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Δ^9-THC stimulates food intake in Lewis rats Effects on chow, high-fat and sweet high-fat diets

James E. Koch*

Department of Psychology, University of Wisconsin Oshkosh, 800 Algoma Boulevard, Oshkosh, WI 54901, USA

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Abstract

Free-feeding adult male Lewis rats were administered intraperitoneal (ip) Δ^9-tetrahydrocannabinol (THC) in doses of 0.5, 1.0 and 2.5 mg/kg, and effects on food intake were measured at 1, 2, 4, 6 and 24 h postinjection. Rats were fed rat chow, a high-fat diet (HF) or a high-fat sweetened (HFS) diet. Small increases in HF and HFS intake following doses of 0.5 or 1.0 mg/kg were seen at 1, 2 and 4 h, but not 6 or 24 h compared to vehicle intake. Increases following 0.5 and 1.0 mg/kg did not differ from each other at any time point and 2.5 mg/kg produced smaller differences at all time points. There was no difference between HF or HFS intake at any time point although larger increases were seen in the HF group compared to both chow and HFS following 0.5 and 1.0 mg/kg. This work confirms previous data in both humans and rats indicating a stimulatory role for cannabinoids in ingestive behavior.

Keywords: Food intake; High-fat diet; Sweet high-fat diet; Lewis rats; Δ^9-THC; Cannabinoids

1. Introduction

While there are numerous reports of marijuana stimulating food intake in humans (Abel, 1971; Foltin et al., 1986, 1988), with the primary target foods being high in fat, sugar or both (Iverson, 2000), it remains to be definitively established that the primary psychoactive component of this drug, Δ^9-tetrahydrocannabinol (Δ^9-THC), is responsible for appetite stimulation. Some early work reported stimulatory effects (Abel, 1971; Greenberg et al., 1976; Hollister, 1971), but other similar reports have been sporadic (Foltin et al., 1986; Mattes et al., 1994) and subsequent applications of these cannabinoid effects include the treatment of wasting diseases in which patients are unable or unwilling to ingest food (Abrams, 1998; Balog et al., 1998; Gross et al., 1983; Mattes et al., 1993). The identification of centrally located cannabinoid receptors (Matsuda et al., 1990), as well as that of anandamide and other endogenous cannabinoid ligands (Devane et al., 1992; Pop, 1999), has provided impetus for new research in the various behavioral effects of cannabinoids. Δ^9-THC interacts with both cannabinoid receptor subtypes, CB_1 and CB_2, the former of which is located primarily in the central nervous system (Matsuda et al., 1990). CB_1 receptors have recently been shown to mediate the hyperphagic effects of anandamide, an effect which is blocked by the CB_1 receptor antagonist SR141617 (Williams and Kirkham, 1999).

Attempts to establish a link between Δ^9-THC and stimulatory effects on food intake in rats have produced disparate results with a number failing to find such a link or reporting anorectic effects (Graceffo and Robinson, 1998; Miczek and Dixit, 1980; Sofia and Knobloch, 1976). Despite these results, there are notable exceptions including Δ^9-THC facilitation of feeding induced by electrical lateral hypothalamic stimulation in rats (Trojniar and Wise, 1991), as well as more direct procedures resulting in intake stimulation (Brown et al., 1977; Glick and Milloy, 1972; Gluck and Ferraro, 1974). Further, two recent studies have reported increases in food intake in rats following oral administration of Δ^9-THC (Williams et al., 1998) and anandamide (Williams and Kirkham, 1999).

Macronutrient and dietary composition studies with peptides such as opioids (Koch and Bodnar, 1994; Koch et al., 1995) and NPY (Altizer, 1999; Glass et al., 1997) have demonstrated a specificity of effect linking receptor types or subtypes to specific dietary components. With the increasing likelihood that cannabinoids play a role in patterns of

* Tel.: +1-920-424-2303; fax: +1-920-424-1204.
E-mail address: kochj@uwosh.edu (J.E. Koch).

