Marihuana

3045 PHARMACOLOGY

EFFECTS OF Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC) ON THE DOG HIND LIMB VASCULATURE. J. Dziak*, C. Chi*, R. Sprecher*, and I. Cavero* (SPON: A. Manian). Sch. of Dental Med. and Pharmacy Univ. of Pittsburgh, Pittsburgh, Pa. 15213.

A vasoconstrictor response was elicited by Δ^9-THC (2.5 mg/Kg, i.v.) in denervated (DHL) or innervated perfused hind limb (IHL) in anesthetized dogs under pentobarbital anesthesia, when mean blood pressure (M.B.P.) was over 85 mm Hg. However, no change in DHL and a decrease in perfusion pressure in IHL occurred in animals in which M.B.P. was below 85 mm Hg. On the other hand, a marked and consistent decrease in perfusion pressure independent of M.B.P. was observed in the IHL of dogs in which the carotid sinus nerves and vagi were bilaterally severed. These findings suggested that the hypotensive effects of Δ^9-THC triggers reflexogenic mechanisms which result in release of vasoactive substances into the blood stream. This conclusion was strengthened by the consistent increase in adrenal venous blood content of epinephrine following Δ^9-THC in dogs with M.B.P. over 85 mm Hg. No impairment on DHL responses to lumbar chain stimulation or to intraarterial administration of norepinephrine, isoproterenol, acetylcholine and histamine occurred following Δ^9-THC, excluding a direct effect of this compound on vascular receptors. These results indicate that Δ^9-THC decreases perfusion pressure in IHL by altering neurogenic tone. (Supported partly by USPHS Grant GM-1217 and partly by DE-00213.)

3046 PHARMACOLOGY

THE INTERACTION OF Δ-9-TETRAHYDROCANNABINOL (THC), PENTOBARBITAL AND SKF-525A WITH THE CARDIOVASCULAR SYSTEM OF THE RAT. Joseph E. Manno* and Barbara R. Manno* (SPON: H. M. Redetzki). Dept. Pharmacology, LSU Medical Center and Vet. Admin. Hosp., Shreveport, La. 71130.

Aqueous suspensions of THC were administered intravenously to male rats in doses of 0.05 mg/kg and 0.5 mg/kg. Direct arterial blood pressure and heart rate were continuously monitored from indwelling carotid catheters in pentobarbital anesthetized and unanesthetized, non-restrained animals. Control rats were administered saline and monitored in the same manner as the experimental animals. A similar series of experiments investigated the effect of pretreatment with the metabolic inhibitor SKF-525A (β-diethylaminoethyl diphenyl propylacetate). A maximal bradycardia was produced in all conditions at 10 minutes after THC administration. The bradycardia reverted to a tachycardia at 60 minutes in unanesthetized rats. The initial bradycardia was greater in anesthetized animals than in unanesthetized rats. Pretreatment with SKF-525A potentiated the initial negative chronotropic action of THC, particularly in unanesthetized rats. The tachycardia at 60 minutes was also potentiated by SKF-525A. The implications of the pretreatment of SKF-525A will be discussed with reference to alterations in THC and 11-hydroxy THC concentrations as described by Gill and Jones (Biochem. Pharm. 21:2237, 1972). (Supported in part by USPHS, NIMH Grant MH 21383 and Veterans Administration funds.)

3047 PHARMACOLOGY

INTERACTION OF THE BEHAVIORALLY ACTIVE DRUG, PHENITRONE, A PURPORTED HASHISH AND LSD ANTAGONIST, WITH SEVERAL CENTRAL NEUROCHEMICAL SYSTEMS. Theodore G. Spaulding* and William L. Dewey. Department of Pharmacology, Univ. of North Carolina, Chapel Hill, North Carolina 27514.

We have previously reported that phenitrone (I) caused unique behavioral effects in dogs and cats. In an attempt to clarify whether one or another discrete central neurochemical system prevailed we have examined individually the interaction of I with cholinergic, serotonergic and noradrenergic systems. Cholinergic interactions were implicated by the findings that the acetylcholine (Ach) response in the isolated frog rectus abdominis was potentiated by small doses of I. I also reversed the anti-Ach effects of tubocurarine. The in vitro hydrolysis of acetylthiocholine (AcSCh) and butyrylthiocholine (BuSCh) by whole rat brain homogenate and the hydrolysis of AcSCh by bovine erythrocyte cholinesterase were inhibited by I. Tacrine, another reported cannabinoid antagonist, has also been shown to have cholinesterase inhibitory properties in this system. Mouse whole brain levels of serotonin were lowered and serotonin turnover rate was decreased by I at doses of 10, 30 and 56 mg/kg. Mouse brain norepinephrine levels were found not to be significantly changed following doses of 10, 30 or 56 mg/kg I. These data suggest that I, like many other centrally acting agonists and antagonists, affect more than one neurochemical system in the brain. (Supported by USPHS Grant #MH-17001 and Fellow of Amer. Foundation for Pharmaceutical Education (T.C.S.)

