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BRIEF REPORT

Δ^9-Tetrahydrocannabinol and Aggressive Behavior in Rats[1]

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Fighting by pairs of albino rats, in a situation without painful shock, was measured by frequency or duration of dominant behaviors (biting attacks, threat postures, allogrooming, autogrooming), defensive-submissive behaviors (defensive-upright, submissive-supine and immobile-crouching postures), and mutual upright postures. Administration of Δ^9-tetrahydrocannabinol (1, 2, or 4 mg/kg, intraperitoneally) to the subordinate rat impaired the defensive-submissive behaviors, while the non-drugged dominant rat's biting attacks became more frequent and injurious. Administration of the drug to the dominant rat greatly reduced attacks and threats toward the non-drugged subordinate rat, and the dominance was weakened but not reversed.

Marihuana extracts or Δ^9-tetrahydrocannabinol (THC)[2] increase aggression in rodents according to some investigators (Carlini and Kramer, 1965; Carlini and Masur, 1969; Masur and Märtz, 1971; Masur, Karniol and Palermo Neto, 1972; Carder and Olson, 1972), decrease it according to others (Carder and Olson, 1972; Kilbey, Fritchie, McLendon, and Johnson, 1972; Santos, Sampaio, Fernandes, and Carlini, 1966), and have no effect according to others (Manning and Elsmore, 1972). Variations in the test situation and in

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[2]An alternative nomenclature for the same compound is Δ^1 tetrahydrocannabinol, using the monoterpene numbering as recommended by R. Mechoulam (1970) instead of the formal numbering.

the measures of aggressive behavior may account for some of these discrepant reports. During fighting episodes between rats, one animal typically establishes dominance by displaying characteristic sequences of offensive postures and movements, whereas the other animal exhibits a pattern of defensive and submissive behaviors (Barnett, 1958; Grant and Mackintosh, 1963). The present paper reports on differential effects of THC on several components of behavior by dominant and subordinate rats in a test situation which reliably generates aggressive behavior.

The subjects were 45 male, albino, adult Sprague-Dawley rats, maintained at 85% of their free-feeding weight, in individual cages. The experiments were conducted at the end of the light period of a daily cycle of 12 hr light, 12 hr dark in an apparatus similar to that described earlier (Miczek and Grossman, 1972). Initially, each rat was trained during a period of 4-6 weeks to run from a Plexiglas chamber (30 X 30 X 28 cm) through a narrow runway to a second identical chamber, each run being reinforced by a food pellet. Ten runs were scheduled each day.

Aggressive encounters were initiated by placing one rat into each of the two chambers at opposite ends of the runway. Sliding doors separating the chambers from the runway were raised simultaneously and the two rats met at the center of the runway. Eventually, one rat forced the other to retreat into the chamber from which it had started. Both rats were confined in the chamber without food pellets during the following 15 min while an experienced observer, behind one-way mirrors in an adjacent room, recorded on a 10-pen event recorder the time of onset and the duration of several components of fighting behavior, as described by Grant and Mackintosh (1963). Checks of the observer's reliability were performed by routinely reviewing selected nondrug fights on videotape.

The dosage conditions were THC (1, 2, or 4 mg/kg) and the control fluid in a volume of 1 ml/kg, injected intraperitoneally, 30 min prior to the start of the test. The THC was injected in a suspension of propylene glycol (5%, 10%, and 20% respectively for THC doses of 1, 2 and 4 mg/kg) in 1% polysorbate-Tween 80-isotonic saline. The control fluid was the vehicle for the highest dose. A minimum of 5 days intervened between each fighting test. Ten food-reinforced training runs were conducted in the absence of an opposing rat on each of those intervening days.

In the first series of experiments, 10 rats which clearly and consistently displayed offensive-dominant behaviors, including attacks and threats in 3 consecutive encounters, were selected as stimulus animals; they were never injected and were tested repeatedly, usually with a different subordinate opponent each time. A group of 11 experienced subordinate animals were given a series of drug tests alternating with control tests; eight of them were tested with all three THC doses in a Latin Square sequence, the others with one or two THC doses.

A second experiment, using different rats, examined the effects of THC when administered to the dominant animals. A total of 17 subordinate rats were used as nondrugged stimulus animals. Nine rats which consistently engaged in the offensive-dominant behavior pattern during at least 3 consecutive encounters were given a single test with 1 of the 3 doses of THC (1 mg/kg for 4 rats; 2 mg/kg for 3 rats; 4 mg/kg for 2 rats), preceded by a test under the control (vehicle) condition.

