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Δ^9-Tetrahydrocannabinol Produced Discrimination in Pigeons[1]

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HENRIKSSON, B. G., J. O. JOHANSSON AND T. U. C. JÄRBE. *Δ^9-Tetrahydrocannabinol produced discrimination in pigeons.* PHARMAC. BIOCHEM. BEHAV. 3(5) 771–774, 1975. – In an operant situation pigeons learned to peck one response key 90 min after an injection of 0.25 mg/kg Δ^9-tetrahydrocannabinol (Δ^9-THC) and another key when trained nondrugged. When tested with doses of Δ^9-THC lower than the training dose the birds discriminated 0.20 mg/kg of the drug from the nondrugged state but not 0.15 mg/kg or lower doses. The animals were able to discriminate the drug state from the nondrugged 180 min but not 360 min after the injection. At a shorter interval (45 min) both drug and nondrug responding appeared. Cannabinol and cannabidiol (4.0 – 8.0 mg/kg) did not elict any drug responses, nor did pentobarbital, ditran or amphetamine. Tests with LSD resulted in both drug and nondrug responding. When administering noncannabinoid drugs in combination with Δ^9-THC 0.15 mg/kg the birds responded at the key associated with the drug state, suggesting interactional effects.

Drug discrimination (StD)-Δ^9-THC Psychotropic drugs Pigeons

THE present investigation was undertaken to study some discriminable properties of Δ^9-tetrahydrocannabinol (Δ^9-THC) in pigeons. To the best of our knowledge no information on drug discriminative controlled responding in non-mammals is available.

By drug discriminative control is meant that the choice behavior of an organism has been made contingent upon the presence or absence of effects of a certain drug. A common way to demonstrate this in rodents is to require the animals to run to e.g. the left side of a T-shaped maze to escape aversive stimulation after drug treatment and to turn to the right side when administered the vehicle [14].

This study was designed to see if choice responding in pigeons, trained in an operant situation, could be made conditional upon the injection of Δ^9-THC, and if so whether or not some other drugs would also elict the drug contingent choice. Dose and time related characteristics of Δ^9-THC were also explored.

METHOD

Animals

Two experimentally naive male pigeons (P 1 and P 2) about 3 years of age were maintained at 80 percent of freefeeding body weight. They were housed in individual home cages.

Apparatus

The experimental space was a Lehigh Valley Electronics pigeon chamber containing 2 translucent plastic response keys, which could be operated by a force of 15 g or more. The experimental chamber was enclosed in a larger ventilated chamber which attenuated most extraneous sounds and a continous masking noise was provided by a white noise generator. Programming was accomplished automatically by a system of switching relays and timers. Data were recorded on magnetic impulse counters and on a cumulative recorder.

Procedure

Throughout the experiment a reinforcement consisted of a 3 sec access to grain. The key light and house light went off simultaneously with the 3 sec operation of the grain magazine and illumination of the food by the magazine light.

The pecking response was shaped in a 1 key chamber, in which the key was placed in the center of the front wall. After shaping the response the birds were trained daily 15 min on a fixed ratio schedule of reinforcement, FR-15, i.e. the birds had to peck the key 15 times in order to get access to food. The drug discriminative training started when the pigeons had shown a well-established FR-15

[1] Numbered Δ^1-THC according to the monoterpenoid system.

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responding during 3 weeks. The drug discriminative training took place in the 2 key chamber every second day.

During drugged sessions (D), when injected IM with 0.25 mg/kg of Δ^9-THC 90 min before the session, the birds were required to peck the left key to be reinforced. During the nondrugged sessions (N), the animals had to peck the right key in order to get food. Occasionally the vehicle was injected before N-sessions. The birds were trained 3 times a week at FR-15 and the order of the 15 min training sessions was D, N, N, D, N, D, D, N etc.

When the experimentally manipulated cues (D and N) differentially controlled the choice behavior of the birds i.e. they responded on the correct key already from the start of the training sessions, test trials were interposed in between the regular training. During test trials the pigeons were allowed to emit only 10 responses after which the programming unit was switched off and the animals were removed from the compartment. A maximum of 10 min was allowed for performing the 10 responses. Test trials were not run unless the responding during the preceeding training sessions had been correct.

