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Effects of Acute and Chronic Administration of Cannabis Sativa and (—)Δ^9-trans-Tetrahydrocannabinol on the Behavior of Rats in an Open-Field Arena*

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Abstract. The effects of acute and chronic administration of Δ^9-THC, cannabis extract and control solution on the behavior of rats repeatedly exposed to an open-field arena have been studied. After the first dose both Δ^9-THC and cannabis extract significantly decreased defecation, grooming and rearing; ambulation was not affected. After 20 injections of both marihuana compounds the rats showed values for defecation, grooming and rearing near to those obtained during the pre-drug phase; control rats, however, showed a significant decrease in these parameters indicating habituation to the open-field. The results are discussed in terms of effects of marihuana on emotional behavior of rats.

Key-Words: Marihuana — Δ^9-Tetrahydrocannabinol — Emotional Behavior — Habituation.

The responses of laboratory animals to marihuana and (—) Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC) seem to depend upon the schedule of drug administration. Acute administration provokes, among others, the following effects: a) delay in climbing rope performance of rats (Carlini, 1968), b) decrease of bar pressing behavior of rats (Silva *et al.*, 1968), c) decrease of spontaneous motor activity of mice (Holtzman *et al.*, 1969; Carlini *et al.*, 1970), d) potentiation of hexobarbital sleeping-time (Garriot *et al.*, 1967), e) catatonic-like state in mice and rats (Carlini *et al.*, 1970; Grunfeld and Edery, 1969), f) suppression of isolated-, induced fighting behavior of mice (Santos *et al.*, 1966; Salustiano *et al.*, 1966), g) decrease of key pecking behavior of pigeons (Siegel, 1969), h) analgesic effect on mice (Bicher and Mechoulan, 1968), i) suppression of conditioned avoidance responses in rats (Grunfeld and Edery, 1969) and j) alteration of maze performance of rats (Carlini and Kramer, 1965;

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Carlini *et al.*, in press). Most, if not all, of these effects are also observed with central nervous system depressant drugs, including tranquilizing agents. On the other hand, it has been reported that chronic administration of marihuana does not produce the effects *a*, *b*, *g* and *j*, because of development of tolerance (Carlini, 1968; Silva *et al.*, 1968; Carlini *et al.*, in press; Frankenheim *et al.*, 1970). Furthermore, when cannabis extract or Δ^9-THC are given chronically to starved rats, the initial depressive effects wear off after a few daily injections, giving place to irritability and aggressive behavior (Carlini and Masur, 1969; Carlini and Masur, 1970).

These data seem to indicate that marihuana and Δ^9-THC might have two different types of action. An acute, depressant action, which subsides rapidly after a number of injections, and effects such as irritability and aggressive behavior which could be better disclosed after tolerance to the former action has developed.

The present work was undertaken in an attempt to shed some light on this subject. Rats were submitted to daily injections of a mariuhana extract and Δ^9-THC and exposed periodically to an open field arena. This method has been used for many years and it is generally accepted that it measures "emotionality" in the rat (Hall, 1934; Brimblecombe, 1963; Broadhurst, 1969; Denenberg, 1969).

Methods

Drugs. Cannabis extract obtained from plants cultivated in the Northeast of Brazil (Mato Grosso State) was prepared and suspended in saline plus tween-80 as described by Carlini and Kramer (1965). Suspensions of Δ^9-THC and the control solution consisting of saline plus tween-80 were prepared in the same way.

Animals. 117 male and female Wistar rats, 70 day old at the beginning of the experiment, were used. Since weaning at 30 days, the animals were housed in groups of five in wooden cages measuring $48 \times 28 \times 20$ cm. Daily handling of the rats consisted of cleaning the cages and providing food and water every morning. All trials were performed in the afternoon.

Apparatus. The open-field arena was constructed according to Broadhurst (1960). It consisted of an arena of plywood measuring 85 cm in diameter and surrounded by a curtain of two layers of muslin. Three 60 watt lamps and three loudspeakers giving a constant white noise of 76 decibels were suspended, respectively, 110 and 140 cm from the floor.

Procedure. The experiment was carried out in two phases. In the first phase only female rats were used; 1 month later the male rats were tested. At the age of 70 days the animals were exposed to the open-field for 2 consecutive days, 3 min a day (exposure 1 and 2). The number of

boluses eliminated, ambulation, grooming and rearing were recorded. The animals were then divided into two groups based on the number of boluses eliminated: rats with a *high* index of defecation, which averaged three or more boluses in the 2 days and animals with a *low* index of defecation, which eliminated less than three boluses. Rearing and grooming were not recorded in female rats with a low index of defecation.

