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# Effects of cannabidiol in animal models predictive of antipsychotic activity

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**Abstract.** The effects of cannabidiol (CBD) were compared to those produced by haloperidol in rats submitted to experimental models predictive of antipsychotic activity. Several doses of CBD (15–480 mg/kg) and haloperidol (0.062–1.0 mg/kg) were tested in each model. First, CBD increased the effective doses 50% (or) $ED_{50}$ of apomorphine for induction of the sniffing and biting stereotyped behaviors. In addition, both CBD and haloperidol reduced the occurrence of stereotyped biting induced by apomorphine (6.4 mg/kg), increased plasma prolactin levels and produced palpebral ptosis, as compared to control solutions. However, CBD did not induce catalepsy even at the highest doses, in contrast to haloperidol. Such a pharmacological profile is compatible with that of an "atypical" antipsychotic agent, though the mechanism of action is uncertain and may not be identical to that of the dopamine antagonists.

**Key words:** Cannabidiol – Cannabinoids – Antipsychotic drugs – Antipsychotic screening – Stereotyped behavior – Prolactin – Catalepsy – Palpebral ptosis

In a study of the interaction between a high $\Delta^9$–THC dose (0.5 mg/kg, PO) and cannabidiol (CBD) carried out in normal volunteers, we observed that the combination of the two cannabinoids significantly attenuated the anxiety and psychotomimetic effects induced by $\Delta^9$–THC (Zuardi et al. 1982). Experimental evidence suggests that the antagonistic effect of CBD did not result from pharmacokinetic interaction between the two cannabinoids (Agurel et al. 1981; Zuardi et al. 1982). Therefore, CBD may have anxiolytic and/or antipsychotic effects.

The hypothesis of a possible antipsychotic effect of CBD has also been suggested by Rottanburg et al. (1982) to justify another type of observation. These investigators, in a study carried out on patients at the time of admission to a psychiatric hospital in South Africa, detected a much higher frequency of acute psychotic episodes associated with the use of *Cannabis sativa* than observed in other countries and attributed this fact to the high potency of $\Delta^9$–THC and to the absence of CBD in the plant variety occurring in that region. On this basis, they suggested that the presence of CBD in *Cannabis sativa* samples consumed in other countries may protect users against the occurrence of acute psychotic episodes.

In the present study, we investigated the possible antipsychotic activity of CBD by studying the effect of this cannabinoid on animal models frequently used in research on new compounds with potential antipsychotic properties. We used apomorphine-induced stereotypy (Janssen et al. 1977), prolactin secretion (Clemens et al. 1974), catalepsy (Janssen et al. 1965), and palpebral ptosis (Janssen and Van Bever 1975). The effects of CBD on these four models were compared with those produced by haloperidol, which is considered to be a representative drug of the group of "typical" antipsychotics.

## Materials and methods

### *Animals*

Male Wistar rats weighing about 350 g and not submitted to any previous treatment or experimental manipulation were used. The animals were kept under the following conditions for at least 1 week prior to the experiment: three to a cage, free access to water and food, a 12-h light/12-h dark cycle, temperature between 22 and 25° C, and daily handling for weighing and cage cleaning.

### *Drugs*

Powdered CBD, kindly supplied by Dr. R. Mecholam (Hebrew University, Jerusalem, Israel), was dissolved in saline with the aid of Tween-80, at concentrations proportional to the CBD dose, ranging from 1.5% (CBD ≤ 60 mg/kg) to 12% (CBD = 480 mg/kg). The same amount of Tween-80 dissolved in saline was used as control.

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Haloperidol (5 mg/ml ampoules, Janssen Pharmaceutica) was diluted with saline, and the vehicle in the ampoules was used as control.

Apomorphine hydrochloride (Merck) was dissolved in distilled water.

All drugs were administered intraperitoneally in a volume of 2 ml/kg body weight.