Drugs

The tetrahydrocannabinol, Δ^9-THC, generously supplied by Dr. O. Braenden, U.N. Office in Geneva, was assayed by glc. to be about 95 percent pure but a subsequent determination by Dr. K. Leander, Stockholm, indicated a Δ^9-THC content of approximately 81 percent. The analyses were carried out as described elsewhere [2]. The doses used were based on the latter analysis. The drug was suspended in a vehicle containing 10 percent propylene glycol and physiological saline plus Tween-80 (1 percent) [16]. Cannabinol (CBN) and cannabidiol (CBD) were suspended in the same way, except that 25–50 percent of propylene glycol was used. The other drugs were dissolved in saline and the doses are expressed in terms of the salts. All drugs were injected in the breast muscle (IM) in a volume of 1 cc/kg.

RESULTS

Drug discrimination was well established after 30 training sessions (15 N- and 15 D-sessions). Thus, the two pigeons responded on the correct, reinforcing key already from the start of the sessions. This acquired behavior was well retained as is indicated in Table 1. In those rare instances where nonreinforced responding occurred this appeared at the end of the training sessions. A comparison between mean number of responses performed during N and D training sessions respectively, interposed between tests, reveals a higher response frequency per session during N conditions (T-test for pair-wise comparisons). However, when separately analysing the first and last blocks of 10 training sessions (5D and 5N) it was found that this differ-

TABLE 1

DOSE AND TIME CHARACTERISTICS OF Δ^9-THC AND SUBSTITUTION TESTS WITH CBD AND CBN

Drug	Dose (mg/kg)	Time (min postinjection)	No. of Tests	Response Choice P1 D-key	P1 N-key	P2 D-key	P2 N-key
No drug (N)*			28	1	27	0	28
Δ^9-THC (D)†	0.25	90	25	24	1	24	1
Δ^9-THC	0.20	90	1	1	0	1	0
Δ^9-THC	0.15	90	3	0	3	1	2
Δ^9-THC	0.10	90	1	1‡	0	0	1
Δ^9-THC	0.05	90	1	0	1	0	1
Δ^9-THC	0.25	45	2	1	1	1	1
Δ^9-THC (D)†	0.25	90	25	24	1	24	1
Δ^9-THC	0.25	180	2	2	0	2	0
Δ^9-THC	0.25	360	2	0	2	0	2
CBD	4.00	90	2	0	2	0	2
CBN	4.00	90	1	0	1	0	1
CBN	8.00	90	1	0	1	0	1

Test trials of 10 responses each with different doses of Δ^9-THC (top section) and different injection-test intervals (middle section. Test trials with cannabidiol (CBD) and cannabinol (CBN) are shown in the bottom section.

*Performance during interposed training: vehicle injections or no injections at all

†Performance during interposed training: Δ^9-THC injections

‡P1 emitted 3 D-, 3 N- and 4 D-responses

TABLE 2

EFFECTS OF SEPARATE AND COMBINED TREATMENTS WITH FOUR PSYCHOTROPIC DRUGS ON THE Δ^9-THC DISCRIMINATION

Drug 1	Dose (mg/kg)	Time (min postinjection)	Drug 2	Dose (mg/kg)	Time (min postinjection)	No. of Tests	Response Choice P1 D-key	P1 N-key	P2 D-key	P2 N-key
Δ^9-THC*	0.25	90				25	24	1	24	1
			P-barb	2.0	20	1	0	1	0	1
			P-barb	4.0	20	1	0	1	0	1
Δ^9-THC	0.15	90	P-barb	4.0	20	1	1	0	1	0
			Amphet	0.5	60	1	0	1	0	1
Δ^9-THC	0.15	90	Amphet	0.5	60	2	1†	0	2	0
			Ditran	0.3	60	1	0	1‡	0	1
			Ditran	0.6	60	1	0	1	0	1
Δ^9-THC	0.15	90	Ditran	0.6	60	1	1	0	1	0
			LSD-25	0.05	60	3	0	3	2§	1
Δ^9-THC	0.15	90	LSD-25	0.05	60	1	1	0	1	0

Test trials of 10 responses each with four non-cannabinoid drugs administered singly and in combination with 0.15 mg/kg Δ^9-THC. P-barb = pentobarbital; Amphet = amphetamine.

