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Influence of Tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on Body Weight, Food, and Water Intake in Rats[1,2]

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SJÖDÉN, P.-O., T. U. C. JÄRBE AND B. G. HENRIKSSON. *Influence of tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on body weight, food and water intake in rats.* PHARMAC. BIOCHEM. BEHAV. 1(4) 395–399, 1973.–Female Wistar rats, six to a group, were injected daily for a 23-day period with Δ^8-THC (5.0 mg/kg), Δ^9-THC (2.5 mg/kg) or vehicle. Body weight, food and water intake were recorded every second day. It was found that Δ^8-THC caused a decrease of body weight, to a level maintained throughout the injection period, with only slight signs of recovery. Both drugs caused a marked decrease of water intake. Food intake was not significantly affected by the drugs. Factors in relation to the effects of THC on body weight, food and water intake are discussed.

Body weight Food and water intake Δ^8-THC Δ^9-THC

WITH respect to the effects of a cannabis extract and tetrahydrocannabinols (THC) on body weight, food and water intake in rats, only two investigations seem to have been performed [4,7].

In the report by Fernandes *et al.* [4], single and repeated injections of cannabis resin caused a 20–25% reduction of food and water intake. A reduction of food intake was also seen after repeated injections of Δ^8-THC, 5 mg/kg. Water intake was not recorded after injections of Δ^8-THC. The reported effects of cannabis resin and Δ^8-THC disappeared after 11 and 8 days respectively, at which time intake of food and water returned to control levels in spite of continued injections. Manning *et al.* [7] observed a similar reduction of food intake, but no effect on water intake as a result of repeated injections of Δ^9-THC in doses of 4 mg/kg, given IP and 8 mg/kg given orally. Pyrahexyl, a marijuana homologue, has been found to depress food but not water intake in rats [1].

Body weight changes were studied in parallel to the observations on food and water consumption in both studies referred to above [4,7]. An initial reduction of body weight was found, followed by a rapid recovery to control levels [4] or a very slow recovery to preinjections weight levels [7].

The present investigation was undertaken in an effort to compare the effects of acute and chronic administrations of Δ^8-THC and Δ^9-THC on body weight, food and water intake, and also to extend previous findings to female rats. In the previous reports, only males were used.

METHOD

Animals

Eighteen experimentally naive Wistar female rats, 190–200 days old, with an initial average weight of 226 g were used. They arrived from the breeder one day prior to the onset of the experiment, and were put into individual cages. The rats in the present experiment were those serving in the short-term acclimation condition in a previous report [9]. Behavioral testing in the open-field, carried out in parallel with the present experiment, is reported separately [9]. The animals were divided into three groups of six, matched according to body weight. The light in the animal

[1] The tetrahydrocannabinols referred to in this paper were obtained by the United Nations Secretariat through the courtesy of the Psychotomimetic Agents Advisory Committee, National Institute of Mental Health (NIMH), U.S.A. and were generously provided to the second author by Dr. Olav Braenden, Chief, United Nations Narcotics Laboratory, Geneva. Thanks are also due to Dr. Gunnar Krook for his arrangements with licences for importing narcotic drugs to Sweden.

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room was switched on at 8:00 a.m. and off at 5:00 p.m.

Drug Injections

The three groups of animals were randomly distributed over the following experimental conditions: (1) Group Δ^8-THC, injected with 5 mg/kg of Δ^8-THC (Δ^8-*trans*-Tetrahydrocannabinol (Δ^8-THC): Batch, QCD-64275, NIMH: Mol.form. $C_{12}H_{30}O_2$; Mol.Wt: 314.5; Specific Rotation, −268° (C, 1.2%; $CHCl_3$); Purity (assay by glc.), 99%.) dissolved in polyethylene glycol-300; (2) Group Δ^9-THC injected with 2.5 mg/kg of Δ^9-THC (Δ^9-*trans*-Tetrahydrocannabinol (Δ^9-THC): Batch, SSC-61516, NIMH; Mol.form., $C_{21}H_{30}O_2$; Mol.Wt., 314.5; Specific Rotation, −164° (C, 1.6%; $CHCl_3$); Purity (assay by glc.), 95.4% (impurity, 4.6% exocyclic THC).) dissolved in propylene glycol; and (3) Group C, given injections of a mixture (1:1) of the two solvents. The drug groups received the compounds from Day 1 to Day 19, the drugs were then withdrawn and the solvent mixture alone was given on Days 20–23. The control group received the solvent mixture for 23 days in succession. Injections were given IP, beginning at 11 a.m. Throughout, the volume injected in cc was equal to the animal's weight in kg. The dosages of the THC used were based on a study by Grunfeld and Edery [5], stating that in rodents, Δ^9-THC is twice as potent as Δ^8-THC.

