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ELECTROENCEPHALOGRAPHIC STUDY OF EFFECTS OF Δ^9 - AND Δ^8 -TETRAHYDROCANNABINOL AND CANNABIS EXTRACT ON SLEEP IN THE RAT. J.E. Moreton* and W.M. Davis. Dept. of Pharmacol., Sch. of Pharm., Univ. of Mississippi, University, Miss. 38677.

The criteria for paradoxical sleep (PS) included activated ECoG, hippocampal (HIP) theta rhythm, rapid eye movement (EM) and low EMG. Daily 3h recordings were made from 3 days before to 6 days after the drugs in non-deprived (ND) rats and for 6 days afterwards in rats PS deprived (PSD) for 72h. Five and 10 mg/kg of synthetic Δ^9 - and Δ^8 -tetrahydrocannabinol (Δ^9 -THC and Δ^8 -THC) and 10 mg/kg of cannabis extract i.p. + PS, + slow sleep (SS) and + wakefulness in ND rats. PS rebound was blocked in PSD rats. Ten mg/kg Δ^9 -THC in studies utilizing recordings 24h/d on the daily schedule as above suppressed PS for 12 h in 2/3 ND rats. A non-significant rise in PS occurred in the next 12h. In PSD rats 10 mg/kg suppressed PS for 6-9h and + SS. Rebound did not occur in the next 12h or subsequent 5 days. Ten mg/kg Δ^9 -THC, daily for 20 days to rats permitted PS only during daily 15h EEG sessions, reduced PS for 3 days after which tolerance developed. No PS rebound occurred in the 10 day post-drug period. Ten mg/kg on the 13th withdrawal day tended to reduce PS. After THC, sleep characterized by HIP theta rhythm, cortical spindles, low EMG and + or absent EM occurred. If such is considered PS, then, THC reduces PS in ND and has little effect in PSD rats. (Supported in part by NIMH Grant MH-19683).

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CHANGES IN EEG VOLTAGE OUTPUT OF THE SLEEP-AWAKE CYCLE IN RESPONSE TO TETRAHYDROCANNABINOLS IN THE RAT. Brenda Colasanti* and Naim Khazan. Mount Sinai School of Medicine, CUNY, New York, N.Y. 10029

Marihuana and the active delta-8- and delta-9- trans-tetrahydrocannabinol (Δ^8 - and Δ^9 -THC) derivatives are generally regarded as psychotomimetics with sedative properties. Since the sympathomimetic hallucinogens have been reported to cause a reduction in the mean voltage output of the EEG and its coefficient of variation, the present study was undertaken to determine whether a similar change would follow the administration of THC. Adult female Sprague-Dawley rats with chronic cortical and temporal muscle electrodes were used. Administration of Δ^9 -THC i.p. at doses ranging from 2.5 to 10.0 mg/kg was followed by a dose-related decrease in the voltage output of the awake state EEG. The sleep and REM sleep states were relatively less affected. Polyspike discharges, reported previously to occur after the administration of marihuana extract or Δ^8 -THC (Masur and Khazan, Life Sci. 9:1275, 1970), were superimposed on the low voltage EEG awake tracings. Administration of Δ^9 -THC resulted in similar EEG changes. The reduction in the voltage output of the EEG in conjunction with the occurrence of the polyspike discharges, unique to this group of psychotomimetics, is presumed to correlate with a state of CNS arousal during which the rat appears behaviorally sedated. (Supported by NIMH Grant MH-16693)

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PHYSIOLOGICAL AND PSYCHOLOGICAL DEPENDENCE TO SYNTHETIC Δ^9 TETRAHYDROCANNABINOL (THC) IN RHESUS MONKEYS, G. A. Deneau and Sukru Kaymakcalan*, Southern Research Institute, Birmingham, Ala. 35205

Six naive monkeys were prepared for iv self-administration of THC. No monkey initiated self-administration over a 3-week period. Automatic injections were then delivered every 6 hours for 1 month at doses increasing from 0.1 to 0.4 mg/kg. Drug effects were: ptosis, blank staring, scratching, and docility. Tolerance developed within a few days of each dosage increment. When injections were discontinued, all monkeys showed abstinence signs. Two of the monkeys then initiated and maintained self-administration of THC. Abstinence signs appeared at 12 hours and lasted 5 days. They were: yawning, anorexia, piloerection, irritability, scratching, biting and licking fingers, pulling hair, tremors, twitches, shaking, sitting in propped-up positions, photophobia and apparent hallucinations (staring in circles, slapping at the cage wall, grasping as if catching flies). (Supported by Grant MH 12277, USPHS)

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Δ^9 -TETRAHYDROCANNABINOL: EFFECTS OF I.V. INFUSION UPON EEG AND BEHAVIOR OF UNRESTRAINED RHESUS MONKEYS. J.L. Martinez, Jr., * S.W. Stadnicki* and U.H. Schaeppi. Mason Research Institute, Worcester, Massachusetts 01608.

