THURSDAY, AUGUST 26 — 1:30 P.M.
Auditorium - Cook Physical Sciences Building
Cochairmen: L. Harris and H. Pars

582

EFFECT OF Δ^9 THC ON CARDIOVASCULAR RESPONSES TO STIMULATION OF VASOPRESSOR LOCI IN THE NEURAXIS OF ANESTHETIZED CATS. M. J. Hosko* and H. F. Hardman. Med. Col. Wis., Milwaukee, Wis.53233.

Two groups of 6 cats anesthetized with chloralose-urethane were used to determine the effects of 1 and 2 mg/kg of Δ^9 THC on heart rate, respiratory rate and blood pressure (BP). Reductions in all parameters were statistically significant in <30 min. Effects at 60 min are presented in table 1 (Tween-80 had no significant effect). The 1 mg/kg animals had bipolar electrodes stereotaxically positioned into vasomotor areas of the hypothalamus (H), reticular formation (RF) and medulla (M). Suprathreshold current to elicit a small BP response was determined for each site. Stimulation at 2x and 4x threshold current was also done. Δ^9 THC (1 mg/kg i.v.) reduced the pressor response to stimulation at all sites. The data indicated that the systolic BP response elicited by H stimulation was suppressed less than that elicited by RF or M stimulation.

Table 1.

	Mean Diff. ± S.E.					
	1 mg/kg i.v.	P[a]	N	2 mg/kg	P[a]	N
Heart rate/min	-38.1± 7.7	<0.01	6	-25.0±6.1	<0.01	6
Resp. rate/min	- 3.6± 1.1	<0.01	6	- 4.3±1.2	<0.01	6
Systolic BP mm Hg	-26.6±10.0	<0.02	6	-26.8±9.1	<0.01	6
Diastolic BP mm Hg	-18.3± 7.0	<0.02	6	-27.5±6.3	<0.02	6

[a]Paired comparison.

(Supported by USPHS #MH17915.)

583

NEUROTOXICITY OF CANNABINOIDS IN CHRONICALLY-TREATED RATS AND MONKEYS. George R. Thompson*, Harris Rosenkrantz*, Mason Research Institute, Worcester, Mass., and Monique C. Braude, NIMH, Rockville, Md.

In chronic trials, Delta-9 and Delta-8-tetrahydrocannabinol (50-500 mg/kg/day) and crude marihuana extract (150-1,500 mg/kg/day) were administered p.o. to rats in sesame oil for 119 consecutive days. Monkeys were similarly treated with Delta-9-tetrahydrocannabinol (Delta-9-THC) for 91 days. Rats showed depression initially, then increased irritability and aggressiveness by day 21. Hyperactivity, detected on day 49, became progressively more severe until tremors and clonic convulsions were prominent by day 70. On the basis of equivalent THC content, behavioral changes in rats were similar for the 3 substances. Preliminary neurochemical findings in rats treated with Delta-9-THC indicated alterations in total brain proteins, RNA and ACHE. All doses in monkeys induced initial depression to which tolerance developed, but, after day 10, hyperactivity occurred only in monkeys treated with 250 mg/kg/day. Tolerance also developed in most hyperactive monkeys. These data indicated that chronic treatment of rats produced cumulative neurotoxicity culminating in convulsions while chronic toxicity in monkeys was less severe.
(Supported by NIMH Contract HSM-42-70-95.)

584

DISSOCIATION BETWEEN BEHAVIORAL EFFECTS AND CHANGES IN METABOLISM OF CEREBRAL SEROTONIN (5HT) FOLLOWING Δ^9-TETRAHYDROCANNABINOL (THC). D.W. Gallager*, E. Sanders-Bush*, and F. Sulser. Dept. of Pharmacol., Vanderbilt Univ. Sch. of Med. and Tenn. Neuropsychiatric Inst., Nashville, Tennessee 37203.

Behavioral changes, reaction times, and effects on metabolism of cerebral 5HT were monitored in male Sprague-Dawley rats following the administration of THC as a propylene glycol-serum complex. THC (5 mg/kg i.p.) produced characteristic and reproducible behavioral effects, including catatonia and squealing, as well as a 100% increase in reaction time in both the hot plate and tail flick tests for analgesia. The levels of 5HT and its principal metabolite, 5HIAA, were measured in forebrain following the i.p. administration of the drug. No significant change in the level of either indole was observed. Moreover, THC did not alter the turnover of cerebral 5HT as determined by the probenecid method and did not change the increase in 5HT following pargyline administration. Following an i.v. injection of 1 mg/kg of THC, behavioral changes correlated well with those elicited by 5 mg/kg i.p. but no change was detected in the levels of 5HT or 5HIAA or in the turnover of 5HT. It may thus be concluded that doses of THC which produce significant and reproducible behavioral changes do not alter the dynamics of the cerebral serotonergic system. (Supported by USPHS grant MH-11468 and 5-T01-GM-00058).

