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Effects of Long-Term Administration and Withdrawal of Tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on Open-Field Behavior in Rats[1]

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SJÖDÉN, P. O., T. U. C. JÄRBE AND B. G. HENRIKSSON. *Effects of long-term administration and withdrawal of tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on open-field behavior in rats.* PHARMAC. BIOCHEM. BEHAV. 1(3) 243–249, 1973.–The behavior of female Wistar rats, injected daily with Δ^8-THC (5.0 mg/kg), Δ^9-THC (2.5 mg/kg) or vehicle was studied in an open-field test both during the two weeks' period of drug administration and after withdrawal. The behavior of rats allowed long-term acclimation to the laboratory (LTA), studied in Experiment 1, was compared with those of Experiment 2, which were subjected to short-term acclimation (STA). Throughout the injection period a depressant effect of both isomers of THC was seen on ambulation, rearing, grooming and latency. Length of acclimation period interacted with the effects of THC:s on ambulation, producing even an increased ambulation for Δ^8-THC in the STA group. Minor indications of tolerance to Δ^9-THC were observed in the LTA condition only. A kind of circling behavior was characteristic of both drug groups, its frequency declining with repeated injections. At drug withdrawal, most open-field measures slowly returned to control levels, whereas rate of grooming showed a manifold increase. Possible implications of the results for behavioral research with the THC:s are discussed.

Open-field Δ^8- and Δ^9-THC Acclimation period Rats

ALTHOUGH findings concerning the effects of cannabis preparations in animals are rapidly accumulating, there is still a lack of information about basic behavioral parameters, such as various forms of exploratory activity.

In a previous report, Masur *et al.* [24] studied the effects of acute and chronic administration of a cannabis extract and Δ^9-tetrahydrocannabinol (THC) on behavior in an open-field arena. The results varied according to the scheme of drug application, i.e., initially the drugs exerted a depressant action which wore off with repeated injections. A marijuana-homologue, pyrahexyl, has shown different actions in the rat depending on the dose given [1]. Low doses increased activity whereas high doses showed depressant effects. Pyrahexyl has also been shown to increase curiosity in rats [2]. More recently, Drew *et al.* [12] investigated the action of Δ^9-THC on open-field behavior with respect to dose-response and time-action effects. It was found that this isomer affected some indices of open-field behavior differently depending on the time after injection, whereas other indices, such as rearing and defecation, were similarly affected independent of the length of the post-injection interval.

Differential effects of Δ^9-THC on spontaneous motor activity as a function of duration of the acclimation period to the laboratory has been reported [3]. The depressant action of tetrahydrocannabinol was less evident in rats which had only one day of acclimation to the laboratory after the shipment from the breeder as compared to those

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having an acclimation period of 5–7 days. At a dose of 4 mg/kg there was even an elevation of the activity scores as measured by an actophotometer. The rationale underlying that experiment [3], is the fact that the effects of hallucinogens like LSD and hashish (marijuana), to a great extent depend on the user's emotional state. An unfriendly and stressful environment will induce agitated and fearful behavioral reactions whereas a supportive and friendly situation counteracts anxiety tendencies.

The present investigation was undertaken in an attempt to extend previous findings about acute and chronic effects of low doses of tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on spontaneous activity in albino rats. In addition to conventional parameters of open-field behavior like ambulation, rearing and defecation, grooming and circling (see below) were included on the basis of preliminary findings. Since signs of behavioral tolerance to THC-preparations have been reported [6, 10, 24, 25, 31], the effect of withdrawal of the drugs was also studied (Withdrawal refers to the procedure of terminating a continuous period of injections of the drugs). A further purpose was to examine whether or not the above mentioned counteracting effect on spontaneous activity, resulting from a very brief period of acclimation, could also be shown in the open-field (O-F) test. Therefore, in Experiment 1 the animals were subjected to a long-term acclimation period to the laboratory milieu (LTA), whereas the rats in Experiment 2 experienced short-term acclimation (STA). The O-F test was employed since it yields several behavioral measurements, whereas the actophotometer cage [3] measures only simple motor activity [20].

