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Effects of Δ^1-Tetrahydrocannabinol[1] on Schedule-Induced Aggression in Pigeons[2]

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CHEREK, D. R. AND T. THOMPSON. *Effects of Δ^1-tetrahydrocannabinol on schedule-induced aggression in pigeons.* PHARMAC. BIOCHEM. BEHAV. 1(5) 493–500, 1973.–The effects of Δ^1-tetrahydrocannabinol (Δ^1-THC) on key-pecking maintained by a response-initiated fixed interval (FI) schedule of food presentation and schedule-induced aggression in the pigeon were studied. The rate of attack responses was suppressed more than the rate of key-pecking, relative to their vehicle control rates, following the administration of Δ^1-THC (Experiment 1). In order to determine if the relatively selective effect of Δ^1-THC on attack rate was the result of a rate-dependent drug effect, the rates of key-pecking and attack responding were equated prior to drug administration in Experiment 2. Again a selective decrease in the rate of attack responses by Δ^1-THC, compared to its effects on key-pecking, was observed when the rate of the two behaviors was comparable. The suppressing effect of Δ^1-THC on attack responses cannot be attributed to a generalized motor impairment, since doses of Δ^1-THC (0.125 and 0.25 mg/kg) which had little or no effect on the rate of key-pecking resulted in substantial decreases in the rate of attack responses.

Aggression Δ^1-tetrahydrocannabinol Pigeon

THE ACUTE administration of marihuana extracts or Δ^1-tetrahydrocannabinol (Δ^1-THC), believed to be the major active principle in marihuana [26], has been found to decrease aggressive behavior in a variety of species. Isolation-induced aggression in mice was markedly suppressed by marihuana extracts [3, 28, 29]. Marihuana extracts and Δ^1-THC also reduced aggressive behavior in large colonies of mice [31]. Gonzales *et al.* [14] reported that marihuana extracts and Δ^1-THC produced a suppression of aggressive-display behavior in the siamese fighting fish. Both facilitation and inhibition of dominance behavior have been observed in rats competing for food, as well as decreases in predatory aggression in rats, following the administration of Δ^1-THC [17, 21, 22]. In contrast, marihuana extracts and Δ^1-THC have been found to have no effect on shock-elicited fighting in rats [2,19]. Increased shock-elicited fighting has been reported only during initial exposure to marihuana extracts [2].

Although numerous studies have determined the effects of various drugs on aggression in infrahuman species [34], two basic problems continue to hinder research in this area; (a) the lack of accurate and objective measurement of aggressive behavior, and (b) the inability to determine selectivity of drug action. Methods previously employed in assessing the effects of drug on aggression (e.g., isolation, predatory attack, etc.) have relied on direct observation to measure aggressive behavior. Recording of aggression by human observers, necessarily involves arbitray decisions regarding the occurrence and/or frequency of attack. Because ambiguous criterion are often employed, the replication of results in other laboratories is one of the major problems confronting research which depends upon direct observation [10]. With the introduction of the methods of schedule-induced aggression in pigeons [1] and shock-elicited biting in squirrel monkeys [15], it was possible to more objectively record aggressive behavior. The development of techniques for automatic recording of aggressive behavior eliminated the necessity of employing direct observational recording, which have hindered previous objective quantification of aggression.

A second problem in aggression research is the evaluation of specificity of drug action. Attempts to determine the selectivity of drug effects are important, since almost all drugs decrease aggressive behavior at some dose [18]. Thus, it is necessary to distinguish between a drug effect on aggressive behavior and an effect, such as sedation or motor impairment, which affects the total behavioral repertoire of the subject. One method of dealing with this problem is to measure the effects of the drug on more than one behavior at the same or approximately the same times [30]. However, a large number of studies have failed to measure drug effects on other behaviors, so that the specificity of the

[1] The monoterpenoid numbering system for tetrahydrocannabinols was employed. Δ^1-tetrahydrocannabinol is equivalent to Δ^9-tetrahydrocannabinol using the pyran numbering system.

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reported effect on aggressive behavior cannot be ascertained. In many investigations the selectivity of drug action has been determined by using rations of doses (ED50) which have an effect on aggressive behavior with doses producing other behavioral effects (e.g., decreased motor activity, impaired rotarod performance, etc.). Often, however, the same drug effect can be classified as selective or nonselective depending on which alternative behavioral measure is employed [9].

