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INDUCTION BY CANNABIS SATIVA (MARIHUANA) OF RHYTHMIC SPIKE DISCHARGES OVERRIDING REM SLEEP ELECTROCORTICOGRAM IN THE RAT*

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Cannabis sativa and Δ^9-tetrahydrocannabinol (Δ^9THC) have been shown to disrupt complex memory patterns in rhesus monkeys and to interfere with visual discrimination in both monkeys (1) and pigeons (2). These drugs alter maze learning (3), bar pressing (4), and climbing rope performances (5), and after chronic treatment in food-deprived rats, they induce agressiveness (6). Administration to mice of Δ^9THC is followed by a slight increase in whole-brain concentration of 5-hydroxytryptamine. Cerebral norepinephrine concentration appears to decrease after low doses and to increase after high doses (7).

Changes in the electroencephalogram (EEG) and in the sleep-awake cycle have been reported to occur after administration of psychotropic drugs to experimental animals (8) and to man (9,10). Studies on the acute effects of Cannabis indica resin on the EEG of the rabbit revealed initial stimulation and subsequent depression, followed by a recovery phase during which repeated high voltage sharp waves were manifest (11). In humans deprived of REM sleep for two nights, REM time tended to be decreased by marihuana extract, THC, or synhexyl (a synthetic analogue of THC), but the change was not significant. In normal subjects, THC had no consistent effect on REM sleep time (12).

The present study describes acute and chronic marihuana-induced changes in the electrocorticogram during longitudinal study of the sleep-awake cycle in the rat.

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Materials and Methods

Five adult female Sprague-Dawley rats (250-300 g) were chronically implanted with cortical and muscle electrodes for recording of the EEG and EMG. EEG bipolar recordings were obtained from stainless steel screws that were placed epidurally through small burr holes over the frontal and parietal cortex. Stainless steel wires were inserted into the temporalis muscles to obtain EMG tracings. The light cycle in the experimental environment consisted of 16 hours of light (6:00 AM to 10:00 PM) and 8 hours of dark (10:00 PM to 6:00 AM). After a correlation was established between the behavioral states of sleep, REM sleep and wakefulness and the recordings of EEG and EMG activity, tracings were collected for twelve days from 9:00 AM to 5:00 PM daily. On the first three days the rats received the vehicle (Tween in water) and on the fourth through twelfth days they received 10 mg/kg Cannabis extract in 1.0 ml vehicle/kg body weight; all injections were given intraperitoneally at 11:00 AM. The extract was prepared from top flowerings of Cannabis sativa according to Carlini and Kramer (3). The rabbit corneal reflex (Gayer test) was abolished by 0.27 ± 0.09 mg of the extract/kg body weight; thus the extract was one-third as potent as Δ^9THC.

Results and Discussion

Cannabis sativa extract induced bursts of polyspikes in the electrocorticogram of all five rats. These high voltage bursts of a frequency ranging from 8 to 12 Hz and an amplitude of up to 600 μV were seen in the awake state as a result of the acute immediate effects of marihuana. The frequency of their appearance then declined during the awake state and they subsequently reappeared toward the end of sleep episodes, overriding partially or totally the REM sleep states which followed. These REM sleep clusters of spike discharges were trains of 6-8 bursts per minute lasting from 30 seconds to 3 minutes and differing from the EEG spindles seen during sleep states.

As had been reported earlier (13), it was noted that in the normal rat

REM sleep is often preceded and followed by EEG bursts which differ from the sleep slow waves. Usually these bursts neither exceeded two in number per REM sleep episode nor were of an amplitude higher than that of the sleep EEG baseline (Fig. 1, 2).