On the following day (third day of the experiment), the animals were either injected with 1.0 ml/kg of control solution or 5.0 mg/kg of cannabis extract or 2.5 mg/kg of Δ^9-THC. They were returned to their home-cages, and 45 min later exposed for the third time to the open-field. The number of boluses eliminated in the home-cages during the 45 min elapsing between drug application and exposure to the open field was also recorded. Table 1 shows the number and sex of animals employed in each drug treatment, according to their index of defecation. Finally, from the 4th to the 22nd day the animals were injected daily and 45 min after injection numbers 5, 10, 15 and 20 they were again exposed to the open field (4th to 7th exposures). As before, defecation in the home-cages and ambulation, grooming, rearing and defecation in the arena were recorded.

Within each group the differences in means between first control exposure and the exposures under drug action were calculated using Student's *t*-test. The differences between values of saline and treated groups were also analysed according to the same test.

Results

Defecation. The results obtained are seen in Table 2. The animals with a high defecation index, regardless of sex, eliminated practically the same number of boluses in the first two exposures. However, when the drugs were injected for the first time (third exposure) there was a slight decrease (non-significant) for the control group, whereas Δ^9-THC and cannabis-treated rats showed a significant reduction in elimination, varying from 45 to 56% of the values of the first exposure. On the other hand, with continuing daily injections the defecation of control rats came down to values significantly smaller. For two of the drug-treated groups (male-Δ^9-THC and female-cannabis extract) elimination returned to levels comparable to those of the first exposure.

Table 2 also shows the results obtained with rats of low index of defecation; male and female animals receiving control solution were joined into one group as they presented similar results. Control solution injections did not affect the animals throughout the treatment. However, rats treated with Δ^9-THC presented an increase in defecation which reached several times the control values at the last two exposures. The

Table 1. *Number, sex and index of defecation of rats which received 1.0 ml/kg of control solution, 2.5 mg/kg of Δ^9-THC or 5.0 mg/kg of cannabis extract*

Drug-treatment	Defecation			
	High index		Low index	
	Male	Female	Male	Female
Control solution	19	19	13	5
Δ^9-THC	12	—	10	—
Cannabis extract	17	13	—	9

Table 2. *Number of boluses (average ± S.D.) eliminated by the rats in an open field. Exposures 1 and 2 are controls (no drug injected): 3 to 7 correspond to exposures in the open field after the first to the 20th injections*

Drug and dosage	Exposure	Injection	Number of boluses ± S.D.			
			High Index		Low index	
			Male	Female	Male	Female
control solution 1.0 ml/kg	1	—	4.3 ± 1.8	4.9 ± 2.2	0.6 ± 1.4	
	2	—	4.3 ± 1.0	4.9 ± 2.1	1.0 ± 1.1	
	3	1	3.8 ± 1.5	3.6 ± 1.5	0.3 ± 0.7	
	4	5	2.6 ± 2.1[a]	3.8 ± 1.1	0.8 ± 1.0	
	5	10	2.6 ± 1.7[a]	3.7 ± 2.1	0.9 ± 0.6	
	6	15	2.1 ± 2.1[a]	3.9 ± 2.5	0.6 ± 0.6	
	7	20	2.8 ± 2.6[a]	3.0 ± 2.1[a]	0.2 ± 0.6	
Δ^9-THC 2.5 mg/kg	1	—	4.8 ± 1.0	—	0.7 ± 0.9	—
	2	—	5.6 ± 2.2	—	0.8 ± 0.7	—
	3	1	2.1 ± 2.4[a]	—	1.5 ± 1.4	—
	4	5	4.4 ± 1.8	—	2.6 ± 2.1[a]	—
	5	10	3.9 ± 1.7	—	2.8 ± 1.5[a]	—
	6	15	4.3 ± 1.2	—	3.2 ± 1.6[a]	—
	7	20	4.4 ± 1.1	—	3.3 ± 1.3[a]	—
Cannabis extract 5.0 mg/kg	1	—	4.4 ± 1.2	4.6 ± 1.4	—	0.0
	2	—	4.8 ± 1.1	5.2 ± 1.5	—	0.0
	3	1	2.2 ± 1.5[a]	2.0 ± 1.4[a]	—	1.0 ± 1.2
	4	5	2.1 ± 1.7[a]	4.3 ± 1.7	—	0.9 ± 1.7
	5	10	2.8 ± 2.5[a]	4.5 ± 2.0	—	0.3 ± 0.6
	6	15	2.5 ± 2.2[a]	4.6 ± 2.8	—	1.2 ± 1.4
	7	20	2.2 ± 2.2[a]	4.5 ± 1.5	—	0.5 ± 0.9

[a] Differs significantly from first control exposure ($p \leqslant 0.05$).