In the present investigation, the effects of Δ^1-THC on schedule-induced aggression in pigeons were studied. This technique has two advantages over other procedures used in evaluating the effects of Δ^1-THC, or other drugs, on aggression. First, this method utilizes an automated objective measure of aggressive behavior, thus avoiding the use of direct observational recording. Secondly, it is possible to compare the effects of Δ^1-THC on two concurrently occurring behaviors, food reinforced responding and aggressive attack. The determination of selectivity of drug action on two behaviors occurring over the same time interval within the same environmental context, affords a more valid estimate of the specificity of drug action.

EXPERIMENT 1: EFFECTS OF Δ^1-THC ON SCHEDULE-INDUCED AGGRESSION

Method

Animals. Three experimentally naive male white Carneaux pigeons (Palmetto, Sumter, So. Carolina) served in this experiment. Two additional pigeons were used as targets, while a taxidermically prepared pigeon was used as a target with one bird (P 46). The experimental animals were food deprived and maintained at 80% of their free-feeding weights; target birds were not food deprived. Each target bird was paired with a specific experimental animal for the entire experiment. All pigeons were housed in individual cages with water and grit continously available.

Apparatus. A standard pigeon operant test chamber (Model 143–05, Lehigh Valley Electronics, Fogelsville, Pa.) containing a single response key and a solenoid-operated food delivery mechanism was used. The response key was transilluminated by a white light. The chamber was illuminated by an overhead light and white noise was present continously to mask extraneous sounds.

The apparatus for recording aggressive attacks was similar to that described by Azrin *et al.* [1]. The target birds were restrained in an opaque box by metal bands fastened over each wing; thus exposing the head, neck and upper breast through the top of the restraining device. The restraining box was mounted on a metal frame containing an adjustable spring and microswitch. A force of at least 100 g exerted against the front of this box by the experimental animal, during periods of attack, resulted in a switch closure. Each switch closure was recorded as an attack response. The restraining box was located on the side of the chamber adjacent to the response key. Plexiglas shields on either side of the restraining box prevented the experimental animals from getting behind the target, since only displacements of the front of the restraining box were recorded. Although target birds make vigorous defensive movements prior to and following periods of attack, such movements, by themselves (i.e., in the absence of attack), did not result in switch closures [6].

The entire apparatus was located in a ventilated, sound-attenuating enclosure. All programming and recording were performed by electromechanical equipment in an adjacent room.

Procedure. Key-pecking on the response key was reinforced with food presentation on a response-initiated fixed-interval (FI) 2 min schedule [25]. On such a schedule, the first response after reinforcement initiated the next fixed interval, and the first response after the interval elapsed was reinforced. During food delivery, the food magazine was illuminated and the response key light was extinguished. Reinforcement consisted of a 3 sec access to Purina poultry pellets. Daily sessions were terminated after 45 min.

Key-pecking was hand-shaped, and birds were stabilized on a FI 2 min food reinforcement schedule. Such a schedule was found to induce aggression [5], and the highest rates of attack were observed at FI values of 2 or 3 min [8]. To prevent the superstitious reinforcement of attack responses, a change-over-delay (COD) of 15 sec was interposed between the occurrence of each attack response and the presentation of food following a key-pecking response [4]. This contingency (i.e., COD) prevented the accidental temporal association of attacks against the target and food presentation.

Synthetic Δ^1-THC in 95% ethanol (200 mg/cc), obtained from NIMH, was suspended in a mixture of 2% Arlacel-20 and Tween-65 in saline [27]. Suspensions were stored in the dark at 4 degrees C. Drug or vehicle injections were administered in a constant volume of 1 ml/kg of body weight. Doses of Δ^1-THC (0.125, 0.25, 0.5, and 1.0 mg/kg) were injected IM two hours prior to the beginning of the session. Dosages were given in a random order, with each dosage level being administered twice.