*Performance during interposed training: Δ^9-THC injections

†At one of the two tests P1 did not emit any responses

‡P1 emitted 2 N-, 2 D- and 6 N-responses

§P2 emitted 1 N- and 9 D-responses in one test and only 3 D-responses in the other

ence was most pronounced during the initial block, N>D 25 percent, $p<0.01$ (P1) and N>D 20 percent, $p<0.05$ (P2) but diminished during the last block D>N 4 percent, $p>0.05$ (P1) and N>D 9 percent, $p<0.05$ (P2). No differential effects between the nondrugged sessions after vehicle treatment and the no injection condition was found and therefore the nondrugged performance constitute a single category in Table 1.

Table 1 further shows the effects of testing doses of Δ^9-THC below 0.25 mg/kg as well as time related characteristics of the training dose. At the dose of 0.20 mg/kg D-responding was still apparent whereas lower doses resulted in N-responding in most test trials.

Varying the injection-test interval resulted in mixed responding after 45 min, complete D-responding after 180 min, and N-responding at the test conducted 360 min after the injection of Δ^9-THC (0.25 mg/kg).

Table 1 also shows that neither cannabidiol (CBD, 4.0 mg/kg) nor cannabinol (CBN, 4.0 and 8.0 mg/kg) elicited any D-key responses. Because of insufficient amounts a further dose of CBD was not tested.

Table 2 shows the results of test trials with pentobarbital (CNS depressant), d-amphetamine (CNS Stimulant), ditran (anticholinergic hallucinogen), and LSD-25 (psychedelic hallucinogen). Except for LSD, the pecking of the pigeons was predominantly on the N-key. After LSD treatment Bird P2 pecked the D-key in 2 out of 3 test occasions. However, during one of these 2 LSD sessions this animal produced only 3 D-key pecks after which it did not peck further during the 10 min period allowed. During the other session this bird emitted 1 N- and 9 D-responses. After treatment with the combination of amphetamine and Δ^9-THC P1 did not peck at all during one test session.

When 0.15 mg/kg of Δ^9-THC was followed by an injection of any one of the non-cannabinoid drugs the pigeons choose the D-key.

DISCUSSION

From this study it is clear that drug discrimination is possible also in a nonmammalian species as demonstrated with two pigeons differential responding in a 2 key operant learning situation. Thus, the tetrahydrocannabinol treatment guided the choice behavior of the birds.

Previous work with rats, girbils, and monkeys has shown that drug discrimination is dose and time related. That is, testing decreasing doses of the training drug or altering the injection–test interval results in a reduction of the drug associated choice behavior [3, 7, 10, 11]. This was also found in the pigeons. The time course for the THC effects is in fairly good agreement with those reported by Abel *et al.* [1], although our data suggest a slightly more rapid onset. They, however, found that key pecking was completely suppressed by IM injections of 0.30 mg/kg whereas 0.10 mg/kg did not produce any appreciable effects. Cherek and Thompson [5], on the other hand, reported no suppression in their pigeons with 0.25 mg/kg of Δ^9-THC, which is in accord with our data. Further comparisons are not warranted because of differences in vehicles, schedules of reinforcement, and degree of drug experience.

Previous work has indicated that the discriminative cues produced by Δ^9-THC are specific in the sense that when other psychotropic drugs are substituted for THC the rats

emit mixed or no drug responding [3,10]. In the pigeon, pentobarbital, amphetamine, and ditran substitution resulted in pecking on the nondrug contingent key whereas the LSD treatment produced variable results. At substitution tests with Δ^9-THC mixed responding in LSD trained rats was seen by Cameron and Appel [4].

Several studies have shown that the two cannabinoids, CBD and CBN, do induce measurable effects [6, 9, 12, 13]. However, the lack of transfer with CBD and CBN in our study corroborates previous findings [3,10]. In addition the two compounds do not produce marijuana-like activity in man [8,15].

The over-all drug responding noted for the birds when 0.15 mg/kg of Δ^9-THC, a dose which predominantly results in nondrug responding, was followed by an injection of the noncannabinoid compounds may be viewed either as potention or an addition of unspecific drug effects. The present experimental design does not permit an evaluation of the specific type of interaction and further research is therefore needed.

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