Table 3. *Ambulation of rats in the open field arena before and after the administration of drugs*

Drug and dosage	Exposure	Injection	Number of floor units entered (average ± S.D.)			
			High index of defecation		Low index of defecation	
			Male	Female	Male	Female
Control solution 1.0 ml/kg	1	—	45.8 ± 20.9	59.8 ± 16.3	42.2 ± 24.5	73.0 ± 9.0
	2	—	36.1 ± 17.8	46.1 ± 21.3	31.8 ± 17.5	70.6 ± 20.5
	3	1	36.2 ± 19.5	47.0 ± 26.8	33.8 ± 22.0	53.4 ± 30.0
	4	5	43.8 ± 25.2	57.6 ± 10.3	23.8 ± 15.3	64.6 ± 34.0
	5	10	37.2 ± 19.5	51.5 ± 23.6	25.9 ± 22.0	40.4 ± 35.6
	6	15	35.6 ± 18.5	49.1 ± 16.9	32.0 ± 15.0	63.9 ± 25.0
	7	20	30.1 ± 18.8	54.0 ± 14.4	31.8 ± 17.0	63.4 ± 28.7
Δ^9-THC 2.5 mg/kg	1	—	31.0 ± 15.6	—	26.9 ± 14.3	—
	2	—	32.3 ± 19.3	—	20.8 ± 14.7	—
	3	1	38.9 ± 19.5	—	26.0 ± 12.3	—
	4	5	26.7 ± 18.5	—	12.9 ± 7.4	—
	5	10	29.1 ± 16.3	—	19.1 ± 15.3	—
	6	15	31.7 ± 24.2	—	20.5 ± 14.1	—
	7	20	34.1 ± 23.0	—	20.1 ± 13.3	—
Cannabis extract 5.0 mg/kg	1	—	54.2 ± 18.0	64.1 ± 19.5	—	89.9 ± 15.4
	2	—	43.2 ± 23.0	46.0 ± 21.2	—	85.9 ± 18.9
	3	1	40.4 ± 20.5	38.7 ± 17.0	—	59.4 ± 22.0[a]
	4	5	29.7 ± 16.1	48.4 ± 24.6	—	57.8 ± 32.5[a]
	5	10	31.3 ± 23.0	34.2 ± 18.7	—	45.5 ± 26.0[a]
	6	15	34.3 ± 15.4	35.6 ± 21.4	—	54.4 ± 24.6[a]
	7	20	29.1 ± 15.1	34.2 ± 19.5	—	64.7 ± 28.1

[a] Differs significantly from second control exposure ($p \leqslant 0.05$).

results with cannabis extract showed a similar trend although they were not significant. Finally, it was observed that all groups of rats showed a similar elimination in the homecages during the 45 min period elapsing between injection and exposure to the apparatus. The average number of boluses eliminated before the 5 exposures varied from 0.3 to 1.0, 0.5 to 1.1 and 0.0 to 1.5, respectively, for control solution, Δ^9-THC and cannabis treated groups.

Ambulation. Results are summarized in Table 3. The first injection of drugs did not affect ambulation in any of the groups; the same negative results were obtained with chronic treatment. However, a few rats treated with Δ^9-THC and cannabis extracted showed periods of "freezing" during the last exposures to the open-field.