Statistical significance of the differences between the drug and vehicle condition was assessed by the Wilcoxon T for matched rank-order scores (Siegel, 1956), using the conservative 2-tail criterion. The three drug doses for the dominant animals were combined because of the small number of these animals tested with any 1 dose.

Figure 1 shows the differential effects of THC injected either in the dominant or the subordinate rat on several components of fighting behavior. Administration of THC to the subordinate rat (dashed line) decreased the time

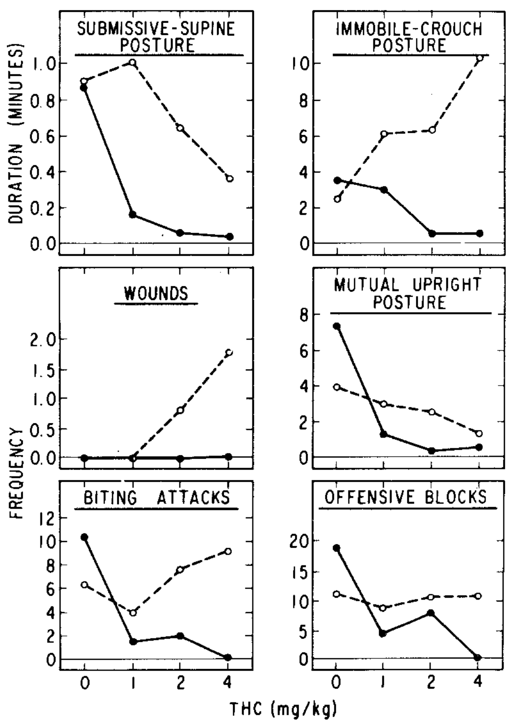

Fig. 1. Effects of THC (1, 2, 4 mg/kg) injected in the subordinate rat (0---0) and in the dominant rat (•——•) on duration of submissive and immobile postures and number of wounds (in the submissive rat), duration of mutual upright posture (by both rats), and frequency of biting attacks and offensive blocks (by the dominant rat).

the submissive rat displayed the submissive-supine posture ($P < .05$ at 4 mg/kg), but prolonged the immobile-crouch posture ($P < .01$ at all 3 doses).

A conspicuous effect of THC when given to the subordinate rat was the high incidence of severe injuries it suffered, whereas in a nondrug fighting episode the dominant animal rarely inflicts wounds in the opponent. Wounds were suffered by 6 of 8 subordinate rats under the 4 mg/kg dose, whereas none were suffered by the same rats in the control tests ($P < .05$). More important, severity of the lacerations was drastically increased at the higher dose levels (2, 4 mg/kg). THC injected in the subordinate rat decreased the frequency of mutual upright postures displayed by both rats simultaneously ($P < .05$ at 4 mg/kg).

The dashed lines in the two bottom panels of Fig. 1 show measures of behaviors by the nondrugged dominant stimulus animal. The frequency of biting attacks was significantly increased when the subordinate animal was injected with 4 mg/kg of THC ($P < .05$). Frequency of offensive blocks by the dominant animal was not significantly altered by the drug condition of the subordinate animal.

Neck grooming (allogrooming) and self-grooming (autogrooming) are responses which characterize the dominant animal, but are rare in the subordinate animal (Spigel, Trivett and Fraser, 1972). These responses continued to be almost absent in subordinate animals after administration of THC (dashed lines, left-hand panels, Fig. 2). However, the dominant animal displayed aggressive neck grooming (allogrooming) for longer periods of time, when the subordinate animals was injected with THC ($P < .05$ at 2 and 4 mg/kg), shown by the dashed line in the bottom right hand panel of Fig. 2.

In the second experiment, THC was administered to the dominant animal only and the results are depicted by solid lines in Figs. 1 and 2. The THC-treated dominant animal attacked less frequently ($P < .01$) and displayed significantly fewer threats ("offensive blocks"; $P < .05$), shown in the bottom panels of Fig. 1. These changes in the attack and threat behaviors of the dominant animal contrast clearly with those seen after administration of THC to the subordinate rat. Due to the drug condition of the dominant animal, both opponents engaged significantly less frequently in the mutual upright posture ($P < .05$).