Birds were run with the target bird present (in the restraining box) every third session: (a) to minimize injury to the target bird, and (b) to avoid the decrease in aggression observed when subjects are exposed to a target over successive sessions [6]. A vehicle or Δ^1-THC injection was also given every third session, when the target bird was present, with two intervening noninjection sessions separating each vehicle and drug session. To minimize the development of tolerance, six days elapsed between each drug session [24]. During the nininjection sessions, birds were run on the FI 2 min food reinforcement schedule with the target bird and restraining box absent.

Results

The effects of Δ^1-THC on the mean rate of key-pecking and the mean rate of attack responses (i.e., switch closures recorded by the restraining apparatus) are shown in Fig. 1. Rates of responding are expressed as a percentage of the mean vehicle control rate. Δ^1-THC produced dose-dependent decreases in the rate of attack and rate of key-pecking. With two of the animals (P 48 and P 57) both rates were decreased to zero at 1.0 mg/kg; with animal P 46 the rate of key-pecking was decreased to 35% of the control rate and the rate of attack was reduced to 10% of the control rate. The rate of attack was suppressed more than the rate of key-pecking, relative to their vehicle control rates, at all other doses of Δ^1-THC. At 0.25 and 0.5 mg/kg, the rate of key-pecking was decreased to 75–95% and 55–65% of the vehicle control rate, while the rate of attack was decreased to 35–55% and 15–25% of the control rate. Thus, Δ^1-THC suppressed the rate of attack, relative to controls, more than the rate of key-pecking.

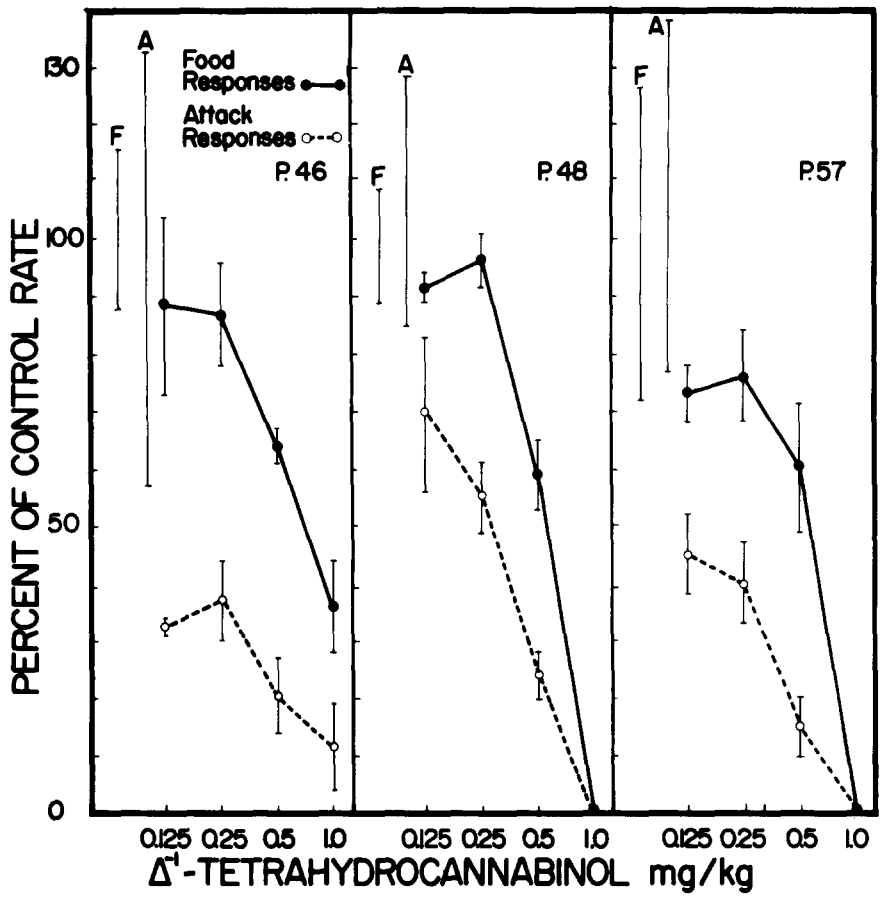

FIG. 1. The effects of Δ¹-THC on mean rate of key-pecking on FI 2 min food reinforcement schedule and the mean rate of attack responding (i.e., switch closures recorded by the restraining apparatus). The vertical lines labeled F (food responding) and A (attack responding) represent the range of response rates observed during vehicle control sessions expressed as a percentage of the mean control value. The mean vehicle control response rates (responses per min) were: 40.11 (P 46), 95.32 (P 48), and 42.11 (P 57) for key-pecking and 6.86 (P 46), 8.49 (P 48), and 5.42 (P 57) for attack responding. The vertical lines at each dosage point represent the range of two observations.

