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Effects of Body Weight Levels on Cannabis Self-Injection[1]

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TAKAHASHI, R. N. AND G. SINGER. *Effects of body weight levels on cannabis self-injection.* PHARMAC. BIOCHEM. BEHAV. 13(6) 877–881, 1980.—Previous findings have shown that naive rats self-inject IV Δ^9-THC 12.5 μg/kg/infusion in the presence of a FT-1 non contingent food delivery schedule. In the present study the effects of three different body weight levels, 80%, 90% and 100%, with and without a FT-1 food delivery schedule, were examined on the THC self-injection behavior. Results confirmed that 80% body weight plus the FT-1 schedule condition leads to the highest intake of THC. In a further experiment, naive rats acquired THC self-injection at 80% body weight with a FT-1 schedule. Rats were then allowed to regain body weight to their free feeding level and were tested again in the same basic paradigm. Animals recovering body weight did not maintain the self-injection rates. The data indicate that the environmental conditions necessary in the acquisition phase are also required to maintain intake of THC 12.5 μg/kg/infusion.

Δ^9-THC Self-injection Schedule-induced Deprivation-induced Body weight Environmental conditions

A RECENT study in this laboratory [17] has presented evidence that experimentally naive rats self-administer intravenously low doses of Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal active constituent in cannabis. Consistent with previous reports using different drugs [8, 10, 11], the Δ^9-THC intake was significant when animals were reduced to 80% of their free feeding body weight and exposed to an intermittent food delivery schedule, fixed-time 1 min (FT-1). Consideration of the interaction of the environmental conditions and pharmacological factors has been neglected in previous studies of cannabis self-administration. It is likely that this neglect explains in part the reported lack of success in inducing laboratory animals to self-inject Δ^9-THC [6,9]. The 80% body weight condition is used in producing most of the schedule induced behaviors such as drinking and intravenous self-injection [5, 8, 20]. It is known that the frequency of these behaviors varies directly with the degree of body weight reduction. Thus, when animals are tested at 80% body weight condition, the amount of schedule induced behaviors is greater in comparison with that observed at 90% or 100% body weight [4, 16, 22]. However, little is known about the effects of body weight reduction on Δ^9-THC intake. The purpose of the present study was to examine in more detail the preliminary findings and to investigate the influence of internal (nutritional factor) and external (FT-1 schedule) environmental conditions on Δ^9-THC self-injection rate.

EXPERIMENT 1

Results of preliminary experiments have shown that animals at 80% body weight tested on a FT-1 min schedule self-injected significantly more Δ^9-THC 12.5 μg/kg/infusion than control solution [17]. These findings suggested that body weight reduction and FT-1 min schedule seem to play an important role in the Δ^9-THC self-injection.

The purpose of the present experiment was to explore the body weight level factor and also the interaction between body weight and schedule on Δ^9-THC self-injection rate. Therefore, the number of infusions of Δ^9-THC 12.5 μg/kg under the three different body weight levels, 80%, 90% and 100% were compared when tested with and without a food delivery schedule.

METHOD

Animals

Four groups of eight and two groups of seven naive male Wistar albino rats weighing approximately 400 g were used. All animals were housed individually in a temperature controlled room with a 12 hr light/dark cycle.

Apparatus

The test environment was identical to that described in a previous paper [17]. The experimental chamber was a modified operant box with a lever and a food cup attached to one side of the walls. The lever triggered the delivery of 0.07 ml of Δ^9-THC or control solution via a syringe infusion pump (Sage Instruments, model 341). A time out of 5 sec was set into the drug delivery system so that any further lever presses by the animals during the 5 sec interval did not result

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in a drug injection. Cumulative records were used to record the number of lever presses and infusions during the test sessions. Noyes food pellets (45 mg) were delivered to the animal every 60 sec when the FT-1 schedule was operating.

Drugs

Solutions of Δ^9-THC, National Institute of Drug Abuse (NIDA), were prepared for intravenous administration prior to each test session by suspending it in an 0.6–1.0 percent solution of Tween-80 in physiological saline [17]. The anaesthetic used for surgery consisted of a combination of pentobarbital sodium and chloral hydrate and the solution was injected intraperitoneally.