EXPERIMENT 1

Method

Animals. Eighteen experimentally naive Wistar females, 180–190 days old, with an initial average weight of 205 g, were used. They had been living in the laboratory from the age of seven weeks, housed in group cages, 4 animals in each. These animals were used in the long-term acclimation condition (LTA). One week prior to the experiment, individual housing was initiated. Free food and water were available at all times.

Drug injections. The animals were randomly divided into the following three groups of 6 animals each: (1) Group Δ^8-THC injected with 5 mg/kg of Δ^8-THC dissolved in polyethylene glycol-300 ((-)-Δ^8-trans-Tetrahydrocannabinol (Δ^8-THC): Batch, QCD-64275, NIMH; Mol.form:, $C_{12}H_{30}O_2$; Mol.Wt., 314.5; Specific Rotation, −268° (C, 1.2%; $CHCl_3$); Purity (assay by glc.), 99%), (2) Group Δ^9-THC injected with 2.5 mg/kg of Δ^9-THC dissolved in propylene glycol ((-)-trans-Δ^9-Tetrahydrocannabinol (Δ^9-THC): Batch, SSC-61516, NIMH; Mol.form., $C_{21}H_{30}O_2$; Mol.Wt., 314.5; Specific Rotation, −164° (C, 1.6%; $CHCl_3$); Purity (assay by glc.), 95.4% (impurity, 4.6% exocyclic THC)) and (3) Group C, given injections of a mixture (1:1) of the two solvents. The drug groups received the compounds from Day 1 to Day 19, the drugs were then withdrawn and the solvent mixture alone was given on Days 20–23. The control group received the solvent mixture for 23 days in succession. Injections were given intraperitoneally 30 min prior to testing in the open-field. Throughout, the volume injected in cc was equal to the animal's weight in kilograms. The dosages of the tetrahydrocannabinols used were based on a study by Grunfeld and Edery [15], stating that in rodents, Δ^9-THC is twice as potent as Δ^8-THC. The dose of Δ^9-THC given (2.5 mg/kg) corresponds to that used by Masur *et al.* [24]. Drug injections and preparations of the animals for open-field testing were not carried out by the experimenter who made the open-field observations.

Apparatus. The open-field (O-F) was an acrylate box (60 x 60 x 26 cm) with an open top, white walls and a brown floor, divided by white lines into sixteen squares (15 x 15 cm). The dividing lines were painted on oil-cloth, which was covered by an acrylate board. The box stood on the floor of a small windowless room, where a faint noise was provided by the air conditioning system. The O-F was illuminated by a frosted 60 W bulb, positioned 170 cm above the center of the field.

Procedure. After being brought into the O-F room, each rat was tested for cannabis-induced vocalization in the manner described elsewhere [17]. This testing was carried out once before and once after O-F testing, at both times with the animal in its home cage.

The rat was gently placed in a corner square of the O-F, closest to where the experimenter sat observing the animal. Upon placement, the rat was allowed to explore the field for 4 min. Records were kept of the following measures: *ambulation* = the number of squares crossed with all four feet, *rearing* = the number of times the animal stood on its hind feet, *defecation* = the number of fecal boluses deposited, *latency* = time in seconds to leave the start square with all four feet upon placement in the O-F, *grooming* = the number of cleaning bouts, including washing of the face with front paws and trimming of the fur, and *circling* = the number of times the animal turned around its vertical axis. The latter behavior pattern, seen in drugged animals only, will be described further in the Results section. The latency was recorded by the experimenter with a stop-watch and scored to the closest one-tenth of a sec. After each test, the fecal boluses and urine were removed and the floor was cleaned with tap water to minimize possible odor cues for the subsequent animal. O-F testing was carried out between 11 a.m. and 3 p.m. The groups were run in an alternate order, animals from the same group never in succession. The order within each group was changed each day, so that all animals were tested three days at the beginning, three days in the middle and three days at the end of a day's session.