Since the nondrugged subordinate opponent never attacked, aggressive behavior was greatly reduced and, consequently, no injuries were inflicted. The subordinate animal spent shorter time in the characteristic defensive-submissive behaviors, including submissive-supine ($P < .01$), and immobile-crouch postures, contrasting again with the changes in these submissive behaviors when the subordinate animals is injected with THC.

The diminished dominance of the THC-treated animal was further evidenced by a marked increase of both autogrooming ($P < .01$) and allogrooming ($P < .05$) by the nondrugged subordinate animal (solid lines in the left hand panels of Fig. 2). However, both kinds of grooming behavior remained unaffected in the drugged, dominant rat (right hand panels of Fig. 2). Thus, when the dominant animal is injected with THC, the difference in grooming behaviors between dominant and subordinate animals is greatly reduced or abolished; (the solid lines in the left compared with the right side of Fig. 2).

These findings indicate both specific and sensitive effects of THC on fighting behavior. Other drugs, including amphetamine and chlordiazepoxide, show different patterns of effects on aggressive and defensive-submissive behavior (Miczek, unpublished data). The same doses of THC used in the present study (1, 2, 4 mg/kg) had no significant effect on running time measured in the same strain of rats with the food-reinforced training procedure in the same apparatus (Miczek and Barry, unpublished data). Other test procedures, with a different strain of rats (Wistar) but similar preparation and administration of the drug, did not reliably alter locomotor activity at doses of 1 and 4 mg/kg (Barry and Kubena, 1969) nor continuous shock-avoidance performance at doses of 1, 2, 4 and 8 mg/kg (Barry & Kubena, 1970).

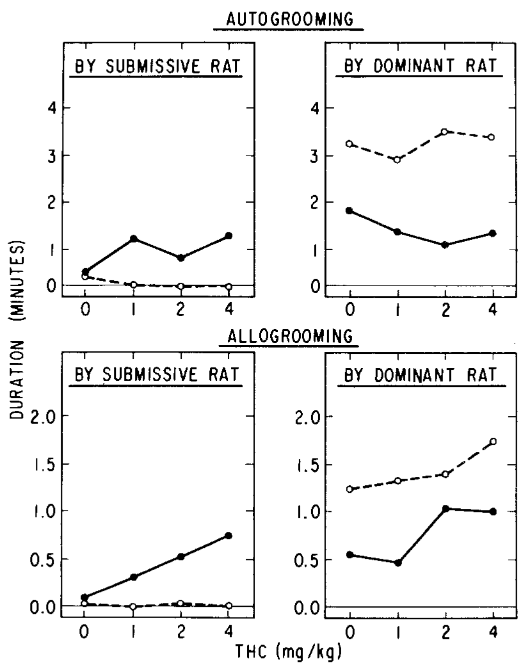

Fig. 2. Effects of THC (1, 2, 4 mg/kg) injected in the subordinate rat (0– – –0) and in the dominant rat (•———•) on duration of autogrooming (self-grooming) and of allogrooming (neck grooming), both shown separately for the behavior by the submissive and dominant rat.

The present results may help to resolve discrepancies in prior reports on effects of THC on aggressive behavior. THC in subordinate rats impaired several crucial components of the defensive behavior, thereby increasing number of attacks and wounds suffered, whereas THC in dominant rats mainly decreased attack and threat behavior. Some experimenters, defining as dominant the animal which forces its opponent to retreat in the narrow runway, have reported that THC induces "winning" behavior (Masur and Märtz, 1971; Masur, Karniol and Palermo Neto, 1972). However, the THC-treated rat tends to "freeze" in the runway until its opponent eventually retreats. The drugged rat usually advances and thus may be classified as the "winner," but the "winner" in the runway is not consistently dominant in the subsequent fighting test. The validity of drug-induced "winning" in the runway test as a measure of dominance has also been questioned by van Riezen and Rijk (1972).

Some prior experiments on aggressive behavior have not attempted to differentiate between the dominant and subordinate rat. The mutual upright boxing-like posture has been used most frequently as the measure of aggression. This type of behavior is usually observed in reaction to painful electric foot shock and probably represents a form of defensive rather than attack behavior (Reynierse, 1971).

The present multi-response analysis of aggressive behavior reveals important differential effects of THC on various components of the stereotypic fighting behavior. These effects clearly depend on whether the drug is administered to the subordinate or dominant rat.

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