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Aggressiveness Induced by Marihuana and other Psychotropic Drugs in REM Sleep Deprived Rats

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ALVES, C. N., A. C. GOYOS AND E. A. CARLINI. *Aggressiveness induced by marihuana and other psychotropic drugs in REM sleep deprived rats.* PHARMAC. BIOCHEM. BEHAV. 1(2) 183–189, 1973. – In 96 hr REM sleep deprived rats given 5–40 mg/kg of Δ^9-THC and several alcoholic extracts of marihuana induce dose dependent aggressive behavior. The aggressiveness appears after the first application of the drugs and is observable for at least 4 hr following the injection. The rats also develop a high degree of irritability. LSD-25 (0.02–0.08 mg/kg), mescaline (80 mg/kg), *d*-amphetamine (1.0 to 4.0 mg/kg) and ethanol (0.8–1.6 g/kg) failed to elicit either aggressiveness or irritability in the REM sleep deprived rats. On the other hand, 8 and 16 mg/kg of *d*-amphetamine induced aggressiveness which was, however, far below that observed in the marihuana treated animals. These data add further support to the previous findings that the acute effects of marihuana can be dramatically changed from depression, as observed in normal rats, to irritability and aggressiveness as observed in stressed animals.

REM sleep deprivation Aggressiveness Marihuana Δ^9-THC Marihuana and aggressiveness Stress and aggressiveness

PREVIOUS work from our laboratory has shown that IP chronic administration of *Cannabis sativa* (marihuana) extracts and of (-) Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC) induces striking fighting behavior in starved rats [7,8]. Other reports confirmed the appearance of aggressiveness in food deprived rats after chronic administration of marihuana compounds [23,27]. A similar increase in aggressiveness of rats was also found when Δ^9-THC was chronically administered either through the oral route [26] or through the lungs (T. Jarbe, personal communication). In addition to this intraspecific aggressive behavior marihuana promotes an interspecific aggressiveness, inducing muricidal behavior in rats; in this case starvation also potentiates the effects [2,27].

Recently, data have been presented suggesting that the stress induced by starvation is the important factor associated with the capacity of marihuana to induce aggressiveness in the starved rats. Thus, rats fed ad lib and stressed by cold [5] or by withdrawal from previous morphine administration [4] react with strong aggressive behavior when first injected with marihuana, which markedly contrasts with the depression shown by normal rats after the first application of the drug.

These data led us to investigate whether deprivation of rapid eye movement (REM) sleep in rats would also make these animals sensitive to the aggressiveness inducing properties of marihuana compounds. REM sleep deprivation produces behavioral changes in animals and in man, such as increased irritability [1, 10, 11, 12, 28], increased shock induced fighting between rats [20] and changes in the response to amphetamine towards aggressiveness [13].

MATERIAL AND METHOD

Drugs. Semipurified extracts of *Cannabis sativa* obtained from top flowerings of 4 different samples of marihuana apprehended by São Paulo State Police and a control solution (0.6 percent solution of Tween-80 in saline) were prepared according to the usual methods employed in our laboratory [6]. Briefly, powdered plant was extracted for 12 hr with petroleum ether in a reflux condenser. The ether was evaporated and the residue resuspended in ethanol. The alcohol solution was left 24 hr at 4°C and filtrated to remove a greenish precipitate. The filtrate was kept at 4°C and used thereafter. To inject the rats the alcohol was evaporated and the residue resuspended in the saline-Tween-80 mixture. (-) Δ^9-*trans*-tetrahydrocannabinol was kindly supplied by the United Nations (we are grateful to Dr. O. Braenden for this generous gift). The compounds

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were analysed by gas chromatography (we are grateful to Drs. J. R. Valle and J. G. Aucelio for the assays) and further assayed by the corneal areflexia method in rabbits [25]. Table 1 gives the percent content of the 3 cannabinoids and the potency in rabbits. Extract 5 was further analysed by gas chromatography at the University of Mississippi (provided by Dr. Carlton Turner to whom we are grateful) and the following percent composition was found: Δ^9-THC 59.9 propyl analog of Δ^9-THC 1.75, cannabidiol 1.4, cannabinol 1.03 and cannabigerol 0.86.

Mescaline sulfate (Sigma Chemical Corporation), *d*-amphetamine sulfate (Nutritional Biochemicals Corporation), ethanol (Merck Laboratories) and LSD-25 (Delysid, Sandoz) were also used. The amounts are expressed in terms of the salts. All injections were given through intraperitoneal route, in a volume of 1.0 ml/kg.

