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Hypnoticlike Effects of Cannabidiol in the Rat

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Abstract. The actions of cannabidiol (CBD), one of the cannabis constituents, were assessed on the sleep-wakefulness cycle of male Wistar rats.

During acute experiments, single doses of 20 mg/kg CBD decreased slow-wave sleep (SWS) latency. After 40 mg/kg SWS time was significantly increased while wakefulness was decreased. REM sleep was not significantly modified. Following the once-daily injections of 40 mg/kg CBD for a period of 15 days, tolerance developed to all the above-mentioned effects.

Key words: Cannabidiol – Cannabis sativa – Slow-wave sleep – Wakefulness

It is known that acute administration of a cannabis extract disrupts the sleep-wakefulness cycle of the rat (Moreton and Davis, 1973; Monti and Carlini, 1975). The changes are characterized mainly by a decrease of slow-wave (SWS) and REM sleep (REM), while wakefulness (W) is increased.

It was initially thought that delta-9-tetrahydrocannabinol (delta-9-THC) was the only active principle of cannabis sativa and that pharmacological actions showing after the injection of an extract were related to the presence of this cannabinoid. There is, however, recent evidence showing that cannabidiol (CBD) directly antagonizes the excitatory effects and indirectly potentiates the depressant effects of delta-9-THC (Karniol and Carlini, 1973; Takahashi and Karniol, 1975). These findings suggest that delta-9-THC and CBD play opposite roles in the actions of cannabis on the sleep-wakefulness cycle, the latter acting as a CNS depressant.

In order to test this hypothesis, we studied the actions of acute and chronic CBD administration on some variables of the sleep-awake cycle of the rat.

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MATERIALS AND METHODS

Experiments were performed on 8 male Wistar rats weighing 250–300 g. They were housed individually and maintained under controlled environmental conditions with a cycle of 12 h light – 12 h darkness. Electrodes were chronically implanted to record the EEG in the frontal and occipital cortices and the EMG of the posterior neck muscles. All the electrodes were wired to a small connector fixed to the skull with dental acrylic. Ten days after implantation the animals were habituated to the recording environment by being placed in a dimly lit sound-proof cage and sleep patterns were recorded. When the animals were fully adapted to their new environment as judged by the consistency of their sleep-awake cycles, experiments were started.

The polygraphic recordings were utilized for recognizing and quantifying W, SWS, and REM as described by Michel et al. (1961) and Lidbrink (1974). Control sessions were also compared to drug sessions for SWS latency (time between beginning the recording and the appearance of high voltage slow waves), REM latency (time between beginning the recording to REM onset), and number of REM periods.

Two sets of experiments were carried out: (1) acute experiments in which single doses of 20 and 40 mg/kg cannabidiol were given; (2) chronic experiments in which once-daily injections of 40 mg/kg cannabidiol were given for a period of 15 days.

The drug was administered as a fine suspension by thoroughly mixing it in a 0.6% solution of Tween-80 in saline. During control experiments the animals received the corresponding volumes of a solution of saline plus Tween-80. All injections were i.p. EEG and EMG recordings were taken for 5 h during the 12-h light phase beginning 20 min after the injections. At least 1 week was allowed to elapse between experiments. Two days before the recording sessions, the chronically treated animals were readapted to the recording procedure.

Differences in mean values of the several variables were tested by analysis of variance for dependent samples, followed by multiple comparisons using the Duncan's new multiple-range test (Steel and Torrie, 1960).

RESULTS

A few minutes after the acute administration of 20–40 mg/kg CBD, the animals showed behavioral quiescence. Soon after they went to sleep and while asleep they always exhibited normal postures. During SWS the cortical EEG was characterized by the

