Effects of Δ^9-tetrahydrocannabinol on a timing behavior in rats

S. N. PRADHAN, PAUL T. BAILEY, and PANKAJ GHOSH
Howard University College of Medicine, Washington, D.C. 20001

Effects of several doses (0.25, 0.5, 1, 5, and 10 mg/kg) of Δ^9-tetrahydrocannabinol were tested on the response and reinforcement (food) in a schedule of differential reinforcement of low rates (DRL) in rats. The response frequency showed a trend to increase with the dose to its peak at 5 mg/kg and to decrease to below normal level at 10 mg/kg. The majority of the increases in response occurred during the first quadrant of the required time (40 sec), although distribution in other quadrants also occurred. The reinforcement decreased gradually with the increase of dose up to 10 mg/kg.

One of the common effects of marihuana intoxication has been distortion of the sense of time. Overestimation of time during marihuana intoxication was observed by several investigators (Weil et al, 1968; Clark et al, 1970; Hollister & Gillespie, 1970). Other related effects due to marihuana include distortion of time (Tart, 1970) and temporal disintegration, inducing Ss to confuse past, present, and future and to lose their goal-directedness (Melges et al, 1970). In view of the above observations, the present investigation was undertaken to study the effect of Δ^9-tetrahydrocannabinol (Δ^9-THC), a potent derivative of marihuana, on a timing behavior in an experimental animal such as the rat.

MATERIALS AND METHODS

Subjects

The Ss were six male rats (Wistar-derived Walter Reed strain) with starting body weight of 200-240 g. Each rat was housed separately with free access to water.

Procedure

The procedure of the experiment was essentially the same as described earlier by Pradhan & Dutta (1970) and is briefly described as follows: Rats deprived of food for 23 h were trained to press a bar in standard Lehigh Valley Skinner boxes for reinforcement with food pellets in a DRL (differential reinforcement of low rates) schedule. The required interval between consecutive responses to be reinforced was gradually raised to and fixed at 40 sec. Each rat was subjected to a 40-min daily session for 6 days a week. After each session, 10-12 g of food pellets were left in the cage. During each session, the response and the reinforcement for each rat were recorded. The interresponse time (IRT) distributions divided into four categories of 10 sec each were also recorded.

When the performance of the rats was stabilized, after training for 2-3 months, a dose (0.25, 0.5, 1, 5, or 10 mg/kg) of Δ^9-THC in 4% Tween was administered intraperitoneally 30 min prior to the session in the above increasing sequence at intervals of at least 2 days. A dose of the drug was given to a rat only when the data on 2 previous control days did not differ from each other by more than 10% of their average and also from the earlier predrug level, in case of a pretreatment with a dose.

The averages of the response and reinforcement from all rats were calculated for 2 predrug and 2 postdrug days, along with those from the drug days at each dose level. The effects of a dose of the drug on the response and the reinforcement in a rat were expressed as the percent change from the data for the corresponding predrug controls (i.e., the average of the data for the 2 corresponding predrug days). Mean and SE (standard error of the mean) were calculated for the respective data on response and reinforcement at each dose and subjected to statistical analysis using Student's t test. The analysis of variance test was performed on the overall data on response and reinforcement. To test the significance of difference between effects (on response or reinforcement) at any two doses, Fisher's least significant difference (LSD) test and Duncan's new multiple-range (NMR) test (Fryer, 1966) were used.

RESULTS

Following administration of 0.25-, 0.5-, 1-, and 5-mg/kg doses of Δ^9-THC, the number of responses was increased and reinforcement decreased in 23 of the 24 drug sessions. At the 10-mg/kg dose, the response was increased in two rats but was reduced or even almost suppressed in four others, while decrease of the reinforcement was most marked. Table 1 shows the effects of the five doses of the drug together with controls for 2 predrug and 2 postdrug days. No drug effect appeared to persist during the 2 successive postdrug sessions. Although some occasional rats might have shown a slight increase in response or decrease in reinforcement, or both, in the postdrug sessions, such effects were not significant.

Dose-Effect Relation

Figure 1 shows the dose-effect graphs for the response and the reinforcement at different doses of Δ^9-THC. It appears that the response rate gradually increased with the dose to its peak at 5 mg/kg. At the 10-mg/kg dose, response was reduced to below normal level. Responses at 0.5 to 5 mg/kg showed a trend to increase, except for those at 0.5 and 1 mg/kg that did not appear to differ. On the other hand, the reinforcement decreased gradually with the increase of dose up to 10 mg/kg. Analysis of variance performed on these data revealed a significant difference in the response and the reinforcement at various doses at the 1% level. However, LSD and NMR tests showed that there was no difference between responses at any two doses from 0.25 to 5 mg/kg, whereas a significant difference existed between those at 5-