In all, O-F testing was performed for nine days with test days distributed according to the following schedule with respect to drug injections. Days 1, 2, 3, 4 of drug/solvent injection correspond to Days 1, 2, 3, 4 of O-F testing. Hereafter, injections alone were performed for an additional 14 days with no O-F testing. Days 19, 20, 21, 22 and 23 of drug/solvent injection correspond to Days 5, 6, 7, 8, 9 of O-F testing. Thus O-F testing on injection Days 20–23 was carried out with all groups in a nondrugged state.

Results

Rats given cannabis extract or synthetic THC vocalize in a characteristic manner when gently pressed bilaterally behind the fore limbs and on the back [17]. Only two rats in the drug groups failed to respond when tested prior to placement in the O-F and this happened only once. All rats in the drug groups vocalized when testing was carried out

TABLE 1

OPEN-FIELD BEHAVIOR OF THC-TREATED RATS IN LONG- AND SHORT-TERM ACCLIMATION (LTA AND STA)

		LTA Blocks†				STA Blocks			
		I	II	III	IV	I	II	III	IV
Ambulation	Δ^8-THC	6.5*‡	2.0*	2.0*	23.0*	70.0	36.5*	56.5*	30.5
	Δ^9-THC	4.5	3.5*	15.5	23.5*	75.0	33.0	20.0	15.0*
	Control	46.0	42.0	42.0	51.0	83.5	17.0	14.0	29.5
Rearing	Δ^8-THC	0.0*	0.0*	1.9*	8.0*	0.0*	0.0*	1.0	8.5
	Δ^9-THC	2.0*	1.5*	6.0	6.0*	5.5*	0.0*	0.5	6.0*
	Control	17.0	19.0	17.0	20.0	23.0	4.5	5.5	10.5
Defecation	Δ^8-THC	1.0	2.0*	3.0*	2.0*	0.0	2.0	1.5	2.0
	Δ^9-THC	0.5	2.0*	3.0*	5.0*	1.0	3.0	2.0	2.0
	Control	0.0	0.0	0.0	0.0	1.5	2.0	5.5	2.5
Latency	Δ^8-THC	46.1*	203.0*	134.6	3.9	6.1*	1.6*	0.8	0.4
	Δ^9-THC	26.2	58.4*	16.8	3.8*	6.2*	1.0*	1.2*	0.5*
	Control	17.3	5.4	14.7	9.9	0.8	0.5	0.5	0.4
Grooming	Δ^8-THC	0.0	0.0*	0.5	5.5*	0.0*	0.0*	0.0	14.5*
	Δ^9-THC	0.0	0.0*	0.0	4.0*	0.0*	0.0	0.0	4.0
	Control	0.0	1.0	1.0	1.0	4.0	0.5	2.5	3.0
Circling	Δ^8-THC	4.0*	1.5*	2.5*	0.0	6.0*	0.5*	0.0	0.0
	Δ^9-THC	4.0*	1.5*	0.0	0.0	2.5*	0.0*	0.0	0.0
	Control	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

*$p<0.05$ for difference from control.

†Block I: Day 1, Block II: Days 2–4, Block III: Day 5, and Block IV: Days 6–9 of open-field testing.

‡Median values.

after O-F performance. None of the rats in the control group vocalized. Results from O-F testing are summarized in Table 1 LTA. Testing for differences between experimental and control groups within blocks was carried out with the Mann-Whitney U-test [30] ($p<0.05$, one-tailed).

Ambulation. Initially, both drugs exerted a depressant effect on ambulation. After an additional 14-day period of injections without O-F testing, ambulation scores were still low for the Δ^8-THC group, whereas an indication of behavioral tolerance or habituation is seen in the Δ^9-THC group (Block III): its median value is however still below that of the control group. After withdrawal of the drugs (Block IV) the rate of ambulation is still significantly below control values for both drug groups.

