. Because of the unequal number of rats in experimental (n=16) and control (n=14) groups, one obese and one lean rat of median weight were dropped from the experimental group prior to the analysis. Comparisons between individual means in this and the two following experiments were made using planned comparison *t*-tests (see [30]).

RESULTS

Baseline

The rats' body weights during the 10-day baseline period are shown in Fig. 1. Obese rats weighed significantly more than lean rats, (Genotype: $F(1,24)=226.82$; $p<0.01$), and gained weight faster than lean rats (Genotype by Days interaction: $F(9,216)=14.56$; $p<0.01$). Measures of food (Fig. 2) and water intakes (Fig. 3) show that obese rats also ate more food (Genotype: $F(1,24)=101.49$; $p<0.01$) and drank more water than lean rats (Genotype: $F(1,24)=26.35$; $p<0.01$) in agreement with data previously reported in the literature [5,10]. No significant Genotype by Days interaction was observed for the food, $F(9,216)=1.45$; n.s., or for the water intake, $F(9,216)=1.13$; n.s.

A comparison of animals assigned to experimental and control groups revealed no significant differences in body weight (Treatment: $F(1,24)=0.04$; n.s.), food intake, $F(1,24)=0.27$; n.s., or water intake, $F(1,24)=0.40$; n.s., and there were no significant interactions. Animals assigned to

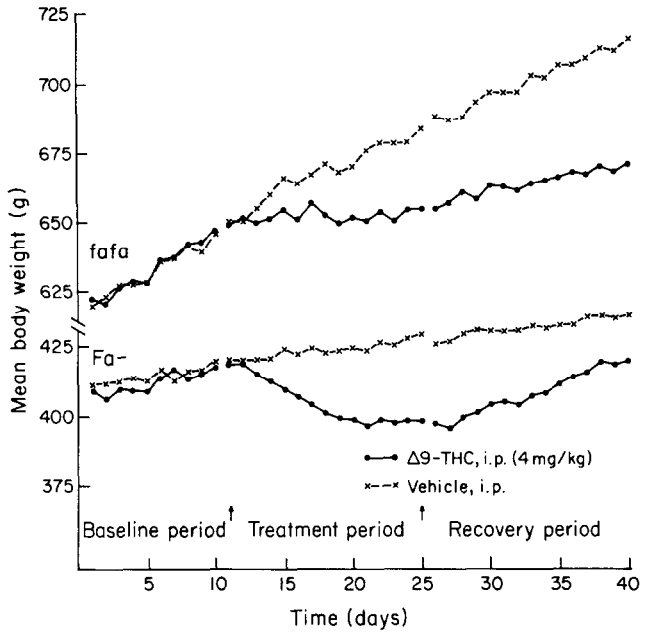

FIG. 1. Mean body weights for each group in Experiment 1 for 10 baseline days, 15 treatment days and 15 recovery days. (Treatment groups: Zucker obese (fa/fa), n=8; Zucker lean (Fa/–), n=8. Vehicle groups: Zucker obese, n=; Zucker lean, n=7). All groups received vehicle during recovery.

experimental and control groups were thus matched not only for body weight, but also for their mean food and water consumption during the predrug period.

Drug Treatment and Recovery

Food intake. Daily food intakes of both obese and lean rats (Fig. 2) were significantly suppressed in the course of drug treatment (Treatment: $F(1,24)=8.72$; $p<0.01$). Although the intake of obese rats was on the average suppressed to a lesser extent (7.0%) than that of lean rats (14.5%), the Genotype by Treatment interaction was not significant, $F(1,24)=0.08$; n.s. Furthermore, the effects of the drug do not appear to be cumulative: there was no significant effect of Days, $F(14,336)=1.47$; n.s. and no Days-related interactions.

Following termination of drug injections, food intakes of lean rats returned to control values, whereas those of obese animals remained suppressed; as reflected in a significant Genotype by Previous Treatment interaction, $F(1,24)=5.26$; $p<0.05$. There was no significant Days effect, $F(14,336)=1.35$; n.s., and no Days-related interactions.

Water intake. Water intakes of obese and lean rats were also suppressed in the course of drug treatment by 13.1% and 10.7%, respectively (Treatment: $F(1,24)=13.58$; $p<0.01$). The Genotype by Treatment interaction was not significant, $F(1,24)=1.09$; n.s. Although there was a main effect of Days, $F(14,336)=5.02$; $p<0.01$, reflecting increased water consumption midway through the drug treatment period, there were no significant Days-related interactions (see Fig. 3).

During the recovery period, water intakes of lean rats returned to control values whereas those of obese rats remained suppressed (Genotype by Previous Treatment interaction: $F(1,24)=7.38$; $p<0.01$). Because the data for the

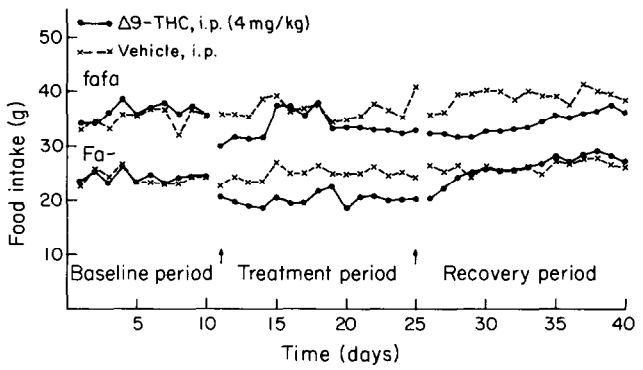

FIG. 2. Effects of chronic administration of Δ⁹-THC on food intake of Zucker obese (fa/fa) and lean (Fa/–) rats in Experiment 1. Average daily food intakes for experimental (4 mg/kg Δ⁹-THC) and vehicle groups are shown for 10 baseline days, 15 treatments days and 15 recovery days. All groups received vehicle during recovery.

