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Effects of Δ^9-THC and a Water Soluble Ester of Δ^9-THC on Schedule-controlled Behavior[1]

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DYKSTRA, L. A., D. E. MCMILLAN AND L. S. HARRIS. *Effects of Δ^9-THC and a water soluble ester of Δ^9-THC on schedule-controlled behavior.* PHARMAC. BIOCHEM. BEHAV. 3(1) 29–32, 1975. – Δ^9-Tetrahydrocannabinol (Δ^9-THC) and one of its water soluble esters (SP-111) decreased the rates of responding by pigeons working under a variable interval 3-min schedule of food presentation, or a multiple fixed-ratio 30, fixed-interval 5-min schedule of food presentation. Δ^9-THC was 3–6 times more potent than SP-111 and had a faster onset of effects on behavior.

Δ^9-Tetrahydrocannabinol   Water soluble THC   Schedule-controlled behavior   Mult FR FI   Pigeon

THE major active component in marihuana, Δ^9-Tetrahydrocannabinol (Δ^9-THC), is not water soluble. Thus, it is necessary to administer Δ^9-THC in solvents and suspending agents that often have pharmacological effects of their own. Recently Δ^9-THC has been converted to a number of water soluble derivatives by preparing esters bearing a basic amino function [7]. The present experiments were designed to compare the behavioral effects of one of these water soluble esters of Δ^9-THC, Δ^9-*trans*-tetrahydrocannabinol-4-mopholinofutyrate (SP-111), with the behavioral effects of Δ^9-THC. The schedule-controlled behavior of the pigeon was used as a measure of drug effect because it has been used previously to study the behavioral effects of a number of tetrahydrocannabinols [2, 4, 5].

METHOD

Animals

The animals were 12 male White Carneaux pigeons weighing between 475 and 538 g when given free access to food and water. They were maintained at 80% of their free feeding weights during this experiment. All the birds had been conditioned to peck a transilluminated key [1]. They had previously performed under various schedules of food presentation.

Apparatus

The apparatus consisted of a standard pigeon chamber, after Ferster and Skinner [1]. It was housed in a sound and light-attenuated chamber. The chamber was illuminated by a 7.5 W bulb (a.c.) and contained one translucent plastic response key, 2 cm in dia. which could be transilluminated by white, red or blue lights. The minimum force required to operate the key was about 15 g. Below the key was a food magazine through which grain was available during 3-sec access periods. White noise was present in the chamber at all times.

Drugs

The Δ^9-THC was stored in the dark at about 4°C. When ready for use, the Δ^9-THC was suspended in an aqueous solution of Triton X-100. SP-111 [7], a water soluble derivative of THC, was dissolved in distilled water. All injections were given in a volume of 1 ml/kg of body weight.

To correspond with the amount of Triton X-100 in the most concentrated Δ^9-THC suspension, a 1% (by volume) solution of the detergent was used as a vehicle control injection. Distilled water was used as a vehicle control for SP-111. Control and drug injections were made in the breast muscle. Two groups of birds were used in the first experiment. One group received Δ^9-THC or SP-111 1 hr

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before the experimental session. The second group received one of the same drugs 2 hr before the session. Doses were given in a mixed order, each dose being separated by at least 6 days without injections. In the second experiment the drug procedure was the same as in the first experiment, except that all birds were injected 1 hr before the session. None of the birds had received Δ^9-THC or SP-111 before these experiments.

Measurement of Drug Effects

Average rates of responding were computed from data recorded on digital counters and elapsed time meters. Quarter life was measured as a percentage of the FI time taken for the first quarter of the FI responses to occur [3]. It provides a numerical description of the pattern of FI responding. Experiments were conducted Monday through Friday with injections usually given on Friday. Data collected on Thursdays were used as noninjection control days.

Procedure

The pigeons in the first experiment performed under a multiple fixed-ratio, fixed-interval schedule (mult FR FI). In the presence of a blue key light, the 30th key peck (FR 30) produced a 3-sec access to grain. In the presence of a red key light the first response after 5 min (FI 5) produced a 3-sec access to grain. The FR and FI components alternated after each food presentation. If a bird did not respond within 40 sec after 5 min had elapsed during the FI component, the schedules changed to the FR component. If the bird did not make 30 responses within 40 sec during the FR component, the schedule changed to the FI component. A session terminated at the first schedule-component change after 60 min.