Procedure

Animals were adapted to their home cages for 10 days with continuous access to food and water. The mean weights over the last 3 days of this period were considered the free feeding body weight. Over a period of 7 days, 2 groups of rats were reduced to 90% and 80% of this body weight, by gradually restricting the daily rations of food. After the weight reduction period animals were held at 90% or 80% body weight. During this phase, body weight reduced animals as well as animals at free feeding body weight were surgically implanted with a jugular cannula under anaesthesia by a method similar to one described elsewhere [8, 10, 17]. Cannula of SP 28 polyethylene tubing were maintained in position by leather jackets worn by each animal. Animals were allowed one week to recover from surgery before being assigned to an experimental group.

After recovery from the surgery the animals were placed in the operant box for 1 hr/day testing sessions for 6 consecutive days at the same time each day and during the light phase of a 12 hr light/dark cycle.

RESULTS

The overall means of infusion/hour/day for the three groups self-injecting Δ^9-THC 12.5 μg/kg is shown in Fig. 1. The response rates were analysed by means of a two-way analysis of variance (ANOVA). The analysis of the number of infusions indicated significant differences between groups, $F(2,40)=8.96$, $p<0.01$, and schedule conditions, $F(1,40)=5.72$, $p<0.05$. The groups by schedule conditions interaction was also significant, $F(2,40)=8.70$, $p<0.01$. A Scheffé post hoc test revealed that 80% body weight animals tested on a FT-1 min schedule self-injected significantly more Δ^9-THC than animals under the other 5 conditions ($p<0.05$). There were no significant differences in the rate of self-injection when comparisons between animals under schedule and no schedule situations were made at 90% and 100% body weight respectively.

DISCUSSION

These results confirm the findings of previous studies which demonstrated that the interaction between the 80% body weight condition and the food delivery contingency, FT-1 min, leads to an increased frequency of drug intake [8, 10, 11, 17]. It is noteworthy that although reduced to 80% of their free feeding body weight, animals when tested without a schedule self-injected negligible amounts of Δ^9-THC. Indeed there was no statistical difference when the number of infusions of these animals were compared to those of animals

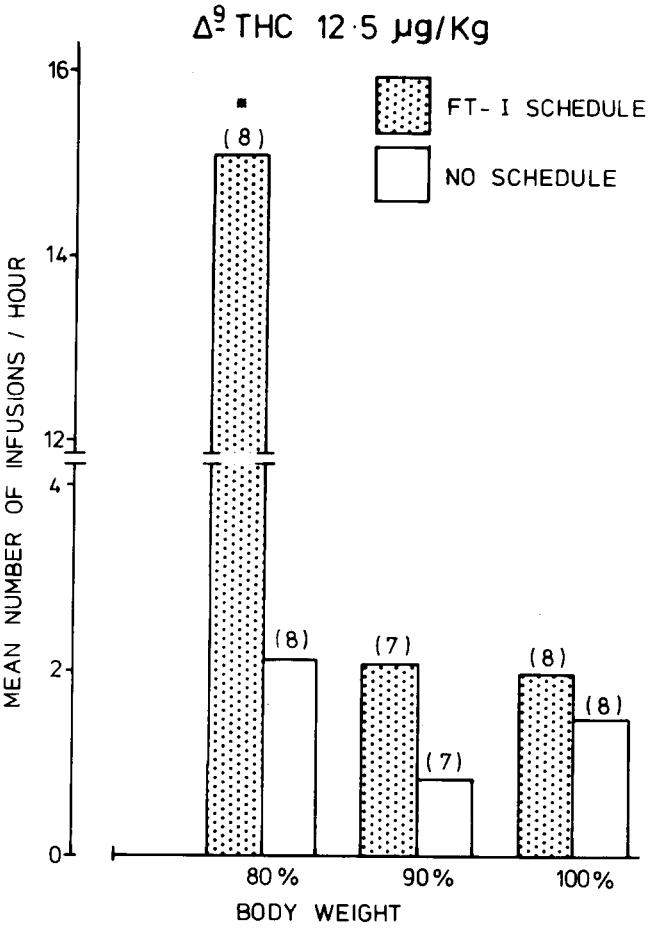

FIG. 1. The overall infusions means of Δ^9-THC 12.5 μg/kg/infusion under the three body weight conditions: 80%, 90% and free feeding. *$p<0.05$, Scheffé post hoc test, compared to other conditions.