TABLE 1

GAS CHROMATOGRAPHY ANALYSIS AND BIOLOGICAL ACTIVITY ON RABBITS (GAYER TEST) OF 4 EXTRACTS OF CANNABIS SATIVA AND OF Δ^9-THC

Drug	Gas chromatography analysis (percentage of constituents)			Gayer test (mg/kg)
	Δ^9-THC	Cannabinol	Cannabidiol	
Δ-THC	100*	0	0	0.09 ± 0.008
Extract 2	44.8	40.1	15.1	0.296 ± 0.04
Extract 4	33.3	38.9	12.2	-
Extract X	35.5			0.410 ± 0.04
Extract 5	83.4	16.7	0	0.118 ± 0.01

*Showed only one peak at the gas chromatography

REM Sleep Deprivation and Aggressive Behavior

Three to four month old female Wistar rats from our own colony were used. Animals were deprived of REM sleep by placing them individually on 7 cm platforms surrounded by water with food ad lib as recommended by others [13,21]. Control animals were left on 14 cm platforms. Twenty-four to 96 hr later the animals were removed from the platforms and kept by pairs in wire cages measuring 16x30x18 cm. Ten min later both animals of each pair were injected with the drugs under study and aggressive behavior was measured for the next 4 hr. In most of the experiments a second injection of the drugs was given 2 hr after the first one. The aggressiveness was scored in seconds and corresponded to the time both animals of each pair remained in an upright position, standing on the hind legs, trying to bite each other [5, 7, 8]. The following experiments were carried out.

Experiment 1. Twenty rats were placed for 96 hr on 7 cm platforms; 10 control rats were left on 14 cm platforms. The REM sleep deprived (7 cm platforms) and the control (14 cm platforms) pairs received 10 min later either 20 mg/kg of extract 2 or control solution. Aggressive behavior was scored for 4 hr beginning immediately after the injection.

TABLE 2

AGGRESSIVE BEHAVIOR INDUCED BY 20 MG/KG OF MARIHUANA EXTRACT 2 AND 1.0 ML/KG OF CONTROL SOLUTION ON 3 MONTH OLD FEMALE RATS DEPRIVED OF REM SLEEP FOR 96 HR

Drug	Number of pairs	REM sleep condition*	Aggressiveness (sec. ± S.E.) during 4 hr after the injections
Control solution	5	7 cm - deprived	0
Extract 2	5	" "	5,000 ± 860‡
Control solution	1	14 cm - control	0
Extract 2	4	" "	160†

*The animals had available either 7 cm (REM deprived) or 14 cm (REM normal) platforms.

†Lack of standard error means that just one pair fought.

‡Differs significantly from control group ($p \leq 0.001$; Student *t*-test).

Experiment 2. One hundred and ninety six rats were left on 7 cm platforms for periods of time which varied from 24–96 hr. After the end of deprivation they were caged by pairs and received 20 mg/kg of either extract 4, 5, X or 1.0 ml/kg of control solution. Aggressiveness was scored during the following 2 hr, at the end of which a second injection was given; aggressiveness was again scored for the next 2 hr. Immediately before the first injection and then at every 30 min up to 4 hr, irritability of the animals was assessed [22]. Briefly, at each assessment the animals were submitted to 4 different nonpainful stimuli and 0–3 points were scored as response to each stimulus. Therefore, a maximum of 12 points of irritability could be attributed to each animal.

Experiment 3. Eighty rats were maintained for 96 hr on 7 cm platforms. After being randomly paired (40 pairs), groups of 5 pairs received the following drugs: control solution, 2.5, 5.0, 10 and 20 mg/kg of Δ^9-THC and 5.0, 10 and 20 mg/kg of cannabis extract 5. The treatments were repeated 2 hr later. Aggressiveness was scored for 30 min intervals during the 2 hr periods following each injection; irritability was also scored at 30 min intervals, as in Experiment 2.

Experiment 4. Ninety six rats were deprived of REM sleep for 96 hr as indicated above. Groups of 3–5 pairs were injected respectively with 40 mg/kg mescaline, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg *d*-amphetamine, 0.01 and 0.04 mg/kg LSD-25 and 400 and 800 mg/kg of ethyl alcohol. Two hr later the injections were repeated. Aggressiveness and irritability were scored as in Experiment 3.