### *Procedure*

*Apomorphine-induced stereotypy.* We studied the effect of CBD on the effective dose 50% ($ED_{50}$) of apomorphine for producing stereotyped behaviors, using the following treatments: control solution, CBD (15, 30 and 60 mg/kg) and apomorphine (0.1, 0.4, 1.6, 6.4 and 25.6 mg/kg) in combination with either control solution or CBD at doses of 15, 30 and 60 mg/kg. Each treatment was administered to groups of six animals. The experimental sessions were always held in the afternoon using 24 animals (1 per treatment). Treatments were administered randomly at 1-min intervals to each animal. Immediately after being injected, the animals were placed in individual cages (16 × 30 × 18 cm), and 30 min after the first animal received the drug, a trained observer who was not aware of the treatments started to observe animal behavior. The animals were observed in the same sequence in which they had been injected for periods of 1 min at 30-min intervals, for a total of six observation periods per animal over a period of 3 h. The occurrence of the following behaviors was recorded during each period: sniffing (vertical oscillation of the head accompanied by movements of nostrils and vibrissae throughout the observation period) and biting (open mouth approaching the cage bars with teeth exposed). The number of animals exhibiting each stereotyped behavior during at least one observation period was computed for each treatment.

For comparison with haloperidol we used the results obtained with the 6.4 mg/kg dose of apomorphine (the dose that induced biting behavior in 83% of the animals) in combination with CBD (0, 15, 30 and 60 mg/kg). During an additional session we tested apomorphine (6.4 mg/kg) in combination with control solution and increasing doses of haloperidol (0.125, 0.25 and 0.5 mg/kg) on groups of six animals each.

*Prolactin secretion.* We tested the effects produced on prolactin secretion by haloperidol (0.062, 0.125, 0.25, and 0.5 mg/kg) and CBD (15, 30, 60, 120, and 240 mg/kg) and by their respective control solutions. The two drugs were tested during independent experimental sessions. Each treatment was administered to groups of ten animals each at random, though care was taken to avoid that the three animals in the same cage would receive equal treatments. The injections were made between 10:00 and 10:30 hours. One hour after drug administration, the rats were taken individually to an isolated room and decapitated with a guillotine. The time spent in removing and sacrificing the three animals from the same cage was less than 1 min in order to avoid the stress of manipulation (Krulich 1974). Blood was collected from the neck with a funnel into a heparinized tube and maintained on ice until centrifugation, which was performed immediately after all animals had been sacrificed. Plasma was stored at −20° C until the time for prolactin measurement. Plasma PRL levels were determined by double-antibody radioimmunoassay (Niswender et al. 1969) using material supplied by NIADDK. Absolute values are shown using RP3 (PRL) reference standards. The measurements were made in duplicate and all samples from each experimental session were measured in the same assay. Intrassay and interassay error were 4% and 12%, respectively. Assay sensitivity was 0.8 ng/tube.

*Catalepsy and palpebral ptosis.* In this experiment we tested the following treatments: CBD (60, 120, 240 and 480 mg/kg), haloperidol (0.125, 0.25, 0.5 and 1 mg/kg) and control solution (a mixture of the vehicles for the two drugs). Each treatment was administered to groups of eight or nine animals distributed at random among seven independent experimental sessions.

After receiving the drugs, the animals were placed in individual cages (30 × 16 × 16 cm) and were tested 1 h later. Testing time (2 h) was divided into six periods of 20 min each and one palpebral ptosis measurement plus one catalepsy measurement were made during each period. At the beginning of each period, one observer unaware of the treatments administered evaluated palpebral ptosis 1 min after a standardized sound stimulus. Palpebral ptosis was classified into four grades by the following criteria: 1 – fully open palpebral fissure, 2 – partial occlusion of < 50% of the palpebral fissure, 3 – partial occlusion of > 50% of the palpebral fissure, 4 – full occlusion of the palpebral fissure. After observation of palpebral ptosis, the animals were positioned with the forepaws resting on a horizontal bar (0.8 cm in diameter) 4.5 cm above the floor surface. We then recorded the time the animals kept their paws on the bar, with up to three attempts made to place the animals' paws on the bar within each 20-min period.

For each animal we calculated one value for palpebral ptosis and one for catalepsy. The highest score among six measurements was considered to be the degree of palpebral ptosis. The catalepsy index was the total time, in seconds, during which the animals stayed with their paws on the bar during the observation period.