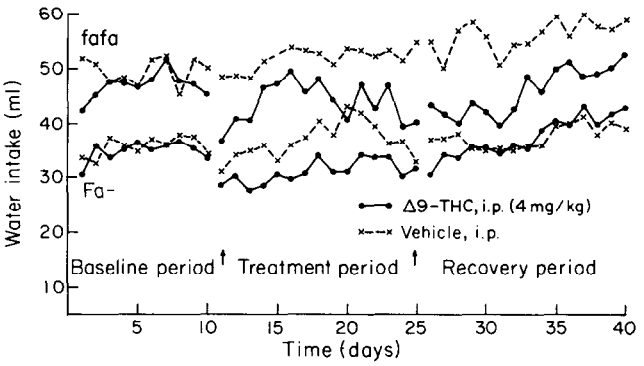

FIG. 3. Effects of chronic administration of Δ⁹-THC on water intake of Zucker obese (fa/fa) and lean (Fa/–) rats in Experiment 1. Average daily water intake for experimental (4 mg/kg Δ⁹-THC) and vehicle groups are shown for 10 baseline days, 15 treatment days and 15 recovery days. All groups received vehicle during recovery.

obese animals were more variable than those for the lean animals, possibly reflecting a greater proportion of water spillage, both the effects of Days, $F(14,336)=9.14$; $p<0.01$, and the Genotype by Days interaction, $F(14,336)=2.74$; $p<0.01$, were significant.

Body weights. The effects of chronic treatment with Δ⁹-THC on the rats' body weight are shown in Fig. 1. Lean Zucker rats lost a significant amount of weight relative to their own baseline levels. While the weight of the obese rats remained constant, their previous rate of growth was arrested (Days by Treatment interaction: $F(14,336)=38.36$; $p<0.01$). Both the obese and lean experimental groups thus weighed less than the vehicle controls. Analysis of variance showed significant effects of both Genotype, $F(1,24)=264.65$; $p<0.01$ and Days, $F(14,336)=5.88$; $p<0.01$, as well as a significant Days×Genotype interaction, $F(14,336)=24.10$; $p<0.01$.

Analyses of body weights during the recovery period showed significant effects of Genotype, $F(1,24)=328.20$; $p<0.01$, Prior Treatment, $F(1,24)=5.10$; $p<0.05$, and Days, $F(14,336)=63.17$; $p<0.01$. Obese Zucker rats regained weight more slowly than lean rats (Genotype by Prior Treatment by Days interaction: $F(14,336)=10.29$; $p<0.01$) so

that at the end of 15 days, their body weights were below those of matched controls, whereas no difference was observed for the lean and matched control rats.

These results suggested that body weights of obese rats might be permanently suppressed following chronic drug treatment. The rats were consequently re-weighed 5 weeks following the completion of the experiment. No difference in mean body weight was found between the experimental group and vehicle controls, $t(13)=0.64$, n.s. Effects of Δ^9-THC on body weight thus appear to be wholly reversible.

DISCUSSION

The present data agree with the majority of previous reports [2] in showing that both food and water intakes of genetically obese and lean Zucker rats are lowered as a result of chronic treatment with 4 mg/kg of Δ^9-THC. Conflicting observations that the drug has no effect on food [24] or water intakes [20] may have resulted from injecting the rats on the morning of the day of treatment, which may have attenuated the anorectic potency of Δ^9-THC. Thus, Manning *et al.* [20] reported a drop in eating but no effect on drinking as a result of daily doses of 4 mg/kg Δ^9-THC injected intraperitoneally in the morning for 30 days, whereas Sjöden *et al.* [24] found that 2.5 mg/kg Δ^9-THC suppressed drinking but not eating in female rats when it was injected daily over a 23-day period. The present data show that the drug affects both eating and drinking.

The paradoxical pattern of the drug's effects on the intakes of obese rats is more difficult to explain. On one hand, the food intake of obese rats is reduced to a somewhat lesser extent than that of lean rats, and the obese rats fail to show any loss in body weight during the drug treatment period. On the other hand, Zucker obese rats are slower to recover from the effects of the drug during the 15-day recovery period when no drug injections are given, and their final intakes and body weights are significantly below those attained by the obese vehicle controls.

The slowness of the obese Zuckers' recovery following the drug treatment period is inconsistent with the notion that they are organically more resistant to the action of anorectic agents [8]. The lesser percentage suppression of their daily food intake compared to lean rats is possibly the result of differences in their circadian meal distribution. Whereas lean rats eat primarily at night, obese rats consume an equivalent proportion of their food during the day [5], by which time the acute effects of Δ^9-THC may have worn off. The present data indicate that the animals' circadian feeding patterns can interact with the effects of pharmacological agents, and point to the importance of obtaining detailed temporal profiles of drug action.

We can only speculate as to why the obese rats are slow to recover following chronic drug treatment. It may be that Δ^9-THC, which is strongly lipophilic [24], selectively accumulates in the adipose tissue of the obese rats and continues to exert its "anorectic-like" action after drug administration is discontinued. This effect would be consistent with the reported cumulative effects of the drug on food intake [25], and with the reported slow rates of elimination of the drug and its metabolites [18,19]. However, this effect is inconsistent with the lower suppression of the obese Zucker rat's food intake on a day-to-day basis. Another explanation may be that the metabolism of the obese Zucker rat is slower to adjust to manipulations of food intake induced by pharmacological agents. Zucker obese rats are reported to adjust more slowly than lean rats to manipulations of food intake by means of dietary dilution using non-absorbable fats [28].

EXPERIMENT 2

The results of the previous experiment confirm reports that chronic treatment with Δ^9-THC suppresses both food and water intakes of laboratory rats [2]. In the present experiment we establish the temporal profile of food intake of Zucker obese and lean rats during the 24 hr following drug injection, and demonstrate drug-induced changes in selected parameters of feeding behavior.

METHOD

Animals

Six genetically obese male Zucker rats (fa/fa) and six lean male littermates (Fa/–) were obtained from the breeding colony at the Biology Department at Vassar College. At the start of the experiment, all animals were approximately six months old, with the obese rats weighing between 617 g and 772 g (mean=684 g) and the lean rats weighing between 374 g and 445 g (mean=413 g). The rats were housed individually in LC34 Wahmann activity wheels and cages, placed in ventilated white-walled boxes in a temperature and humidity controlled room with the temperature maintained at 68°F. A computer controlled light/dark cycle (6 a.m. to 6 p.m.) was employed [5].

Diet

All rats were maintained on a diet of 45 mg Noyes pellets and water. The pellets contain 23.9% protein, 5.6% fat and 52.9% carbohydrate according to the manufacturer's specifications and have a caloric density of 4.5 kcal/g.

Drug

Delta-9-THC was injected intraperitoneally in a volume of 1.0 mg/kg of body weight. The vehicle for injection was the same as described in Experiment 1 and the dose (4 mg/kg) was identical.