Rearing. These results closely parallel those for ambulation, i.e., an initial depression in both groups, followed by a slight recovery in the Δ^9-THC group after 14 additional injections and significantly lower scores for both drug groups after withdrawal.

Defecation. Both drugs acted to increase the frequency of defecation in comparison to controls, not significantly for Block I, but significantly so for Block II. The controls had a median value of 0.0 for defecation. A continued increase of defecation is seen in Block III, which is followed by an additional increase for the Δ^9-THC group during Block IV. The defecation score for Group Δ^8-THC remains high after drug withdrawal.

Latency. During the initial testing, both drug groups show longer latencies than controls; the group treated with Δ^8-THC appearing more affected by the treatment than the Δ^9-THC group.

Signs of behavioral tolerance to Δ^9-THC for ambulation and rearing are reflected in the latency scores for Block III, whereas the Δ^8-THC group still seems more affected by the drug. Upon withdrawal of the drugs, the latency scores returned to control levels (Block IV).

Grooming. During O-F testing on Day 1 (Block I), neither group showed any grooming behavior. In Block II the action of the drugs was to completely suppress this behavior pattern as compared to controls. By Block III, grooming behavior seems to have recovered somewhat in the Δ^8-THC group. The low score for the control group for Block III makes further comparisons difficult. A marked increase is seen after withdrawal of the drugs; the median values being four to five times higher in the drug groups than in the controls (Block IV). Median values for the 9 days of O-F testing treated separately are shown in Fig. 1.

Circling. Other experiments with the THC:s in this laboratory have indicated that drugged animals tend to move around their vertical axis in a stereotyped manner. Circling was scored when the rat showed the described pattern, one point given for each complete 360 degree turn.