*Statistical analysis.* The $ED_{50}$ doses and the 95% confidence limits for the stereotyped sniffing and biting behaviors induced by apomorphine plus control solution and by apomorphine in combination with the three CBD doses were calculated by the method of Weil (1952). We considered the $ED_{50}$ values for the groups that received CBD to differ significantly from those obtained for the control group when there was no overlapping between their 95% confidence limits and those of the control group. The effects of haloperidol (0.5 mg/kg) and CBD (60 mg/kg) on the stereotyped biting behavior induced by apomorphine (6.4 mg/kg) were compared with the effects of the control solutions by the Fisher test (Siegel 1956). The prolactin, catalepsy and palpebral ptosis data were submitted to Kruskal-Wallis analysis of variance. Comparison between the results obtained with each drug and their control groups were done by multiple comparison based on the Kruskal-Wallis rank sum test (Hollander and Wolfe 1973). The significance level was $P < 0.05$.

## Results

### *Apomorphine-induced stereotypy*

The control solution or CBD (15, 30 and 60 mg/kg) did not induce any stereotyped behavior during the entire period of observation.

Figure 1 shows the $ED_{50}$ values and their 95% confidence limits for apomorphine in combination with the control solution and with CBD (15, 30 and 60 mg/kg) in terms of induction of the sniffing and biting stereotyped behaviors. For the sniffing behavior (Fig. 1A), the $ED_{50}$ values of apomorphine plus CBD at the doses of 15, 30 and 60 mg/kg (1.3, 1.0 and 1.6, respectively) ranged around a higher value than the $ED_{50}$ for apomorphine plus the control solution (0.7). For the biting behavior (Fig. 1B), the addition of increasing CBD doses to apomorphine produced progressively higher $ED_{50}$ values (4.8, 8.4 and 12.8) than those for the control group (4.0). On the basis of the criterion used, the differences obtained in relation to the control group were significant after the highest CBD dose (60 mg/kg) both for sniffing and biting.

The results obtained for biting in the groups that received a combination of apomorphine (6.4 mg/kg,

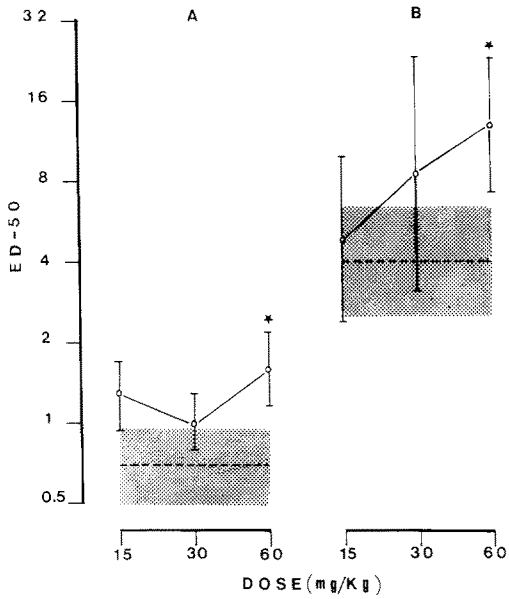


**Fig. 1A, B.** Effective doses 50% (–○–) and 95% confidence limits *(vertical bars)* of the combinations of apomorphine with CBD (15, 30 and 60 mg/kg) for the induction of the sniffing (**A**) and biting (**B**) stereotyped behaviors in rats between 30 and 180 min after drug ingestion. The effective 50% doses of apomorphine in combination with control solution are represented by the *broken lines* and the 95% confidence limits by the *shaded areas*. The *asterisk* (*) indicates a significant difference compared to the control

the $ED_{83}$ for biting behavior) with: CBD (15, 30 and 60 mg/kg), haloperidol (0.125, 0.25 and 0.5 mg/kg), and the respective control solutions are presented in Fig. 2A. With increasing doses of both haloperidol and CBD, the number of animals showing biting behavior was reduced, and this reduction was statistically significant compared to controls at the highest doses of haloperidol ($P<0.01$) and of CBD ($P<0.05$).

*Prolactin secretion*

Analysis of variance showed that plasma prolactin levels changed significantly with the various doses of CBD ($H=25.1$, $df=5$, $P<0.001$) and of haloperidol ($H=25.8$, $df=4$, $P<0.001$).

Figure 2B shows the mean plasma prolactin levels detected in animals injected with the various doses of haloperidol, CBD and the respective control solutions. Haloperidol induced a significant increase in plasma prolactin levels when compared with the control group at the doses of 0.125, 0.25 and 0.5 mg/kg, whereas CBD induced a significant increase in plasma prolactin levels only at the doses of 120 and 240 mg/kg.