reduced to 90% body weight and to animals in the free feeding condition. The implication from this experiment is that the physiological imbalance caused by food deprivation alone is not a decisive factor in inducing Δ^9-THC self-injection. Although no significant increase was found, the addition of a FT-1 min food delivery schedule at 90% and 100% body weight situations induced a slightly higher intake of Δ^9-THC compared to animals tested without a schedule. These results are also in accordance with other studies which have shown that schedule induced behavior varies directly with body weight deficit [4, 5, 14]. Thus, in animals tested on a FT-1 schedule a clear effect was seen at 80% body weight, but no difference was found when the highest body weight levels, 90% and 100% were examined.

EXPERIMENT 2

The previous experiment has shown that the co-occurrence of reduced body weight condition and the FT-1 min schedule is a decisive factor in establishing Δ^9-THC intake. Recent studies have shown that following a sufficient exposure to the appropriate schedule at reduced body weight, schedule induced behaviors persist when body weight is returned to free feeding condition [15,21]. In rela-

TABLE 1

SELF-ADMINISTRATION OF Δ^9-THC 12.5 μg/kg WITH BODY WEIGHT CHANGES

	Phase 1 Acquisition period Days 1–5	Phase 2 Body weight recovery period 6–10	Phase 3 Maintenance period 11–15
Group A (7)	80% B.W.+FT-1	80% B.W.+FT-1	80% B.W.+FT-1
Group B (7)	80% B.W.+FT-1	Food rations increased FT-1	Free feeding situation FT-1

tion to Δ^9-THC, it is not known whether food deprived animals will maintain the acquired rate of self-injection when the body weight is returned to normal. If a similar response rate for Δ^9-THC is maintained under these circumstances it may be of some significance in evaluating Δ^9-THC reinforcing properties. Thus, in order to provide insight into the role of the nutritional factor during the maintenance of Δ^9-THC self-injection, a second experiment was carried out. Naive rats were allowed to initiate Δ^9-THC self-injection at 80% body weight with a FT-1 min schedule. After the acquisition phase, body weights were gradually returned to free feeding levels. The rates of responding were recorded over 15 consecutive days.

METHOD

Animals

Two groups of seven Wistar male rats were reduced to 80% of their free feeding body weight and were implanted with intravenous jugular catheters by methods similar to those described in Experiment 1. The test box and all other equipment were the same as in the preceding experiment.

Procedure

Animals at 80% body weight were allowed to self-inject Δ^9-THC 12.5 μg/kg/infusion for 1 hr/day for 5 days. On day 5, animals were divided into two groups of 7 each. Group A was maintained at 80% body weight and tested daily for Δ^9-THC self-injection throughout the next 10 days while animals in Group B were allowed to regain body weight by gradually increasing the daily ration of food for the next 5 days. By day 10, animals in Group B were in a free feeding condition in their home cages. During these different phases, all animals were tested daily on a FT-1 min schedule for Δ^9-THC self-administration.

The basic experimental design used in this study is shown in Table 1.

RESULTS

The mean numbers of infusions/hr for the two groups are shown in Fig. 2.

A two-way ANOVA for these data between days 5 and 15 showed significant main effects of the body weight factor $F(1,120)=34.87$, $p<0.01$ and the interaction between the body weight factor and days, $F(9,120)=2.13$, $p<0.05$. The factor days was not significant, $F(9,120)=1.03$, $p>0.05$. These results suggest that the rate of Δ^9-THC self-injection in Group A, 80% body weight animals, is significantly higher than in Group B, animals recovering body weight. It is important to note that from day 10, when animals in Group B were fed ad lib, the rate of drug intake was low and quite constant, Fig. 2. It is clear also that even over 15 days, animals in Group A displayed the erratic pattern of self-injection that has been reported in a previous paper [17].

