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Chronic Δ^9-Tetrahydrocannabinol[1] Administration and Schedule-Induced Aggression[2]

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CHEREK, D. R., T. THOMPSON AND T. KELLY. *Chronic Δ^9-tetrahydrocannabinol administration and schedule-induced aggression.* PHARMAC. BIOCHEM. BEHAV. 12(2) 305–309, 1980.—The effects of 0.5 mg/kg and 1.0 mg/kg of Δ^9-tetrahydrocannabinol (Δ^9-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. Initially, following the administration of Δ^9-THC both the rate of key-pecking and attack responding were markedly reduced. Over sessions, tolerance developed to the suppressant effect on key-pecking, with the rate returning to the predrug level. The suppressing effect of Δ^9-THC on the rate of attack remained at or near zero throughout the series of Δ^9-THC injections.

Δ^9-tetrahydrocannabinol Aggressive behavior Chronic Schedule-induced

THE acute administration of marijuana extracts of Δ^9-tetrahydrocannabinol (Δ^9-THC) has been found to decrease aggressive behavior in a variety of species. Isolation-induced aggression in mice [11,24], spontaneous fighting in large colonies of mice [26], predatory aggression in rats [17,19], schedule-induced aggression in pigeons [8,9], and intruder conspecific aggression in mice, rats and squirrel monkeys [23] have all been observed to decrease following the acute administration of marijuana extracts or Δ^9-THC. In contrast to the effects of Δ^9-THC or marijuana extracts on aggressive behavior following acute administration, chronic injections have been reported to increase aggression in rats [4, 5, 30]. In the present experiment, the effects of chronic administration of Δ^9-THC on schedule-induced aggression in pigeons was studied.

METHOD

Animals

Four male white Carneaux pigeons (Palmetto, Sumter, So. Carolina) served in this experiment and were maintained at 80% of their free-feeding weights. Taxidermically prepared pigeons served as targets for all subjects. The subjects were housed in individual cages with water and grit continuously 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 mechanisms was used. The response key was transilluminated by white light. The chamber was illuminated by an overhead light and white noise was present continuously to mask extraneous sounds.

The apparatus for recording aggressive attacks was similar to that described by Azrin, *et al.* [2]. The stuffed target birds were held 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 subject (during periods of attack) resulted in a switch closure. Each switch closure was recorded as an attack response. The restraining box was located in the side of the chamber adjacent to the response key. Plexiglas shields on either side of the restraining box prevented the experimental subjects from getting behind the target, since only displacements of the front of the restraining box were recorded.

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 was reinforced with food presentation on a

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

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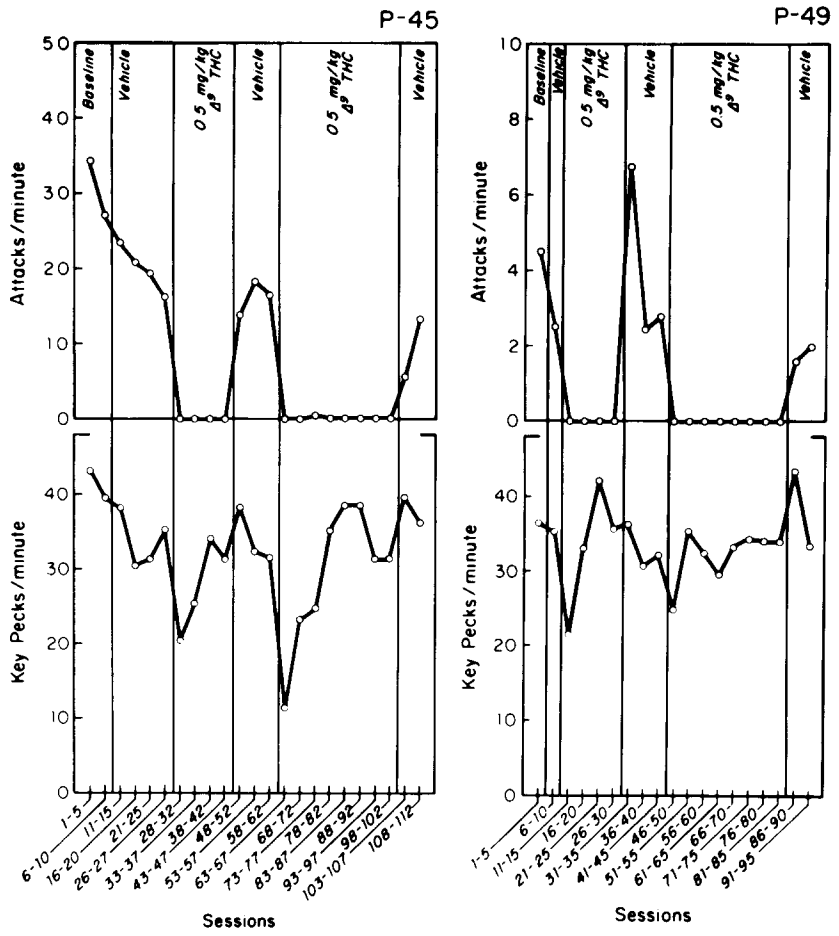