*Catalepsy and palpebral ptosis*

Analysis of variance showed significant differences between experimental groups both in terms of catalepsy indices ($H=36.6$; $df=8$; $P<0.001$) and the degrees of palpebral ptosis ($H=31.2$; $df=8$; $P<0.001$).

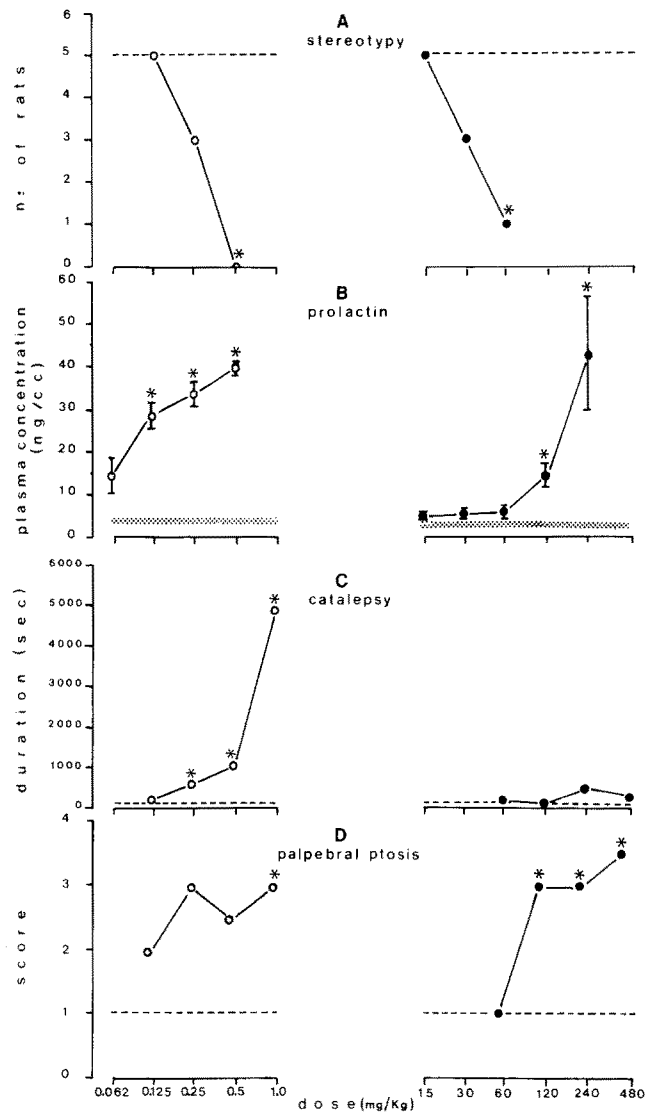


**Fig. 2A–D.** Profile of the effects of haloperidol (–○–), CBD (–●–) and control solution (- - -) in models predictive of antipsychotic activity applied to male Wistar rats. The *asterisk* (*) indicates statistically significant differences compared to the control. **A** Number of animals exhibiting biting stereotyped behavior 30–180 min after receiving 6.4 mg/kg apomorphine in combination with each treatment. **B** Plasma prolactin levels (means ± SEM) 60 min after treatment. **C** Median values of the catalepsy indices recorded 60–180 min after each treatment. **D** Median value of the degree of palpebral ptosis observed 60–180 min after each treatment

Figure 2C shows the median times, in seconds, during which the animals kept their paws on the bar (catalepsy index) after receiving the control solution and the various doses of CBD and haloperidol. Catalepsy time increased progressively with increasing haloperidol doses, with a significant difference from the control group at the doses of 0.25, 0.5 and 1 mg/kg. CBD did not increase the catalepsy index in a significant manner at any of the doses used.

The median values of degree of ptosis for the control group and for the groups that received the various doses of CBD and haloperidol are shown in Fig. 2D. There

were significant increases in relation to the control group at the doses of 120, 240 and 480 mg/kg CBD and 1.0 mg/kg haloperidol.

## Discussion

As expected, the animal models predictive of antipsychotic activity used in the present study proved to be sensitive to the effects of a "typical" antipsychotic drug, i.e., haloperidol.