3048 PHARMACOLOGY

FURTHER STUDIES ON THE HEMODYNAMIC EFFECTS OF Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC). Icilio Cavero* and Bhagavan S. Jandhyala* (SPON: N. Watzman). Sch. of Pharmacy, University of Pittsburgh, Pittsburgh, Pa. 15213.

We previously reported that Δ^9-THC (2.5 mg/Kg, i.v.) induced a sustained decrease in blood pressure, heart rate, cardiac output (C.O.) and a transient decrease in total peripheral resistance in pentobarbital anesthetized dogs. The change in C.O. was related to the bradycardia since there was no alteration in stroke volume (Fed. Proc. 31: 1647, 1972). However, prevention of bradycardia by pacing the atria at a constant rate or by selective cardiac denervation failed to completely abolish the effects of Δ^9-THC on cardiac output. In these studies Δ^9-THC also significantly decreased stroke volume. On the other hand, pretreatment with chlorisondamine abolished the cardiovascular effects of Δ^9-THC. Since Δ^9-THC neither significantly altered right ventricular contractile force in chlorisondamine pretreated or cardiac denervated animals nor interfered with the positive inotropic response to calcium and isoproterenol nor depressed left ventricular function curves, it appears that direct myocardial depression is not primarily responsible for the effect of Δ^9-THC on C.O. A decrease in venous tone indicative of an alteration in venous compliance was demonstrated in the major vessel occlusion preparation following Δ^9-THC. These studies suggest that Δ^9-THC induces cardiovascular modifications resulting in a reduction in venous return to the heart. (Supported by PHS Research Grant GM-15587.)

3049 PHARMACOLOGY

MECHANISM OF THE NEGATIVE CHRONOTROPIC AND INOTROPIC EFFECTS OF Δ^1-TETRAHYDROCANNABINOL (Δ^1-THC OR Δ^9-THC). M. Barnard* (SPON: R.H. McDonald, Jr.) Department of Pharmacology, University of Pittsburgh, Pittsburgh, Pennsylvania 15213.

The indirect and direct influences of Δ^1-THC were studied in anesthetized cats and rabbits in vivo and in isolated rabbit hearts in vitro in an attempt to separate the possible underlying mechanisms of the negative chronotropic and inotropic actions of Δ^1-THC. Intravenous administration of Δ^1-THC (2.5 to 10 mg/Kg) produced bradycardia and hypotension. The negative chronotropic action of Δ^1-THC was partially abolished after vagotomy. Previously reported data from our laboratory demonstrated that decreases in blood pressure and myocardial function were concomitant with a decrease in efferent sympathetic discharge and an increase in vagal activity to the heart (Fed. Proc. 31: 505, 1972). In isolated rabbit hearts, the effect of albumin with and without Δ^1-THC was examined. In all doses (0.05 to 0.4 mg), Δ^1-THC decreased ventricular pulse pressure (VPP) with only slight change in heart rate. Per cent recovery of VPP was less with the higher dose (0.4 mg); however, with the lower doses (0.05 to 0.2 mg) recovery was complete or near complete. Ethanol and albumin, the vehicles, did not have appreciable effects. It is postulated that Δ^1-THC decreases heart rate primarily by influencing nerve activity and decreases myocardial force by direct and possibly indirect actions. (Supported by USPHS Grant MH-21323 from NIMH).

3050 PHARMACOLOGY

HYPOTHERMIC ACTION OF Δ^9-TETRAHYDROCANNABINOL, 11-OH-Δ^9-TETRAHYDROCANNABINOL AND 11-OH-Δ^8-TETRAHYDROCANNABINOL (Δ^9-THC, 11-OH-Δ^9-THC and 11-OH-Δ^8-THC) IN MICE. C. O. Haavik* and H. F. Hardman. Med. Col. of Wis., Milwaukee, WI 53233.

Metabolism of Δ^9-THC in vivo to 11-OH-Δ^9-THC occurs in several species. Mechoulam has speculated (Science, 169: 611, 1970) that pharmacological activity resides in 11-OH-Δ^9-THC rather than in Δ^9-THC. We have compared these two agents in regard to production of hypothermia in the mouse. Drugs were administered i.v. to male Cox mice at an ambient temperature of 20°C. Both Δ^9-THC and 11-OH-Δ^9-THC lower body temperature immediately: a significant fall ($p < 0.05$) occurs within 30 seconds after administration. Magnitude and duration of the hypothermic response are dose related. At low dose levels Δ^9-THC and 11-OH-Δ^9-THC do not differ significantly in onset, magnitude and duration of hypothermic action. 11-OH-Δ^8-THC also lowers body temperature significantly within 30 seconds after administration, but is less potent than is 11-OH-Δ^9-THC and has a shorter duration of action. The rapid onset of hypothermia following i.v. administration of Δ^9-THC suggests that this drug possesses intrinsic activity. A quantitative comparison of Δ^9-THC and 11-OH-Δ^9-THC indicates that both substances have similar hypothermic efficacy. (Supported by USPHS Grant No. MH 21174.)