Procedure

During the entire experiment, free food and tap water were available to the rats. The animals were kept in a room maintained at approximately 23° C. The food consisted of a commercial type pelleted diet (laboratory chow No. 210), marketed by Anticimex AB, Sollentuna, Sweden. A list of the ingredients of the diet is available from the first author. The animals had been raised on the same diet as used in the present study, a regimen which seems important in view of findings [8] concerning food-avoidance in rats. The pellets and a bottle of tap water were positioned in a concave space in the roof of the cages, in which the animals lived. Every second day throughout the experiment, body weight, food and water intake in g were recorded. The recordings were carried out at 11 a.m.

RESULTS

Body Weight

Data showing the influence of acute and chronic administrations of THCs on body weight are illustrated in Fig. 1. Analysis of variance (Groups x Days split-plot design, mixed model) [6] was performed.

Significant effects were obtained for Days ($F = 22.2$, $df = 11/165$, $p<0.01$) and for the Groups x Days interaction ($F = 3.1$, $df = 22/165$, $p<0.01$). A simple main effects analysis, employing a pooled within-cell variance (see [6]), showed significant differences among the groups for Blocks 8–11 (F-values ranging from 3.1–4.4, $df = 2/180$, $p<0.05$). Pairwise comparisons (Tukey's HSD-test) of the overall means for body weight showed no significant effect of drug administration. Pairwise testing of differences between the means of the three groups for Blocks 8–11 showed that the Δ^8-THC-treated rats weighed significantly less ($p<0.05$) than controls in all four Blocks (Block 8: q = 4.20, Block 9:

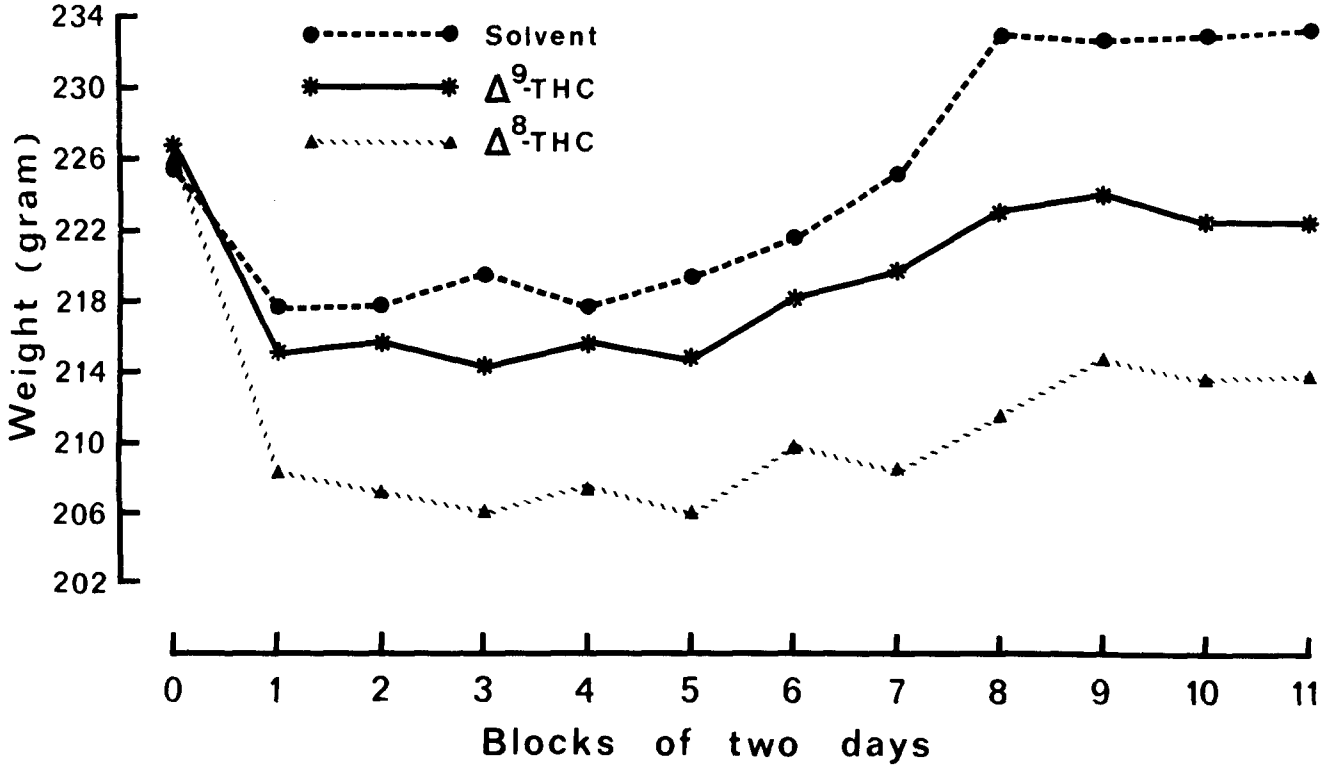

FIG. 1. Mean weight of rats treated with Δ^8-THC (5.0 mg/kg) and Δ^9-THC (2.5 mg/kg) and controls over a period of 22 days. Session 0 = preinjection values. From Day 20 and onwards only the solvent mixture was given to all groups.

q = 3.49, Block 10: q = 3.78, Block 11: q = 3.78, $q'_{0.05}$ = 2.99). In the within-groups factor (Days) all three groups changed significantly (Δ^8-THC: F = 9.5; Δ^9-THC: F = 5.2; Control: F = 13.8, df = 11/165, $p<0.01$).

Food Intake

Analysis of variance of food-intake scores in Fig. 2 showed a significant effect of Days only (F = 4.0, df = 10/150, $p<0.01$). Further analysis indicated an increase of food intake in both the Δ^8-THC group (F = 2.68, df = 10/150, $p<0.01$) and the control group (F = 2.62, df = 10/150, $p<0.01$). The Δ^9-THC group did not increase its food intake during the experimental period. Mean food intake/day for the groups were: Δ^8-THC = 24.6 g, Δ^9-THC = 23.7 g, and controls = 28.2 g.

Water Intake

A plot of the water intake data, showing the effects of THC and days of injection is found in Fig. 3. Analysis of variance indicated significant Groups (F = 8.8, df = 2/15, $p<0.01$), Days (F = 15.8, df = 10/150, $p<0.01$) and Groups x Days effects (F = 2.1, df = 20/150, $p<0.01$). A simple main effects analysis yielded significant differences among the groups in all Blocks, except No. 2 and No. 5 (F-values from 3.6–12.9 df = 2/165; Block 3: $p<0.05$, other Blocks: $p<0.01$). There was also a significant change over time for all groups (Δ^8-THC: F = 4.8; Δ^9-THC: F = 4.5; Controls: F = 10.7, df = 10/150, $p<0.01$).

Pairwise comparisons, using Tukey's HSD-test, among overall means for the three groups showed significant differences ($p<0.05$) between the Δ^8-THC group and controls (q = 5.70, $q_{0.05,3,15}$ = 3.67) and between the Δ^9-THC group and controls (q = 4.26). Tests of pairwise differences ($p<0.05$) between groups for all Blocks except No. 2 and No. 5, showed significant differences between Δ^8-THC and controls for Blocks 1, 3, 4, and 6–11, and between Δ^9-THC and controls for Blocks 4 and 6–11 (q-values ranging from 3.45–6.39, $q_{0.05}$ = 2.94). Also, a significant difference appeared between Δ^8-THC and Δ^9-THC in Block 1.

From an inspection of Fig. 3 it is evident that the control group consumed approximately 45% more water per block than the Δ^8-THC group and 30% more than the Δ^9-THC group throughout the experimental period. For all groups, there was an increase in water consumption during the experiment.