Table 1
Effects of Δ^9-Tetrahydrocannabinol on Response and Reinforcement in a DRL Schedule in Rats

Dose (mg/kg)*	Data (Mean ± SE)				
	−2 Day	−1 Day	0 Day	1 Day	2 Day
			Response		
0.25	87 ± 11	88 ± 9	102 ± 10	92 ± 17	97 ± 11
0.5	73 ± 7	82 ± 9	106 ± 15	82 ± 11	87 ± 10
1	87 ± 8	83 ± 7	114 ± 11	81 ± 9	81 ± 5
5	85 ± 8	83 ± 6	130 ± 12	84 ± 12	88 ± 10
10	79 ± 9	83 ± 11	64 ± 33	80 ± 11	86 ± 11
			Reinforcement		
0.25	30 ± 3	29 ± 3	21 ± 3	28 ± 5	27 ± 3
0.5	32 ± 2	33 ± 3	22 ± 4	29 ± 4	29 ± 3
1	28 ± 3	28 ± 4	16 ± 4	31 ± 4	29 ± 3
5	31 ± 4	31 ± 3	11 ± 3	29 ± 4	29 ± 3
10	30 ± 3	28 ± 2	5 ± 3	28 ± 3	27 ± 3

Injected intraperitoneally on 0 day 30 min before the session.

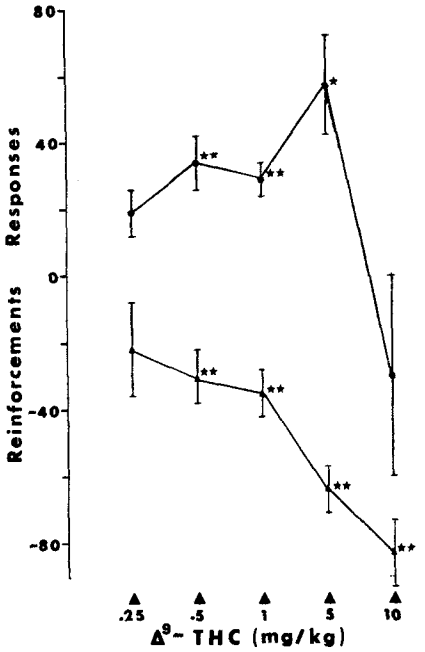

Fig. 1. Dose-effect graphs showing effects of several doses of Δ^9-THC on response (—•—) and reinforcement (—▲—) in DRL schedule. Figures in the ordinate represent percent change from the control. Each point represents mean of the data from six rats, and the vertical bar about each point represents one SE. * indicates $p < .05$ and ** indicates $p < .01$.

and 10-mg/kg doses at the 1% level. Similarly, no difference was observed between reinforcements at the 0.25- to 1-mg/kg dose and between those at the 5- and 10-mg/kg doses; however, there was a significant change from the 1- to the 5-mg/kg doses at the 1% level.

IRT Categories

In the control sessions, most of the IRT categories were very brief, so that maximum distribution of the response occurred in the first quadrant (10-sec category). Next large group of categories was the one very close to the required time (40-sec category). Thus, the IRT distribution was usually bimodal and sometimes unimodal (peak occurring at the 10-sec category). Figure 2 illustrates the average distribution of IRT categories in six rats in the control as well as drug sessions at 0.5-, 1-, and 5-mg/kg doses that increased the response significantly. Analysis of the effects at the three doses in different IRT categories shows that the responses increased by 62, 37, 30, and 12 and that the numbers of sessions showing the increase were 16, 14, 14, and 11 (out of a total of 18), respectively. It thus appears that the increase in response occurred mostly during the 10-sec category, although such increase also occurred in other categories, particularly the 20- and 30-sec categories. In the 40-sec category, the increase was minimal and disproportionate.

DISCUSSION

Marihuana and its derivatives have been reported to decrease responses in the majority of the behavioral situations in experimental animals (see Pradhan & Bailey, 1972; see also Marihuana and Health, 1971). Investigations from our laboratory (Pradhan et al, 1972) also demonstrate similar behavioral depression in intracranial self-stimulation, fixed-ratio food reinforcement, and conditioned shock avoidance schedules in a majority of the rats. In contrast to these observations, the present experiment shows a trend to increase in DRL responses following 0.25- to 5-mg/kg doses of Δ^9-THC in rats.

