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PROSTAGLANDINS AND CANNABIS XIII. CANNABINOID INDUCED ELEVATION OF LIPOXYGENASE PRODUCTS IN MOUSE PERITONEAL MACROPHAGES. Sumner Burstein*, Sheila A. Hunter, Kent Ozman and Lori A. Renzulli. University of Massachusetts Medical School, Worcester, MA 01605.

The phospholipases controlling the release of arachidonic acid in mouse peritoneal macrophages have been shown to be stimulated by the natural psychoactive cannabinoids such as tetrahydrocannabinol (THC) and its metabolites. A close correlation was observed between the potencies of these substances in elevating arachidonate levels in vitro and the reported activities in a behavioral assay in monkeys and in producing a "high" in humans. The order of activity with the macrophages was Δ^1-THC > 7-OH-Δ^1-THC > 6α-OH-Δ^1-THC > 6β-Δ^1-THC >> Δ^6-THC-7-oic acid. It is suggested that this effect, which has now been shown in several diverse cell types, may serve as a model for studying the mechanism of action of THC.

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COMPETITIVE DISPLACEMENT OF TESTOSTERONE FROM HUMAN SEX BINDING GLOBULIN BY Δ^9-TETRAHYDROCANNABINOL AND CANNABINOL. J.L. Valentine* and S.P. Murray* (SPON. N.P. Plotnikoff) Oral Roberts University, Tulsa, OK 74171

An in vitro study was conducted to assess the possibility of competitive displacement and/or binding between testosterone (I) and two components found in marijuana smoke, viz. Δ^9-tetrahydrocannabinol (II) and cannabinol (III) to human male sex binding globulin (SBG). Radiolabeled I was added to plasma obtained from a male non-marijuana smoker at a concentration of 10ng/ml and incubated at 25° for 20 min. These conditions were found to be sufficient to saturate binding sites for I on SBG. Displacement studies were conducted using 0, 5, 7.5, 10, 15, and 20 ng/ml of unlabeled I; or 50, 90, 120, 150, and 300 ng/ml of either II or III using the same incubation protocol. Extent of displacement was assessed by electrophoresis using gradient polyacrylamide gels followed by determination of activity present in individual gel slices. Significant displacment of labeled I was found with 120, 150, and 300 ng/ml of II, whereas III exhibited significant displacement at all levels studied.

3902

OCULAR HYPOTENSION, OCULAR TOXICITY AND NEUROTOXICITY AFTER MARIHUANA EXTRACT, DELTA-9-TETRAHYDROCANNABINOL (Δ^9-THC) AND CANNABIDIOL. B.K. Colasanti, R. Brown* and C.R. Craig. Depts. of Ophthalmol. and Pharmacol., West Virginia University Medical Center, Morgantown, WV 26506

Δ^9-THC (20 µg/hr), marihuana extract of equivalent THC content (1 µl/hr), or the polyethylene glycol vehicle (PEG; 1 µl/hr) was delivered unilaterally to eyes of cats via osmotic minipumps over 9 days. Cat eyes treated chronically with PEG ranged less than 1 mm Hg lower in pressure than fellow eyes, and no ocular toxicity became evident. In contrast, pressure differences between pairs of eyes treated with marihuana extract remained 3-4 mm Hg lower than those of vehicle controls, while differential values for the THC-treated group remained reduced by 4-6 mm Hg; data for the latter 2 experimental groups did not significantly differ. Ocular toxicity after THC was quite severe, while that after marihuana extract was comparatively much reduced. Cannabidiol lowered ocular tension by 3-4 mm Hg during the initial treatment days, but tolerance developed by the 6th day; ocular toxicity was lacking. Both marihuana extract and THC produced a dose-related increase in the appearance of 8-13 Hz polyspike discharges in the EEGs of rats. Both PEG and cannabidiol were devoid of this effect. These results substantiate our earlier findings of dissociation between the tension lowering and toxic effects of marihuana cannabinoids. (Supported by NIH (NEI) Grant No. EY03520).