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ingestion, it is of interest to find out if these latter substances also affect the distribution of intake of fat, carbohydrate and protein. Reports of ingestion in humans following marijuana intake include a predomination of foods high in sugar and fat (Abel, 1971; Foltin et al., 1986, 1988; Iverson, 2000), and some animal studies have done so also (Brown et al., 1977; Sofia and Knobloch, 1976), although there is little agreement in the results.

In an effort to further clarify the parameters of a Δ^9-THC-induced stimulation of food intake, and to address the issues described above, the present study used Lewis rats and three diets: pelleted rat chow, a powdered high-fat diet (HF) and the same high-fat diet sweetened with saccharine (HFS). It was hypothesized that Δ^9-THC would, over a short time frame and in a dose-dependent manner, increase intake in all diet groups with the largest increases being in the HFS-fed rats and the lowest being in the chow-fed rats.

2. Methods

2.1. Animals

A total of 26 male Lewis rats (Harlan Sprague–Dawley) weighing 200–220 g at the start of the experiment were housed individually and maintained on a 12:12 light/dark cycle (light onset at 07:00 hours). Food (one of the three diets, see below) and tap water were continuously available.

2.2. Drugs

Δ^9-THC was obtained from NIDA (Bethesda, MD) in concentrations of 50 mg/ml in absolute ethanol. Δ^9-THC was diluted to injection concentrations in a mixture of 0.9% saline and alkamuls EL-620 (ethoxylated castor oil; Rhone-Poulenc, NJ) combined in a ratio of 18:1 (vehicle) and was injected intraperitoneally (ip) at volumes of 1 ml/kg body weight.

2.3. Diets

The chow diet was standard laboratory pellets (Harlan Teklad, diet no. 8604) providing 4% of calories as fat, 24% as protein and 46.6% of calories as carbohydrate (3.93 kcal/g). The HF and HFS were powdered and custom-made by Dyets Inc. (Bethlehem, PA). The HF provided 63% of calories as fat (corn oil), 13% of calories as carbohydrate (corn starch) and 24% as protein (4.7 kcal/g) while the HFS was identical except for being sweetened with 0.1% sodium saccharine.

2.4. Procedure

Rats were randomly assigned to one of the three diets (chow: $n=9$; HF: $n=9$; HFS: $n=8$), maintained on these diets for 3 weeks prior to testing and were handled and weighed every third day. Following establishment of stable baseline food and H_2O intake (10 consecutive days of statistically identical 24-h consumption), and starting at 08:00 hours (1 h into the light cycle), rats were injected intraperitoneally with either vehicle or Δ^9-THC (0.5, 1.0 and 2.5 mg/kg). Intake, in grams (adjusted for spillage), was measured at 1, 2, 4, 6 and 24 h following injection. Injections were spaced at weekly intervals and counterbalanced within each diet group. For each data collection time point (1, 2, 4, 6 and 24 h), intake in grams was converted to kilocalories (kcal) consumed, and a mixed ANOVA was used to analyze cumulative intake for main (diet group and drug dose) and interaction effects (Diet × Dose) with Scheffe post hoc comparisons used where appropriate. There were small nonsignificant baseline differences in the amount in kilocalories consumed by rats in the three diet groups with the HF and HFS being consumed in amounts equal to each other but slightly greater than chow.

3. Results

At 1 h following injections of Δ^9-THC, significant main effects with differences in both Diet [$F(2, 92)=13.99$, $P<.0001$] and Dose [$F(3, 92)=31.84$, $P<.0001$] and a significant Diet × Dose interaction [$F(6, 92)=3.51$, $P<.0036$] (see Table 1 for Diet × Dose cumulative intake for 1, 2 and 4 h) were produced. With respect to main diet effects, rats fed chow ($X=4.09+0.93$; all values are mean in kcal ± S.E.M.) and the HFS ($X=4.75\pm0.87$) ate significantly less food than rats fed the HF ($X=7.64\pm0.93$). For the main effect for dose, 0.5 and 1.0 mg/kg resulted in significant increases in intake ($X=7.31\pm1.02$ and $X=8.98\pm1.25$, respectively) for all diet groups compared with vehicle ($X=1.6\pm0.46$) and the 2.5 mg/kg dose ($X=4.08\pm0.91$). With respect to significant interactions at

Table 1
Cumulative intake in kilocalories for Diet × Dose conditions (means ± S.E.M.)