Cumulative records of the performance of pigeon P 46 are shown in Fig. 2. The effects of Δ¹-THC on responding on FI 2 min food reinforcement schedule were similar to those reported by Frankenheim, *et al.*, [12]. Δ¹-THC had little or no effect on the FI pattern of responding. The slight decrease in response rate observed at 0.125 and 0.25 mg/kg, was due primarily to increased postreinforcement pausing (i.e., time between reinforcement presentation and the initiation of the next fixed interval). Higher doses (0.5 and 1.0 mg/kg) produced a dose-dependent cessation of responding, after periods of responding at near vehicle control rates earlier in the session.

Attack responses occurred primarily during the postreinforcement pause and early portions of the fixed interval, as has been previously reported [5]. A dose of 0.125 or 0.25 mg/kg of Δ¹-THC had little or no effect on food reinforced responding, while producing a marked decrease in the attack rate. Following vehicle injections, attack occurred during almost every postreinforcement pause (refer to Fig. 2). Attacks continued to occur during most of the postreinforcement pauses after the administration of 0.125 and 0.25 mg/kg of Δ¹-THC, however, the number of attacks during each postreinforcement pause was greatly reduced. The number of postreinforcement pauses during which no attacks occurred, increased as the dose of Δ¹-THC increased.

EXPERIMENT 2: RATE-DEPENDENT EFFECTS OF Δ¹-THC

The ongoing rate of behavior is known to be an important determinant of the behavioral effects of drugs. Numerous drugs have been shown to have rate-dependent effects, in that, the effect of the drug (i.e., an increase or decrease in response rate) is dependent upon the ongoing rate of behavior prior to drug administration [16,32]. Such rate dependent effects have been demonstrated for amphetamine, methamphetamine, barbiturates, morphine, cocaine, imipramine, meprobamate, and chlordiazepoxide [9, 10, 13, 33].