585

BIOCHEMICAL INTERACTIONS OF Δ^9-TETRAHYDROCANNABINOL. J.V. Dingell, H.G. Wilcox*, and H.A. Klausner*. Dept. of Pharmacol., Vanderbilt Univ. Sch. of Med. and Tennessee Neuropsychiatric Inst., Nashville, Tennessee 37203.

Fractionation of proteins of rat and human plasma by zonal ultracentrifugation after addition of Δ^9-tetrahydrocannabinol (THC) (10 µg/ml) showed that as much as 90% of the drug is associated with the total protein; over 2/3 of this with lipoprotein (chylomicra, VLDL, LDL, HDL). The rapid distribution of THC from plasma into tissues, previously observed in this laboratory (Life Sci. 10:49, 1971), thus suggested its intracellular binding. Using the isolated perfused rat liver, THC was found localized in nuclei and microsomes. Intracellular binding of THC affects hepatic drug metabolism: metabolism of THC by liver homogenates is only about 1/3 of that in 600 or 9000 g supernatants; THC (10^{-4}M) inhibits microsomal oxidation of aminopyrine (50%) and hexobarbital (58%) conjugation of estradiol (25%) and p-nitrophenol (18%), but enhances reduction of p-nitrobenzoic acid (33%). Metabolism of THC, in vitro, is inhibited by SKF-525 A (76%), nortriptyline (31%) and DMI (20%) at concentrations of 10^{-4}M. (Supported by USPHS Grants MH-11468 and GM-15431).

586

THE PHARMACOLOGICAL EFFECTS OF AND THE LACK OF Δ^9-THC BLOCKING ACTIVITY OF PHENITRONE. Theodore C. Spaulding*, William L. Dewey, and Louis S. Harris, Dept. Pharmacology, University of North Carolina, Chapel Hill, N.C. 27514

It has previously been reported (Farmakol. Tokikol. 31: 549, 1968) that (3-(hexahydro-1H-azepin-1-yl)-3'-nitropropiophenone HCl), phenitrone (I) blocked and reversed the overt behavioral effects of hashish in dogs. The intravenous injection of 20 mg/kg I produced a short duration behavioral syndrome resembling in some ways that seen after Δ^9-THC injection. There was no antagonism of the behavioral effects of Δ^9-THC when given to this dog 10 minutes after I. Doses of 20 or 40 mg/kg I given I.P. 15 or 30 minutes prior to 2 mg/kg Δ^9-THC were also without inhibitory activity. I (2 mg/kg) produced a transient fall in blood pressure in the anesthetized dog but did not block the hypotension or bradycardia produced by 6 mg/kg Δ^9-THC. Neither a single injection nor 5 daily injections of 40 mg/kg I blocked the hypothermia produced in mice by 10, 30, or 100 mg/kg Δ^9-THC. However, when I was given simultaneously, a dose dependent inhibition of high doses of Δ^9-THC induced activity in the tail flick test was observed. I produced hypothermia, a decrease in spontaneous activity and had an I.P. LD-50 in mice of 175 mg/kg.
Supported by MH17001.

587

SOME ACUTE AND CHRONIC INTERACTIONS BETWEEN Δ^9-THC AND ETHANOL AND BETWEEN Δ^9-THC AND MORPHINE IN MICE. W.L. Dewey, L.S. Harris, B.Dennis*, S. Fisher*, J. Kessaris*, L. Kersons*, J. Watson*. Dept. of Pharmacology, Univ. of North Carolina, Chapel Hill, N.C. 27514.

The I.P. administration of 3.75 g/kg ethanol (I) produced a loss of righting reflex (LRR) in mice which had a mean duration of 32 minutes. An I.P. injection 10 mg/kg of Δ^9-THC (II) given immediately after I reduced the LRR to 19 minutes. If the injection of II was given 30 minutes prior to I or if 10 mg/kg II was given daily for 4 days prior to the day of testing, the reduction in LRR was not observed. A higher acute dose of II (30 mg/kg) did not alter the LRR induced by I; however, 100 mg/kg II significantly prolonged the LRR induced by I. The activity of morphine sulfate in the tail flick test was not significantly altered by a simultaneous injection of either 10 or 100 mg/kg II. If mice were treated daily for 7 days with 10 mg/kg II, injections of morphine sulfate were significantly less active on day 8 than in acute experiments. The degree of this reduced effect approached the tolerance observed to daily single injections of morphine in this procedure. II, which is without activity in this test at doses below 100 mg/kg, appeared to have more activity in animals treated chronically with morphine than in controls.
Supported by MH17001 and 19759.