The pigeons in the second experiment were trained to respond under a VI 3-min schedule. In the presence of the white key light, responses were reinforced (on the average every 3 min) with 3-sec access to grain. The session terminated after the first presentation of grain after 2 1/2 hr had elapsed.

RESULTS

Effects of Δ^9-THC and SP-111 on Performance under the Multiple Schedule

Figure 1 shows the dose-response curves for Δ^9-THC and SP-111 on the rate of responding under the two components of the multiple schedule. The control injection and 0.3 mg/kg of Δ^9-THC had no effect on response rate under either component of the schedule when given either 1 or 2 hr before the experimental session. Dose-dependent decreases were seen with the 3 higher doses of Δ^9-THC on both components of the schedule. These decreases in response rate were similar 1 and 2 hr after administration.

The effects of SP-111 on the rate of responding were much smaller. Although rate decreases were seen with the 10 and 18 mg/kg of SP-111 when given 1 hr before the session, the decreases were not as large as those produced by Δ^9-THC at this time. Large decreases in the rate of responding were seen when SP-111 was given 2 hr before the session, but 10–18 mg/kg of SP-111 were required to produce decreases in responding comparable to those produced by 1.8 or 3 mg/kg of Δ^9-THC.

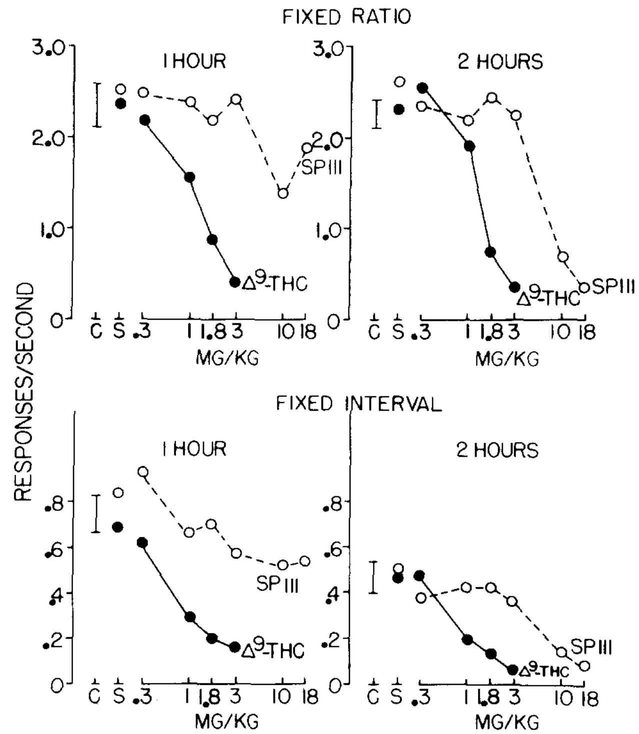

FIG. 1. Effects of Δ^9-THC and SP-111 given 1 hr or 2 hr before testing on rate of responding under mult FR 30 FI 5. Abscissa: mg/kg of Δ^9-THC or SP-111, log scale. Ordinate: rate of responding during an entire session. The brackets at C represent the range of control values (Thursdays). Points at S show the effects of control injections on rate of responding. ●——● is the dose-response curve for Δ^9-THC; ○– – –○ is the dose-response curve for SP-111. Each point is the mean of a single injection in each of four birds.

Figure 2 shows the effect of the two drugs on the quarter life. Before drugs were given, the quarter life values were between 0.44 and 0.50; that is, 25% of the responses emitted during the 5-min FI component occurred during the first 2 1/2 min of the interval. Small changes in quarter life were seen after the two largest doses of Δ^9-THC, especially when given one hour before the session. SP-111 had no effect on the quarter life.

Effects of Δ^9-THC and SP-111 on Performance under the Variable-Interval Schedule

Figure 3 shows the effect of one dose of Δ^9-THC and of two doses of SP-111 on responding under a variable-interval schedule. Average response rates under the VI schedule are shown for 15 min intervals. With 3 mg/kg of Δ^9-THC it can be seen that response rate decreased rapidly about 30 min after the session started, but 3 mg/kg of SP-111 does not decrease responses rates until about 2 hr after administration. A dose of 10 mg/kg SP-111 decreased the rate to the same extent as 3 mg/kg of Δ^9-THC, although the rate of decrease was slower with SP-111 than with Δ^9-THC.