In Experiment 1 the effects of Δ¹-THC on two

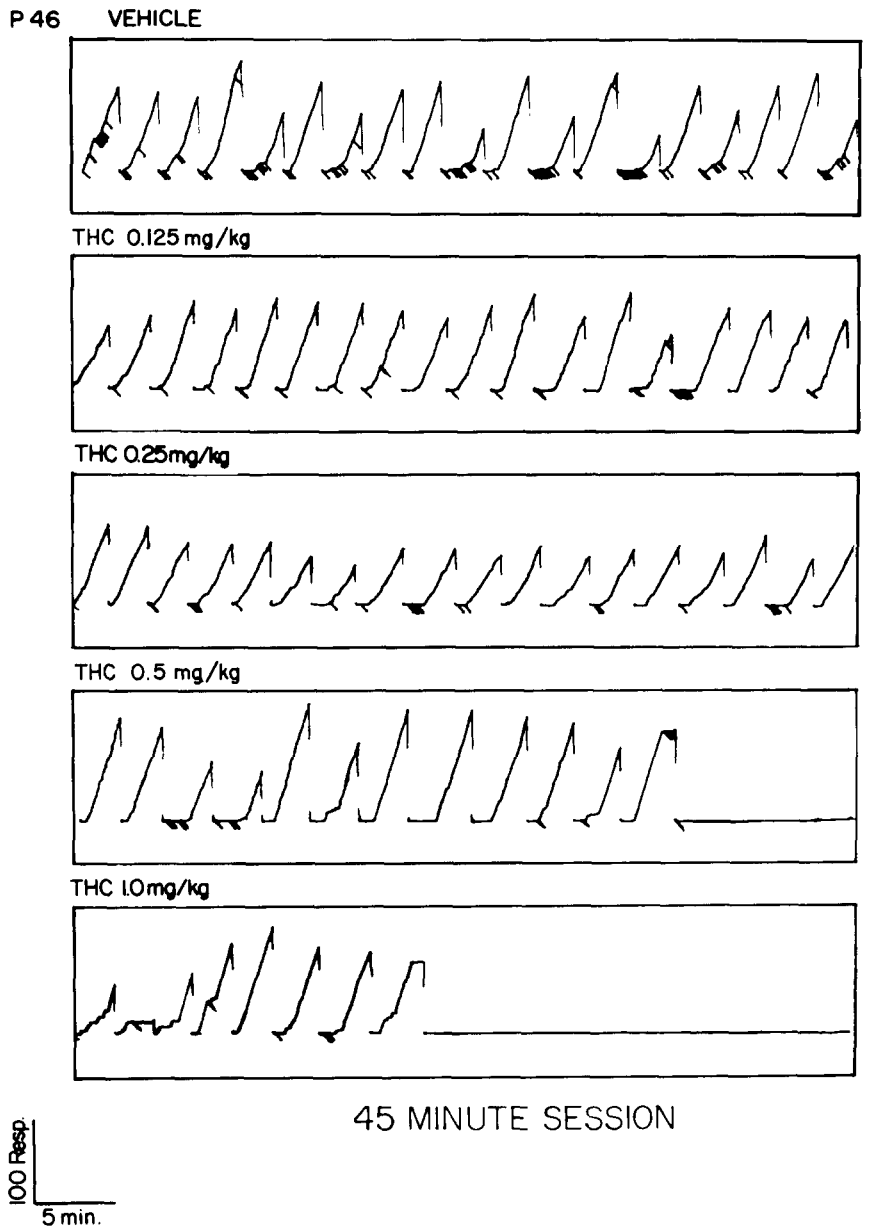

FIG. 2. Sample cumulative records for pigeon P 46 responding on FI 2 min food reinforcement schedule following the administration of vehicle or Δ^1-THC. Following the presentation of food, the recording pen reset to the baseline. Attack responses are indicated by a brief downward deflections of the response pen.

behaviors occurring at different rates were studied; key-pecking maintained by food presentation (40–95 responses per min) and attack responses (4–12 responses per min). The observed selective effect of Δ^1-THC on attack responses may have been the result of a rate-dependent effect (i.e., Δ^1-THC selectively suppresses low rate behaviors as opposed to high rate behaviors), rather than a selective effect on schedule-induced aggressive behavior. In order to determine if the effect of Δ^1-THC on aggression might be the result of a rate-dependent effect, the rates of the two behaviors (key-pecking and attack responding) were equated prior to drug administration in Experiment 2.

Method

Animals. Three experimentally naive male white Carneaux pigeons served in this experiment. Three other pigeons were used as targets.

Apparatus. The apparatus was the same as described in Experiment 1.

Procedure. In order to decrease the rate of key-pecking to a rate comparable to the rate of attack, a 6–8 sec DRL (i.e., differential reinforcement of low rate responding) contingency was added in tandem with the FI 2 min food reinforcement schedule. With this schedule, the first res-

ponse after the 2 min interval elapsed was reinforced (as in Experiment 1), provided at least 6–8 sec had elapsed since the previous response (i.e., tand FI 2 min DRL 6–8 sec). This resulted in the bird spacing all responses throughout the fixed interval about 6 sec apart, thus resulting in a lower overall rate of key-pecking.

Pigeons were hand-shaped to key-peck, and then responding was reinforced on a response-initiated fixed-interval (FI) schedule. Birds were run on an FI 2 min schedule, and after two weeks the DRL contingency was added. The birds were exposed to an FI 2 min DRL 5 sec schedule for one week and then the DRL value was increased to 6 sec. The pigeons were then run in the presence of an accessible target bird every third day as in Experiment 1. If the rate of attack and the rate of key-pecking were comparable, the DRL value remained unchanged. If the rate of key-pecking was still higher, the DRL value was increased to 8 sec.

Following this, the birds were administered either vehicle or drug on every third session, with two intervening sessions in which there were no injections and the target bird was absent (refer to Table 1). Δ¹-THC (0.25, 0.5, and 1.0 mg/kg) was injected IM two hr prior to the beginning of the drug session, with each dosage level being administered twice.

