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BRIEF COMMUNICATION

Parameters Influencing the Effect of Δ^9-THC on Activity Wheel Behavior

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FRIED, P. A. *Parameters influencing the effect of Δ^9-THC on activity wheel behavior.* PHARMAC. BIOCHEM. BEHAV. 2(3) 435–438, 1974. – In 2 studies the effect of Δ^9-THC on activity wheel behavior in rats was examined. The amount of laboratory acclimation prior to testing was manipulated and either 4 mg/kg or 8 mg/kg Δ^9-THC was given intraperitoneally. Activity counts were taken 15 minutes, 1, 6, 24, 48 or 72 hr after the injection. Those animals that received 4 mg/kg Δ^9-THC and had little laboratory acclimation were significantly more active than their controls during the first 15 min but, after 1 hr were, like the other 3 experimental groups, less active than the appropriate controls. The time course for the depressant action of the Δ^9-THC at both dose levels was quite similar and lasted for approximately 24 hr.

Δ^9-THC Activity wheel Laboratory acclimation

THE ADMINISTRATION of marihuana-like compounds or constituents of marihuana has been reported to affect spontaneous motor activity but it is apparent that the type of behavioral alteration is contingent upon a number of parameters. In the majority of studies it has been found that an injection in rodents of Cannabis constituents results in a depression of motor activity [3, 9, 10, 15, 17] but under particular conditions the cannabinoids may not decrease the activity and, in fact, in certain circumstances actually increase it.

Repeated injections of Δ^9-tetrahydrocannabinol have been found to attenuate the initial depressant action observed in spontaneous motor tasks [6, 14, 15]. In a similar behavioral vein, acclimation to the laboratory [2,17] or the apparatus [4] lessened the depressant action of Δ^9-THC. In fact, at a dose level of 4 mg/kg the drug increased activity when measured by an actophotometer following acclimation to the laboratory [2] and an injection of 1.5 or 6 mg/kg resulted in a significant increase in the number of wheel revolutions if the animals had received several sessions in the activity wheel prior to the drug administration [2]. The time elapsing between receiving the drug and testing is an important parameter as the maximum depressant action appears to be between twenty minutes and three hours after an injection [5, 8, 16] with both the dosage and the type of dependent variable influencing the time-course action of the drug. A dose-related depressant effect has also been found by a number of workers [1, 4, 5, 8, 15]. Abel [1] reported a biphasic dose effect on ambulatory scores when using a marihuana homologue, pyrahexyl. At 2.5 and 5 mg/kg pyrahexyl increased motor scores, at 10 mg/kg there was no apparent effect and at 15 mg/kg activity was depressed.

The present studies were undertaken to examine the interaction of some of the parameters which apparently influence whether Δ^9-THC has an excitatory or depressant effect on spontaneous motor activity. The variables to be considered include the time-course of the drug and the amount of laboratory acclimation with two dosage levels being employed.

EXPERIMENT 1

The purpose of this study was to examine the effect of 4 mg and 8 mg/kg Δ^9-THC on rats in activity wheels with the animals having little time to acclimatize themselves to the laboratory and handling.

Method

Animals. Thirty two experimentally naive male Wistar rats with an initial average weight of 300 g were used. They arrived from the breeder one week prior to the onset of the experiment and were placed in individual cages with water and food available ad lib.

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Drug injections. The animals were randomly assigned to one of 2 experimental groups or one of 2 control conditions with each group consisting of 8 animals. In the experimental conditions the animals received an intraperitoneal injection of either 4 mg or 8 mg/kg Δ^9-THC suspended in propylene glycol (1 mg Δ^9-THC/0.5 cc propylene glycol). The control groups received an intraperitoneal injection of propylene glycol equal in volume to either the 4 mg or 8 mg/kg experimental animals.

Apparatus. Modified Wahmann activity wheels, housed individually in sound attenuating ventilated chambers, were used to monitor the animal activity with indirect lighting from 8:30 a.m. until 7 p.m. The wheels were automated by replacing the counter-trip arms by cam-operated micro switches which, in turn operated counters mounted exterior to the chambers.

Procedure

Immediately after receiving the appropriate injection an animal was placed in an activity wheel and the chamber was shut. The activity was recorded at 15 min, 1 hr, 6 hr, 24 hr, 48 hr and 72 hr after being placed in the apparatus. Prior to analyzing the data, individual activity counts (at each interval described above) were converted to revolutions per hour and then were converted to their square root [11]. Subsequently the data were subjected to a 2 × 2 × 6 analysis of variance with the dose levels and drug type constituting the between variables and the 6 activity counts contributing to the within factor. A Newman-Keul [18] test was used to examine the differences in treatment means in greater detail.