DISCUSSION

When Δ^9-THC was given one hour before an experimental session, it markedly decreased the rate of responding maintained by a VI schedule or by a mult FR FI

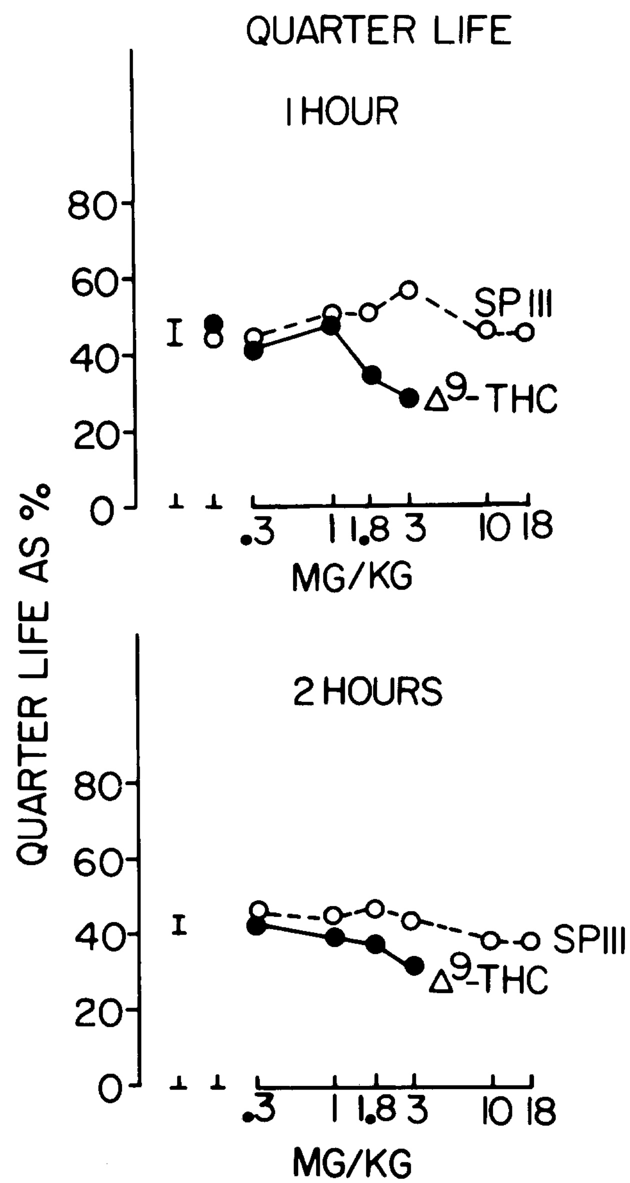

FIG. 2. Effects of Δ^9-THC and SP-111 given 1 hr or 2 hr before testing on the quarter-life. Abscissa: mg/kg of Δ^9-THC or SP-111, log scale. Ordinate: quarter-life as a percentage during an entire session. The brackets at C represent the range of control values (Thursdays). Points at S show the effects of control injections on rate of responding. •——• is the dose-response curve for Δ^9-THC; ○– – –○ is the dose-response curve for SP-111. Each point is the mean of a single injection in each of 4 birds.

schedule during the first hour of the session. The same doses of SP-111 decreased the rate under these schedules only slightly. When responding was measured 2 hr after injection, both Δ^9-THC and SP-111 decreased the rate of responding maintained by the VI schedule and by both components of the multiple schedule to the same extent, but Δ^9-THC was 3 to 6 times more potent than its water soluble ester. Thus, Δ^9-THC has a more rapid onset of action and a greater potency than SP-111.

Zitko *et al.* [7] have suggested that the principle activity of SP-111 results from its in vivo hydrolysis to Δ^9-THC by the liver. They reported that the hydrolysis of SP-111 to Δ^9-THC occurs rapidly in dogs, so that the onset of action by both SP-111 and Δ^9-THC occurs within 10 min after intravenous injection. Further, SP-111 was as potent or two-thirds as potent as Δ^9-THC in a variety of tests in dogs and mice. In contrast, in our pigeons SP-111 was only one-third to one-sixth as potent as Δ^9-THC.