Apparatus

Two different food delivery systems were used in conjunction with the standard Grayson-Stadler pellet dispenser. The first system was the photobeam-triggered eatometer, with each new pellet delivered 1 sec following pellet removal [16]. The second system employed (BCI) food cups: shallow chambers into which a pellet was dispensed when the animal touched a metal baffle hanging in front of the chamber. The delivery systems were connected to a PDP-8 computer via a solid state digital I/O interface. Water intakes were read daily from 100 ml graduated cylinders.

Data Collection

Food intake and activity responses were continuously monitored with each dispensed pellet and each revolution of the activity wheel recorded by an on-line PDP-8 computer. A time-keeping mechanism was triggered at the onset of each bout of feeding and each bout of activity. Once the minimum threshold criterion had been met, a second timer, measuring the interbout interval, was activated. For the purpose of data collection, we defined the lowest threshold of a bout of feed-

ing as a minimum of one pellet dispensed during 1 min, and the lowest threshold of a bout of activity as one revolution of the running wheel occurring within 1 min. A feeding bout was considered as having terminated when no pellets were dispensed for at least 1 min. Similarly, a bout of activity was considered as having terminated when no revolutions of the running wheel occurred for at least 1 min. The minimum interbout interval (IMI) criterion in data collection was thus 1 min for both feeding and activity records.

Teletype and paper tape printouts of the collected data were obtained at the end of every 24 hr period. Analyses of the temporal course of intake and the parameters of feeding behavior were carried out on a PDP-10 computer at the University of Pennsylvania. Following inspection of the data, these analyses employed meal thresholds and intermeal interval criterion that differed from those of the data collection program [2]. A minimum of 5 pellets (0.2 g) was taken to constitute a meal and the minimum intermeal interval was set at 2 min.

Procedure

The rats were accustomed to the pellet diet during 1 wk prior to the start of the experiment. They were maintained on the diet for a baseline period of 6 to 12 days during which their intake remained stable. Following the baseline period, the rats were injected with the vehicle, were given one day of recovery, and were injected on the third day with Δ⁹-THC. The animals were always injected between 5:45 and 6 p.m., at the beginning of the 12-hr dark phase of the light/dark cycle.

RESULTS

Food and Water Intakes

Cumulative food and water intakes for baseline, vehicle and drug conditions are shown in Table 1. Vehicle injections did not affect food or water intakes relative to the baseline data. In contrast, a comparison of baseline and drug conditions showed that Δ⁹-THC suppressed daily food intakes of both the obese, paired $t(5)=3.53$; $p<0.01$, and lean rats, $t(5)=2.95$; $p<0.05$, and the water intake of the lean, $t(5)=5.58$; $p<0.01$, but not the obese rats, $t(5)=1.19$; n.s. Percentage suppression of food intakes relative to baseline was 17.2% for the lean and 14.5% for the obese rats, while percentage suppression of water intakes was 17.6% for the lean and 7.0% for the obese rats; both sets of values were similar to those obtained in Experiment 1 in the course of chronic drug treatment.

The temporal profile of action of Δ⁹-THC on food consumption was established by measuring the rats' food intake during 8 consecutive 3-hr periods following drug injection. Because the effects of vehicle injection were negligible, the principal comparison was made between baseline and drug conditions. Data in Fig. 4 show that obese rats eat significantly more food than do lean rats (Genotype: $F(1,10)=14.49$; $p<0.01$) and that the amount of food eaten depends on the time of day, with more food eaten during the dark cycle (6 p.m.–6 a.m., indicated in Fig. 4 by a solid bar on the abscissa) than during the subsequent light cycle (Time: $F(7,70)=6.09$; $p<0.01$).

The suppressive effects of Δ⁹-THC on food intake depend strongly on the time postinjection. The "anorectic-like" action of the drug appears to be delayed, with no changes in intake observed during the initial 3 hr postinjection.

TABLE 1

MEAN(± STANDARD ERROR) FOOD AND WATER INTAKES OF OBESE AND LEAN RATS IN EXPERIMENT 2

Condition	Zucker Obese (fa/fa) Food (g)	Zucker Obese (fa/fa) Water (ml)	Zucker Lean (Fa/–) Food (g)	Zucker Lean (Fa/–) Water (ml)
Baseline	31.7*	49.7	22.0†	36.8‡
	(1.6)	(6.4)	(1.3)	(2.2)
Vehicle	30.1	48.2	21.9	35.0
	(1.9)	(6.4)	(1.4)	(3.7)
Δ⁹-THC	27.1*	46.2	18.2†	30.3‡
	(2.6)	(5.0)	(1.5)	(2.5)

*†‡Similar subscripts indicate conditions that are significantly different ($p<0.05$) (two tailed t-test).

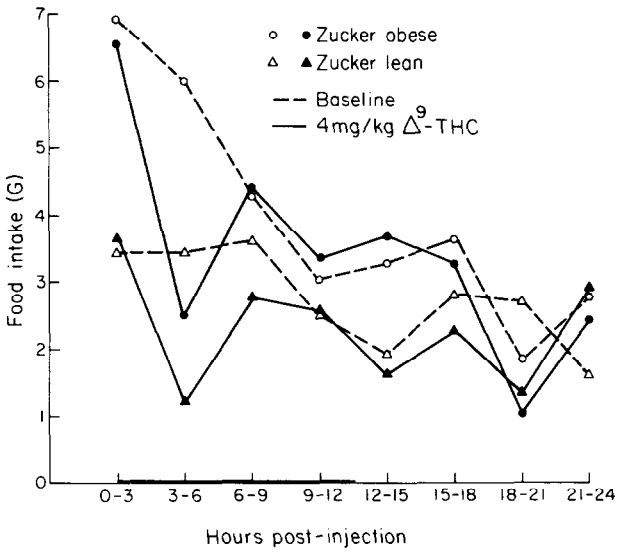

FIG. 4. Temporal effects of IP administration of Δ⁹-THC (4 mg/kg) on food intake of Zucker obese (n=6) and lean (n=6) rats in Experiment 2. Eight consecutive 3 hr periods are shown. The solid bar along the abscissa indicates the 12-hr dark cycle.

Moreover, the suppression in intake observed between 3–6 hr postinjection is not followed by rebound or compensatory feeding during the monitored 24 hr period. Analysis of variance shows both the main effect of Drug, $F(1,10)=20.95$; $p<0.01$, and the Drug by Time interaction, $F(7,70)=3.15$; $p<0.01$, as being significant. Subsequent planned comparison t-tests confirm that food intake is significantly suppressed relative to baseline only between 3 and 6 hr postinjection (obese: $t(10)=4.16$, $p<0.01$; lean: $t(10)=2.62$; $p<0.05$) and that no significant differences in intake are obtained at any other time.