TABLE 1

DESIGN FOR EXPERIMENTS 1 AND 2

Session	Food Reinforcement Schedule Exp. 1	Exp. 2	Target	Drug
1	FI 2 min	FI 2 min DRL 6–8 sec	Absent	No
2	FI 2 min	FI 2 min DRL 6–8 sec	Absent	No
3	FI 2 min	FI 2 min DRL 6–8 sec	Present	Vehicle
4	FI 2 min	FI 2 min DRL 6–8 sec	Absent	No
5	FI 2 min	FI 2 min DRL 6–8 sec	Absent	No
6	FI 2 min	FI 2 min DRL 6–8 sec	Present	Δ¹-THC
7	Sequence repeated			

Results

The rate of key-pecking and attack responding as a function of dosage of Δ¹-THC is shown in Fig. 3. At 0.25 mg/kg of Δ¹-THC, the rate of key-pecking was essentially unchanged, and the rate of attack responding was decreased to approximately one-half the vehicle control rate at 0.5 mg/kg, while there was a decrease in the rate of attack to a little more than 10% of the control rate. Both rates were decreased to nearly zero at 1.0 mg/kg of Δ¹-THC.

Figure 4 shows sample cumulative records for pigeon P 78. At 0.25 and 0.5 mg/kg of Δ¹-THC, there were only slight decreases in the rate of key-pecking, while the rate of attack responses was markedly suppressed. At 1.0 mg/kg, both rates were substantially decreased.

Again attack responses occurred primarily during the post-reinforcement pause. More attack responses were observed early in the fixed interval than in Experiment 1, resulting in a slightly higher rate of attack. The rate of attack was greatly reduced at all doses of Δ¹-THC.

DISCUSSION

The results of Experiments 1 and 2 indicate that low doses (0.125 and 0.25 mg/kg) of Δ¹-THC appear to have a relatively selective effect of decreasing the rate of attack responding when compared to its effects on the rate of key-pecking. Although Δ¹-THC produce a dose-dependent decrease in the rats of both responses, the rate of attack was suppressed more at a given dose of Δ¹-THC than the rate of key-pecking, relative to their vehicle control rates. At higher doses of Δ¹-THC (0.5 and 1.0 mg/kg) the rate of attack and key-pecking were both markedly decreased, so that any decrease in attack rate may have been the result of a decrease in the number of food presentations, rather than a direct effect of Δ¹-THC on the rate of attack.

In Experiment 1, key-pecking and attack responding were occurring at markedly different rates prior to drug administration. The relatively selective effect on the rate of attack may have been the result of a rate-dependent drug effect, in that, Δ¹-THC selectively decreased a low rate behavior (i.e., attack responding) as opposed to a high rate behavior (i.e., key-pecking). The rates of key-pecking and attack responding were equated prior to Δ¹-THC administration in Experiment 2, to determine if such a rate-dependent effect was responsible for the selective decrease in attack rate. The same selective suppressing effect of Δ¹-THC on the rate of attack responding was observed when the rate of key-pecking and attack were comparable. Thus, the suppressing effect of Δ¹-THC on the rate of attack does not appear to be due to a rate-dependent drug effect.

Another possible interpretation of the effect of Δ¹-THC on schedule-induced aggression, is a direct effect on the level of food deprivation, which in turn produces a decreased rate of attack. Δ¹-THC has been reported to decrease food intake in dogs and rats [20,23]. Also, slight decreases in deprivation level have been found to decrease the rate of other schedule-induced behaviors (e.g., air-licking and polydipsia), while having minimal effects on food maintained responding [11]. This supposition was tested in a previous experiment [7], by determining the effects of changes in the level of food deprivation on schedule-induced aggression in pigeons. Slight decreases in food deprivation level, were found to have no effect or produce increases in the rate of responding maintained by the opportunity to attack, and the rate of attack responding. Thus, it appears that the decreased rate of attack following Δ¹-THC administration in the present experiment, is not the result of an alteration in the effective level of food deprivation. One problem confronting aggression research is evaluating the selectivity of a drug which decreases aggressive behavior, since the effect may represent a generalized depressant action (i.e., ataxia, impaired motor function, etc.). the results of Experiments 1 and 2 indicate that the suppressing effect of Δ¹-THC on schedule-induced aggression cannot be attributed to a generalized motor impairment. Doses of Δ¹-THC (0.125 and 0.25 mg/kg) which have little or no effect on food maintained responding result in substantial decreases in the rate of attack responses.