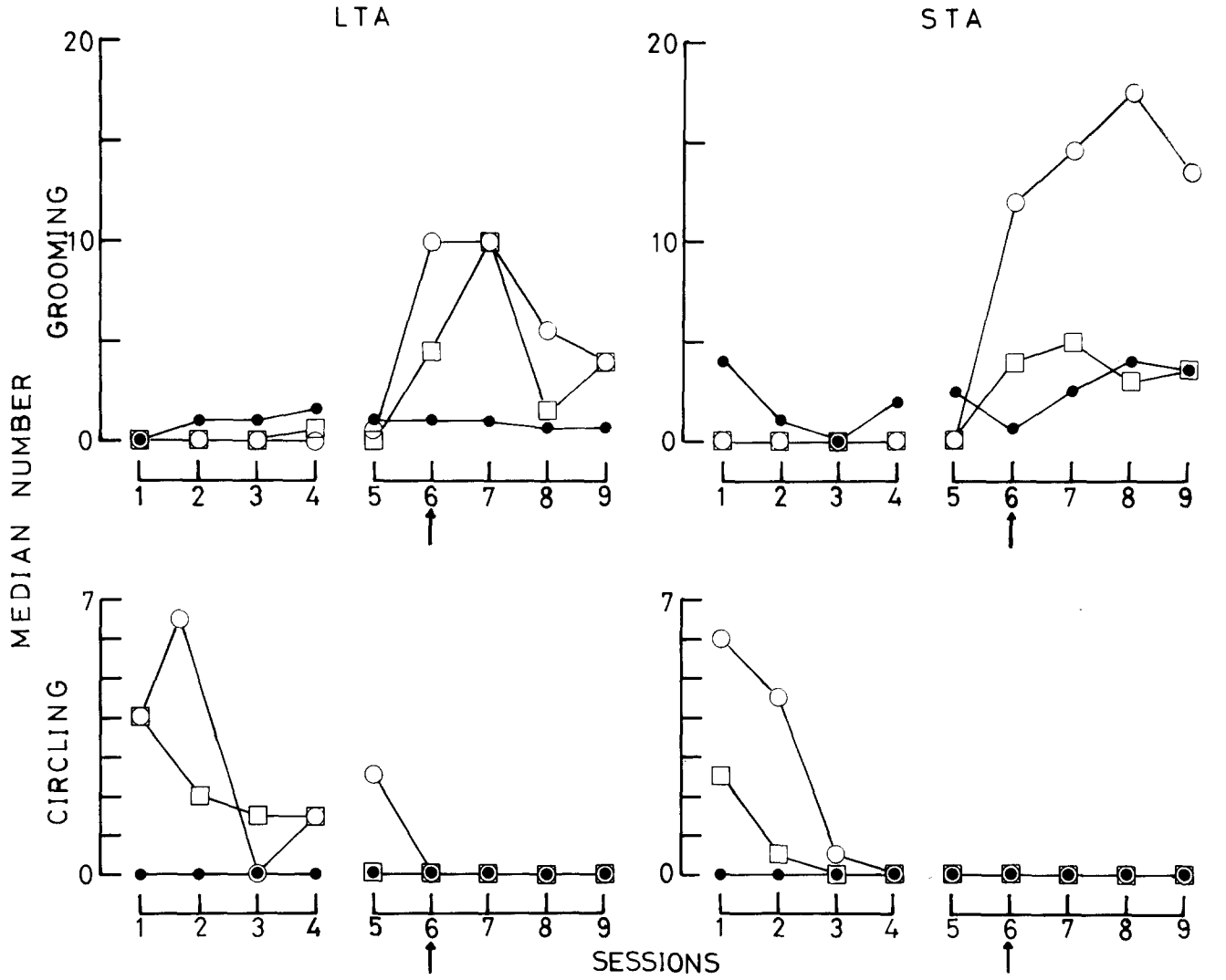

FIG. 1. Median values of grooming and circling for rats treated with THC:s and controls over nine sessions of testing. LTA = long-term acclimation, STA = short-term acclimation. ○ = Δ^8-THC, □ = Δ^9-THC, and ● = Controls. A fourteen-day pause in open-field testing is interpolated between Sessions 4 and 5. Arrow at Session 6 indicates withdrawal of drugs.

This behavior is easily distinguished from normal exploration, in that several rotations around the vertical pole usually follow immediately upon each other. Only drugged animals showed this behavior, to a comparable degree in both drug groups (Blocks I and II). By Block III circling remained frequent in the Δ^8-THC group only. After drug withdrawal, no circling was seen (Block IV). The changes over time for this behavior pattern are presented in detail in Fig. 1.

EXPERIMENT 2

Method

Animals. Eighteen experimentally naive Wistar female rats, 190–200 days old, with an initial average weight of 226 g were used. These animals were of the same genetic stock as those in Experiment 1. They arrived from the breeder one day prior to the onset of the experiment, were put into individual cages, and were thus subjected to short-term acclimation (STA). The animals were divided into three groups of six, matched according to body weight. Food and water were available ad lib. during the entire experiment. Body weight, food and water-intake for these animals will be reported in a separate paper [32].

Drug injections. Injections were carried out as in Experiment 1.

Apparatus. The same O-F situation as in Experiment 1 was used, with the modification that a 15 x 15 cm square was marked in the center of the field. The modification in no way changed the O-F for the rats, since the square could only be seen in the light from the 60 W bulb from the position of the experimenter.

Procedure. Vocalization was tested in the same way as described in the first experiment. The O-F procedure was

identical to the one used in Experiment 1, with the exception that the rat was placed in the center square of the O-F instead of in a corner square. This change was instituted because of an observation in the previous experiment, that circling behavior seemed more prevalent when the rats were not close to the walls of the O-F apparatus.

Results

The results from vocalization testing agree with those of the previous experiment. With the exception of two rats on three occasions in all, each rat in the drug groups vocalized both before and after O-F performance. None of the rats in the control group vocalized. Testing for differences between experimental and control groups were carried out as in Experiment 1.

Ambulation. In contrast to the data in Experiment 1, no depressant effect on the rate of ambulation was evident in the drug groups (Table 1 STA). Both the Δ^8-THC and the Δ^9-THC groups were more active than controls in Block II, the Δ^8-THC group significantly so. This pattern is also seen after 14 additional injections (Block III). After withdrawal, the Δ^9-THC group ambulated significantly less than controls.

