Δ⁹-THC as a Discriminative Stimulus in Rats and Pigeons: Generalization to THC Metabolites and SP-111*

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Abstract. In a drug discrimination paradigm pigeons and rats were trained with an operant procedure to discriminate between the presence and absence of the effects of Δ⁹-THC (1.0 and 3.0 mg/kg, injected IM 90 min and I.P. 30 min before the start of the session). Once trained, various THC metabolites as well as a water-soluble derivative of THC (SP-111), were substituted for Δ⁹-THC to test for generalization to the training drug. Generalization to Δ⁹-THC occurred with the 11-hydroxy metabolites and the potency order was 11-OH-Δ⁹-THC > 11-OH-Δ⁸-THC > Δ⁹-THC. Among the other metabolites tested (8α-OH-Δ⁹-THC, 8α, 11-di-OH-Δ⁹-THC, 8β-OH-Δ⁹-THC, 8β, 11-di-OH-Δ⁹-THC), it was only 11-di-OH-Δ⁹-THC that completely substituted for Δ⁹-THC in pigeons, albeit at very high dose levels (rats were not tested with these metabolites). SP-111 generalized to Δ⁹-THC in both species. However, the onset of action of SP-111 was slower than that for Δ⁹-THC, especially in pigeons. These studies show the importance of obtaining complete dose-effect determinations over time when assessing structure-activity relationships with drug-discrimination procedures.

Key words: Δ⁹-THC stimulus — THC metabolites — SP-111 — Rats — Pigeons
Balster and Ford (1978) reported on effects of THC metabolites in rats and, therefore, most of our tests were restricted to pigeons. A water-soluble derivative of THC, SP-111, was tested in both species but a more thorough test program was scheduled for rats to illustrate the importance of obtaining separate dose-effect curves at different postinjection intervals to compare drug potencies accurately when the time-course of the effect of a test compound is not well known.

Materials and Methods
The subjects were eight mature, male White Carneaux pigeons, experimentally naive at the beginning of these experiments. The animals were maintained at about 80%–85% of their initial free-feeding weights by the food presented during the sessions and by postsession supplemental feedings. Water and oyster shell grit for the pigeons were always available in the home cages. The average free-feeding weights after 10 days in the laboratory for rats and pigeons were 371 g (SD ± 17.5) and 513 g (SD ± 25.7), respectively.

The experimental chambers were sound attenuating and ventilated. In the pigeon chamber the response keys, 2 cm in diameter and dimly illuminated with white light, were mounted horizontally, 10 cm apart on the front panel in the chamber, each about 19 cm above the chamber floor. The minimum force to operate the keys was about 15 g. Opening of the key contacts defined the key-pecking response. The food magazine was located in between the response keys, 4 cm above the floor of the chamber. The reinforcer was a 4-s access to mixed grain (Purina pigeon grain). The key light and house light went off simultaneously with the 4-s operation of the grain magazine and illumination of the food by the magazine light. The chamber was illuminated by a 7.5-W, 110-V A.C. bulb.

In the middle of the front panel (20 cm) of the two rat test cages was mounted a receptacle into which 97-mg Noyes pellets could be dispensed by a Gerbrands' pellet feeder. On either side (4.5 cm) of the food receptacle and, 4 cm above the grid floor of the chamber, was a Gerbrand's rat lever. A force of 30 g or more was required to register a lever press response. Each rat cage was illuminated by a 28-V D.C. bulb.

White noise was present in the chambers at all times. Chambers were ventilated by exhaust fans. Conventional relay programming and recording apparatus, located in a room adjacent to that of the chambers, were used.