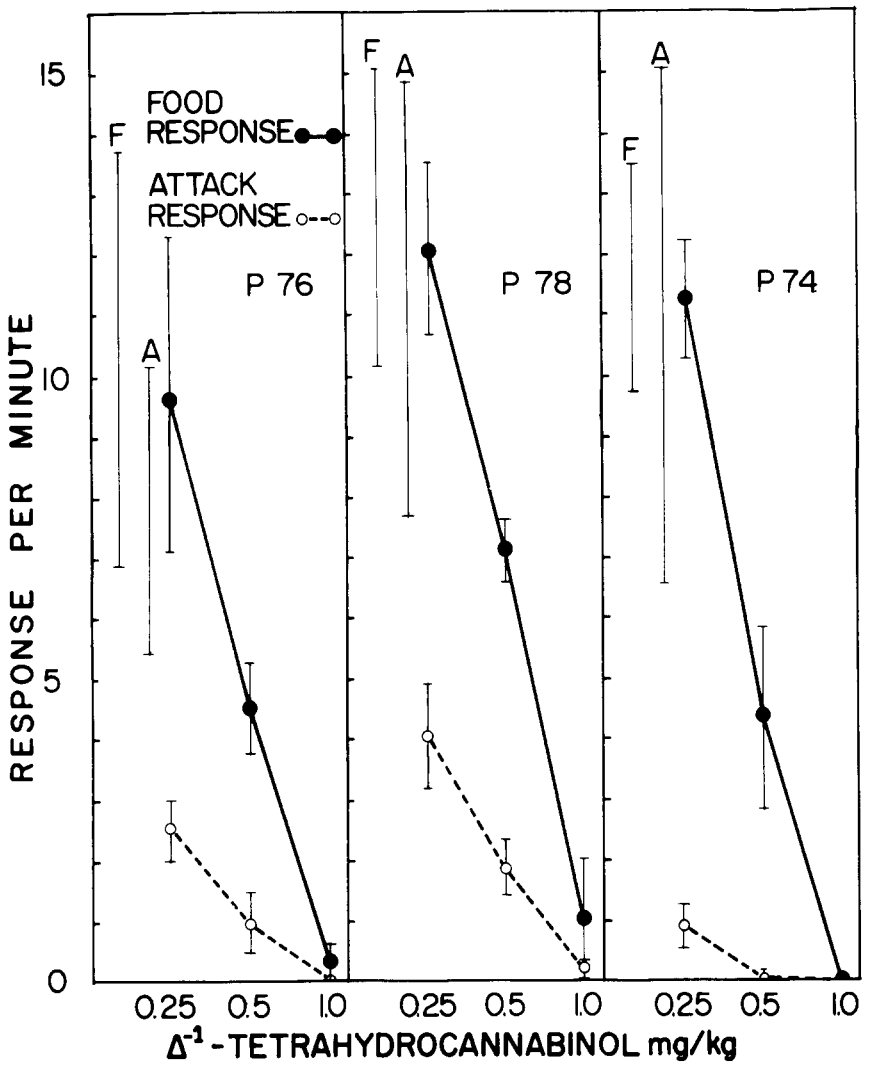

FIG. 3. The effects of Δ¹-THC on the mean rate of key-pecking on FI 2 min DRL 6–8 sec food reinforcement schedule and the mean rate of attack responding. The vertical lines labeled F (food responding) and A (attack responding) represent the range of response rates observed during vehicle control sessions. The mean vehicle control response rates (responses per min) were: 10.14 (P 76), 12.93 (P 78), and 11.60 (P 74), for key-pecking and 8.08 (P 76), 11.08 (P 78), and 10.79 (P 74) for attack responding. The vertical lines at each dosage point represent the range of two observations.