FIG. 1. The effects of Δ^9-THC (0.5 mg/kg) and vehicle injections on mean rate of key-pecking on FI 2 min food reinforcement schedule and the mean rate of attack responding (i.e., switch closures recorded by the restraining apparatus) for subjects P45 and P49. To conserve space the data points represent the mean rates of key-pecking or attack responding averaged over five or fewer consecutive sessions under a given condition (vehicle or Δ^9-THC).

response-initiated fixed-interval (FI) schedule [21]. On such a schedule, the first response after reinforcement intiated the next fixed-interval, and the first response after a specified interval elapsed was reinforced. During food delivery, the food magazine was illuminated and the response key light was extinguished. Reinforcement consisted of 3-sec access to Purina Poultry Pellets. Daily sessions were terminated after 45 min.

Subjects were gradually introduced to a FI 2 min food reinforcement schedule. Such a schedule was found to induce aggression [6], and the highest rates of attack were observed at fixed-interval values of 2 or 3 min [10]. 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. This contingency (COD) prevented the accidental temporal association of attacks against the target and food presentation.

After the rate of key-pecking had stabilized, subjects were run with a stuffed target present on every session (6 days/week). A stuffed target bird was employed to avoid the decrease in aggression observed when subjects are exposed to a live target bird over successive sessions [7]. An initial baseline period was conducted to determine the rate of key-pecking and attack responding prior to vehicle or drug injections. Following this, an ABAB design was initiated, with either vehicle (A) or 0.5 mg/kg or 1.0 mg/kg of Δ^9-THC (B) being injected intramuscularly (IM) two hr prior to the beginning of the daily session. The first series of Δ^9-THC injections were administered for 20 sessions and the replication for 40 sessions.

Synthetic Δ^9-THC in 95% ethanol, obtained from the National Institute of Mental Health was suspended in saline using polyvinyl pyrrolidone [13]. Suspensions were stored in the dark at 4°C. Drug or vehicle injections were administered in a constant volume of 1 ml/kg of body weight.

RESULTS

Figure 1 shows the rate of key-pecking maintained by food presentation and rate of attack responding for subjects P45 and P49 during sessions following the administration of vehicle or 0.5 mg/kg of Δ^9-THC. To conserve space the data points represent the average of five or fewer consecutive