DISCUSSION

The results support the findings of Manning *et al.* [7], and Fernandes *et al.* [4] with regard to body weight. Thus, the fact that significant differences appeared between the Δ^8-THC group and the controls in the last four Blocks of testing, favors the conclusion that treatment with Δ^8-THC

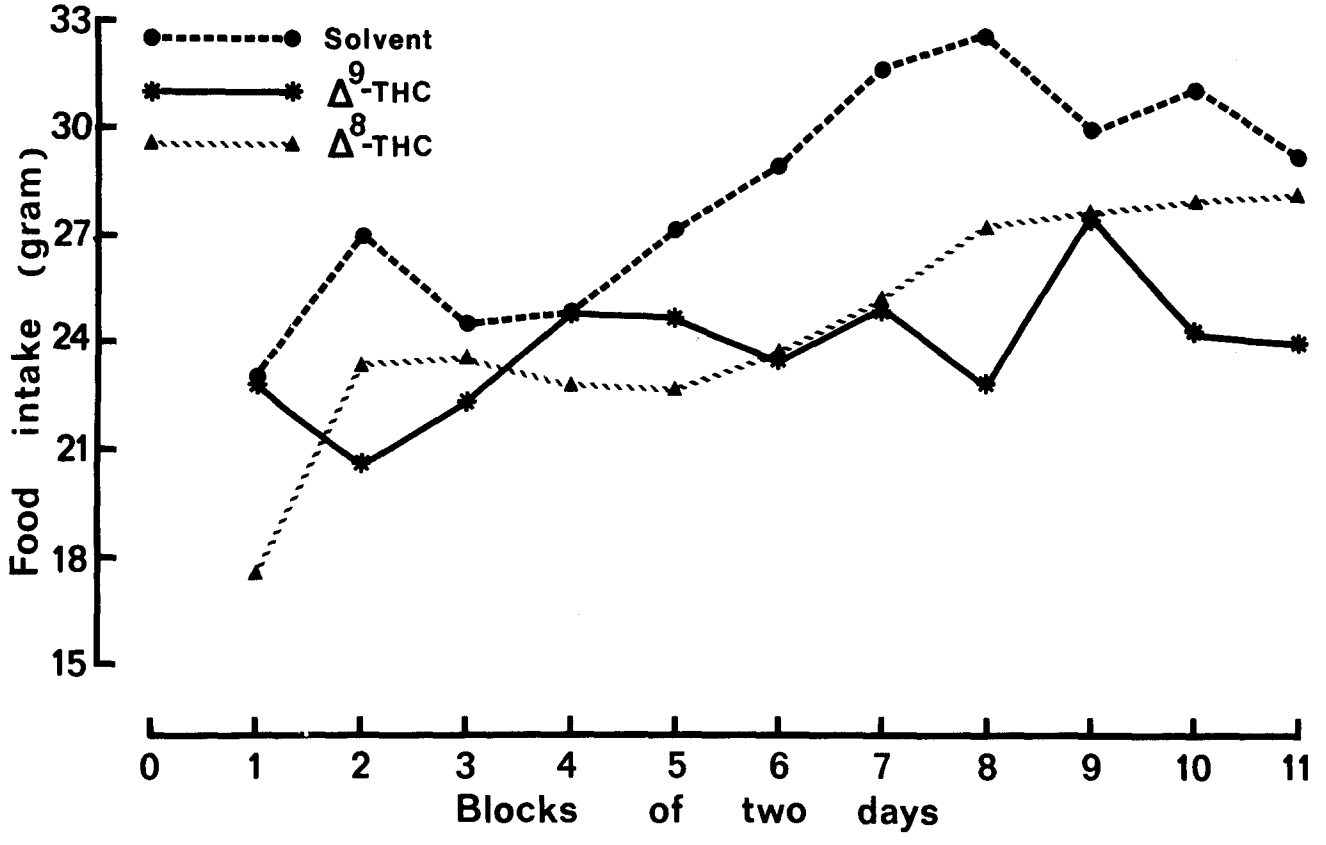

FIG. 2. Mean intake of food of rats treated with Δ^8-THC (5.0 mg/kg) and Δ^9-THC (2.5 mg/kg) and controls over a period of 22 days. From Day 20 and onwards only the solvent mixture was given to all groups.