Four Rhesus monkeys were infused i.v. (4 min.) with Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) in doses of 0.05-12.8 mg/kg emulsified in 0.4% Tween-80, 10% sesame oil and normal saline. The monkeys were provided with chronic brain electrodes (cortex, amygdala, hippocampus, thalamus, pons and cerebellum). Infusion of Δ^9 -THC elicited dose related drowsiness, ptosis, immobility, muscle rigidity, slow wave EEG activity and rhythmic 12-20 cps (burst) activity of intermediate voltage which appeared in trains of varying duration. Maximal EEG changes occurred within 1/2 hour. With larger doses (1.6-12.8 mg/kg) bursts occurred in the amygdala, pons, putamen, and cortex, but not in the hippocampus. With a dose as low as 0.05 mg/kg, burst activity was solely restricted to the cerebellum. Often, the frontal cortex and amygdala exhibited trains of synchronized rhythmic slow waves of high amplitude. It appears that the motor impairment including slowness of movement and muscle rigidity may be related to the subconvulsive activity that occurred throughout the brain, but primarily in the cerebellum. (Supported in part by PHS Training Grant No. MH-10625 to the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.)

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TOLERANCE TO EEG EFFECTS OF MARIJUANA IN RATS. J. H. Pirch, P.R. Barnes*, and E. Barratt*, Dept. of Pharmacol. and Toxicol., Univ. of Texas Med. Branch, Galveston, Texas 77550.

This investigation was designed to determine if tolerance develops to EEG changes induced by marijuana extract distillate (MED, with known Δ^9 THC content) in female albino rats. EEGs were recorded from parietal cortex and were quantified by voltage integration. Following oral treatment with MED (20 mg/kg Δ^9 THC), the integrated EEG voltage showed a significant decrease which was maximal after one or two daily doses. This MED effect diminished gradually with daily treatment so that after 5-12 doses the integrated voltage was no longer significantly lower than the pre-drug placebo control (6% Tween 80 in distilled water). No significant decrement in response was seen during three months of treatment when only one dose per week was administered. Thus, the development of EEG tolerance depends upon the dosage interval. An additional EEG effect of MED was the appearance of high voltage "spindle-like" activity to which no tolerance developed with either dosage schedule. This study demonstrates that tolerance develops in rats to certain, but not all, EEG effects of marijuana. (Supported by a grant from U. S. Dept. Justice).

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THE ANTICONVULSANT ACTIVITY OF Δ^1 -TETRAHYDROCANNABINOL IN MICE. R. Duane Sofia*, Thomas A. Solomon*, and Herbert Barry, III. Dept. of Pharmacol., Univ. of Pittsburgh Sch. of Pharmacy, Pittsburgh, Pa. 15213.

Electroshock and chemically induced seizures were used for comparing protective effects of Δ^1 -tetrahydrocannabinol (Δ^1 -THC) with three clinically effective anticonvulsant drugs (diphenylhydantoin, phenobarbital and chlorthalidoxepoxide). All four drugs at sufficiently high doses prevented seizures (ED_{50} = 54.5 mg/kg i.p. for Δ^1 -THC) with supramaximal electroshock intensity (50 mA, 0.2 sec.). Lethality was prevented by lower doses of all drugs (0.3 mg/kg for Δ^1 -THC). A dose inactive against supramaximal electroshock seizure (10 mg/kg for Δ^1 -THC) increased by 20% the threshold convulsive intensity (10.9 mA, 0.2 sec. for the control animals). Seizures and lethality induced by pentylenetetrazol and strychnine were prevented by phenobarbital and chlorthalidoxepoxide but enhanced by Δ^1 -THC and diphenylhydantoin. With a nicotine dose inducing seizure and death in control animals, all four anticonvulsant agents prevented lethality but did not prevent seizures. These data indicate that Δ^1 -THC closely resembles diphenylhydantoin in spectrum of anticonvulsive activity. (Supported by PHS grants MH-13595 and K2-MH-5921 from NIMH and GM-1217 from NIGMS.)