Meal Parameters

Because changes in total food intake are accomplished through variation either in meal frequency or in meal size, further analyses examine the influence of Δ⁹-THC on the parameters of feeding behavior. Table 2 shows meal fre-

TABLE 2

EFFECTS OF Δ^9-THC ON SELECTED MEAL PARAMETERS (2 MIN IMI CRITERION) (MEAN ± SEM) IN EXPERIMENT 2 DURING THE INITIAL 6 HOURS POSTINJECTION

	Zucker Obese (fa/fa)				Zucker Lean (Fa/–)			
	Meal Size		Meal Frequency		Meal Size		Meal Frequency	
Hours postinjection	0–3	3–6	0–3	3–6	0–3	3–6	0–3	3–6
Baseline	2.98*	3.79*	2.38†	1.96	2.05	2.69*	2.08	1.50
	(0.56)	(0.72)	(0.13)	(0.49)	(0.40)	(0.59)	(0.56)	(0.42)
Vehicle	2.49	2.81	2.50	2.16	1.89	2.65	2.00	2.33†
	(0.56)	(0.59)	(0.50)	(0.65)	(0.44)	(0.75)	(0.52)	(0.49)
Δ^9-THC	1.80*	1.76*	4.00†	1.33	1.41	1.28*	2.83*	1.00†
	(0.51)	(0.57)	(0.86)	(0.42)	(0.36)	(0.32)	(0.70)	(0.26)

*,†=Similar subscripts indicate conditions that are significantly different. Planned comparison t-tests: $p<0.05$, (one tailed).

quencies and meal sizes established on the basis of a 2-min intermeal interval (IMI) criterion during the initial 6 hr following drug administration.

The drug reduces meal sizes during both time periods. The main effect of Treatment is significant, $F(2,20)=20.05$; $p<0.01$, but the effect of Time is not, $F(1,10)=2.54$; n.s., nor is the Treatment by Time interaction, $F(2,20)=1.34$; n.s. In contrast, meal frequency increases during the initial 3-hr period and decreases during the subsequent 3 hr.: the effects of Time, $F(1,10)=5.08$; $p<0.05$, and the Treatment by Time interaction, $F(2,20)=9.40$; $p<0.01$, are both significant. Planned comparison t-tests confirm that the main effect of Treatment is due to significant differences between baseline and drug or vehicle and drug conditions. No differences on any of the measures are obtained between vehicle and baseline conditions (see Table 2).

The early increase in number of small meals is reflected in the 24-hr distribution of meal sizes. Table 3 shows the percentage distribution of meal sizes, established on the basis of a 2-min IMI criterion, for baseline, vehicle and Δ^9-THC conditions. The data suggest that small meals or "nibbles" (<1 g) may arise at the expense of large meals (>4 g), the proportion of which is reduced following Δ^9-THC administration. The proportion of meals in the middle size range (1–4 g) remains relatively unaffected by the drug. The largest meals thus appear to be most vulnerable to disruption, and the drug seemingly shifts the animals' feeding pattern toward smaller feeding bouts or "nibbles".

TABLE 3

PERCENTAGE DISTRIBUTION OF MEAL SIZES (2 MIN IMI) IN EXPERIMENT 2

	Zucker Obese (fa/fa)			Zucker Lean (Fa/–)		
Meal Size (g)	<1	1–4	>4	<1	1–4	>4
Baseline	56.1	31.8	12.1	49.3	44.8	5.9
Vehicle	52.6	41.6	5.8	49.0	46.1	4.9
Δ^9-THC	61.2	36.2	2.6	58.8	41.2	0.0

DISCUSSION

The present data show that the "anorectic-like" effect of 4 mg/kg of Δ^9-THC observed with both obese and lean Zucker rats over a 24 hr period following injection is due entirely to a transient suppression in food intake between 3 and 6 hr postinjection that is not followed by rebound or compensatory eating.

The observation that meal frequency actually increases during the initial 3 hr suggests that one of the early effects of Δ^9-THC may be the stimulation of appetite. However, the concomitant reduction in average meal size might equally be interpreted as reflecting an increase in satiety [7]. The effects of Δ^9-THC on food intake therefore seem paradoxical, since both appetite and satiety appear to be enhanced simultaneously, while the total caloric intake is not affected, at least during the initial 3 hr. Since the observed increase in the number of small meals appears to occur at the expense of large meals, it may be that small meals arise as a result of pauses within larger bouts of feeding so that neither appetite nor satiety are affected by the drug. These possibilities are investigated in the following experiment, in which we also examine the effects of a range of doses of Δ^9-THC on the consumption of liquid food.

EXPERIMENT 3

The results of the previous experiment show that Δ^9-THC has delayed and short-lasting effects in suppressing the intake of solid food. An initial increase in small meals or "nibbles" is followed by transient anorexia, with the drug exerting its effects on food intake wholly within 3–9 hr postinjection. In the present experiment we investigate the temporal profile of intake and changes in meal parameters following different doses of Δ^9-THC. In addition, we examine the possible contributing effects of caloric density and diet palatability on food intake by maintaining rats on a sweetened condensed milk diet. We also examine whether Δ^9-THC acts initially as an appetite stimulant by measuruing the latency and size of the first meal, as well as the rate of feeding.

METHOD

Animals

Five genetically obese male Zucker rats (fa/fa) and 6 male lean littermates (Fa/–) were obtained from the Biology Department at Vassar College. (A preliminary description of this experiment has appeared in reference [10].) The animals

TABLE 4

EFFECTS OF INCREASING DOSES OF Δ⁹-THC ON LIQUID FOOD INTAKES (ML) (±SEM) DURING DARK AND LIGHT PERIODS IN EXPERIMENT 3

	Zucker Obese (fa/fa)			Zucker Lean (Fa/–)		
	Dark	Light	Total	Dark	Light	Total
Baseline	25.12 (2.40)	22.72 (1.15)	47.84 (2.10)	19.29 (1.35)	14.90 (1.47)	34.19 (2.31)
Vehicle	24.86 (7.87)	22.21 (1.21)	47.07 (7.45)	15.55 (1.66)	12.73 (1.23)	28.27 (1.80)
1 mg/kg Δ⁹-THC	22.03 (5.24)	17.51 (1.28)	39.54 (5.16)	13.19 (2.03)	13.05 (2.98)	26.24 (3.02)
4 mg/kg Δ⁹-THC	21.19 (4.34)	17.91 (2.07)	39.10 (2.99)	11.41 (1.18)	12.44 (2.62)	23.85 (1.95)
8 mg/kg Δ⁹-THC	17.99 (5.00)	16.44 (2.86)	34.66 (3.24)	13.17 (1.65)	13.23 (1.93)	26.40 (3.39)

were approximately 8 months old. The obese rats weighed between 694–908 g (mean=787.8 g), while their lean littermates weighed between 403 g–522 g (mean=484.1 g).