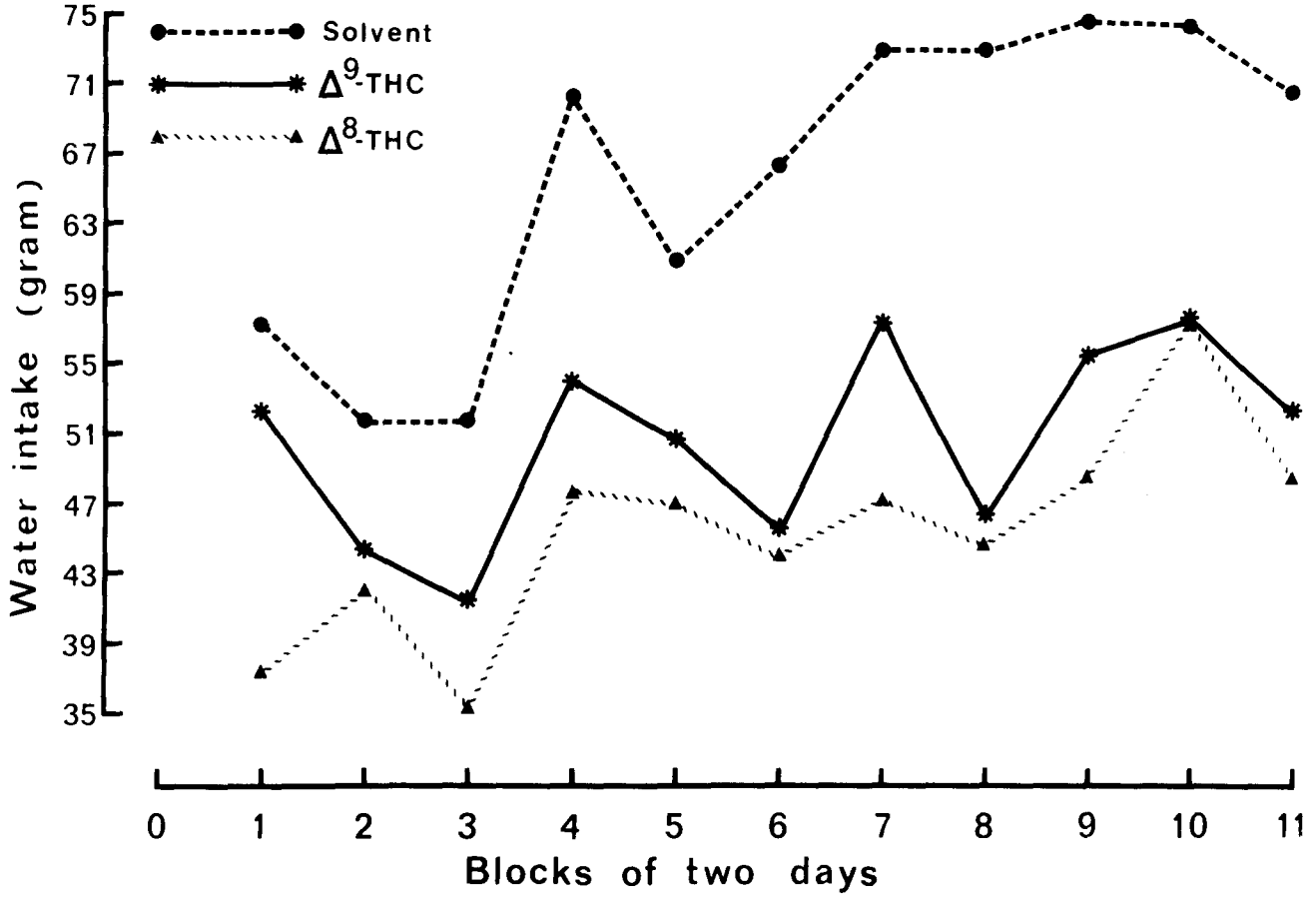

FIG. 3. Mean intake of water of rats treated with Δ^8-THC (5.0 mg/kg) and Δ^9-THC (2.5 mg/kg) and controls over a period of 22 days. From Day 20 and onwards only the solvent mixture was given to all groups.