Rearing and Grooming. Cannabis extract and Δ^9-THC had a similar effect, as may be seen in Tables 4 and 5. There was a decrease in both

Table 4. *Grooming of rats in the open field arena before and after the administration of drugs*

Drug and dosage	Exposure	Injection	Number of grooming behavior (average ± S.D.)		
			High index of defecation		Low index of defecation
			Male	Female	Male
Control solution	1	—	3.2 ± 1.1	2.8 ± 1.8	3.1 ± 2.1
	2	—	3.8 ± 1.8	3.5 ± 1.4	2.3 ± 2.6
1.0 mg/kg	3	1	4.9 ± 2.7	3.9 ± 1.8	2.9 ± 2.0
	4	5	4.7 ± 3.3	4.1 ± 2.2	2.2 ± 1.9
	5	10	4.2 ± 2.7	3.0 ± 1.5	3.3 ± 1.4
	6	15	3.9 ± 2.3	2.7 ± 1.5	2.7 ± 2.9
	7	20	5.4 ± 2.5	4.1 ± 1.7	2.4 ± 1.7
Δ^9-THC	1	—	3.3 ± 1.5	—	2.2 ± 2.0
2.5 mg/kg	2	—	4.8 ± 1.6	—	2.1 ± 1.5
	3	1	1.4 ± 1.1[a]	—	0.5 ± 0.9[a]
	4	5	3.0 ± 2.6	—	1.2 ± 1.6
	5	10	2.1 ± 1.6	—	0.6 ± 1.0
	6	15	2.7 ± 2.3	—	1.6 ± 1.3
	7	20	2.5 ± 2.3	—	1.4 ± 1.1
Cannabis extract	1	—	3.5 ± 1.6	3.6 ± 1.8	—
	2	—	3.2 ± 1.6	3.5 ± 1.1	—
5.0 mg/kg	3	1	2.2 ± 1.4[a]	1.3 ± 1.5[a]	—
	4	5	1.4 ± 1.3[a]	2.0 ± 1.8[a]	—
	5	10	2.0 ± 1.4[a]	3.8 ± 2.6	—
	6	15	2.1 ± 1.4[a]	2.3 ± 1.7	—
	7	20	2.2 ± 1.7	2.8 ± 2.3	—

[a] Differs significantly from first control exposure ($p \leqslant 0.05$).

parameters after the first injection. At the end of the experiment, however, the values for grooming and rearing showed a tendency to return to levels near the predrug phase.

Discussion

5 mg/kg of marihuana extract and 2.5 mg/kg of Δ^9-THC, acutely given, decreased rearing and grooming of male and female rats exposed to an open field arena; ambulation was not affected. These effects were clearer with Δ^9-THC probably because of its stronger activity. The effects on defecation varied according to the previous level of elimination. The first injection reduced defecation of animals eliminating three or more boluses daily; however, it did not affect rats with a low index of defecation. These effects are not common to other psychotomimetic drugs.

Table 5. *Rearing of rats in the open field arena before and after the administration of drugs*

Drug and dosage	Exposure	Injection	Number of rearing behavior (average ± S.D.)		
			High index of defecation		Low index of defecation
			Male	Female	Male
Control solution	1	—	13.8 ± 8.5	17.5 ± 9.1	12.0 ± 9.4
	2	—	10.4 ± 7.9	12.1 ± 7.5	5.9 ± 6.7
1.0 mg/kg	3	1	12.0 ± 10.8	16.7 ± 8.4	8.3 ± 7.9
	4	5	11.9 ± 8.0	17.6 ± 5.8	12.7 ± 3.4
	5	10	10.1 ± 7.0	14.0 ± 9.2	6.3 ± 8.1
	6	15	9.5 ± 6.7	12.5 ± 5.4	9.0 ± 5.5
	7	20	8.6 ± 7.9	14.8 ± 7.0	8.8 ± 8.2
Δ^9-THC	1	—	10.2 ± 6.2	—	5.9 ± 3.6
2.5 mg/kg	2	—	8.6 ± 7.4	—	3.7 ± 3.3
	3	1	2.0 ± 3.0[a]	—	1.1 ± 1.7[a]
	4	5	4.9 ± 4.4	—	1.3 ± 2.1
	5	10	4.5 ± 5.1	—	2.1 ± 3.7
	6	15	7.2 ± 6.7	—	4.1 ± 5.1
	7	20	6.9 ± 5.0	—	4.3 ± 4.9
Cannabis extract	1	—	14.8 ± 7.2	24.6 ± 5.9	—
	2	—	8.9 ± 6.0	14.0 ± 8.0	—
5.0 mg/kg	3	1	4.0 ± 4.5[a]	10.9 ± 7.0	—
	4	5	5.3 ± 6.9	12.7 ± 9.4	—
	5	10	7.6 ± 7.1	13.1 ± 7.7	—
	6	15	8.3 ± 5.5	15.3 ± 8.3	—
	7	20	5.5 ± 4.3	12.1 ± 8.5	—

[a] Differs significantly from second control exposure ($p \leqslant 0.05$).