Statistics. Aggressive behavior among the several experimental groups was analysed through analysis of variance; when the groups were found to differ significantly among them, the Student *t*-test was used for further comparison.

The scores of irritability were first analysed through the Kruskal-Wallis one-way analysis of variance by ranks; for further comparisons the Mann-Whitney U test was used.

RESULTS

Experiment 1. Animals deprived of REM sleep for 96 hr and injected with control solution did not fight, in contrast to the strong aggressiveness observed in the group similarly deprived and treated with 20 mg/kg of cannabis extract 2 (Table 2). Of the four pairs of control animals (96 hr on 14 cm platform) injected with extract 2, only one pair showed discreet fighting totaling 160 sec during the 4 hr period of observation. The behavior of the REM sleep deprived marihuana treated animals was peculiar. They jumped when stimulated by puffs of air, showed vocalization during fightings and sometimes just by seeing an object approaching them, such as the experimenter's hand, they stood upright and fell backwards remaining in that position in the corner of the cage, vocalizing and rapidly moving the forepaws. This was in contrast with the control marihuana injected rats or with the REM sleep deprived control solution injected animals, which remained most of the time depressed or sleeping in the cages. The 96 hr sleep deprived animals lost 12.1±1.2 g (average±S.D.) during the deprivation period; control animals lost 3.9±0.1 g. To verify whether the weight loss was playing a role, 8 other rats were starved for 36 hr losing 9.1±1.0 g. Twenty mg/kg of cannabis extract 2 did not induce aggressive behavior; on the contrary, only depression was observed.

Experiment 2. As it is known that biological activity of cannabis varies from sample to sample [25] and may not be due solely to their Δ^9-THC content [14], this experiment was performed with 3 different extracts. Concomitantly, the influence of time of deprivation of REM sleep was also studied. Table 3 shows the results. Analysis of variance performed with the four groups of animals revealed significant differences at all periods of REM deprivation ($p \leq 0.02$ to $p \leq 0.001$); same statistical analysis performed among the 3 groups of cannabis treated rats showed significant differences at 24, 48 and 96 hr of REM deprivation ($p \leq 0.05$ to $p \leq 0.01$). Extract 5 was the most potent of all in inducing the aggressive behavior. On the other hand, with the exception of rats treated with extract 4, it was observed that the longer the period of REM sleep deprivation the greater the aggressiveness induced by marihuana. Weight loss of 24, 48, 72 and 96 hr REM deprived animals was, respectively, 11.6±2.4, 11.6±1.9, 9.8±1.7 and 11.9±1.7 g. Finally, Table 3 shows again that REM sleep deprived rats treated with control solution did not present aggressive behavior; the few seconds of fighting postures occasionally observed were the result of the stimuli given at every 30 min to assess irritability. Table 4 shows irritability scores (medians) for control and extract 5-treated rats as well as for Δ^9-THC (see Experiment 3). Analysis of variance performed among all 96 hr REM deprived groups showed that the results differed significantly ($p \leq 0.001$). It is seen that control solution injected rats showed an irritability degree which was small when compared to the marihuana treated animals. Thus, 96 hr deprived control animals showed a maximum of 5.0 degrees of irritability; 72 and 96 hr deprived rats treated either with extract or Δ^9-THC showed the maximum degree of irritability (12 degrees) during almost all experiment.

Experiment 3. Once determined that extract 5 and 96 hr of REM sleep deprivation were the best conditions to induce aggressiveness in the rats, a comparative study was carried out using several doses of extract 5 and of Δ^9-THC. Figure 1 shows the results expressed as the total aggressiveness scored during the 4 hr period of observation. It is seen that 5.0 mg/kg (given in 2 doses of 2.5 mg/kg each, spaced by 2 hr) did not induce significant fighting. There was, however, a proportional increase of aggressive behavior as the doses of both substances were raised. Extract 5 showed a tendency to be more active than Δ^9-THC, but the difference did not reach statistical significance.

