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Self-Administration of Δ^9-Tetrahydrocannabinol by Rats

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TAKAHASHI, R. N. AND G. SINGER. *Self-administration of Δ^9-tetrahydrocannabinol by rats.* PHARMAC. BIOCHEM. BEHAV. 11(6) 737–740, 1979.—The present study examines the dose-response pattern of Δ^9-tetrahydrocannabinol self-injection in naive rats at 80% reduced body weight and 100% body weight, both conditions with a fixed-time 1 min (FT-1) food delivery schedule. The results indicated that food deprived animals tested on a FT-1 min schedule self-injected low doses of Δ^9-THC at a higher rate than those animals at 100% body weight and on a FT-1 min schedule. Animals at 80% reduced body weight without a schedule did not differ from rats self-injecting Δ^9-THC at free feeding situation. These findings suggest that rats without previous history of drug dependence self-administer low doses of Δ^9-THC and that the interaction between the food deprivation state and the environmental contingencies introduced by a FT-1 min schedule is a critical variable in the acquisition period.

Self-injection Body weight reduction Food delivery schedule Δ^9-tetrahydrocannabinol

ALTHOUGH cannabis compounds (marihuana, hashish) have been widely used by man primarily for their behavioral effects, they seem to be either not self-administered or poorly self-administered by animals [9,14]. Marihuana self-administration by infra-human organisms has been reported in only two studies but both of them used experienced drug taking animals [11,18]. Δ^9-trans-tetrahydrocannabinol (Δ^9-THC) is commonly accepted as the major psychoactive constituent of cannabis sativa and it was first isolated in pure form from hashish in 1964 [8,16]. Probably because of the insolubility of this drug in water, its delayed onset of action and its induction of taste aversion, experimental self-administration of cannabis has been less successful than other classes of drugs such as stimulants and opiates [4, 7, 15].

Food deprived rats and other experimental animals tested on intermittent schedules of food reinforcement develop concurrent patterns of excessive fluid intake [5]. This phenomenon, known as schedule-induced polydipsia, has been used as a procedure for inducing oral self-administration of drugs by substituting a drug solution for water [6,13]. In our laboratory an extensive series of experiments for inducing voluntary intake of large quantities of drugs has been carried out using a technique which combines an intermittent food delivery schedule consisting of one food pellet each minute (FT-1 min) and an intravenous self-injection procedure [12,17]. This schedule-induced self-injection method overcomes the problems associated with the oral ingestion methods and it has advantage over other techniques because it allows the study of the interaction of environmental, nutritional and pharmacological factors in drug-taking behavior. Using this methodology the present study was undertaken to examine whether rats without drug pre-treatments initiate and maintain self-administration of Δ^9-THC.

METHOD

Animals

Eighty-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. Food and water were available ad lib. In experiments requiring rats at 80% of their body weight these were reduced prior to surgery and then maintained at that weight with water available ad lib.

Apparatus

The experimental chamber was a modified operant box (35×32×32 cm) with a bar and a food cup attached to one side of the walls. The bar operated a syringe infusion pump (Sage Instruments, model 341) which delivered 0.07 ml of Δ^9-THC solution or saline when triggered. A timing device set for a fixed interval of 5 sec was incorporated into the drug delivery system so that any further bar presses by the animals during the 5 sec infusions were not rewarded with drug injections. Cumulative records were used to record the number of bar presses and infusions during test sessions. Noyes food pellets (45 mg) were delivered regularly, one each minute, to the animal when the fixed time-1 min (FT-1) schedule was operating.

Drugs

Solutions of Δ^9-THC (NIDA-USA) were prepared for intravenous administration prior to each test session by suspending it in an 0.6 percent solution of Tween-80 in physiological saline. The control solution consisted of the Δ^9-THC vehicle [1,11]. The anaesthetic used for the surgery consisted

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of a combination of pentobarbital sodium and the chloral hydrate and the solution was injected intraperitoneally.

Procedure

All animals were surgically implanted with a jugular cannula under anaesthesia. Cannulae of SP28 polyethylene tubing were maintained in position by leather jackets worn by each animal. The catheter was connected to a flexible swivel system allowing each animal unrestricted movement. Animals were allowed one week to recover from surgery before being assigned to an experimental group.

Following recovery the animals were placed in the operant box for 1 hr/day testing sessions for 6 consecutive days at the same time each day. Each experiment commenced by priming the animal with an initial dose of drug or control solution.

In the first experiment, the dose-response pattern of Δ^9-THC self-injection was determined. Seventy-five experimentally naive rats were allowed to self-inject 6.25, 12.5, 25 and 50 μg/kg/infusion of Δ^9-THC at 100% body weight and 80% reduced body weight, both conditions with a FT-1 min schedule.