Thus, 2 to 136 μg/kg of LSD-25, increase ambulation, rearing and grooming, whereas 500 μg/kg decrease rearing and grooming and increase ambulation (Dandiya *et al.*, 1969). Brimblecombe (1963) reported that 100 and 500 μg/kg of LSD-25, injected either 1.5 or 3 h before exposure to the open field, did not alter rearing and ambulation, and slightly increased grooming; on the other hand, 0.5 mg/kg significantly decreased defecation. The same effect was also obtained with mescaline, harmine, dimethyltryptamine, diethyltryptamine and bufotenine; however, these drugs increased defecation before the exposure to the open field (Brimblecombe, 1963). Therefore, it is possible that the decrease observed in the apparatus was not due to the drug action on the emotional defecation of the rats. Our results are not open to this criticism, because cannabis and Δ^9-THC did not change defecation before testing.

The acute effects of Δ^9-THC and cannabis seem to resemble those of depressant and tranquilizing agents. Thus, amitriptyline, chlorproma-

zine and haloperidol are strong depressors of grooming behavior in mice (Rohte, 1969); pentobarbital sodium inhibits rearing activity of rats (Garg, 1969); reserpine, chlorpromazine and haloperidol reduce ambulation, rearing, grooming and defecation of rats (Ryall, 1958; Janssen *et al.*, 1960).

Defecation in the unfamiliar environment of the open field is considered as a measure of the emotional reactivity of rats (Hall, 1934; Broadhurst, 1958; Ryall, 1958); Δ^9-THC and cannabis effects were observed on animals with a high index of defecation or high index of anxiety motivated emotional defecation, according to the terminology employed by Hall (1934), Broadhurst (1958), Ryall (1958) and Janssen *et al.* (1960). This suggests that marihuana compounds, acutely administered, could decrease influences of environmental stress on animals of high emotionality, an effect which would be expected from drugs with tranquilizing properties. It is interesting in this respect that cannabis extracts and Δ^9-THC are as active as chlorpromazine in suppressing the isolation-induced aggressiveness of mice (Santos *et al.*, 1966; Salustiano *et al.*, 1966; Carlini *et al.*, 1970). As further support to our contention is the decrease of rearing and grooming observed in the rats. It is conceded that rearing is a function of the central nervous system (CNS) excitability level (Lat, 1963; Holland and Gupta, 1966; Garg, 1969). Therefore, Δ^9-THC and cannabis extract, acutely given, could decrease the excitability of the CNS or block the input of environmental stimuli to it. The lack of effect of Δ^9-THC and cannabis on ambulation is not in disagreement with this possibility, because, as stated by Candland and Nagy (1969), the relationship between motor activity and fear is unclear.

On the other hand, Δ^9-THC and *Cannabis sativa* extract, chronically given, have effects different from those observed after acute administration. Thus, rearing and grooming, which were depressed by the first injection, showed a tendency to return to values near the predrug levels after several injections. Whether or not this could be due to tolerance to the depressing effects of marihuana is open to discussion; it has been described before that such tolerance can occur in several experimental situations (Carlini, 1968; Silva *et al.*, 1968; Carlini *et al.*, in press; Frankenheim *et al.*, 1970). Defecation, after the initial decrease, also increased with continuation of injections. Thus, rats with a high index of defecation treated repeatedly with Δ^9-THC and cannabis did not show the known decrease in elimination after several exposures to the apparatus, as was observed with control animals. This habituation of rats to the open field has been considered as an indication that elimination is emotional (Hall, 1934). However, this effect of marihuana compounds cannot be considered merely as a result of tolerance; if this was the case treated rats, as controls, should also show habituation to the open field.

Neither can it be considered as a result of an increase of intestinal activity, because the drug did not change defecation in the 45 min before exposing the rats to the open field. It is also improbable that marihuana acted by blocking habituation; the large increase in defecation of rats of low index of defecation show clearly that this did not happen. One possible explanation is that marihuana compounds given chronically enhance the emotional reactivity of rats, or alternatively that the effects on emotional behavior would be present since the first injection but were only disclosed after tolerance had developed to the depressant effects. The increase of "curiosity" (Abel and Schiff, 1969) and of aggressive behavior (Carlini and Masur, 1969) in rats treated chronically with marihuana compounds, together with the present results, show that the effects of *Cannabis sativa* on animals can be very different according to the scheme of drug application.

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