Discrimination Training and Testing. The animals were trained initially to respond on either of the two manipulanda to obtain food according to an 1 Fr 1 schedule of reinforcement; the requirement for obtaining the food was then gradually increased until an FR 10 (rats) or an FR 15 (pigeons) schedule was in operation, i.e., the rats had to press the lever 10 times and the birds had to peck the key 15 times to produce food. This requirement was met during a median of 2.5 sessions in the pigeons and in 5 sessions for the rats. When injections were given before a session, the inappropriate manipulandum (left or right) for a given training condition was covered during five Δ⁨^2⁧^THC sessions and five vehicle sessions, after which the free-choice discrimination training began with both manipulanda available. The animals had to respond on the appropriate manipulandum to produce food. Which manipulandum was correct was dependent upon whether Δ⁨^2⁧^THC or the vehicle had been administered prior to the start of the session. Responses on the inappropriate manipulandum had no programmed consequences. Discrimination training was similar to the protocol outlined by Colpaert et al. (1977). The animals were trained once a day 5–6 days/week for a maximum of 20 min/session or, in the case of the pigeons, until grain had been presented 35 times. For rats, the drug training condition (D) consisted of an injection of 3 mg/kg of Δ⁨^2⁧^THC and the nondrug training (N) condition was 1 ml/kg of the vehicle, injected intraperitoneally (I.P.) 30 min prior to training sessions. For pigeons the final training dose of Δ⁨^2⁧^THC was 1 mg/kg and the drug and vehicle solutions were given intramuscularly (I.M.) 90 min prior to the start of sessions. The birds were placed in the chamber 80 min after the injection and remained there for 10 min until the session started which was signaled by the onset of the house light and illumination of the response keys. The rats were placed in the chambers immediately after the injections and remained there until the sessions started 30 min later. The onset of the house light signaled the start of a session. The masking noise and exhaust fans were always in operation.

When the animals selected the correct manipulandum (left or right) at the onset of each training session during at least 8 of 10 consecutive training days, the animals were switched from the training procedure to the test procedure. During the test procedure, the pigeons could obtain 18 reinforcements if all responses (270 pecking responses) were directed to the key on which the bird first completed 15 responses. Once one key was selected, pecking on the other, nonselected key, did not activate the food magazine. Test probes for the rats were similar to those of the pigeons. However, the rats were tested for the regular 20-min period, and no constraints were put on the number of reinforcements that could be earned during a session. Test sessions were preceded by at least one Δ⁨^2⁧^THC and one vehicle training session. Tests were not conducted unless the performance during the preceding training sessions had been on the correct manipulandum.

Drugs. All drugs were stored under nitrogen at –4 °C. The drugs had a purity of > 95% as measured by gas-liquid chromatography (National Institute of Drug Abuse, Research Triangle Institute, N.C., USA). Once the drug vials were opened, their contents were dissolved in pure ethanol (95.5%) and, shortly before testing the ethanol was evaporated under a stream of nitrogen before the suspensions (5% propylene glycol, 4% Tween-80 and, physiological saline) were prepared. SP-111, the structure of which is depicted in Pars et al. (1977, p. 159), was dissolved in physiological saline (0.9%) only (Sharps Associates, Ma., USA). It may be noted that glass syringes rather than the regular plastic ones were used for injections of SP-111 since it appeared possible that this drug might adhere to plastic materials. Except where otherwise indicated the injection volume was 1 ml/kg for both species.

Data Analyses. The data recorded and the calculations made were: position selection (left or right manipulandum) expressed as the number of animals selecting the drug (Δ⁨^2⁧^THC) associated position (symbol: DP selected); accuracy of the selection which is expressed as the number of responses emitted before the first reinforcement (symbol: FRF; possible values for the rats, 10 to 19, and for the pigeons, 15 to 29); the percentage of responding on the selected manipulandum out of the total number of responses emitted during a session (symbol: % on selected position). The two-tailed, 95% confidence limits (C.L.) for the two last measures are based on the tables by Owen (1962) and with a N < 8, correspond to the range of observations. Therefore, the baseline data (D- and N-session performances) were weighted (N ≤ 8) to be comparable to the test data. The mean percentage of responses on the Δ⁨^2⁧^THC (D) associated position is symbolized by RDP (%). Response rate (rate of responding) and latency (time in seconds to initiate responding) are expressed as the quotient between the most recently preceding vehicle session and the drug session. It should be noted that the latency scores were subtracted from the total session time since in this situation the latency to initiate responding may depend on the generalized depressant effect of the drugs and/or a decision-making period. The statistics used are indicated in the appropriate sections.