RESULTS AND DISCUSSION

Figure 1 presents the overall means of infusions/hour/day for the two groups self-injecting Δ^9-THC at each dose and saline. Statistical comparisons were made using the Student's t-test.

Rats reduced to 80% body weight and tested on a FT-1 min schedule self-injected significantly more Δ^9-THC at doses of 6.25 and 12.5 μg/kg than control solution (Fig. 1). There was no significant increase in the rate of self-injection of the two higher doses of Δ^9-THC compared to the rate of control animals. Animals at normal body weight self-injecting Δ^9-THC at all doses available did not differ from control animals (Fig. 1).

The Δ^9-THC self-injection pattern of food deprived rats throughout 6 days was not constant (Fig. 2). These results are interesting because they display the same sawtooth type self-injection pattern obtained with nicotine and d-amphetamine [12,20], drugs usually considered to have psychological addiction potential. Narcotic analgesics tested on the same basic design showed a different self-injection pattern across the sessions [17]. Again it is clear that at higher doses, 25 and 50 μg/kg/infusion, rats lever-pressed for Δ^9-THC at rates which were not different from rats self-injecting the control solution (Fig. 2).

These results demonstrate significant rates of Δ^9-THC self-injection of 6.25 and 12.5 μg/kg/infusion. Although there was no significant difference between these two doses, Δ^9-THC 12.5 μg/kg induced the higher rate of self-injection. The overall mean number of infusions, 15.14 ± 4.31, was not as high as is seen with narcotic analgesics and d-amphetamine [17,20]. Taking this into account and assuming that drugs with a high reinforcement potential are those which have properties leading to their self-administration under different conditions and over a range of doses, Δ^9-THC in rats seems to have weak reinforcing properties. It is interesting to note that we did not find a monotonically increasing dose-dependent self-injection pattern. A dual effect was observed: a stimulant effect inducing self-injection at low doses and a depressant effect starting with a dose of 25 μg/kg (Fig. 1, 80%+FT-1 group). However, in this paradigm,

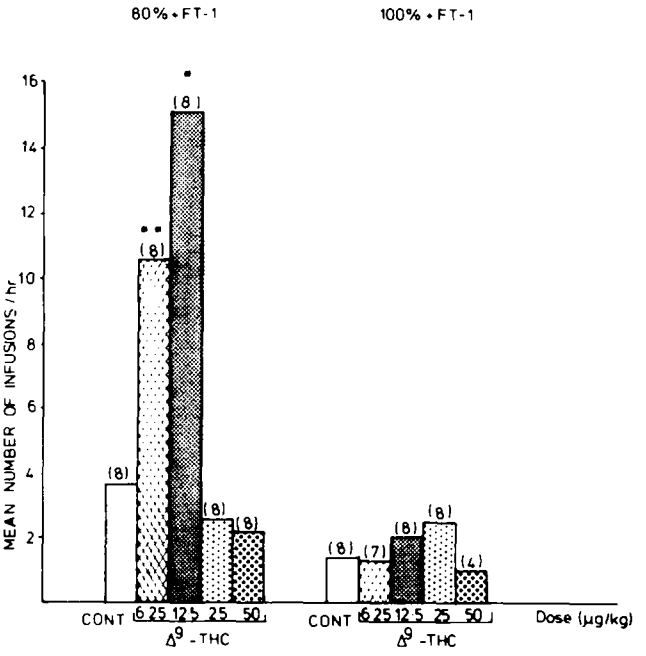

FIG. 1. The overall means of infusion for the control and Δ^9-THC solutions under conditions: 80%+FT-1, 80% reduced body weight animals with a FT-1 min schedule and 100%+FT-1, 100% body weight animals with a FT-1 min schedule. $*p<0.05$, $**p<0.01$, Student's t-test, one-tail, compared to control group. ( ) number of animals.

