Effects of Δ^8 -THC on dissociation of conditioned avoidance responding in tolerant and nontolerant rats*

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Previous work in this laboratory with tetrahydrocannabinol (THC) on conditioned avoidance responding (CAR) have indicated a possible symmetrical dissociative effect on CAR retention. The results of the present study indicate that Δ^8 -THC (15 mg/kg) induces asymmetrical dissociation given that rats are made tolerant to the acutely disruptive effects of the drug. After a 15-day drug-free period, previously tolerant animals also showed disruption of established CAR.

Using the shuttlebox conditioned avoidance response (CAR) in a 2 by 2 factorial design, it was noted that rats given tetrahydrocannabinol (THC) showed state-dependency (StD) effects, possibly of a symmetrical character (Henriksson & Järbe, 1971a). However, most data bearing on change-of-state effects indicate asymmetrical StD, i.e., the change from a drugged (D) to a non-drugged (ND) state results in greater impairment at the CAR retention test than the ND to D change condition (Overton, 1968). In our hands, such an asymmetry has been noted for diazepam (Henriksson & Järbe, 1971b).

Using the reversal learning paradigm, it was found that rats trained ND, but given daily postsession injections of Δ^8 -THC (20 mg/kg), showed facilitation of a reversal task while drugged, whereas other ND-trained rats, which experienced the first THC injection at the start of reversal learning, performed even worse than the drugged controls, i.e., the D-D condition (Järbe & Henriksson, 1973a).

Thus pretest drug experience seems to be an influential factor when assessing StD properties of THC. The present experiment was undertaken to shed light on the issue of whether the impaired CAR test performance seen for the former ND-D group (cf. Henriksson & Järbe, 1971a) would also be apparent in rats that received daily postsession injections of THC before being exposed to the CAR test in a drugged state.

MATERIALS AND METHODS

Subjects

Experimentally naive male albino Sprague-Dawley rats, purchased from a commercial breeder (Anticimex AB, Sollentuna, Sweden) and housed individually with free access to food and water, were used. The average weight was 355 g at the start of CAR training.

*This research was supported by the Swedish Council for Social Science Research (185/72P). The drug was generously supplied by T. Petrzilka, University of Zurich. The help from I. Dureman and G. Ohlin is appreciated.

Apparatus

A two-way-hurdle shuttlebox, where the separate grid floors could be activated by a scrambled shock (2 mA) appearing immediately after the termination of the CS tone (8 sec), was used. Further details are given elsewhere (Henriksson & Järbe, 1971a).

The CAR-acquisition phase, 10 trials/session, lasted for 8 days; both Groups 1 (N = 7) and 2 (N = 7) were trained in a nondrugged state but Group 1 received daily intraperitoneal (IP) injections of Δ^8 -THC (15 mg/kg) and Group 2 the corresponding vehicle [polyethylene glycol - 300 (75%) and saline (24%) plus Tween-80, 1 ml/kg] 2 h after the completion of the sessions. Neither training nor injections were run on Day 9. At Days 10 and 11, both groups were CAR tested in a drugged state (Δ^8 -THC, 15 mg/kg, IP 30 min before the sessions). The THC dose was the same as had been used previously (Henriksson & Järbe, 1971a).

Twelve days after the second CAR test day, both Groups 1 (N = 6) and 2 (N = 7) were retrained (ND) for 3 days, followed by a third CAR test (D). Neither of the groups were THC-treated during this retraining.

RESULTS

There were no significant differences, except at Day 3, between the two groups during the acquisition phase (Days 1-8). When tested drugged, a marked suppression of CAR was evident for Group 2 ($t = 5.2$, $df = 12$, $p < .001$, t test). The difference was reduced below significance on the next day, when both groups were once again tested while drugged ($t = 1.23$, $df = 12$, $p > .05$). This is due to the fact that half of the animals in Group 2 were still being maximally suppressed by the drug while the other half showed complete recovery of CAR-responding, as indicated by the great within-group deviation, cf. Table 1. When THC-tested after 15 drug-free days, i.e., the third CAR test, both groups showed approximately equal and significant decreases in the number of CARs as compared to the response number seen during the preceding day ($t = 4.6$ and 4.3 , $df = 5,6$, $p < .01$ for Groups 1 and 2, respectively). Great within-group deviations indicate that some animals are still tolerant while most animals are again maximally

Table 1
Mean Number and Standard Deviations of Conditioned Avoidance Responses (CAR) Out of Ten Possible

	Day 8		Test Day 1		Test Day 2		Day 26		Test Day 3	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Group 1	8.3	1.90	7.0	2.52	7.4	1.90	9.7	0.52	3.7	3.33
Group 2	8.9	2.27	1.0	1.73	5.0	4.80	9.3	1.11	4.6	4.51

Note—Both groups were CAR trained in a nondrugged state, but Group 1 ($N = 7$) received daily postsession injections of Δ^8 -THC (15 mg/kg) and Group 2 ($N = 7$) the vehicle (Days 1-8). At Test Days 1 and 2, both groups were THC treated prior to the sessions. Day 26 refers to the last retraining (ND) session and Test Day 3 to the drugged session that followed immediately after Day 26. At Days 26 and 27, $N = 6$ for Group 1.

suppressed by the drug. The results are summarized in Table 1.

DISCUSSION

The suppressive effect of THC on established CAR performance in drug-naïve rats confirms previous findings (Grunfeld & Edery, 1969; Henriksson & Järbe, 1971a; Delini-Stula, 1973).

That the performance of the pretreated group was unaffected at Sessions 9 and 10 supports the notion that THC also induces asymmetrical dissociation in the CAR task, nota bene when the animals are rendered tolerant to the disruptive effects of the drug. That tolerance is somehow involved is further indicated by the fact that both groups were equally depressed at the third drugged CAR test, i.e., an increased sensitivity to the drug was noted for Group 1. It may be argued that complete tolerance to the central effects of THC had been achieved for Group 1 during the pretreatment period (Days 1-8) and therefore the first CAR-test could be considered another ND training session (Day 10). Such an objection seems unlikely, however, since it has been shown that rats are able to discriminate the cannabis state from the ND state, although these animals were marihuana-tolerant, as defined by a rope-climbing test (Bueno & Carlini, 1972). Similar findings have been obtained by us (Järbe & Henriksson, 1973b). In addition, the THC-treated rats vocalized in response to touch, an effect not likely to occur in unaffected rats (Järbe & Henriksson, 1973c).

After submitting this study for publication, the results from two other reports also indicate development of tolerance to the disruptive effects of THC on active avoidance behavior (Goldberg, Hefner, Robichaud, & Dubinsky, 1973; Webster, LeBlanc, Marshman, & Beaton, 1973).

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(Received for publication September 10, 1973;
revision received June 4, 1974.)