leads to a reduction of body weight in rats. The observation that the difference between the Δ^9-THC group and controls is not significant for overall means or for any single block of testing, might be understood with reference to the fact that the controls showed an initial decrease of body weight as well as the drug groups. This is likely to be an effect of the short acclimation period but effects of the behavioral testing carried out on all animals in the present study (see [9]) or the injections per se could not be ruled out. Also, the dose of Δ^9-THC used in the present analysis (2.5 mg/kg) is lower than the doses used by Manning *et al.* [7] in their main experiment. As is evident from Fig. 1, both drug groups show an initial decrease of body weight and remain on approximately the same level during the entire period of injections. The significant differences between the Δ^8-THC group and controls in the last four Blocks stem from the fact that the control group shows a marked increase of body weight during these blocks. A point of difference between the present data and those of Fernandes *et al.* [4] is the relatively rapid return to normal body weight levels during the injection period, reported by the latter authors. An impression from Fig. 1 is that the drug groups show only a slight recovery of body weight during the latter part of the experiment.

We thus conclude that acute treatment with Δ^8-THC leads to a sharp decrease of body weight to a level which is maintained throughout the period of chronic administrations. Slight signs of recovery may appear after 12–14 injections.

Whereas Manning *et al.* [7] reported that there is a close correlation between the loss of body weight and the decrease of food intake, we find no statistically significant effect of drug treatment on food consumption. The mean intake/day for the three groups indicates a slight lowering of the food consumption of the drug groups. The absence of significant effects of drug treatment on food intake might be accounted for with reference to the fact that we used female rats, whereas Manning *et al.* [7] used males. It has been observed in this laboratory, that whereas most male rats show a continuous incease of body weight and food intake during the entire adult period, females show a much slower increase or no increase at all after having reached adult age. These differences may have a hormonal basis [3]. Unfortunately, the age of the animals in the study by Manning *et al.* [7] is not reported. The body weight range (250–300 g) given would suggest an approximate age of 90–100 days. In the present study, older animals were used (190–200 days), which might be an additional factor in relation to effects of THC on food intake.

Manning *et al.* [7] reported that the differences in body weight between groups, were caused by a lower food intake in the Δ^9-THC group than in the control group. Their line of reasoning was partly based on the use of an analysis of covariance, with food intake as the covariate. Controlling total food consumption in this way, the significant effect of Δ^9-THC on body weight disappeared. However, this use of an analysis of covariance can be severely criticized. Since both the covariate (food intake) and the dependent variable (body weight) are influenced by the drug treatment, an adjustment of the body weight scores for differences in food intake removes the effects of the drug from the dependent variable (cf. [6]). Thus, the conclusion by Manning *et al.* [7] on this point cannot be substantiated by their use of the analysis of covariance.

Our data on water intake, showing strong effect of both THCs during the entire period of injections are in opposition to the observations by Manning *et al.* [7], who found no effect of Δ^9-THC at doses as high as 32 mg/kg. However, the results support the findings by Fernandes *et al.* [4], with respect to Δ^8-THC and also extend them to Δ^9-THC. The reduction of water intake in the present data is close to twice the effects reported by Fernandes *et al.* [4], using the same dose of Δ^8-THC.

A finding of a dose-related decrease of body weight in pregnant female rats after injections of Δ^9-THC in doses ranging from 10–200 mg/kg, has been reported by Borgen *et al.* [2]. These authors have found (unpublished, cited in [2]) that the effect of Δ^9-THC in these animals is primarily an inhibitory action on water consumption, with a secondary decrease of food intake. The present results point to the identical conclusion. It is of interest to note that the explanation of a decrease of food intake offered by Manning *et al.* [7], that THC given IP causes intraperitoneal tissue lining lesions, cannot account for the results by Borgen *et al.* [2], since the latter authors used the subcutaneous route of administration. Thus, it seems likely that our finding of a decrease of body weight and water intake as a result of THC injections depends on other factors as well.

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