		Time period		
Diet	Dose	1 h	2 h	4 h
Chow	Vehicle	1.29 ± 0.5	2.73 ± .44	8.21 ± 0.71
	0.5	4.64 ± .82	8.92 ± .83	9.62 ± 0.71
	1.0	6.01 ± 1.75	10.04 ± 1.11	11.66 ± 1.02
	2.5	4.41 ± 1.09	7.34 ± 0.97	9.83 ± 0.98
HF	Vehicle	1.39 ± 0.71	3.07 ± 0.69	9.43 ± 1.09
	0.5	10.96 ± 1.27	13.31 ± 1.6	14.67 ± 1.5
	1.0	12.36 ± 0.9	16.58 ± 0.71	17.18 ± 0.73
	2.5	5.59 ± 0.84	7.01 ± 0.8	10.54 ± 0.6
HFS	Vehicle	2.12 ± 0.62	3.72 ± 0.62	11.33 ± 1.05
	0.5	6.33 ± 0.96	12.16 ± 1.15	13.32 ± 1.13
	1.0	8.3 ± 1.11	16.1 ± 0.9	16.83 ± 0.7
	2.5	2.25 ± 0.79	6.76 ± 0.64	9.9 ± 1.24

See Fig. 1a–c for significant differences between means.

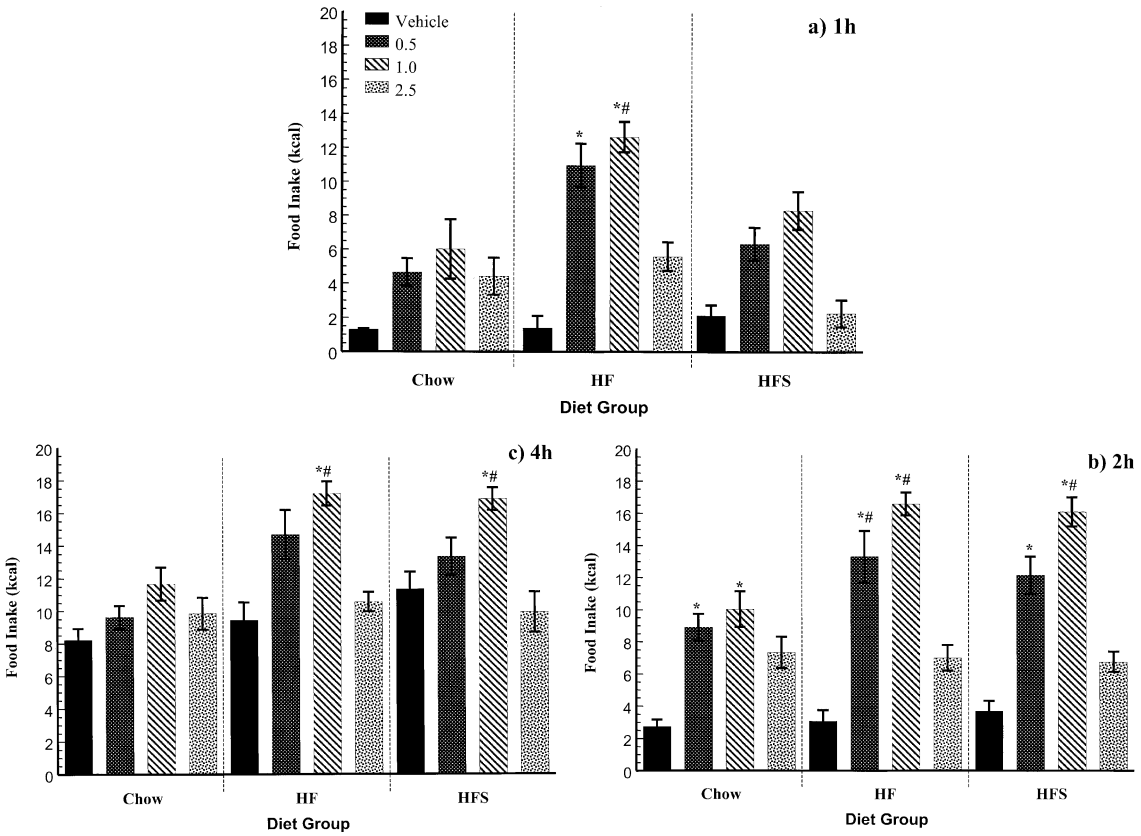

Fig. 1. Diet by dose interactions for 1 h (a), 2 h (b) and 4 h (c) of cumulative intake in kilocalories of chow, HF and HFS diets. * Significant differences from vehicle ($P<.01$); # Significant increases compared to 2.5 mg/kg ($P<.01$).

1 h (see Fig. 1a), in rats fed the HF, doses of 0.5 and 1.0 mg/kg increased intake compared to vehicle and doses of 2.5 in both other diet groups. HF-fed rats receiving 1.0 mg/kg also increased intake significantly more than chow-fed rats receiving 0.5 and 1.0 mg/kg. In rats fed the HFS, 1.0 mg/kg produced a significant increase compared only to the chow-fed vehicle condition. Within the chow group, even though the 1.0 dose produced a modest increase, it did not differ significantly from intake levels following other Δ^9-THC doses or vehicle within the chow group.

At 2 h following Δ^9-THC injections, significant main effects for both Diet [$F(2, 92)=10.41$, $P<.0001$] and Dose [$F(3, 92)=82.60$, $P<.0001$], as well as a significant Diet × Dose interaction [$F(6, 92)=3.785$, $P<.002$] were produced. HF ($X=9.99\pm0.95$)- and HFS ($X=9.68\pm0.83$)-fed