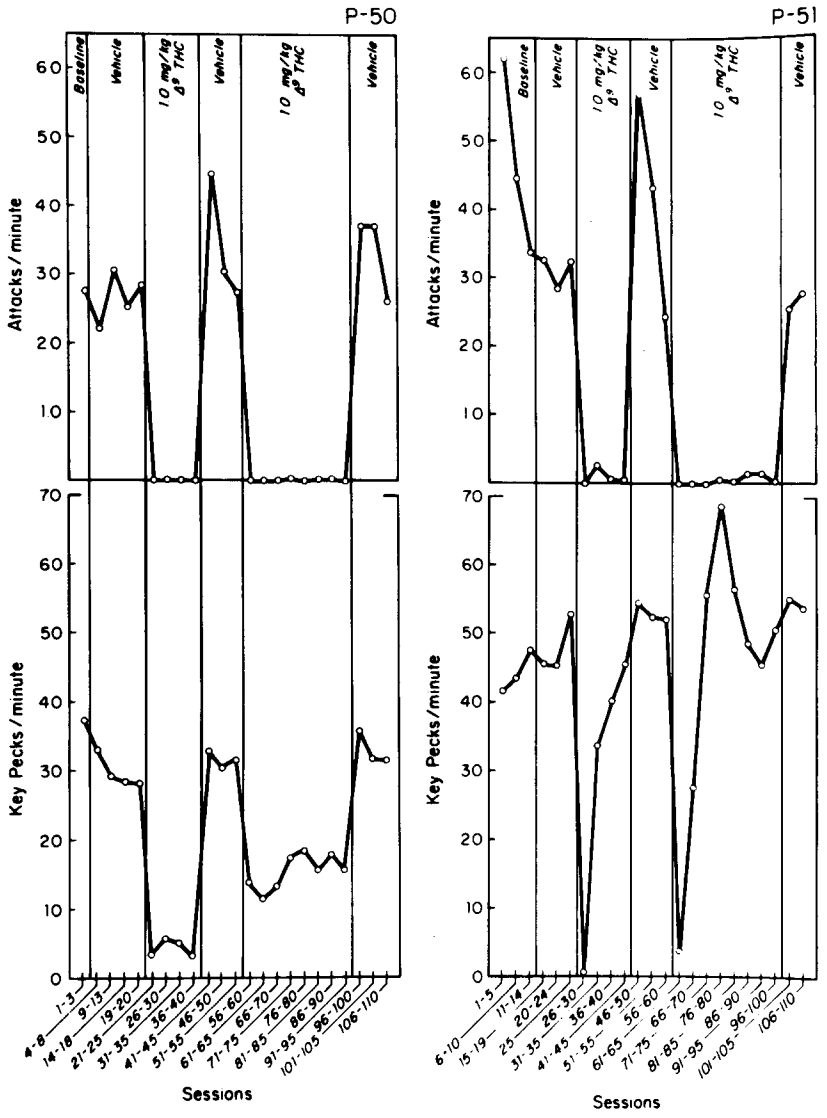

FIG. 2. The effects of Δ⁹-THC (1.0 mg/kg) and vehicle injections on mean rate of key-pecking on FI 2 min food reinforcement schedule and the mean rate of attack responding (i.e., switch closures recorded by the restraining apparatus) for subjects P50 and P51. To conserve space the data points represent the mean rates of key-pecking or attack responding averaged over five or fewer sessions under a given condition (vehicle or Δ⁹-THC).

sessions under a given condition. Following a baseline condition in which no injections were given, injections of the vehicle solution resulted in no significant changes in the rate of either behavior. After the administration of 0.5 mg/kg of Δ⁹-THC, the rate of key-pecking was reduced to approximately 30 to 50% of the vehicle control rate and the rate of attack responding was decreased to zero. Over sessions, tolerance developed to the suppressant effect on key-pecking with the rate returning to the predrug level within 8 to 10 sessions. The suppressing effect on the rate of attack responding showed no tolerance development and the rate of attack remained at zero throughout the series of 0.5 mg/kg Δ⁹-THC injections. Following 20 sessions of Δ⁹-THC injections, return to vehicle injections resulted in a return of attack responding to the pre-drug levels and had little or no effect on key-pecking since tolerance had already developed to this suppressant effect. Subject P49 showed a dramatic increase in attack responding during the first few sessions of vehicle injections following the Δ⁹-THC injections. A second treatment with 0.5 mg/kg of Δ⁹-THC again resulted in a suppression of key-pecking which returned to vehicle control levels within a few sessions. Again attack responding showed no tolerance to the suppressant effects of Δ⁹-THC over 40 sessions. Following the 40 sessions of Δ⁹-THC, a return to vehicle injections resulted in a return of attack responding to a slightly lower rate than during the previous vehicle injections.