Rearing. Initially, the frequency of rearing was lower in both drug groups than in controls. By Block III, rearing was still low in the experimental groups. After drug withdrawal, rearing seems to have recovered in the Δ^8-THC group, but the Δ^9-THC group still reared significantly less than controls.

Defecation. No differences between groups with regard to defecation appeared.

Latency. Drug-treated groups had longer latencies, several times that of the controls during the initial blocks of testing. The absolute values for latency were smaller than in the previous experiment. This is an effect of the change in the procedure of placing the rat in the O-F. In Blocks III and IV, only the Δ^9-THC group was slower than controls to leave the start square. The differences are however minute with respect to absolute values.

Grooming. For this behavior pattern, the drug groups show significantly lower frequencies than controls for the initial blocks, with the exception of Δ^9-THC group in Block II. In Block III, no significant differences appeared. As in Experiment I, grooming showed an increase upon withdrawal of the THC:s. The Δ^8-THC group showed approximately five times as much grooming as the controls in Block IV, whereas there is no difference between the other two groups. A more detailed picture of the changes in grooming behavior for all nine days of testing is shown in Fig. 1.

Circling. Circling shows a pattern of effects similar to that obtained in Experiment 1. The drug groups showed this behavior during the initial blocks of the experiment. As can be seen in Fig. 1, the median values for circling fell to 0.0 for both groups on Day 4. In Block III and after withdrawal (Block IV) no circling was seen.

DISCUSSION

1. Drug Effects

As is evident from the data, the THC:s exert an acute depressant action on several behavioral parameters, such as ambulation, rearing, grooming and latency. The effect was expected from previous work on acute administration of THC [12, 18, 24, 26]. However, the total activity of THC is dependent upon such factors as length of acclimation period to the laboratory and, in certain cases, the duration of drug administration.

2. Length of Acclimation Period

In accordance with Barry and Kubena [3], it was found that the acute depressant action of THC is not evident in the STA groups for *ambulation.* There is even an increase of rate of ambulation for the Δ^8-THC group as compared to the controls. Thus, the results indicate an interaction of length of acclimation period with the effects of THC on ambulation.

There are reports in the literature of stimulating behavioral effects of Δ^8-THC [11, 28]. The results from the present study further support this finding. It seems as if a drastic change of living-environment for the animals, prior to O-F testing, potentiates the stimulant action with regard to ambulation. A mechanism, involving a higher level of catecholamines in the STA groups, might be responsible for these phenomena [3]. Also, interactions of THC with amphetamine have been reported [9, 14, 21]. Further data, relating cannabis to an increased nor-adrenaline content of the terminal axonal varicositites of the hypothalamus, are found in a study by Constantinidis and Miras [8], using the fluorescence method. These observations would seem to form a basis for the interaction of stress-inducing manipulations with the action of THC:s on behavior.

An interaction of drug effect with period of acclimation is also evident for *defecation.* In the LTA condition, an increase of defecation frequency was seen throughtout the period of injections with both THC:s. These results agree with data reported by Masur *et al.* [24] who found a progressive increase of defecation frequency with repeated O-F performance and Δ^9-THC-injections in male rats having a low defecation-index. Since no effect of THC was evident for defecation in the STA condition, we tentatively conclude that repeated injections of THC increase the level of defecation in normally low-defecating rats, but leaves defecation unaltered in rats subjected to a stressful environment also outside the O-F situation.

The results from the LTA condition indicate a general increase of emotionality[34], which is however not substantiated by the STA-results. This makes it unlikely that the THC-produced irritation of the peritoneal lining tissue which has been reported by Manning *et al.* for the i.p. route [23], can entirely account for the results, unless an interaction of this factor with stress-inducing procedures is proposed.