rats ate significantly more than chow-fed rats ($X=7.26\pm0.84$). Doses of 0.5, 1.0 and 2.5 mg/kg ($X=11.46\pm1.19$, $X=14.24\pm1.19$ and $X=7.04\pm0.80$, respectively) resulted in significant increases in intake for all diet groups compared with vehicle ($X=3.17\pm0.58$), and intake following doses of 0.5 and 1.0 was significantly greater than that following 2.5 mg/kg. With respect to Diet × Dose interactions (see Fig. 1b), doses of 0.5 and 1.0 mg/kg produced significant increases in intake in all diet groups compared to vehicle injections, and in HF- and HFS-fed rats receiving 1.0 mg/kg, significant increases compared to 2.5 mg/kg. Doses of 1.0 mg/kg produced the largest increases in intake in all diet groups, and HF-fed rats receiving 1.0 mg/kg ate significantly more than their chow-fed counterparts receiving the same dose. While a dose of 2.5 mg/kg produced some increases in intake, these never differed from vehicle in any of the diet groups.

At 4 h following injections of Δ^9-THC, significant Diet group differences [$F(2, 92)=16.65$, $P<.0001$] and Dose [$F(3, 92)=20-51$, $P<.0001$] effects remained. There was no significant Diet × Dose interaction although there remained some significant post hoc group comparisons. Intake in the HF- and HFS-fed rats remained significantly higher than that in chow-fed rats ($X=13.23\pm0.98$, $X=13.41\pm1.03$ and $X=9.83\pm0.86$, respectively). The 1.0 dose significantly increased intake compared to all other doses, none of which were different from one another (vehicle $=15.49\pm0.82$, 0.5 mg/kg $=12.9\pm1.11$, 2.5 mg/kg $=10.36\pm0.94$). Specifically, 1.0 mg/kg produced significant increases compared to vehicle, but not 0.5 mg/kg, in HF- and HFS-fed rats (see Fig. 1c).