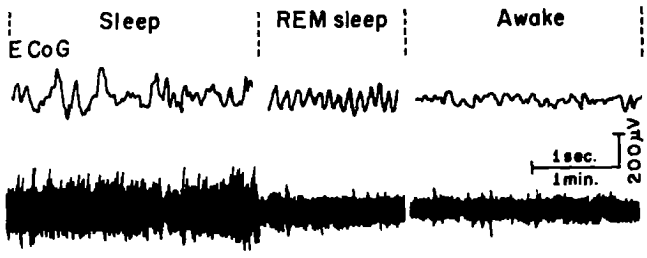

FIG. 1

Comparison of the cortical EEG activity (ECoG) during sleep, REM sleep and wakefulness in the control rat. Very low EMG baseline (not shown here) as well as the frequent movements of the vibrissae and lower jaw with muscle twitches occurred during all REM sleep episodes recorded.

After daily treatment with the Cannabis extract these EEG bursts were associated with practically all REM sleep episodes. They reached a peak during the second and third hour after treatment before declining. The average number of these bursts per minute REM sleep time increased from 2.5 on the first day of treatment to 4 bursts on the second day. This increase persisted throughout the whole period of marihuana administration.

A preliminary study of three rats given Δ^8THC, in Tween water, at doses of 2.5 and 5 mg/kg i.p. revealed the presence of EEG spike discharges of wave form, frequency and amplitude similar qualitatively to those seen after treatment with Cannabis extract. These polyspikes were likewise seen initially during the awake state and then during the REM sleep states.

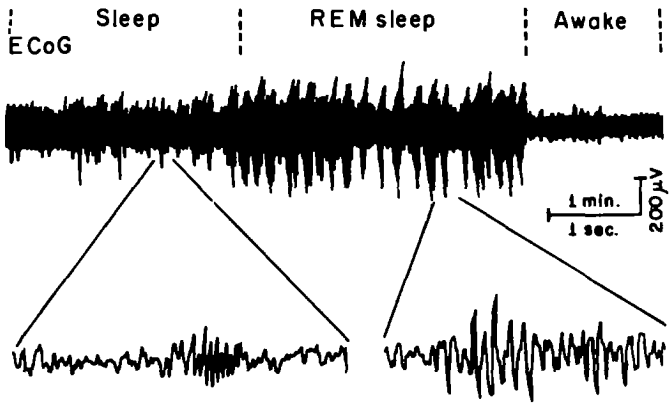

FIG. 2

The development of rhythmic polyspike EEG discharges in the REM sleep state after Cannabis extract treatment is shown. In this example, these bursts override the entire duration of the REM sleep episode. The higher speed tracing compares the sleep spindle and the marihuana-induced burst.

REM sleep episodes have been shown to be preceded by pontine-geniculate-occipital (PGO) activity. This activity represents spike discharges which are associated with the REM sleep phasic event. PGO spikes are significantly increased in the cat following REM sleep deprivation (14) and after reserpine treatment (15). While these PGO spike discharges have not been noticed in the rat (16), high voltage spikes were recorded in the prepyriform cortex of the rat after reserpine treatment (17). It is postulated that the marihuana-induced rhythmic EEG bursts represent facilitation of those bursts preceding REM sleep (13) which may be related to the PGO spikes described above. The latter have been noticed in the awake state also and are presumed to correlate closely with the hallucinatory behavior of the para-chlorophenylalanine (PCPA) treated cat (18). Deep electrode implantation should shed further light on

the origin of these marihuana bursts and would thus clarify their relation, if any, to the PGO spikes.

We found that acute and chronic morphine injections given i.v. to rats precipitated high voltage EEG "slow bursts" which were scattered rather than rhythmic and prevailed mainly during the awake state, but also occurred, although less frequently, during the REM sleep state (19,20). No similar REM sleep spike discharges were noted during our earlier studies of the effects of several psychotropic agents on EEG and sleep-awake cycle in the rat (21-24). The study of changes in REM sleep time induced by marihuana and THC treatment in man (12) did not report REM sleep spike discharges similar to those observed in the rat.

In conclusion, abnormal rhythmic polyspike discharges of the EEG, which override REM sleep episodes, occur in the rat treated both acutely and chronically with a marihuana extract and Δ^8THC.

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