The animals were maintained on Borden's sweetened condensed milk, diluted 3:1 with water and supplemented with vitamins and minerals [5,10]. The caloric concentration of the diet was 3.17 kcal/ml. The animals had free access to water at all times.

Apparatus

Glass drinking tubes (100 ml) containing the liquid diet were attached to each cage. Each tube ended in a stainless steel spout, which was encased in a length of plastic tubing to prevent accidental grounding, and was connected to a drinkometer circuit, which was in turn connected to a PDP-8 computer [5,10].

Data Collection

Data collection proceeded as described previously. The lowest threshold for a feeding bout or meal was defined as 20 licks occurring within 1 min. The meal was considered to have terminated when no licking occurred for a period of 2 min. Two values of the minimum intermeal interval (IMI) criterion: 2 min and 15 min, were used in the analysis programs. The criteria for activity bouts were the same as those used in Experiment 2.

Procedure

The animals were maintained on the liquid diet for a baseline period of 5–12 days during which no injections were given. The rats were then given intraperitoneal injections of Δ⁹-THC at doses of either 1.0, 4.0 or 8.0 mg/kg, with the dose order counterbalanced in a Latin Square design. Drug injections, prepared and administered as described above, were spaced 2 days apart, with the rats receiving an equivalent volume of vehicle on the intervening days.

RESULTS

Total Intakes

Intakes of liquid food separated by the dark and light phases are shown in Table 4 for the obese and lean rats. An initial analysis of baseline data shows that obese rats eat more food than lean rats (ANOVA: $F(1,18)=16.78$; $p<0.01$) and that both groups show a temporal distribution of feeding, eating more during the 12 hr dark cycle than during the 12 hr light cycle, $F(1,18)=4.34$; $p<0.05$.

Liquid food intake is reduced following drug injection, particularly during the dark period. A comparison of baseline, vehicle and the 3 drug conditions shows significant main effects of Treatment, $F(4,80)=2.53$; $p<0.05$, and Genotype, $F(1,80)=29.89$; $p<0.01$. The present data thus confirm the results of Experiment 2 in showing that Δ⁹-THC exerts its anorectic effect within the initial 12 hr following drug injection.

Somewhat unexpectedly, the percentage reduction in food intake does not appear to be a function of drug dose. A separate analysis of variance, with Genotype, Time and Drug dose as the main variables shows a main effect of Genotype, $F(1,46)=12.62$; $p<0.01$, but no effect of Time, $F(1,46)=0.62$; n.s., or of Drug dose, $F(2,46)=0.15$; n.s. However, since the maximal effects of the drug occur within the first few hours postinjection, the effects of dose may be masked by the present measures of 12 hr intake. A comparison of the effects of the two extreme drug doses (1.0 and 8.0 mg/kg) on food intake during the 4 consecutive 3-hr periods following drug injections shows no significant effect on Drug dose for lean rats but does show a significant Dose by Time Period interaction for the obese rats, $F(3,18)=18.62$; $p<0.01$. Thus there is a dose effect but it is limited to the obese rats.

Meal Parameters

The effects of Δ⁹-THC on the two principal meal parameters: meal frequency and meal size, are shown separately in Table 5 for the obese and lean rats and for the dark and light periods. The table shows meal parameter values established on the basis of both 2- and 15-min IMI criteria.

Analysis of the 2-min IMI data shows that obese rats eat more frequently than lean rats (Genotype: $F(1,80)=8.43$; $p<0.01$), and that more food is consumed during the dark period (Time: $F(1,80)=18.86$; $p<0.01$). Obese rats also tend to eat larger meals than lean rats (Genotype: $F(1,80)=4.25$; $p<0.05$). The drug significantly reduces meal sizes (Treatment: $F(4,80)=5.18$; $p<0.01$), especially during the dark period (Time: $F(1,80)=7.96$; $p<0.01$), but does not appear to

TABLE 5

EFFECTS OF Δ^9-THC ON SELECTED MEAL PARAMETERS (2 AND 15 MIN IMI) (±SEM) DURING DARK AND LIGHT PERIODS IN EXPERIMENT 3

IMI Criterion	Zucker Obese (fa/fa) Frequency		Size (ml)		Zucker Lean (Fa/–) Frequency		Size (ml)	
	Dark	Light	Dark	Light	Dark	Light	Dark	Light
2 min								
Baseline	10.96	9.47	2.96	2.62	9.10	5.89	2.36	2.75
	(2.56)	(0.82)	(0.63)	(0.24)	(1.81)	(0.46)	(0.35)	(0.34)
Vehicle	11.50	7.50	3.02	3.89	9.33	5.83	1.87	2.56
	(5.50)	(1.94)	(0.65)	(1.34)	(1.14)	(0.75)	(0.33)	(0.29)
1 mg/kg	15.25	11.00	1.69	2.24	9.83	6.67	1.52	2.30
	(4.25)	(3.03)	(0.60)	(0.88)	(1.60)	(1.23)	(0.33)	(0.68)
4 mg/kg	16.80	8.40	1.27	2.42	11.00	5.67	1.08	2.15
	(3.25)	(1.12)	(0.06)	(0.62)	(1.26)	(0.67)	(0.14)	(0.34)
8 mg/kg	13.00	7.25	1.40	2.32	11.00	10.00	1.26	1.43
	(3.00)	(1.11)	(0.34)	(0.21)	(1.47)	(1.87)	(0.22)	(0.25)
15 min								
Baseline	6.94	7.10	4.00	3.38	6.68	5.44	2.90	2.99
	(1.17)	(0.46)	(0.49)	(0.21)	(0.80)	(0.32)	(0.26)	(0.32)
Vehicle	7.00	6.50	3.43	4.15	8.30	5.80	2.03	2.36
	(1.78)	(1.32)	(0.38)	(1.25)	(0.96)	(0.75)	(0.37)	(0.31)
1 mg/kg	10.25	8.75	2.41	2.47	7.17	5.33	2.10	2.67
	(2.69)	(1.89)	(0.73)	(0.79)	(1.17)	(0.67)	(0.42)	(0.72)
4 mg/kg	8.60	7.60	2.48	2.61	4.00	6.00	2.11	2.58
	(1.29)	(0.81)	(0.37)	(0.60)	(0.68)	(0.68)	(0.41)	(0.65)
8 mg/kg	7.00	6.50	2.51	2.59	5.50	7.75	2.58	1.67
	(0.95)	(0.96)	(0.56)	(0.24)	(0.50)	(1.11)	(0.41)	(0.19)

affect meal frequency; no significant effect of Treatment on meal frequency, $F(4,80)=0.93$; n.s., nor a Treatment by Time interaction is observed in the present experiment, $F(4,80)=0.67$; n.s.