Results

The mean square root of revolutions per hour for the various groups at the different post-injection times are plotted in Fig. 1. The overall analysis of variance indicated that a significant dose effect was present, $F(1,28) = 6.719$, $p = 0.014$, a significant interaction of dose × time after injection, $F(5,140) = 4.020$, $p = 0.002$, and drug × time after injection $F(5,140) = 2.288$, $p = 0.048$, and a significant triple interaction of drug × dose × time after injection, $F(5,140) = 2.822$, $p = 0.018$. The analysis of the individual means revealed that during the first 15 min the 4 mg/kg Δ^9-THC animals made significantly more revolutions than any other group ($p<0.05$) whereas the 8 mg/kg Δ^9-THC animals were significantly less active than their controls during the first 15 min ($p<0.05$).

As graphically illustrated in Fig. 1 the injection of 8 mg/kg Δ^9-THC had its maximum depressant effect between 15 min and 24 hr after the administration. By 48 hr the experimental and control animals in the 8 mg/kg group were indistinguishable. Except for the initial excitatory effect, the 4 mg/kg injection of Δ^9-THC paralleled the time course of the higher dose although the depressant effect was not quite as pronounced.

EXPERIMENT 2

In this study, the effect of injections of 4 mg/kg and 8 mg/kg Δ^9-THC on activity wheel behavior of rats with

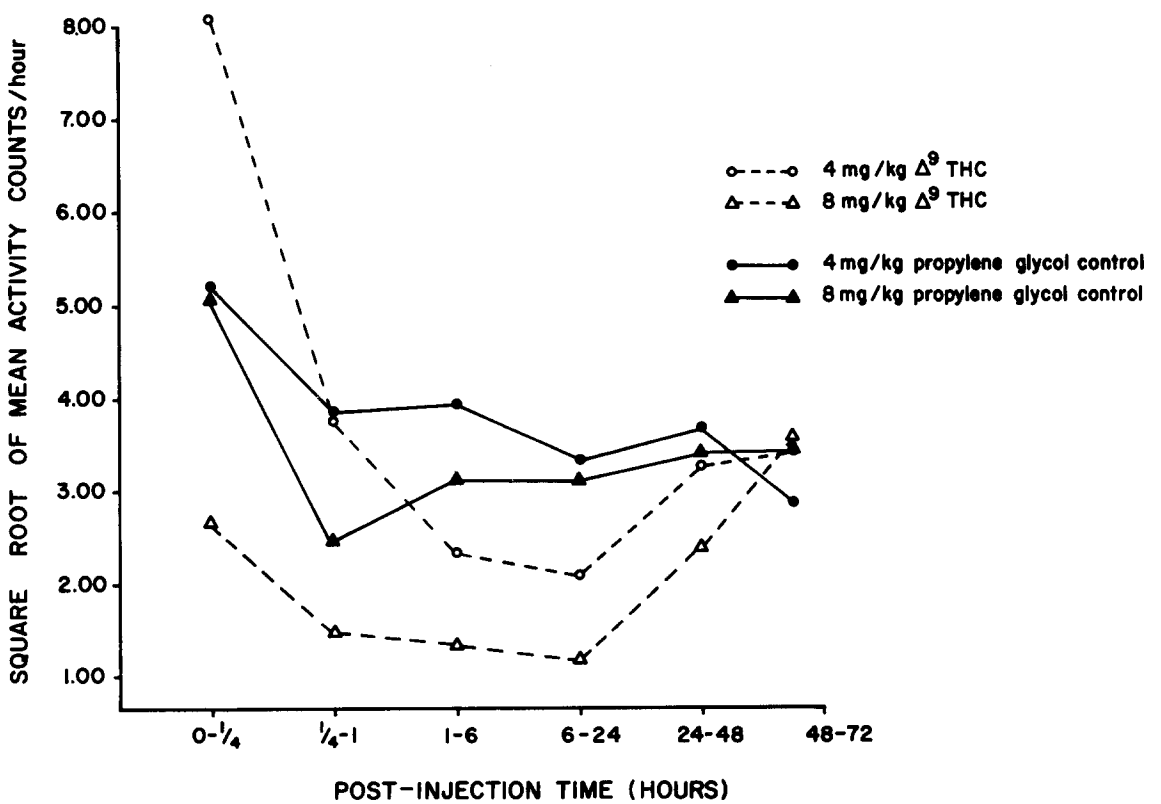

FIG. 1. Effects of Δ^9-THC on the wheel activity of rats with little laboratory acclimation. Each curve represents the mean activity of 8 animals.