Figure 2 shows the results for 20 and 40 mg/kg of both compounds, scored at every 30 min, throughout the 4 hr of

TABLE 3

INFLUENCE OF DURATION OF REM SLEEP DEPRIVATION ON THE AGGRESSIVENESS INDUCED IN RATS BY 2 DOSES OF 20 MG/KG OF 3 DIFFERENT EXTRACTS OF *CANNABIS SATIVA*

Drug	Total aggressiveness in sec (average ± S.E.) during 4 hr induced by cannabis extracts in rats deprived of REM sleep by different periods of time (hr)			
	24	48	72	96
Control solution	0(7)*	7 ± 5.8 (7)	0(7)	2.8 ± 2.4 (8)
Extract 4	0(4)	692 ± 269(6)†,‡	1190 ± 217(9)†	472 ± 440(6)†'‡
Extract X	1422 ± 552(5)†	784 ± 367(9)†,‡	1895 ± 455(5)†	2055 ± 853(5)†,‡
Extract 5	97 ± 43(5)†	3182 ± 1008(5)†	3722 ± 1561(5)†	8008 ± 1896(5)†

*Within parenthesis: number of pairs tested
†Differs significantly from control by at least $p \leq 0.05$ (Student t-test);
‡Differs significantly from extract 5 by at least $p \leq 0.05$ (Student t-test).

TABLE 4

IRRITABILITY SCORES (MEDIANS) OF REM SLEEP DEPRIVED RATS TREATED WITH CANNABIS EXTRACT 5 AND Δ^9-THC

Drug	Dose (mg/kg)*	REM deprivation (hr)	Number of rats	Irritability (medians) at several time intervals (min) after injection					
				0	30	60	120	180	240
Control solution	1.0 ml/kg	24	8	1.0	1.0	1.0	0.5	0.5	0.5
"	"	48	14	1.0	2.0	1.5	0.5	2.0	0.5
"	"	72	14	1.0	2.0	1.0	1.0	1.0	1.0
"	"	96	16	3.0	5.0	5.0	3.0	4.0	3.0
Extract 5	40	24	10	1.0	5.0	7.0	9.0	9.0	11.0
"	"	48	10	2.5	5.5	10.0	9.5	12.0	12.0
"	"	72	10	1.0	8.0	12.0	12.0	12.0	12.0
"	"	96	10	1.5	12.0†	12.0‡	12.0‡	12.0†	12.0‡
Extract 5	10	96	16	1.0	10.5‡	12.0‡	9.0‡	12.0‡	12.0‡
"	20	"	10	1.0	12.0‡	12.0‡	12.0‡	12.0‡	12.0‡
Δ^9-THC	5	"	6	0.5	10.0‡	10.5†	7.5‡	8.5‡	10.5‡
"	10	"	6	3.0	10.0‡	12.0‡	9.5‡	9.0‡	9.0†
"	20	"	6	3.5	11.5‡	9.0‡	10.5†	10.0‡	12.0‡
"	40	"	10	1.5	11.5‡	12.0‡	12.0‡	12.0‡	12.0‡

*Dose applied in 2 injections spaced by 2 hr.

‡Differs significantly from 96 hr REM deprived control group ($p \leq 0.01$; Mann-Whitney U test); statistical analysis was not performed among the 24, 48 and 72 hr REM sleep deprived rats.

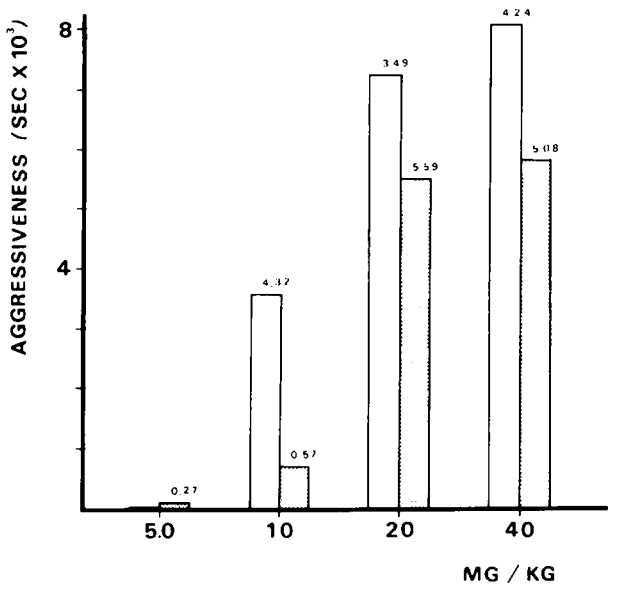

FIG. 1. Aggressive behavior induced by several doses of marihuana extract 5 (open columns) and Δ^9-THC (hatched columns) on 96 hr REM sleep deprived rats. Numbers above columns are the standard errors of the means. The total dose of each drug was applied in two injections spaced by 2 hr. The aggressive behavior was scored during 4 hr, beginning immediately after the first application of drugs.