Meal parameters calculated on the basis of the 15-min IMI criterion show a similar reduction in meal size (Treatment: $F(4,80)=2.70$; $p<0.05$) but no significant change in meal frequency (Treatment: $F(4,80)=1.04$, n.s.). The principal effect of the drug is therefore on meal sizes rather than on meal frequencies, in agreement with the data reported in Experiment 2. However, there may be effects of the drug on meal frequency which are too short-lasting to be revealed with a 12-hr measure of food intake.

Temporal Profile of Drug Action

Analysis of intake profiles shows that Δ^9-THC suppresses feeding (Treatment: $F(4,320)=2.93$; $p<0.05$) and that its effects vary with time (Treatment by Time interaction: $F(28,320)=1.57$; $p<0.05$). Concomitant changes in meal parameters during this period, as established on the basis of the single 2-min IMI criterion, are shown in Figs. 5 and 6. (Because no effect of drug dose on total intakes has been observed, the data shown have been averaged over the three drug doses.) The observed increase in meal frequency is seen only during the initial 3 hr, with the number of meals subsequently declining to baseline levels. The main effect of Treatment is not significant, $F(4,320)=1.63$; n.s., but there is a significant effect of Time, $F(7,320)=32.50$; $p<0.01$, and a significant Treatment by Time interaction, $F(28,320)=2.58$; $p<0.05$.

This transient increase in meal number is attenuated using the 15-min IMI criterion. The main effects of Genotype, $F(1,320)=14.04$; $p<0.01$, and Time, $F(7,320)=12.08$; $p<0.01$, are significant, but the effect of Treatment is not, $F(4,320)=1.48$; n.s. In contrast, the influence of the drug in reducing meal size is more robust, and the main effect of Treatment is significant (2 min IMI: $F(4,277)=4.70$; $p<0.01$; 15 min IMI: $F(4,269)=3.70$; $p<0.01$).

The data thus indicate that Δ^9-THC reduces meal size, an effect which persists across two different IMI criteria. In contrast, the effect of Δ^9-THC on meal frequency depends on the value of the IMI criterion (2 or 15 min), which suggests that the apparent increase in "nibbles" may be due to extended pauses within larger bouts of feeding rather than to a transient stimulation of appetite. The following analysis of the time of onset of the first meal is designed to test further the hypothesis that Δ^9-THC is an appetite stimulant; subsequent analysis of feeding rates tests the hypothesis that animals injected with Δ^9-THC pause more frequently within bouts of feeding.

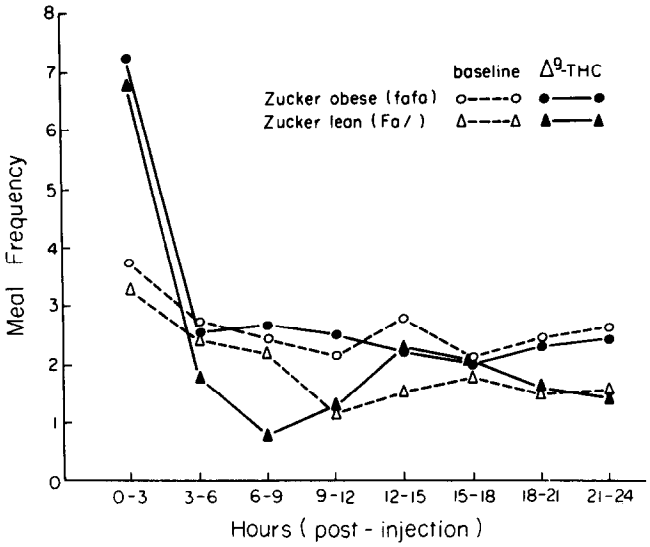

FIG. 5. Temporal effects of acute administration of Δ⁹-THC (IP) on meal frequency (2 min IMI) of obese (fa/fa) and lean (Fa/–) Zucker rats in Experiment 3. Data are averaged over drug doses (1, 4, 8 mg/kg). Eight consecutive 3-hr periods are shown.

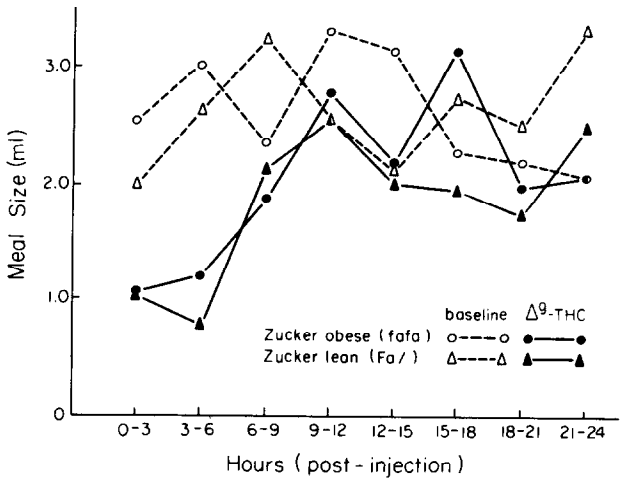

FIG. 6. Temporal effects of acute administration of Δ⁹-THC (IP) on meal sizes (2 min IMI) of obese (fa/fa) and lean (Fa/–) Zucker rats in Experiment 3. Data are averaged over drug doses (1, 4, 8 mg/kg). Eight consecutive 3-hr periods are shown.