Figure 2 shows the effects of vehicle and 1 mg/kg injections of Δ⁹-THC on attack responses and key-pecking for subjects P50 and P51. One mg/kg of Δ⁹-THC produced a

greater decrease in key-pecking, reducing all responding to zero with subject P51. During the first 20 sessions of Δ^9-THC 1 mg/kg injections, subject P50 showed little or no tolerance to suppressant effects on key-pecking or attack responding. Key-pecking was occurring at a very low rate; attack response not at all. A return to the vehicle injections resulted in a return of key-pecking to the pre-drug or vehicle control levels and a marked increase in attack responding which returned to pre-treatment levels after the first few sessions. A return to 1 mg/kg Δ^9-THC injections with subject P50 for the next 40 sessions again resulted in total suppression of attack responding for the entire 40 sessions. Key-pecking showed little or no tolerance, with Δ^9-THC producing less suppression than during the initial exposure. A final return to the vehicle injections resulted in an increase of attack responding to near vehicle control levels and also a return of key-pecking.

Subject P51 showed tolerance to the suppressant effects of Δ^9-THC injections over sessions. By the end of the 20th session following 1 mg/kg of Δ^9-THC injections, the rate of key-pecking had almost returned to vehicle control rates. During the second exposure of Δ^9-THC, there was an initial suppression followed by a large increase in key-pecking which returned to vehicle control rates in the later part of the 40 drug treatment sessions. Attack responding for subject P51 differed from all other subjects in that some attack responding did occur, although the rate was very low, during the first and also the second longer 40 session drug treatment. The attack responses were very minimal, and a return to vehicle injections following the first and second drug treatments showed a substantial increase in attack responding which usually fell to vehicle controls levels.

DISCUSSION

Results of the present experiment indicate that the chronic administration of Δ^9-THC to pigeons resulted in a marked decrease in aggressive behavior. No tolerance developed to this suppressing effect of Δ^9-THC on the rate of attack responding over as many as 40 sessions. This is similar to the lack of tolerance to the suppressant effect of Δ^9-THC on aggression in mice after 30 daily injections [27,28]. These results are in direct contrast with the increase in intraspecies aggression reported in rats following the chronic administration of cannabis [4] and Δ^9-THC [5]. An important difference between these studies and the present experiment was the route of administration. The rats were injected interperitoneally (IP), a route of administration which results in poor absorption and distribution to other tissues with most of the drug remaining in the abdominal cavity [16]. In addition, chronic IP injections of Δ^9-THC produced a diffuse chemical peritonitis in rats [18]. The observed increase in aggressive behavior following chronic injections of Δ^9-THC in rats may have been due to the irritation resulting from peritonitis, since pain is known to be a reliable elicitor of aggression. An observation that adds support to this interpretation is that following IP cannabis injections, tactile stimulation of the peritoneal area elicited vocalizations in rats, a response commonly elicited by painful stimulation [15]. Thus, the reported increase in aggressive behavior following chronic Δ^9-THC administration may be the result of chemical irritation produced by the drug. The increase in intraspecies aggression in rats following chronic Δ^9-THC injections is dependent upon concurrent food deprivation [4,5], which by reducing body fat could further inhibit IP distribution and increase the likelihood of peritonitis. In contrast, chronic injections of Δ^9-THC have been found to induce predatory aggression in non food deprived rats [22,30], and examinations have indicated no evidence of chemical peritonitis [22]. Ultimately, the role of chemical peritonitis in the increased intraspecies aggression in the rat following chronic IP Δ^9-THC administration is an empirical question which can only be answered by utilizing different routes for the chronic administration of Δ^9-THC.

The observation that tolerance developed to Δ^9-THC suppressant effect on the rate of key-pecking but not attack responding is another example of behavioral tolerance [23,27]. Tolerance to the suppressant effect of Δ^9-THC on key-pecking in pigeons has been reported [19]. As in previous research, tolerance to the response suppressant effects of Δ^9-THC or marijuana extracts has resulted in an increase in probability of food reinforcement [2,13].

The suppressant effect of Δ^9-THC on schedule-induced aggressive behavior could represent an effect on schedule-induced or adjunctive behaviors as a class of behaviors rather than a specific effect on aggression [11]. The results of the present experiment are related to intraspecies aggression induced by a schedule of food reinforcement. Comparisons with the effects of chronic Δ^9-THC administration on predatory aggression or spontaneous and shock-elicited aggression in rats is confounded by different types of aggressive behavior studied and the environmental manipulations employed to induce the aggression [1].

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