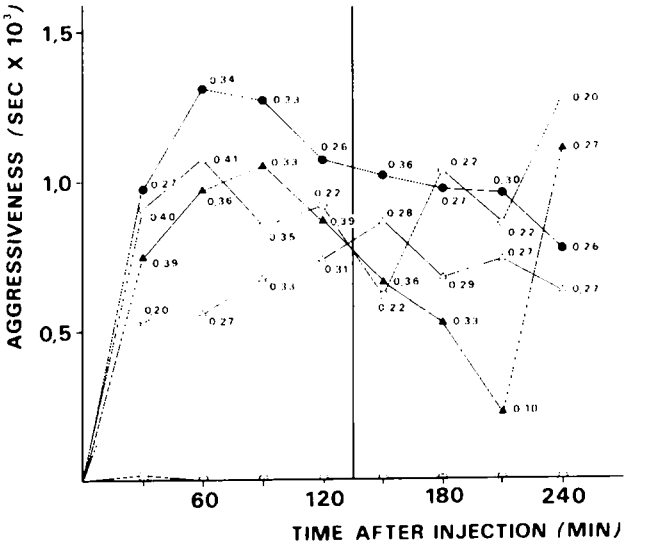

FIG. 2. Aggressive behavior, scored at 30 min intervals, of 96 hr REM sleep deprived rats injected with control solution (○——○), 20 and 40 mg/kg of Δ^9-THC (△——△); ▲——▲), and 20 and 40 mg/kg of marihuana extract 5 (●——●). The total dose of the drugs was applied in two injections spaced by 2 hr (the vertical line in the figure indicates the results obtained during 2 hr period after each dose). Number above each point represent the standard errors of the means.

TABLE 5

AGGRESSIVENESS AND IRRITABILITY INDUCED BY SEVERAL DRUGS IN RATS DEPRIVED OF REM SLEEP FOR 96 HR

Drug	Dose* (mg/kg)	Number of pairs	Aggressiveness in sec (average ± S.E.) during 4 hr	Irritability (median) at several time intervals (min) after injections					
				0	30	60	120	180	240
Control solution	1.0 ml/kg	4	8†	4.0	6.5	6.0	3.5	6.5	7.0
LSD-25	0.02	5	13†	1.5	8.5	7.0	5.5	7.0	6.5
"	0.08	4	22 ± 9.9	3.0	8.0	7.5	5.0	8.0	8.0
Mescaline	80	5	158 ± 139	2.5	2.0	3.5	5.0	6.0	9.0
d-Amphetamine	1.0	3	0	1.5	2.0	4.5	3.0	2.5	3.0
"	2.0	3	7†	0.5	5.0	7.5	7.5	6.5	7.5
"	4.0	4	862 ± 838‡	0.5	9.5	8.5	8.0	5.0	9.5
"	8.0	5	3†	1.0	8.5	8.0	7.0	7.5	8.5
"	16	5	90-38‡	3.0	6.5	10.0	9.0	9.5	8.0
Ethanol	800	5	0	0.5	2.5	6.5	5.0	6.5	7.0
"	1,600	5	0	2.0	5.5	7.5	8.0	7.5	7.5

*Dose applied in 2 injections spaced by 2 hr.
†Lack of standard error means that just one pair fought.
‡Differs significantly from control solution group ($p \leq 0.05$; Student *t*-test).

observation. During the first two hours, when the animals were under half of the total dose applied, animals treated with extract 5 showed more fighting than Δ^9-THC-treated rats; the same was also observed in the two hours following the second application of drugs. The difference, however, was not significant. Table 4 shows also that under Δ^9-THC or cannabis extract 5 a strong irritability appeared as shown by the large number of animals which scored the maximum of 12 points of irritability.

Experiment 4. The results of are summarized in Table 5. None of the substances employed were able to induce an aggressiveness similar to that observed either with extract 5 or Δ^9-THC. The largest value found was 862 seconds of fighting for 4.0 mg/kg of amphetamine which was far below the aggressiveness elicited by the marihuana compounds. Irritability was slightly increased but not as remarkably as with the marihuana compounds.

DISCUSSION

The present data show that the first application of marihuana compounds induces irritability and aggressive behavior in REM sleep deprived rats. The effects were obtained with 4 different extracts of *Cannabis sativa* and with Δ^9-THC, in doses ranging from 5--40 mg/kg.