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EFFECTS OF CANNABINOIDS ON CYCLOPHOSPHAMIDE-INDUCED TASTE AVERSIONS IN MICE. Michael R. Landauer*, Steven T. Phillips*, Robert L. Balster and Louis S. Harris. Dept. of Pharmacol., Med. Col. of Virginia, Richmond, VA 23298

A series of experiments were performed with adult CD-1 male mice to evaluate the antiemetic effects of several compounds using the conditioned taste aversion procedure. The antiemetics were administered IP immediately prior to a 30-min conditioning trial in which a novel tasting solution (0.3% saccharin) was presented to the subjects. The emetics, apomorphine and the cancer chemotherapeutic drug cyclophosphamide, were given IP immediately after the conditioning trial at doses that we had shown to induce taste aversions. Three days later the mice received a two bottle preference test (saccharin vs. water) and the percent saccharin consumed was calculated. Doses of the phenothiazine antiemetic, prochlorperazine (1 and 3 mg/kg), attenuated the aversions produced by 0.3 and 1.0 mg/kg apomorphine. Doses of drugs currently approved or under clinical investigation as antiemetics in conjunction with cancer chemotherapy, i.e. prochlorperazine (1.0 mg/kg), delta-9-tetrahydrocannabinol (0.3 and 1.0 mg/kg) and nabilone (0.1 and 0.3 mg/kg), significantly attenuated the taste aversions induced by 30 mg/kg cyclophosphamide. Levonantradol at doses of 0.03 and 0.06 mg/kg, however, did not attenuate cyclophosphamide-induced taste aversions. Conditioned taste aversions produced by emetic drugs warrants investigation as a model for evaluating potential antiemetics. (Supported by N.I.D.A. Grant DA-00490 and N.I.E.H.S. Grant ES-07087)

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DISCRIMINATIVE STIMULUS PROPERTIES OF INTRAVENTRICULAR Δ^9-TETRAHYDROCANNABINOL. Mary Jeanne Kallman, George L. Kaempf* and Louis S. Harris. Dept. of Pharmacology & Toxicology, Medical College of Virginia Commonwealth University, Richmond, Virginia 23298

The discriminative properties of intraventricular (IVT) Δ^9-tetrahydrocannabinol (THC) were assessed in rats initially trained to discriminate 3 mg/kg Δ^9-THC injections (ip.) from an ethanol-Emulphor vehicle in a standard 2-lever operant discrimination procedure. Once discrimination of the training cue stabilized, rats were prepared under anesthesia with chronic lateral IVT cannulas. Following recovery from cannulations, rats were tested for generalization of the Δ^9-THC training cue to other ip. doses of Δ^9-THC and to 11-OH-Δ^9-THC. Reductions of the Δ^9-THC dose produced concomitant reductions in drug-lever responding. 11-OH-Δ^9-THC substituted for the training cue with equivalent stimulus control produced by a dose of approximately .75 mg/kg. IVT administration of Δ^9-THC at a dose of 80 µg generalized to the peripheral cue while the IVT injection of the vehicle did not produce drug-lever responding. IVT Δ^9-THC doses which produced generalization also produced some response suppression while discriminable doses of ip. Δ^9-THC did not produce suppression. The IVT administration of 11-OH-Δ^9-THC also generalized with the training stimulus although both cannabinoids were about equipotent when administered IVT. These data suggest that route of administration is important in the availability of cannabinoids to brain sites. (Supported by DA-004900 funds).

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BEHAVIORAL DEPENDENCE OF RHESUS MONKEYS ON INTRAVENOUSLY-ADMINISTERED DELTA 9-TETRAHYDROCANNABINOL. Patrick M. Beardsley, Robert L. Balster and Louis S. Harris. Dept. of Pharmacol., Med. Col. of Virginia, Richmond, VA 23298

Studies were conducted to determine whether discontinuation of a continuous intravenous infusion regimen of delta 9-tetrahydrocannabinol (delta 9-THC) would disrupt food-maintained performance of rhesus monkeys. Four rhesus monkeys lever pressed for food-pellet deliveries on fixed-ratio schedules (either FR 100 or FR 150) during 0.5 hr sessions at 10:00 a.m., 4:00 p.m., 10:00 p.m. and 4:00 a.m. daily. During one phase of the study, the monkeys were either infused with vehicle (10% Emulphor 620/10% ethanol in 0.9% saline) or 0.05 mg/kg/hr delta 9-THC. After 10 days of continuous delta 9-THC administration, substitution with vehicle resulted in markedly reduced food-reinforced responding by the second day of withdrawal followed by a two-week recovery period to baseline rates in three of the four monkeys. Only minor observable effects on response rates occurred during the 10-day infusion regimen. One monkey that did not initially show a withdrawal effect later did so following a higher-dose regimen. Behavioral dependence upon delta 9-THC, defined as disruptions of operant behavior during withdrawal, can be produced within 10 days of administering as little as 1.2 mg/kg/day. (Supported by N.I.D.A. grants DA-00490 and DA-07027)