3. Duration of Drug Administration

In apparent contrast to data reported by Masur *et al.* [24], (cf also Davis *et al.* [10]) we found only slight signs of behavioral tolerance to Δ^9-THC, although the total number of drug-injections is the same in both studies. With this isomer, possible tolerance effects were observed for *ambulation*, *rearing*, and *latency* in the LTA condition. For Δ^8-THC no signs of tolerance were observed. Several methodological differences between the two studies make direct comparisons of results difficult. Masur *et al.* [24] used a high level of visual and auditory stimulation during O-F runs and O-F sessions spaced five to six days apart.

Circling is another behavior pattern, where possible

tolerance is observed. The diminishing rate of circling with repeated injections is more evident in the STA than in the LTA condition. It should be noted that a circling-like behavior, pivoting, has been observed in rats treated with other hallucinogenic drugs, e.g. levallorphan tartrate [33], phencyclidine, psilocybine, cyclazocine and high doses of amphetamine [29].

4. Withdrawal Effects

A comparison of Blocks III and IV reveals a progressive increase of *ambulation* and *rearing* frequency for most groups. The only exception to this is the Δ^8-THC group in the STA condition, which shows a progressive decrease with respect to ambulation during these days. As a point of interest, this group showed a stimulant effect of drug treatment on ambulation during the injection period. Thus, after withdrawal of the drug, this action progressively ceases. From an analysis of scores from Days 5–9, each day treated separately, it is evident that the stimulant action of Δ^8-THC diminished progressively until, on Days 8 and 9, there is no difference between drug groups for ambulation. The progressive increase for ambulation and rearing in other groups is similar to findings by Cole and Dearnaley [7] who found a slow wearing-off of effects of chlorpromazine and chlordiazepoxide on rearing and locomotion after withdrawal.

The most dramatic change of behavior after drug withdrawal is that reflected by the *grooming* scores, which increase rapidly and to a comparable degree in both experiments. The interpretation of this finding is complicated by the lack of agreement with regard to the significance of this behavior pattern, which characterizes most of the literature [4, 5, 16, 19].

In some studies concerning withdrawal of cannabis-derivatives [22, 25] no effect, comparable to the increase of grooming has been reported. Recently [27], it has been shown that withdrawal of a marijuana extract after repeated daily administrations resulted in a marked increase of an integrated voltage recording of the electrocorticogram in rats. The possibility that this finding is related to the changes in grooming behavior deserves further attention.

CONCLUSIONS

It can be assumed [12] that ambulation, rearing and latency reflect exploratory behavior directed towards the external environment. From the data on the LTA condition, we conclude that both THC:s cause a decrease of exploratory behavior. This decrease develops concomitantly with an increase of defecation, a presumed index of emotionality [12, 34]. In the groups subjected to STA, a decrease of exploratory behavior is present for all indices except ambulation, which is unaltered or increased by the drug treatment. This observation suggests that exploratory behavior, defined in the above manner, is not a unitary concept as far as underlying mechanisms are concerned. In addition to reflecting behavior, aimed at investigating the external environment, ambulation might also contain a component of general activity, which is unaltered or increased by THC-treatment in the STA condition.

The implications of the above findings with regard to behavioral research with the THC:s seem to be as follows: (1) It would seem mandatory to control shipment and acclimation procedures for animals used for behavioral research with THC. In the light of the comparison of data from the LTA and STA conditions, multiple behavioral testing of the same rats in different situations is not recommended. (2) The changes of exploratory behavior and emotionality reported for the THC-groups in the LTA condition point to the possibility that such changes may constitute part of the effects of THC on learning. This would seem to be particularly the case in situations where locomotor exploration and rearing can be assumed to be important for the efficient learning of the task at hand.

The lack of tolerance observed for some indices of O-F behavior must not lead to the conclusion that tolerance will not develop to these kinds of behavior in other situations. Ferraro [13] has emphasized that tolerance may not develop when the initial drug effects are benign i.e., when no compensatory behavioral adjustment are necessary to avoid or remove stressful stimulation. Thus, in learning tests utilizing aversive stimuli, tolerance may well develop both for rearing and ambulation.

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