TABLE 6

MEAN (±SEM) LATENCY AND SIZE OF THE FIRST MEAL AND THE FIRST MEAL ABOVE ONE ML FOLLOWING INCREASING DOSES OF Δ⁹-THC IN EXPERIMENT 3

	Zucker Obese (fa/fa)				Zucker Lean (Fa/–)			
	First Meal		First Meal above 1 ml		First Meal		First Meal above 1 ml	
	Latency (min)	Size (ml)	Latency (min)	Size (ml)	Latency (min)	Size (ml)	Latency (min)	Size (ml)
Baseline	42.0 (11.0)	3.54 (0.91)	51.0 (9.4)	3.96 (0.80)	22.4 (15.2)	2.24 (0.55)	43.7 (18.6)	3.17 (0.74)
1 mg/kg	47.8 (18.0)	2.18 (1.52)	62.6 (14.9)	3.00 (1.32)	22.8 (10.8)	2.29 (0.61)	56.1 (30.7)	2.63 (0.46)
4 mg/kg	43.7 (16.3)	3.66 (1.29)	46.2 (18.2)	4.14 (1.01)	21.7 (10.4)	1.61 (0.59)	75.5 (54.1)	2.41 (0.43)
8 mg/kg	32.5 (10.9)	1.76 (0.79)	134.2 (98.4)	3.29 (0.70)	19.2 (11.0)	1.34 (0.71)	76.7 (57.6)	2.23 (0.52)

Onset Time

Data shown in Table 6 indicate that Δ⁹-THC does not affect the onset of feeding following service time and the presentation of fresh food. A comparison of baseline and drug conditions is not significant at any dose level either for the onset time of the first meal, or for the onset time of the first meal exceeding 1.0 ml ($p>0.10$). The size of the first meal is significantly lower only for the highest drug dose (paired $t(7)=2.41$; $p<0.05$), while the size of the first meal above 1 ml remains unaffected by the drug. Unchanged onset of feeding thus argues against Δ⁹-THC acting as an appetite stimulant. Since the onset of feeding remains unaffected, the subsequent anorectic action of Δ⁹-THC cannot be due to conditioned aversion to food, avoidance behavior or general malaise as has been suggested previously [11]. Moreover, the present pattern of results does not conform to the data obtained with d-amphetamine, which has been reported to delay the onset of the first meal, or with fenfluramine, which has been reported to reduce the initial meal size [7].

Feeding Rates

Feeding rates (ml/min) of the Zucker obese and lean rats were calculated by dividing the average meal size obtained on the basis of the 15-min IMI by the average meal duration in minutes. Because the measure of meal duration used here represents not the time spent eating but rather the time from the first feeding response to the response followed by 15 min of no feeding, it is particularly sensitive to within-meal pauses. Data shown in Table 7 demonstrate that Δ⁹-THC does indeed reduce feeding rates during the dark period, the

TABLE 7

EFFECTS OF Δ^9-THC ON FEEDING RATES (ML/MIN) (±SEM) ESTABLISHED USING A 15-MINUTE IMI IN EXPERIMENT 3

	Zucker Obese (fa/fa)		Zucker Lean (Fa/–)	
	Dark	Light	Dark	Light
Baseline	0.38 (0.08)	0.45 (0.09)	0.47 (0.09)	0.66 (0.11)
Vehicle	0.31 (0.08)	0.62 (0.25)	0.45 (0.11)	0.79 (0.14)
1 mg/kg	0.26 (0.05)	0.47 (0.18)	0.34 (0.07)	0.61 (0.21)
4 mg/kg	0.25 (0.06)	0.65 (0.29)	0.14 (0.02)	0.86 (0.24)
8 mg/kg	0.16 (0.04)	0.49 (0.11)	0.17 (0.03)	0.59 (0.23)

analysis of variance for the dark period showing a significant main effect of drug treatment, $F(4,39)=4.25$; $p<0.01$. The observed transient increase in small meals thus seems to be due to slower feeding rates and more frequent pauses within feeding bouts, and is unlikely to be due to appetite stimulation.

DISCUSSION

The present data confirm those obtained in Experiment 2 in showing that the anorectic effects of Δ^9-THC are short-lived, with intakes falling significantly below baseline only within the initial 12 hr postinjection. The effects on meal parameters are even more short-lasting. Meal frequency initially increases and then drops to baseline levels within 3–6 hr, while meal size initially drops but recovers within 9–12 hr postinjection. Neither meal frequency nor meal size differ from baseline values during the subsequent light cycle and no compensatory or rebound feeding is observed.

The effects of Δ^9-THC on meal parameters seem inconsistent with the established models of anorectic action. The observed increase in meal frequency cannot be readily interpreted as reflecting a transient increase in appetite, since onset time of the first meal is unchanged relative to the baseline condition. Although rats injected with Δ^9-THC appear to eat more frequently, they do not eat sooner than non-injected animals. Similarly, the decrease in meal size cannot be interpreted as reflecting an increase in satiety because the total amount of food eaten within the initial 3 hr is not significantly different from the baseline level. This shift in the rats' feeding pattern towards more, smaller meals becomes less paradoxical if we interpret small meals as arising as a result of frequent pauses within larger bouts of feeding. Meal frequency established on the basis of the more conservative 15-min IMI criterion [21] does not change substantially following injections of Δ^9-THC, so that the number of larger feeding bouts remains unchanged. However, the duration of bouts established on the basis of the 15-min IMI becomes disproportionately long in relation to the increase in bout size, leading to the observed significant decreases in feeding rates.

One explanation of the reduced feeding rates that would be in line with anectodal reports of a craving for sweets following cannabis administration [2] is that the animals may savor the highly palatable diet [26]. However, a similar increase in "nibbles" was also observed with solid food, so the effect is probably independent both of the caloric density and the palatability of the diet. A more likely explanation involves the rats' state of arousal: Δ^9-THC has been shown to have a sedating effect at higher doses [12]. It may be that frequent pauses within feeding bouts, followed by a subsequent drop in the number of meals, reflect the tranquilizing effects of Δ^9-THC. The following experiment deals, therefore, with the temporal pattern of spontaneous running-wheel activity of the obese and lean rats following injections of Δ^9-THC.

EXPERIMENT 4

If the observed suppression in food intake is an indirect consequence of the sedating effects of Δ^9-THC, then its temporal course might be expected to be reflected in a parallel suppression of the rats' spontaneous activity. Moreover, one would expect to obtain with measures of the animals' activity a dose-response curve to Δ^9-THC that was not obtained with measures of food intake in Experiment 3. We therefore present concomitant measures of running wheel activity of rats described in Experiments 2 and 3 and we investigate both the temporal pattern of activity and the effects of increasing drug doses.