The relatively selective decrease in schedule-induced aggression in the pigeon produced by Δ¹-THC in the present experiments, supports previous reports of the effects of marihuana extracts and Δ¹-THC on aggressive behavior in other species. Measuring fighting time in isolated mice, Santos *et al.*, [29] also found evidence for a high degree of selectivity, in that doses of marihuana extract that decreased fighting time by 80%, had little or no effect on spontaneous motor activity. Likewise, Kilbey *et al.*, [17] reported decreases in predatory aggression in the rat by Δ¹-THC at doses which did not impair rotarod performance. The apparently highly selective action of marihuana and Δ¹-THC in decreasing aggression is in marked contrast to the effects reported for most other drugs [34].

Schedule-induced aggression, schedule-induced escape, and polydipsia are members of a class of behaviors termed "adjunctive" [11]. The effects of Δ¹-THC on the other adjunctive behaviors (i.e., schedule-induced escape and polydipsia) have not been studied. The effects of Δ¹-THC on schedule-induced aggression reported in these experiments may represent a selective effect on aggression, or on schedule-induced behaviors as a class of behaviors. This alternative is feasible, although the selective effects of Δ¹-THC on isolation-induced and predatory aggression would seem to indicate specificity regarding aggressive behavior.

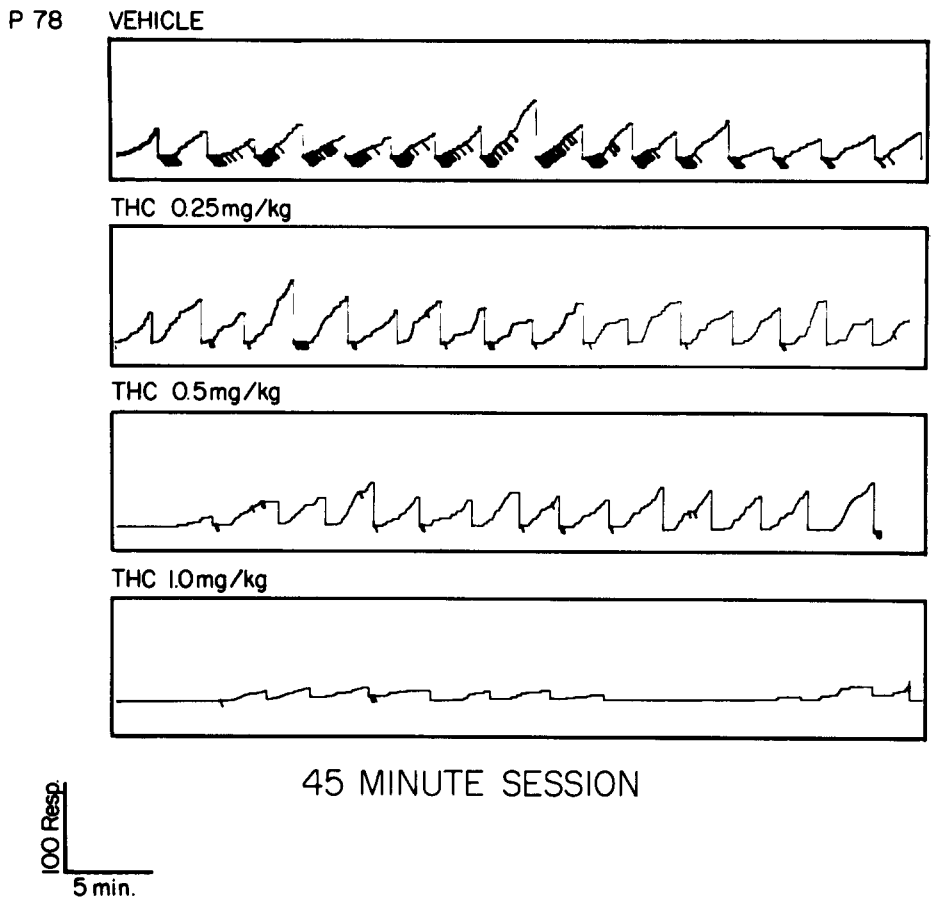

FIG. 4. Sample cumulative records for pigeon P 78 responding on FI 2 min DRL 8 sec food reinforcement schedule following the administration of behicle or Δ¹-THC. Following the presentation of food, the recording pen reset to the baseline. Attack responses are indicated by the brief downward deflections of the response pen.

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