Δ^9 -Tetrahydrocannabinol used as discriminative stimulus for rats in position learning in a T-shaped water maze*

BENGT G. HENRIKSSON and TORBJÖRN JÄRBE
University of Uppsala, Slottsgård 3, S-752 20 Uppsala, Sweden

Rats were trained to swim differentially to either of the two arms of a T-shaped water maze on the basis of Δ^9 -tetrahydrocannabinol or solvent only. The two states, drugged (D) and nondrugged (ND), were changed from day to day. After 11-13 sessions, the animals performed the task at virtually the 100% level, i.e., the imposed state (D or ND) determined the choice of arm in the T-maze. After 2 weeks of rest, the animals were retested in both the D and ND states, and the results indicate that this differentially controlled performance is very well retained.

In a previous paper by Henriksson & Järbe (1971b) it was shown that Δ^9 - and Δ^8 -tetrahydrocannabinol produce state-dependent learning in rats in a conditioned avoidance learning situation. Drugs known to produce state-dependent learning are usually effective as discriminative stimuli, i.e., the imposed internal chemical state determines the choice of response in a given learning situation (Overton, 1968). Since the cannabinoids, at least initially, exert a depressant action in the rat both on motility and on feeding behavior, we found it convenient to avoid methods based on food reinforcement. In our experiment, a T-shaped water maze was used, in which correct responding was reinforced by allowing the rats to get out of the water tank in either of its two arms. The two states, drugged (D) and nondrugged (ND), were the only indicators of which arm would be the correct choice.

METHOD

The animals, experimentally naive male Sprague-Dawley albino rats, with an average weight of 350 g, were housed in individual cages with free access to food and water. The animals were purchased from a commercial breeder, Anticimex AB, Sollentuna, Sweden. As a general routine in our laboratory, the rats were handled every day during the week preceding experimentation.

The tank was made of stainless steel, and the internal dimensions were: length, 105 cm; width, 45 cm; height, 40 cm. The training sessions consisted of 10 trials per day, which were spaced for each animal with an

intertrial interval of about 3 min. Immediately after the training, the animals were placed for 2 h in a room which was about 5°C warmer than their usual living conditions. The water in the maze had a temperature of 16°C.

The intraperitoneal injections (1 cc/kg) of Δ^9 -THC, dissolved in propylene glycol, or of the solvent only were given 30 min before the sessions. The two states, drugged and nondrugged, were changed from day to day. The rats were trained 5 days a week, i.e., no sessions were run on Saturdays and Sundays. The aim with the present investigation was to find out if it is possible to establish differential responding in a simple position learning situation when the

Fig. 1. Learning curves for differential responding controlled by the difference between drug state and nondrug state. Ordinate, percent of rats performing correctly on the first trial of the daily training session; abscissa, drug (uneven days) and nondrug (even days) training sessions. Groups I and III were injected with 5 mg/kg Δ^9 -THC and Group II with 10 mg/kg of the same drug. Before the nondrug sessions, injections of propylene glycol were given. Group III was initially trained with forced responding. Retest was after 14 days.

*This work was supported by research grants from the Swedish Medical Research Council (B72-27P-2904-03) and the Swedish Council for Social Science Research (181/71P). Δ^9 -THC was kindly supplied by Dr. O. J. Braenden, Division of Narcotic Drugs, United Nations Office, Geneva.

Δ^9 -THC-induced state acts as a discriminative stimulus. If differential responding appears, it should be possible to investigate whether or not the animals can discriminate between the cannabis state and other drug states when using the present method.

Twenty animals were divided into three groups: Group I (N = 7) was injected with 5 mg/kg Δ^9 -THC and Group II (N = 7) with 10 mg/kg on uneven days (D) and with propylene glycol on even days (ND). Group III (N = 6) received the same dosage of Δ^9 -THC as Group I, but during the first six training sessions, these rats were forced into the correct arm, i.e., a barrier prevented the entrance to the incorrect arm of the maze.

On three occasions, the vocalization test (Henriksson & Järbe, 1971a) revealed absence of effect of the injection of THC, and therefore these animals were excluded from these particular training sessions.

RESULTS

The percentage of correct first-trial responses in each group indicates the degree of response control acquired between the drugged and nondrugged states. As can be seen in Fig. 1, the animals had acquired a differential responding at virtually the 100% level after 11-13 sessions. The response control is somewhat easier to establish

in the nondrugged state, as compared to the drugged state. After 2 weeks of rest, the rats were retested in both the drugged and nondrugged states. The figure shows that the differentially controlled performance is well retained. In fact, in Groups II and III, there still was correct responding at the level of 100%. Group III, which was initially forced to respond correctly, did not acquire response control faster than the two self-correcting groups. However, it is interesting to note that the external change induced by the shift from the forced to the self-correcting procedure had a more deleterious effect in the drugged state than in the nondrugged state. This effect is more evident when analyzing the total number of responses during the first 10-trial sessions, maybe indicating difficulties to cope with changes in the external milieu. There was no difference in the acquisition rate between the two self-correcting groups (5 mg/kg vs 10 mg/kg of Δ^9 -THC). Usually a higher dose is more effective, i.e., produces a faster response control, than a lower one (Overton, 1968). This lack of difference between the groups might be a result of using the intraperitoneal route of administration (Ho et al, 1971).

The purpose of using the

differential responding technique is that it gives an opportunity to investigate similarities or dissimilarities between tetrahydrocannabinols and other psychotropic drugs. That is, if the experienced effects of a certain test drug are similar to those of THC, it is presumed that the animal will swim to the THC-associated position of the water maze.

REFERENCES

- HENRIKSSON, B. G., & JÄRBE, T. Cannabis-induced vocalization in the rat. *Journal of Pharmacy & Pharmacology*, 1971a, 23, 457-458.
- HENRIKSSON, B. G., & JÄRBE, T. The effect of two tetrahydrocannabinols (Δ^9 -THC and Δ^8 -THC) on conditioned avoidance learning in rats and its transfer to normal state conditions. *Psychopharmacologia* (Berlin), 1971b, 22, 23-30.
- HO, B. T., FRITCHIE, G. E., ENGLERT, L. F., McISAAC, W. M., & IDÄNPÄÄN-HEIKKILÄ, J. E. Marijuana: Importance of the route of administration. *Journal of Pharmacy & Pharmacology*, 1971, 23, 309-310.
- OVERTON, D. A. Dissociated learning in drug states (state dependent learning). In D. H. Efron (Ed.), *Psychopharmacology: A review of progress, 1957-1967*. Washington, D.C.: U.S. Government Printing Office, 1968. Pp. 918-930.

NOTE

1. (-)-trans- Δ^9 -Tetrahydrocannabinol (Δ^9 -THC). Mol. formula $C_{21}H_{30}O_2$; mol wt, 314.5; assay (glc) 95.4% Δ^9 -THC; specific rotation, -164° (C. 1.6%; $CHCl_3$); impurities, 4.6% exocyclic THC (by glc).