DISCUSSION

The results of Experiment 2 indicate that 80% body weight animals tested on a FT-1 min schedule maintain Δ^9-THC self-administration response throughout 15 days. It is not clear if the increase seen in the final 5 days is due to a tolerance effect (Fig. 2, Group A). However, more interesting is the finding that animals recovering body weight, Group B, did not maintain the acquired Δ^9-THC self-injection behavior. The diminution of self-injection response in this study seems to be related to the nutritional factor. When the food ration was gradually increased over days 5 to 10, the self-injection rate was lowered (Fig. 2, Group B). The failure to maintain Δ^9-THC self-administration under this condition suggests that the interaction between the schedule, the reduced body weight and some pharmacological property of the drug is crucial, not only during the acquisition period, but also throughout the maintenance period. In contrast, in a recent study of nicotine self-injection using a similar paradigm, it has been reported that mechanisms for acquisition differ from those responsible for maintaining the behavior. Food deprived rats which had initiated self-injection of nicotine with a schedule continued self-injection behavior on recovery of body weight [15].

GENERAL DISCUSSION

The results of these experiments demonstrate that the acquisition and the maintenance of significant amounts of Δ^9-THC self-administration as a function of a schedule induced behavior involve a three-way interaction: body weight reduction, food delivery schedule and the pharmacological effect of the drug.

The present data also indicate that regardless of the physiological and/or hormonal changes, body weight deficit *per se* cannot fully account for the Δ^9-THC intake, i.e., deprivation-induced Δ^9-THC self-injection is marginal at 80% and 90% of free feeding body weight.