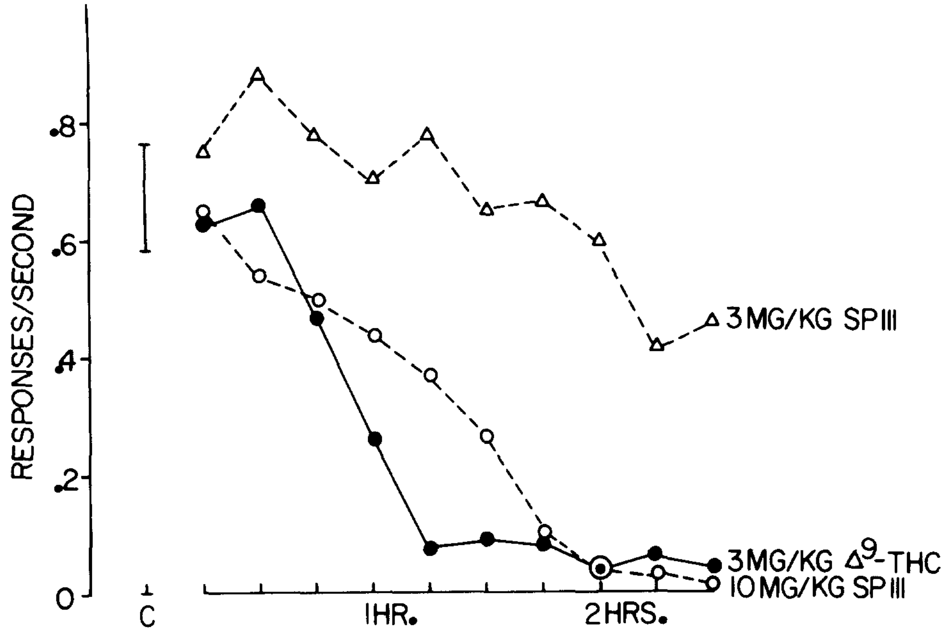

FIG. 3. Effects of 3 mg/kg of Δ^9-THC and 3 or 10 mg/kg of SP-111 on rate of responding under the VI 3 min schedule. Abscissa: 15 min intervals of the 2 1/2 hr VI session. Ordinate: mean rate of responding during 15 min intervals. The brackets represent the range of response rates in each 15 min interval under saline conditions. ●——● is the dose-response curve for 3 mg/kg of Δ^9-THC; ○– – –○ is the dose-response curve for 10 mg/kg SP-111; △– – –△ is the dose-response curve for 3 mg/kg SP-111. Each point is the mean of a single injection in each of 2 birds.

The slower onset of action of SP-111, relative to Δ^9-THC in the pigeon, might have occurred because of (1) species differences in the response to the behavioral effects of the active tetrahydrocannabinols, Δ^9-THC and SP-111; (2) a slow hydrolysis of the inactive SP-111 to the active Δ^9-THC; or (3) a slower absorption of SP-111 than Δ^9-THC from the pectoral muscle of the pigeon. These same factors might also explain the potency difference between SP-111 and Δ^9-THC. Our experiments do not permit a choice among these possibilities; however, McMillan *et al.* [6] have shown that tetrahydrocannabinols are absorbed fairly rapidly from pigeon pectoral muscle.

Zitko *et al.* [7] have also reported that Δ^9-THC is only 1 to 1.5 times more potent than SP-111, which is consistent with a conversion of SP-111 to Δ^9-THC. In the pigeon Δ^9-THC is 3–6 times more potent than SP-111. It is difficult to reconcile this large potency difference between Δ^9-THC and SP-111 on the basis of hydrolysis of SP-111 to Δ^9-THC.

Frankenheim *et al.* [2] have reported that Δ^9-THC and Δ^8-THC have little tendency to disrupt the temporal pattern of FI responding. In the present experiments there were small changes in the quarter life after large doses of Δ^9-THC, while SP-111 did not produce changes in the quarter life. This is further evidence that tetrahydrocannabinols have little effect on the temporal patterning of FI responding.

ACKNOWLEDGEMENTS

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