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Antianxiety effect of cannabidiol in the elevated plus-maze

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Abstract. In order to assess the presence of anxiolytic properties in cannabidiol (CBD) the drug was tested in an elevated plus-maze model of anxiety, in rats. Doses of 2.5, 5.0 and 10.0 mg/kg significantly increased the entry ratio (open/total number of entries), an anxiolytic-like effect. CBD at a dose of 20.0 mg/kg was no longer effective. None of the doses of CBD used changed total number of entries, a measure of total exploratory activity. Diazepam (2.0 mg/kg) also caused an anxiolytic-like effect in this model. These results indicate that CBD causes a selective anxiolytic effect in the elevated plus-maze, within a limited range of doses.

Key words: Cannabidiol – Anxiety – Elevated plus-maze

Cannabidiol (CBD) is a major component of *canabis sativa*, making up to 40% of cannabis extracts (Grlie 1962). Unlike Δ^9-tetrahydrocannabinol (Δ^9-THC), it is devoid of psychotomimetic activity. In fact, reported results show that in addition to its anticonvulsivant properties (Cunha et al. 1980), CBD antagonizes the decrease in body temperature, the increase in heart rate and respiration and the decrease in response rate induced by Δ^9-THC in rats, pigeons and monkeys (Dewey 1986). In man also, Zuardi et al. (1982) showed that CBD attenuates the subjective effects induced by high doses of Δ^9-THC, including enhanced anxiety. Therefore, CBD may have anxiolytic properties. However, the results reported so far in laboratory animals are contradictory (Silveira Filho and Tufyk 1981; Zuardi and Karniol 1983).

The recently developed elevated plus-maze test seems to be a reliable animal model of anxiety, since it detects both anxiolytic and anxiogenic-like drug effects, correlating with subjective reports in humans (Pellow et al. 1985; Pellow and File 1986). Therefore, in the present study we used the elevated plus-maze to access the anxiolytic action of CBD.

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Material and methods

Animals. Male Wistar rats (200–240 g) were housed in groups of six to ten with free access to food and water on a 12 h light cycle (7:00–19:00 hours) at 24 ± 1° C. Each animal was used only once.

Apparatus. An elevated plus-maze, as described by Pellow and File (1986), was used. Briefly, it consists of two opposed open arms, 50 × 10 cm, and two enclosed arms, 50 × 10 × 40 cm, made of wood, elevated 50 cm above the floor. The central square formed by the arms was open. Before exposure to the maze the rats were placed in a wooden arena (60 × 60 × 35 cm) for 5 min. The experiment took place in a sound isolated room illuminated by a dim light. The observer sat in the same room.

Drugs. Cannabidiol was supplied by Dr. R. Mechoulam from Hebrew University, Jerusalem. It was dissolved in a solution of 10% proplyene glycol – 1% Tween 80 – saline, as proposed by Sofia et al. (1971) for Δ^9-THC. A suspension of diazepam was prepared by adding a drop of Tween 80 in saline. All solutions, including vehicles, were injected in a volume of 1 ml/kg.

Procedure. The rats were injected IP and placed in an individual cage. CBD was injected 60 min, and diazepam 20 min, before the test. Each animal was then placed in the wooden arena for 5 min and, immediately thereafter, placed at the centre of the maze, facing a closed arm. For the 10-min test period, the number of entries into each arm was recorded and the entry ratio (open/total arm entries) was calculated.

Statistical analysis. The data of CBD were analyzed by a completely randomized analysis of variance (ANOVA), followed by the multiple range test of Duncan. The results of diazepam were analyzed by a t test. The significance level was set at $P < 0.05$.

Results

As shown in Fig. 1, CBD caused a significant increase in the entry ratio ($F4, 45 = 5.137$, $P = 0.002$), as compared to vehicle, at doses of 2.5, 5.0 and 10.0 mg/kg. However, the dose-effect curve had an inverted U shape, so that 20.0 mg/kg CBD was no longer effective. No drug effect occurred on total number of entries ($F4, 45 = 0.238$, NS).

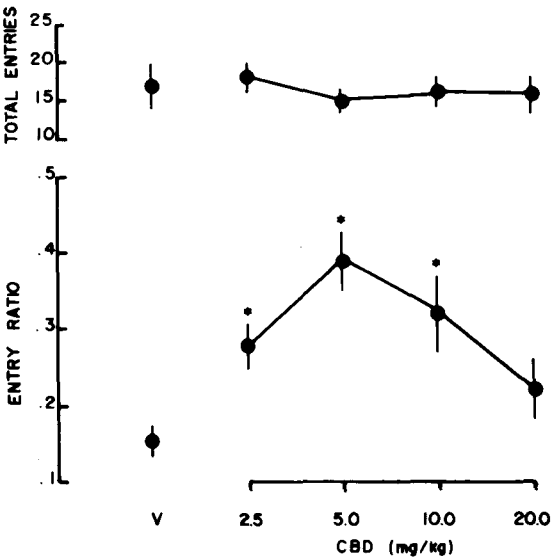

Fig. 1. Effect of cannabidiol (*CBD*) and vehicle (*V*) on entry ratio (open/total number of entries) and total entries. Points in figure represent means ± SE of ten animals. The asterisks indicate a significant difference from vehicle (Duncan test, $P<0.05$)

The dose of 2.0 mg/kg diazepam used significantly increased ($t=3.423$, $df=18$, $P<0.005$) the entry ratio (0.52 ± 0.07) as compared to vehicle (0.26 ± 0.02), without affecting the total number of entries ($t=0.33$, $df=18$, NS).

Discussion

The increases in the ratio of open arm entries per total entries in the elevated plus-maze caused by the three lower doses of CBD used (2.5, 5 and 10 mg/kg) indicate that this drug has anxiolytic properties. Moreover, this anxiolytic effect of CBD does not seem to be associated with sedation or impaired locomotion, since the number of entries in either closed or open arms of the maze was not significantly decreased.

However, the dose-effect curve obtained shows that the range of anxiolytic doses of CBD is narrow. Thus, the maximum effect was caused by 5 mg/kg, and 20 mg/kg no longer increased the entry ratio. The last dose also did not significantly decrease the total number of entries. Therefore, the inverted U shape of the dose-effect curve of CBD, shown by the present results, is unlikely to be due to the interference of sedative effects that might be caused by the highest doses. Also, the maximum effect of CBD (entry ratio $=0.39\pm0.04$) was smaller than that of 2 mg/kg of the prototype anxiolytic diazepam (entry ratio $=0.52\pm0.07$).

Such a limited range of anxiolytic doses of CBD may help to explain the contradictory results of the two studies published so far which have assayed the cannabinoid in animal models of anxiety. Thus, in the study by Zuardi and Karniol (1983) where positive results were obtained, as indicated by a drug-induced decrease of suppression of lever-pressing behaviour maintained by water presentation caused by a conditioned stimulus warning of an inevitable electric foot shock, a dose of CBD was used (10 mg/kg) which also produced an anxiolytic effect in the present experiment. In contrast, Silveira Filho and Tufik (1981) reported that doses above 100 mg/kg CBD were ineffective in releasing punished responding in a Geller-Seifter type of conflict test as well as in increasing eating suppressed by neophobia. Accordingly, in the present results a dose of only 20 mg/kg CBD was no longer anxiolytic.

In conclusion, the present as well as previously reported results with animal models of anxiety indicate that CBD causes anxiolytic effects of moderate intensity and within a limited range of doses.

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