It appears from this and earlier observations with heroin,

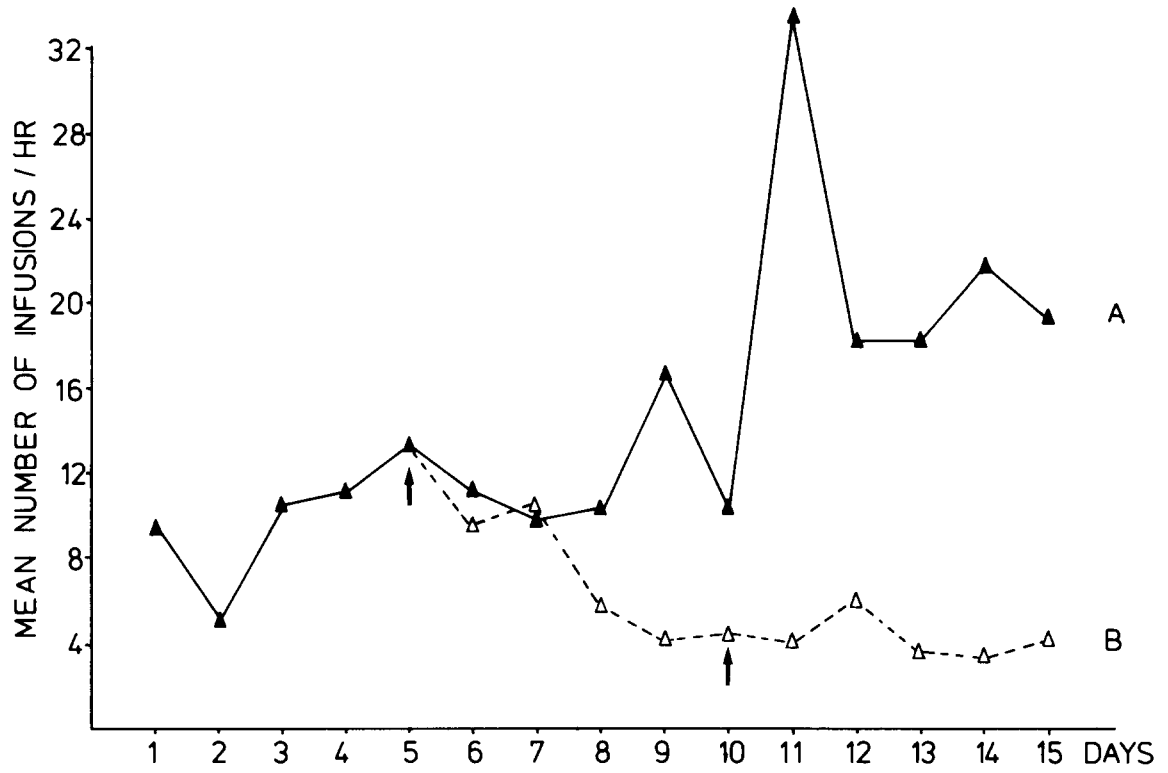

FIG. 2. Mean number of Δ^9-THC 12.5 μg/kg/infusion per hour. Group A—80% reduced body weight animals. Group B—80% reduced body weight animals regaining body weight. Days 1 to 5, acquisition period. The arrow on day 5 (Group B) indicates the gradual increase in food ration, while the subsequent arrow, day 10, indicates that animals reached the free feeding situation. All 14 animals were tested on a FT-1 min food delivery schedule.

methadone [10], amphetamine [16] and alcohol [11] that external environmental conditions affect the acquisition of drug self-injection differently. For all drugs except amphetamine the schedule-induced condition leads to the highest rates of drug intake. These findings also confirm the utility of the schedule-induced self-injection paradigm in isolating patterns of interaction as suggested by Jefferys *et al.* [7].

It is quite clear from these studies with different classes of drugs that interpretations based on specific properties of psychoactive drugs such as central depressant or appetite suppressant effects are untenable. Apparently the different environmental variables (internal and external) provide the necessary preconditions for the different compounds to maximize voluntary drug administration. The recent attempt to provide a general explanation invoking a mechanism such as learning to account for increased drug intake by food deprived animals seems unsatisfactory [2]. The suggestion of Wayner [19] that schedule-induced behavior involves a nonspecific increase in the excitability of motor pathways through the lateral hypothalamus (LH) appears to be more plausible. It has been suggested that Na and glucose cells in the LH respond to changes in the composition of the circulating blood producing an increase in excitability [20]. Δ^9-THC reportedly influences blood glucose levels [13,20]. Therefore, it could be postulated that the increased responsiveness observed with the self-administration of THC in this study may stem from activation of these cells at the level of the LH and that this excitability is enhancing the high level of activity induced by environmental conditions. Further support for this hypothesis comes from the results of Wayner *et al.* that low doses of Δ^9-THC IP increased the schedule-induced polydipsia [20]. An earlier report from Pickens *et al.* is also of relevance in the present context. They reported hashish smoking by monkeys only when the animals were tested under a food pellet contingency. When food was available ad lib hashish smoking was not maintained [12]. These findings, together with those which suggest that drug addiction represents an adaptive behavioral response by an animal to changes in its environment [3], provide interesting and testable hypothesis concerning drug seeking behavior.

Contrary to the notion that schedule-induced behavior is difficult to extinguish [4,21] animals in this study decreased the rate of THC intake when the nutritional factor was manipulated. Interpretation of the results of Experiment 2 in terms of the influence of the nutritional factor is difficult since THC effects on food intake are contradictory [1]. The finding that animals regaining body weight decreased barpressing responses, tends to suggest that THC intake was primarily brought about because it suppressed hunger. However, if so, one would expect a similar rate of deprivation-induced self-injection by 80% body weight animals without a schedule. However, Experiment 1 showed that those

animals presented a negligible THC self-injection rate. An alternative explanation for the decreased response in animals recovering body weight is that the period of exposure to the inducing schedule at reduced body weight was not long enough. Conversely, one can consider an explanation in terms of THC pharmacological properties. It is likely that the small dose of THC had such minimal reinforcing effect that any changes in the precondition state, schedule or 80% body weight, would affect self-injection response. The last explanation is in agreement with previous reports of the poor reinforcing capability of cannabis compounds [6,12].

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