The increase in response may be due to low basal response rates, as reported for amphetamine by Dews (1958) and for amphetamine and meprobamate by Kelleher et al (1961). LSD also caused facilitation of responses only on one of two DRL schedules that had a lower response rate (Appel, 1971). However, no change in DRL response rates had been observed with some other drugs, e.g., ethyl alcohol (Sidman, 1955, 1956), chlorpromazine, prochlorperazine, mephenesin (Kelleher et al, 1961). The increase in response may also be attributed to inhibition of behavioral performance suppressed during learning of DRL behavior, since marihuana and its derivatives were shown to cause depression of learned responses in many behavioral situations (loc. cit.). Similar increase has been caused by certain depressant drugs such as pentobarbital (Sidman, 1956), meprobamate, and phenobarbital (Kelleher et al, 1961), but not by ethyl alcohol (Sidman, 1955, 1956), chlorpromazine, or prochlorperazine (Kelleher et al, 1961). Finally, with reference to distortion of time sense caused by marihuana in man (loc. cit.), Δ^9-THC may alter the time sense in rats, as also in the case of LSD, another psychotomimetic agent (Appel, 1971). It may be suggested from the fact that an increase in response following administration of Δ^9-THC occurred mostly during the shorter IRT categories and was not equally distributed over all the time categories. One or more of these factors may be involved in disrupting the timing behavior following administration of Δ^9-THC.

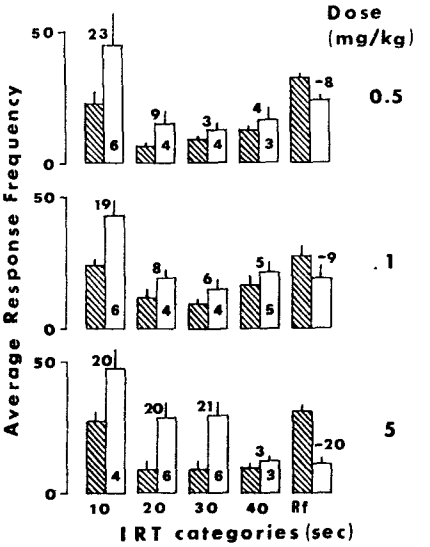

Fig. 2. Effects of 0.5, 1, and 5 mg/kg of Δ^9-THC on the response frequency during the four IRT categories and on the reinforcement in six rats. The required interval for DRL, 40 sec, was divided into four IRT intervals. Bars with vertical lines at their top represent the mean and the SE of responses from the control (hatched bars) and the drug (open bars) sessions. The control was taken as the average of the respective data from the two daily sessions prior to the drug sessions. The figures within the open bars indicate the number of sessions (out of six, one for each animal) showing increase of response, and those at the top of these bars show the number of responses increased over the controls at each category at each dose.

REFERENCES

APPEL, J. B. Effects of LSD on time-based schedules of reinforcement. Psychopharmacologia (Berlin), 1971, 21, 174-186.

CLARK, L. D., HUGHES, R., & NAKASHIMA, E. N. Behavioral studies of marihuana. Archives of General Psychiatry, 1970, 23, 193-198.

DEWS, P. Studies on behavior: IV. Stimulant actions of methamphetamine. Journal of Pharmacology & Experimental Therapeutics, 1958, 122, 137-147.

FRYER, H. C. *Concepts and methods of experimental statistics.* Boston: Allyn & Bacon, 1966.

HOLLISTER, L. E., & GILLESPIE, H. K. Marihuana, ethanol and dextroamphetamine. Archives of General Psychiatry, 1970, 23, 199-203.

KELLEHER, R. T., FRY, W., DEEGAN, J., & COOK, L. Effects of meprobamate on operant behavior in rats. Journal of Pharmacology & Experimental Therapeutics, 1961, 133, 271-280.

Marihuana and health. A report to Congress from the Secretary, U.S. Department of Health, Education, and Welfare. Washington, D.C: U.S. Government Printing Office, 1971.

MELGES, F. T., TINKLENBERG, J. R., HOLLISTER, L. E., & GILLESPIE, H. K. Temporal disintegration and depersonalization during marihuana intoxication. Archives of General

Psychiatry, 1970, 23, 204-210.
PRADHAN, S. N., & BAILEY, P. T. Behavioral effects of marihuana and its derivatives. In J. M. Singh, H. Lal, and L. Miller (Eds.), *Drug addiction: Experimental pharmacology.* North Miami: Symposia Specialists, 1972.
PRADHAN, S. N., BAILEY, P. T., & GHOSH, B. Some behavioral effects of Δ^9-tetrahydrocannabinol in rats Research Communications in Chemical Pathology & Pharmacology, Vol. 3, March 1972.
PRADHAN, S. N., & DUTTA, S. N. Comparative effects of nicotine and amphetamine on timing behavior in rats. Neuropharmacology, 1970, 9, 9-16.
SIDMAN, M. Technique for assessing the effects of drugs on timing behavior. Science, 1955, 122, 925.
SIDMAN, M. Drug behavior interaction. New York Academy of Sciences, 1956, 65, 282-302.
TART, C. T. Marihuana intoxication, common experience. Nature, 1970, 226, 701-704.
WEIL, A. T., ZINBERG, N. E., & NELSON, J. M. Clinical and psychological effects of marihuana in man. Science, 1968, 162, 1234-1242.