METHOD

The animals, apparatus and procedures used were the same as those already described for Experiments 2 and 3, with the number of running bouts (defined on the basis of a 2-min IMI criterion), and the mean number of revolutions per bout serving as the dependent variables.

RESULTS

Data presented in Table 8 show a reduction in the rats' running wheel activity following Δ^9-THC. A comparison of the drug and baseline conditions for the 1.0 mg/kg Δ^9-THC dose level shows no significant differences on either of the two measures used (Wilcoxon's signed-ranks, matched pairs tests: $p>0.10$), whereas the same comparison for the 8.0

TABLE 8

EFFECTS OF INCREASING DOSES OF Δ^9-THC ON ACTIVITY PARAMETERS IN EXPERIMENT 3*

		Number of Bouts	Revolutions/bout
Zucker Obese (fa/fa)			
Baseline		4.68†	2.34‡
Δ^9-THC	1 mg/kg	7.33	2.76
	4 mg/kg	2.33	2.67
	8 mg/kg	2.00†	1.50‡
Zucker Lean (Fa/–)			
Baseline		15.37†	5.93‡
Δ^9-THC	1 mg/kg	11.16	3.89
	4 mg/kg	12.50	4.05
	8 mg/kg	7.80†	3.19‡

*Data for the obese and lean Zucker rats were pooled for statistical analysis.

†‡similar subscripts indicate conditions that are signficantly different ($p<0.05$) (two tailed t-test).

TABLE 9

EFFECTS OF Δ⁹-THC ON ACTIVITY PARAMETERS IN EXPERIMENTS 2 AND 3*

Hours postinjection	Number of bouts 0–3	Number of bouts 3–6	Revolutions/bout 0–3	Revolutions/bout 3–6
Solid Diet (Expt. 2)				
Zucker Obese (fa/fa)				
Baseline	3.73	3.83	5.25	5.44
4 mg/kg	3.50	3.25	2.81	1.83
Zucker Lean (Fa/–)				
Baseline	4.00	4.49	9.16	9.75
4 mg/kg	4.00	2.50	3.13	7.36
Liquid Diet (Expt. 3)				
Zucker Obese (fa/fa)				
Baseline	3.15	1.80	4.26	4.11
Δ⁹-THC†	2.50	0.83	3.76	2.66
Zucker Lean (Fa/–)				
Baseline	4.18	4.35	9.56	8.37
Δ⁹-THC	4.20	2.06	5.54	4.29

*Data for the obese and lean rats were pooled for statistical analysis.

†Data for Experiment 3 were combined over the three doses of Δ⁹-THC.

mg/kg dose is significant both for the number of bouts ($p<0.02$, two-tailed), and the mean number of revolutions per bout ($p<0.05$, two-tailed).

A question now arises as to whether the temporal course of suppression of activity parallels that of suppression of food intake. Measures of activity were therefore obtained for two consecutive 3-hr time periods following drug injection. Since food intake was found to have been maximally suppressed during that time (Experiments 2 and 3), we might expect this effect to be reflected in the suppression of concomitant activity.

The temporal profile data are shown in Table 9. The drug does suppress the rats' activity during the initial 6 hr postinjection. The effect is significant for the initial 3 hr for the number of revolutions per bout in Experiment 2 (Wilcoxon's test: $p<0.05$, two-tailed), and for both measures during the initial 3-hr postinjection in Experiment 3 (Wilcoxon's test: $p<0.05$, two-tailed). Because the data in Experiment 3 were pooled over the 3 drug doses (1.0, 4.0 and 8.0 mg/kg Δ⁹-THC, whereas Experiment 2 employed only a single dose of 4.0 mg/kg Δ⁹-THC), this effect is consistent with the notion of a slower recovery following larger doses of Δ⁹-THC. The data show that the temporal patterns of suppression of activity coincides with the previously discussed pattern of intake suppression.

GENERAL DISCUSSION

This series of experiments documents the suppression in daily food and water intakes of non-deprived obese and lean Zucker rats following treatment with Δ⁹-THC. The observed anorexia is delayed and short-lasting, with no suppression in intake observed during the initial 3-hr postinjection and with full recovery, unaccompanied by rebound eating, occurring by the end of the 12-hr dark period. These effects are observed for both solid and liquid diets, which differ from each other both in palatability and in caloric density.

Examination of meal parameters (meal frequency and meal size) shows that Δ⁹-THC does not follow the patterns exemplified by d-amphetamine and by fenfluramine, thought to be the principal models of anorectic action [6,7]. The present data show an initial increase in the frequency of small meals or "nibbles" occurring within the initial 3-hr postinjection period, that is followed by an overall decrease in both meal frequency and in meal size. Unlike d-amphetamine, Δ⁹-THC does not appear to affect appetite, since the onset time of the first meal is unchanged relative to baseline. Unlike fenfluramine, Δ⁹-THC does not appear to enhance satiety, since the size of the first meal is not decreased and no reduction in intake is observed during the initial 3-hr. Increased pausing within larger bouts of feeding (as seen with a 15-min IMI) leads to an apparent increase in the number of small meals or nibbles (as seen with a 2-min IMI) and is also reflected in the apparent reduction in the overall feeding rate.

Since the temporal pattern of reduction in food intake exactly parallels the temporal pattern of reduction in running-wheel activity, the altered pattern of feeding following Δ⁹-THC may be a direct consequence of the rats' altered state of arousal. The drug may thus exert its "anorectic-like" action by tranquilizing the rats, rather than by directly influencing central mechanisms concerned with the control of food intake. This intrepretation is consistent with the following observations. First, a greater suppression in activity occurs with the 8 mg/kg dose than with the 1 mg/kg dose but there are no differences in the suppression of food intake. Secondly, the food and water intakes are equally affected by the drug. Thirdly, the drug has equivalent effects on both obese and lean rats. This hypothesis is also consistent with the previously noted similarities among the actions of Δ⁹-THC and tranquilizers and barbiturates [22].

The present data show that reductions in food intake can be produced by a variety of mechanisms. Agents earlier classed as "anorectic" simply because they produce a decrease in daily food intake can be shown upon detailed examination to have modes of action which may cause suppression of food intake but which otherwise are not properly classifiable as anorectic. The present study demonstrates an experimental approach to the investigation of potential anorectic agents and illustrates the importance of continuous intake and activity measures in behavioral pharmacology.

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