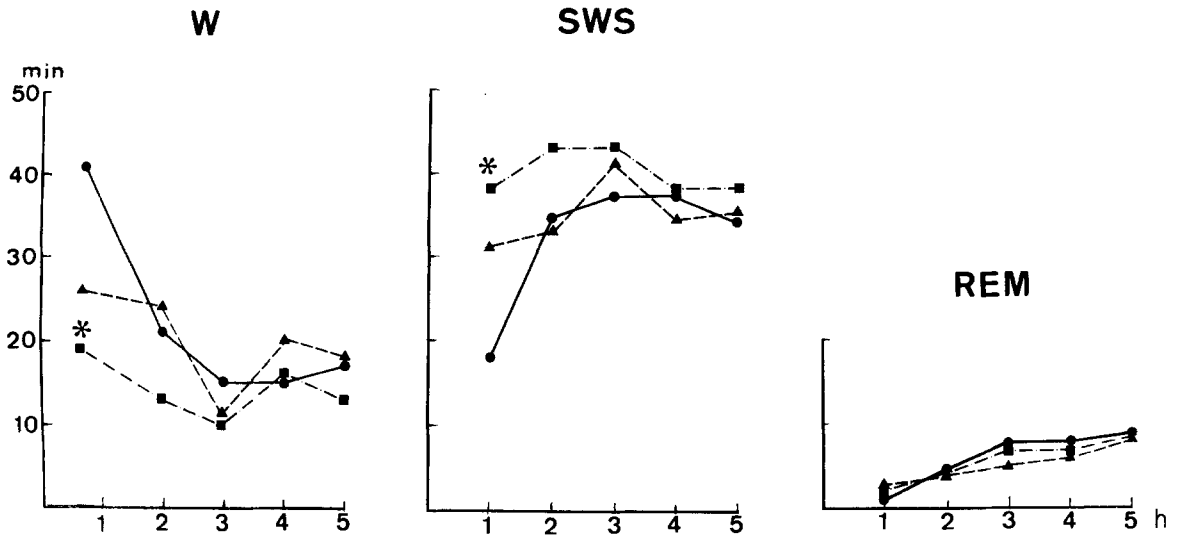

Fig. 1. Amounts of waking, slow wave sleep, and REM sleep during the 5-h sessions after acute cannabidiol administration. *Abscissae:* time in h. *Ordinates:* time in min. ●——● Control solution (Tween 80-saline); ▲——▲ CBD 20 mg/kg; ■·-·-■ CBD 40 mg/kg. * Significantly different from control: $P < 0.01$ (Duncan's new multiple-range test)

Table 1. Effects of acutely administered cannabidiol on some variables of the sleep-wakefulness cycle during 5-h sessions

Treatment	W (min ± SEM)	SWS (min ± SEM)	REM (min ± SEM)	SWS latency (min ± SEM)	REM latency (min ± SEM)	No. of REMP (± SEM)
Control	109 ± 11	161 ± 9	30 ± 3	19 ± 5	87 ± 16	13 ± 1
CBD 20	97 ± 12	174 ± 9	29 ± 3	3 ± 1**	52 ± 12	11 ± 1
CBD 40	70 ± 6**	200 ± 6**	30 ± 3	6 ± 3*	68 ± 16	14 ± 2

W, wakefulness; SWS, slow wave sleep; REM rapid eye movement sleep. Doses of CBD in mg/kg. Differences in mean values were compared to control values and tested for significance by applying Duncan's new multiple-range test. * $P < 0.05$; ** $P < 0.01$

presence of high-voltage, irregular slow waves. When the animals were in the REM phase of sleep, the frontal EEG showed the usual desynchronized pattern, while theta waves were recorded at the occipital level. The high-voltage polyspikes described after delta-9-THC injection were not observed here.

Both doses of CBD significantly decreased SWS latency while REM latency and the number of REM periods were not substantially modified. Furthermore, 40 mg/kg CBD significantly decreased W and increased SWS during the 5-h recordings (Table 1). Figure 1 shows that the largest increase of SWS occurred during the first 3 h. REM time values did not differ from those of control. These values of the different variables corresponding to the records obtained after chronic CBD administration did not differ significantly from control (W 106 ± 12; SWS 169 ± 11; REM 26 ± 8, and SWS latency 13 ± 7 min).

DISCUSSION

Our results show that acutely administered CBD behaves as a short-acting hypnotic in the rat. The gross behavior and EEG patterns of the injected animals were similar to those observed during physiological sleep. The sleep-inducing effect of CBD was already evident after a dose of 20 mg/kg, while its sleep-maintaining effect was manifest only after 40 mg/kg. Total sleep time increase was related to only an increment of SWS. Tolerance to all these effects developed after chronic administration of CBD.

Unexpectedly, REM sleep was not decreased. In this connection, CBD contrasts with most CNS depressant and hallucinogenic drugs, including delta-9-THC, which depress REM sleep (King, 1971; Monti and Carlini, 1975).

Acutely administered delta-9-THC and CBD show opposite effects on the rat's sleep-awake cycle. While the first compound presents an alertogenic effect (Moreton and Davis, 1973) CBD induces SWS.

It can be suggested that the decrease of SWS and REM following a cannabis extract injection would produce different values depending not only on its content of delta-9-THC but also on the percentage of CBD present, which probably partially antagonizes the arousing effect of delta-9-THC.

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