Interval intake (kcal) was also analyzed for 0–1, 1–2 and 2–4 h following Δ^9-THC (see Table 2 for means ± S.E.M.). Results for 0–1 h are identical to those described for the 1-h cumulative intake described above. From 1 to 2 h, HFS-fed rats ate significantly more than HF- or chow-fed rats [$F(2, 92)=13.39$, $P<.0001$], and 0.5 and 1.0 mg/kg doses pro-

Table 2
Effects of THC on interval kilocalorie intake

		Time interval		
Diet	Dose	0–1 h	1–2 h	2–4 h
Chow	Vehicle	1.29 ± 0.5 (16)	1.44 ± 0.21 (18)	5.48 ± 0.66 (66)
	0.5	4.64 ± .82 (48)	4.27 ± 0.05 (44)	0.71 ± 0.37 (8)
	1.0	6.01 ± 1.75 (52)	4.03 ± 0.84 (35)	1.62 ± 0.42 (13)
	2.5	4.41 ± 1.09 (45)	2.93 ± 0.46 (30)	2.49 ± 0.44 (25)
HF	Vehicle	1.39 ± 0.71 (15)	1.68 ± 0.63 (18)	6.36 ± 0.92 (67)
	0.5	10.96 ± 1.27 (75)	2.34 ± 0.51 (16)	1.37 ± 0.46 (9)
	1.0	12.36 ± 0.9 (74)	3.95 ± 1.07 (23)	0.6 ± 0.2 (3)
	2.5	5.59 ± 0.84 (53)	1.43 ± 0.4 (14)	3.54 ± 0.77 (33)
HFS	Vehicle	2.12 ± 0.62 (19)	1.61 ± 0.49 (14)	7.61 ± 1.0 (67)
	0.5	6.33 ± 0.96 (48)	5.82 ± 1.3 (44)	1.16 ± 0.41 (8)
	1.0	8.3 ± 1.11 (49)	7.8 ± 0.84 (46)	0.73 ± 0.47 (5)
	2.5	2.25 ± 0.79 (23)	4.51 ± 0.83 (46)	3.14 ± 1.07 (31)

Tabled values represent group means ± S.E.M.

Numbers inside parentheses represent, within each interval, the percentage of the total 4-h intake.

duced significant increases compared to those following vehicle and 2.5 mg/kg [$F(3, 92) = 14.43$, $P < .0001$], but there was no Diet × Drug interaction. Diet differences from 2 to 4 h reached significance [$F(2, 92) = 3.2$, $P < .05$] with HFS-fed rats eating more than chow rats. Dose differences also remained with the largest intakes following vehicle [$F(3, 92) = 46.08$, $P < .0001$].

Differences between diet groups and doses of Δ^9-THC were not present at 6 or 24 h after drug administration (data not shown) for either cumulative or interval intake.