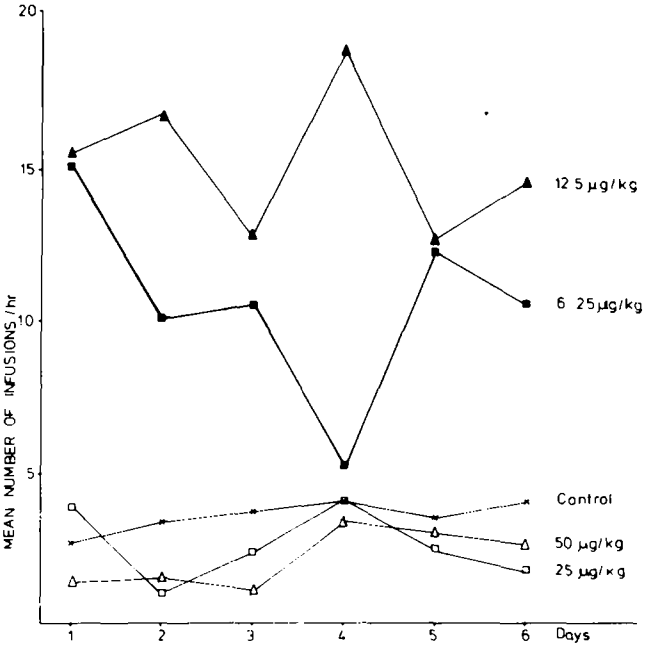

FIG. 2. The mean number of infusions for the control solution and Δ^9-THC at 6.25, 12.5, 25 and 50 μg/kg/infusion for each session of the animals at 80% reduced body weight and FT-1 min schedule.

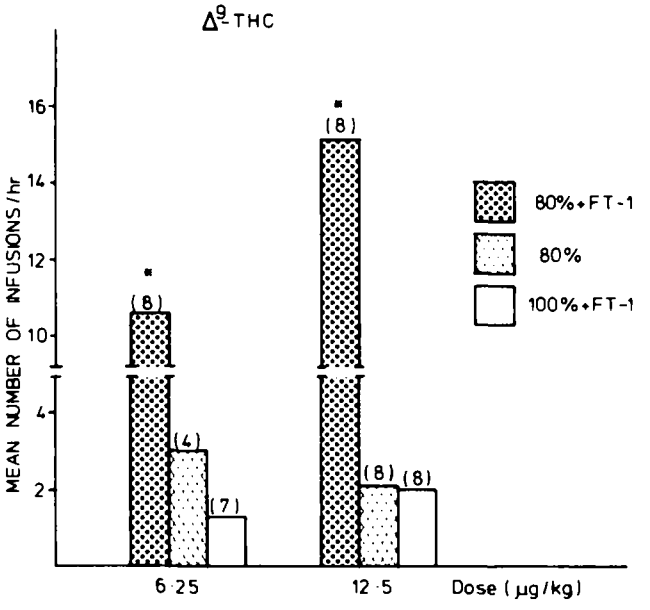

FIG. 3. The overall means of infusion for Δ⁹-THC 6.25 and 12.5 μg/kg/infusion under the three schedule conditions: 80%+FT-1, 80% reduced body weight animals with a FT-1 min schedule; 80%, 80% reduced body weight animals without a schedule and 100%+FT-1, 100% body weight animals with a FT-1 min schedule. *$p<0.02$, at least, Student's t-test, two-tail, compared to 80% and 100%+FT-1 groups. ( ) number of animals.

rats did not show a "superimposed biphasic effect", hyperactivity followed by depression in the same animal, reported elsewhere [2,21]. Towards the end of the daily sessions most of the animals tested on Δ⁹-THC showed behavioral responses described in the literature: abnormal posture, general sedation and hyperreactivity characterized by vocalization when held [1,19]. The low performance found at higher doses may be due to the "novelty" effect or "fear reaction" and/or the general depression of operant responses induced by Δ⁹-THC [3,10].

The present data do not clarify whether the physiological imbalances caused by food deprivation and/or the environmental contingencies introduced by a FT-1 min schedule are the critical variables in inducing Δ⁹-THC self-administration. In order to further examine this point, twelve animals in the second experiment were reduced to 80% of their normal body weight and tested without a FT-1 min food delivery schedule. Rates of self-injection of Δ⁹-THC 6.25 and 12.5 μg/kg from both groups, 80%+FT-1 and 100%+FT-1 min were again compared with the rates of animals from this second experiment. Figure 3 indicates that there is no significant difference between animals at the 80% reduced body weight without a schedule and animals at free feeding body weight condition. The present findings suggest that the food deprivation state by itself is not a decisive factor in inducing self-injection of Δ⁹-THC. Also these results are in agreement with our recent studies suggesting that animals at 80% reduced body weight and tested on a FT-1 min schedule are differentially sensitive to the pharmacological property of drugs [12,17].

In conclusion, the results demonstrate that naive rats self-administer small doses of Δ⁹-THC and that the interaction between food deprivation state and the environmental factor introduced by a FT-1 min schedule is a critical variable in the acquisition period. They also provide suggestive evidence that different techniques are required to assess the self-injection of different classes of drugs and thus to examine their dependence liability.

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