Of the 4 extracts of *Cannabis sativa* used, extract 5 was by far the most active. Its potency was equal to that of pure Δ^9-THC. Taking into consideration the percentage of Δ^9-THC present in this alcohol extract (Table 1) and the yield of resin obtained from the petroleum ether extraction, it was calculated that this particular sample of marihuana plant contained approximately 7 per cent of Δ^9-THC. To the best of our knowledge this is one of the highest amounts of Δ^9-THC found in one plant.

The aggressiveness observed after a first dose of marihuana in REM sleep deprived rats is remarkable if it is taken into consideration that acute effects of cannabis compounds in normal animals are characterized mainly by depression [9,18]. This constitutes, therefore, another example of change in direction of cannabis effects by manipulation of previous conditions of the organism. It has been reported before that such direction also depends upon whether the animal is naive or not to the drug; thus, when some effects disappear due to development of tolerance, other effects, sometimes in opposite direction to the former ones, are unmasked [3, 15, 18].

The mechanisms through which REM sleep deprivation facilitates the induction of aggressiveness by marihuana is at present obscure. Certainly the body weight loss occurring during deprivation was not involved. The rats lost the same amount of body weight regardless of the time of deprivation (Experiment 2) but marihuana did not induce clear aggressiveness in the 24 hr deprived animals; furthermore, confirming our previous data [7], in rats food deprived for 36 hr and with the same loss of body weight as 96 hr REM deprived rats, marihuana induced only depression (Experiment 1). REM sleep deprivation alone did not induce aggressiveness although an increase of irritability was observed in the 96 hr deprivation condition (Table 4). Control animals submitted during 96 hr to the 14 cm platforms and injected with marihuana also did not present

aggressive behavior. Therefore, marihuana only induced this abnormal behavior in the REM deprived rats, suggesting that deprivation per se is stressful to the animals. We have recently obtained aggressiveness after the first injection of marihuana in rats stressed by cold [5] or by withdrawal from previous morphine administration [4]. On the other hand, comparable increases in plasma corticosterone levels have been reported in both REM sleep deprived (7 cm platforms) and control (11 cm platforms) animals which would indicate that both situations are equally stressful [13]. The possibility remains, however, that a ceiling corticosterone response was obtained in both situations obscuring an eventual difference in the intensities of stress.

Acute administration of mescaline, LSD-25 and ethanol failed to induce aggressiveness or to clearly increase the irritability of 96 hr REM sleep deprived rats (Tables 4 and 5). We have previously showed that chronic administration of mescaline, caffeine, amphetamine and amylobarbitone also failed to induce aggressiveness in starved rats [8]. These data show that induction of aggressive behavior is a rather peculiar property of marihuana which pharmacologically differentiates it from the other drugs. On the other hand, 4 mg/kg of *d*-amphetamine provoked irritability and aggressiveness in the 96 hr REM deprived rats, which were, however, far below those observed with marihuana. This effect of amphetamine had been reported before [13]. It is interesting that in 2 other behavioral situations marihuana and amphetamine effects were also similar. Both induce aggressiveness in rats undergoing morphine withdrawal [4] and also increase winning behavior of rats competing for food in a straight runway [17]; Terada and Masur, to be published).

It has been recently suggested that the direction of drug effects are apparently highly specific and as consequence effects of marihuana should be in the same direction regardless the number of injections given to the animals [16]. It was further stated that aggressiveness observed after chronic IP administration of marihuana to starved rats could be easily explained on the basis of a discomfort caused by a peritonitis produced by the chronic administration [19]. This has been suggested in an attempt to reconcile the blockade of aggressive behavior obtained in some experimental conditions by acute administration of cannabis [19, 24, 25] with the induction of aggressiveness observed by chronic administration to starved rats. According to these authors [16,19] if the psychoactive properties of marihuana were responsible for the aggressive behavior, an increase in aggression should be observed following the first injection. However, several recent reports on cannabis are against this suggestion. The present work and the observations of aggressiveness after the first application of marihuana to cold stressed rats [5] and to rats undergoing withdrawal from previous morphine administration [4] strongly speak against it. On the other hand, chronic administration of marihuana *per os* [26] and through the lungs also provokes aggressiveness in rats. Furthermore, in formulating that hypothesis the authors [16,19] did not take into consideration the complexity of the psychoactive properties of marihuana which induces sometimes opposite effects depending upon the previous state of the organism [9,18]. As an example of these complex actions and pertinent to this case, are the recent reports showing that acute administration of cannabis suppresses muricidal behavior of spontaneous killer rats whereas chronic administration elicits the same behavior in previously nonkiller rats [2,27].

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