4. Discussion

The stimulatory effects of intraperitoneal administration of Δ^9-THC can be addressed from a number of angles. Doses of 0.5 and 1.0 mg/kg produced similar increases in intake with those following 1.0 doses slightly higher in all diet groups while 2.5 mg/kg produced nonsignificant increases. These latter data are in contrast to a number of previous reports, which have shown intake suppression following 2.5 mg/kg (Foltin et al., 1986; Glick and Milloy, 1972; Graceffo and Robinson, 1998; Sofia and Knobloch, 1976), as well as conditioned taste or place aversions (Lepore et al., 1995; Parker and Gillies, 1995). The hyperphagic effects of the two lower doses support previous reports of a similarly narrow effective dose range for Δ^9-THC (Brown et al., 1977; Glick and Milloy, 1972; Manning et al., 1971; Sjoden et al., 1973; Sofia and Barry, 1974; Sofia and Knobloch, 1976; Williams et al., 1998) and anandamide (Williams and Kirkham, 1999). The increase in intake in the present study is modest, both overall and in comparison to that produced by other applications of Δ^9-THC (Williams et al., 1998) and by other stimulatory compounds in free-feeding paradigms, such as peptides. The dose-dependent pattern of intake at 1, 2 and 4 h following Δ^9-THC is an "inverted U" shape, a biphasic effect most likely produced by reported motor deficits at doses of 2.5 mg/kg and above (Foltin et al., 1986; Miczek and Dixit, 1980). No such deficits were observed (nor systematically measured) in the present groups of rats following this dose, and some stimulation of intake was observed compared to vehicle. While 2.5 mg/kg-induced intake was not different from vehicle intake at any time point, suppressions compared to vehicle were not seen either, a departure from the anorectic results previously reported to follow this dose (Glick and Milloy, 1972; Manning et al., 1971; Sjoden et al., 1973; Sofia and Barry, 1974), although food palatability may impact the effects on ingestion of higher doses as 20% sucrose solution consumption failed to be suppressed by higher doses of Δ^9-THC (Sofia and Knobloch, 1976). Indeed, recent data from our lab indicate that intracerebroventricular injections of doses up to 25 μg do not suppress intake of a palatable food.

The time course of the dose-dependent effects shows most significant differences abating by 4 h and no long-term effects on intake. One reason may be satiety. Table 2 shows kilocalorie intakes for each interval up to 4 h, demonstrating that over the first 2 h after Δ^9-THC administration, an average of 85% of the eventual total 4-h intake was consumed across all diets, and by 6 h, all dose group intakes are essentially the same (data not shown). These data parallel recent reports of cannabinoid-induced stimulation (Williams and Kirkham, 1999; Williams et al., 1998) but do not appear to support reports of compensatory decreases in intake (Brown et al., 1977), as long-term intake was not suppressed. A second reason for this pattern of stimulation may be that sedative side effects may appear more strongly in the latter part of the measured time course, leading previously stimulated animals to enter a period of relative quiescence. Finally, in humans, a feeling of contentment (and subsequent inactivity) is reported to follow ingestive "binges" induced by marijuana intake (Iverson, 2000), although support for parallel emotional states in animal models does not presently exist.

With respect to dietary composition, it was hypothesized that the greatest increases in intake would be seen in rats fed the HFS and the smallest effects seen in rats fed chow. Only the latter part of this hypotheses was supported as HF-fed rats ate significantly more at 1 h compared to both other diets. At 2 and 4 h, HF- and HFS-fed rats consumed food in equal measure and in amounts markedly greater than chow-fed rats. Table 2 reveals a slightly different ingestion pattern between diets with HFS- and chow-fed rats consuming steadily over 2 h, while significant increases in HF-fed rats occurred predominantly during the 0–1 h interval. It is possible that the 0.1% saccharine added to make the HFS affected the rate at which ingestion occurred, creating a gustatory experience that made intense "bingeing" less likely compared to the HF, but not creating overall differences in intake over the effective time course of the drug.

Lewis rats appear to be responsive to both appetite stimulating and overall rewarding effects of Δ^9-THC both alone, facilitating feeding induced by hypothalamic stimulation (Trojniar and Wise, 1991), and in comparison to Sprague–Dawley, Long–Evans or Fischer strains (Gardner et al., 1988). Lewis rats respond to opiate agonists with larger increases in food intake compared to F344 rats (Gosnell and Krahn, 1993) and also show the largest increases in enhancement of brain reward activity in the medial forebrain bundle following 1.0 mg/kg Δ^9-THC compared to both Sprague–Dawley and F344 strains (Lepore et al., 1996). Thus, Lewis rats may prove useful in cannabinoid system/ingestion studies in the future. In addition, different routes of drug administration (such as intracerebroventricular), use of highly palatable foods (although see Graceffo and Robinson, 1998), manipulating palatability levels of available food or using multiple-diet free-choice paradigms may reveal further characteristics of cannabinoid/ingestion relationships.

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