CBD attenuated the stereotypy induced by apomorphine, as demonstrated by the increase in apomorphine $ED_{50}$ values for the induction of sniffing (Fig. 1A) and biting behaviors (Fig. 1B), and by the significant decrease in the number of animals that exhibited biting behavior after the 6.4 mg/kg dose of apomorphine (Fig. 2A). This effect can be observed with most of the antipsychotic drugs available (Janssen et al. 1977).

Another effect shared by antipsychotic drugs is the induction of prolactin secretion (Clemens et al. 1974), which was also observed in the present study with haloperidol and CBD (Fig. 2B). However, it can be seen that the variability of the response obtained with CBD increased with increasing doses, contrary to what occurred with the groups that received haloperidol. The animals receiving the highest CBD doses (120 and 240 mg/kg) tended to show two types of response, i.e., either low or very high prolactin levels, resulting in high standard errors of the means. The responses to haloperidol were close to normal distribution. This observation suggests that the effects of CBD and haloperidol on prolactin secretion may involve different mechanisms.

The palpebral ptosis induced by both haloperidol and CBD is also compatible with the effects produced by antipsychotic drugs (Janssen and Van Bever 1975), though it reflects a sedative activity that is not specific of these drugs. This result agrees with previous reports of the sedative effects of CBD (Monti 1977; Pickens 1981; Colassanti et al. 1984).

The results obtained with CBD in the catalepsy model differed from those expected for a "typical" antipsychotic drug (Janssen et al. 1965). Contrary to haloperidol, CBD did not induce a significant increase in catalepsy index (Fig. 2C). This absence of catalepsy induction by CBD in rats confirms data reported by Fernandes et al. (1974). Reports of catalepsy induction with CBD in mice are contradictory, with both negative results (Jones and Pertwee 1972; Fairbairn and Pickens 1979) and one positive result (Karniol and Carlini 1973).

Taken as a whole, the present results show that the CBD profile was not exactly the same as observed with haloperidol, suggesting that CBD does not belong to the group of "typical" antipsychotic drugs. The effects of CBD may be compatible with those of an "atypical" antipsychotic drug such as sulpiride, clozapine or thioridazine (Jenner and Marsden 1983). These drugs stimulate prolactin secretion (Meltzer et al. 1979); reduce stereotypy induced by apomorphine (Zivkovik et al. 1980; Robertson and MacDonald 1986), though they have also been reported to exert weak antistereotypic abilities (Costall and Naylor 1975; Puech et al. 1976; Jenner et al. 1978); but do not induce significant catalepsy (Costall and Naylor 1975; Jenner et al. 1978; Zivkovic et al. 1980). In addition, the potency of CBD in increasing prolactin levels was very low, as is also the case for clozapine (Meltzer et al. 1979). Indeed, the minimum effective dose of CBD for prolactin secretion was 3- to 24-fold higher than that needed to produce other effects in rats such as decreased locomotor (Karniol and Carlini 1973), anticonvulsive (Izquierdo et al. 1973) and hypnotic (Monti 1977) activity, and increased corticosterone levels (Zuardi et al. 1984).

The mechanism of action of CBD, which is responsible for the effects observed in the present study, is not clear. Evidence about the cellular effects of cannabinoids reviewed by Martin (1986) suggests that CBD may not act as a typical dopaminergic antagonist. Other actions of CBD may explain the present results, such as blockade of serotonin reuptake (Johnson 1976) or increased GABA activity (Revuelta et al. 1979; Benedito and Leite 1981). Drugs that increase serotonergic activity may attenuate the stereotypy induced by apomorphine (Carter and Pycock 1981; Costall et al. 1981) and stimulate prolactin secretion (Weiner and Ganong 1978). Drugs that increase GABAergic activity have less consistent effects on stereotypy (Scatton and Bartholini 1982; Dougherty and Ellinwodd Jr. 1983) and on prolactin secretion (Casanueva et al. 1981). The effects of CBD may also be due to its interaction with specific cannabinoid receptors (Nye et al. 1985; Herkenham et al. 1990).

In conclusion, the present results reveal a profile of CBD effects compatible with that of "atypical" antipsychotic drugs, although its mechanism of action is unknown and may involve neurotransmitter systems other than the dopaminergic one.

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