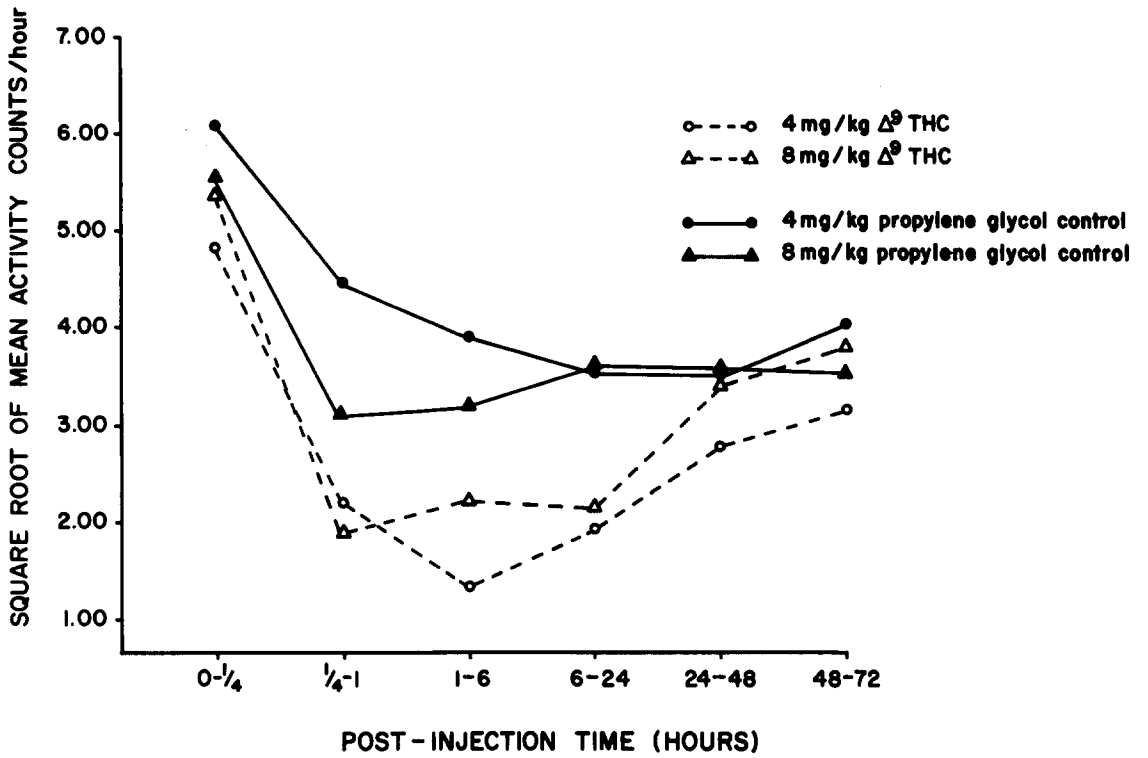

FIG. 2. Effects of Δ^9-THC on the wheel activity of rats with extensive laboratory acclimation. Each curve represents the mean activity of 10 animals.

extensive laboratory and handling experience was examined.

Method

Forty male Wistar rats with an average weight of 300 g were used. Prior to being tested in the activity wheels, the animals had been used in an open field situation and had received several weeks of daily handling. The drug injections, apparatus, procedure and analysis were identical to those described in the first study. Ten animals were used in each of the 4 groups.

Results

The mean square root of revolutions per hr for the 4 groups at the various recorded post-injection times are plotted in Fig. 2. The overall analysis of variance indicated that there was a significant drug effect, $F(1,36) = 4.970$, $p = 0.030$, but no dosage effect. As can be seen in Fig. 2 the 2 groups receiving Δ^9-THC made fewer revolutions than the control groups. Individual tests indicated that at no point did either the 2 experimental or 2 control groups differ significantly from one another. The time course of both 4 mg and 8 mg/kg Δ^9-THC was quite similar with the depressant effect evident after 15 min and lasting for approximately 24 hr.

DISCUSSION

One of the major findings of the present studies was the differential effect of 4 mg/kg Δ^9-THC as a function of laboratory experience. Those animals with very limited acclimation (Study 1) demonstrated an initial spurt of activity lasting for approximately 15 min before motor depression became evident, whereas rats with extensive handling prior to an injection of 4 mg/kg Δ^9-THC did not display any increase in wheel activity. At the higher dose of 8 mg/kg Δ^9-THC differential pretest experience did not result in differential wheel activity. The depressant effect of this dose is in accord with other reports as described in the Introduction.

The initial increase of the 4 mg/kg Δ^9-THC animals with limited laboratory experience may be interpreted as the drug effect interacting with the organism's emotional state [2]. Presumably, those animals who had not been handled prior to being placed in the activity wheel were considerably more aroused in the experimental situation than the remaining animals and 4 mg/kg Δ^9-THC enhanced this arousal. There is considerable neurophysiological data suggesting that the effect of low doses of Δ^9-THC do result in a fluctuation between sedative and excitatory states [7, 12, 16] and, possibly, the situation in which testing occurs determines which state predominates.

The time course of the depressant action of both dose levels of Δ^9-THC was quite similar in both studies, with the maximum effects lasting from approximately 1 hr–24 hr after the injection and, except for the initial two points in the first study (little laboratory experience), the two drug dosages did not differ significantly from one another.

The results of this study together with work previously cited [2, 4, 17] indicate the care experimenters must take both in conducting research investigating motor effects of Δ^9-tetrahydrocannabinol and in generalizing the findings. The need for reporting such parameters as the amount of pre-test handling and the time elapsing between drug administration and testing are clearly demonstrated by the present findings.

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