460

COMPARISON OF THE MONOMETHOXYAMPHETAMINES ON THE UPTAKE AND RELEASE OF BIOGENIC AMINES IN BRAIN TISSUE. Liang-fu Tseng* (SPON: V.C. Sutherland). Dept. of Pharmacol. Univ. California, San Francisco, CA 94143.

Para-methoxyamphetamine (PMA) is the most potent compound among monomethoxyamphetamines in disrupting the food reinforced behavior in rats (Snell et al., these proceedings). Meta-methoxyamphetamine (MMA) produces moderate d-amphetamine (A)-like locomotor stimulation but ortho-methoxyamphetamine (OMA) is not active. To investigate the reasons for the different behavioral effects among them, a comparison was made on the uptake and spontaneous release of ^{3}H-5HT, ^{3}H-NE and ^{3}H-DA in tissue slices of cerebral cortex and corpus striatum of rat brain. The potencies for inhibiting the uptake of ^{3}H-5HT in cerebral cortex and corpus striatum were PMA>MMA>A>OMA and of ^{3}H-NE in cerebral cortex A>PMA>MMA>OMA and of ^{3}H-DA in corpus striatum A>MMA>PMA>OMA. The potencies for the increased release of ^{3}H-5HT in cerebral cortex was found to be PMA>MMA>A>OMA and of ^{3}H-NE, A>PMA = MMA>OMA and of ^{3}H-DA in corpus striatum, A>MMA>PMA>OMA. The high effectiveness of PMA on inincreasing the release and blocking the uptake of 5HT and of A and MMA on DA suggest that 5HT may be involved in the production of hallucinogenic effects of PMA and DA is important in the locomotor stimulation of A and MMA. (Supported in part by MH-25487).

461

CORRELATION OF THE INCREASE IN BRAIN TRYPTOPHAN PRODUCED BY AMPHETAMINE-LIKE DRUGS WITH AN INCREASE IN BODY TEMPERATURE. David A. Brase* and Horace H. Loh. Dept. of Pharmacol., Univ. of California, San Francisco, California 94143.

Two effects of amphetamine (A), hyperthermia and increased serum unesterified fatty acids (UFA), were considered as having possible roles in the A-induced increase in brain levels of tryptophan (Trp). Male Sprague-Dawley rats received i.p. injections of 50 μmoles/kg of the following: dl-A, dl-β,β-difluoroA (DFA), dl-p-hydroxyA (PHA), dl-p-methoxyA (PMA), dl-p-chloroA (PCA), methA (MA), benzphetamine (BP), methylphenidate (MP), or chlorphentermine (CP). Changes in rectal temp., serum UFA and train Trp compared to saline-injected control rats were measured at 1 hr. All drugs significantly increased UFA except MP. Effects on temp. and Trp were more variable. Concerning increases in Trp, the drugs ranked in order of decreasing effect: A, PMA, MA, PCA, MP, PHA, DFA, CP and BP. For temp. increase the rank was A, MA, PCA, DFA, PMA, MP, PHA, CP and BP. The change in brain Trp was highly correlated with changes in body temp. ($r = 0.89$) but not with changes in serum UFA ($r = 0.04$). Also, changes in temp. did not correlate with UFA changes ($r = 0.01$). The A-induced increase in brain Trp also appeared to correlate with temp. increases in several mouse strains. The mechanism by which hyperthermia increases Trp is unknown. (Supported by NIMH Fellowship MH-02435).

462

BRAIN BUFOTENINE FROM ADMINISTERED ACETYLBUFOTENINE: COMPARISON OF ITS TREMORGENIC ACTIVITY WITH THAT OF N,N-DIMETHYLTRYPTAMINE AND 5-METHOXY-N,N-DIMETHYLTRYPTAMINE. Peter K. Gessner and Jana B. Dankova*. Dept. of Pharmacol., State Univ. of N.Y. at Buffalo, Buffalo, NY 14214.

Interest in the effects of bufotenine (Bu) on the CNS stems from its possible in situ formation by N-methylation of 5-hydroxytryptamine. The low lipid solubility of Bu (Gessner et al. Life Sci. 7,267,1968), however, limits its ability to cross the blood-brain barrier and has hindered direct investigation of its central activity. To circumvent this problem mice were administered i.v. 30 μmoles/kg of the acetyl ester of Bu (AcBu), which is more lipid soluble, and were killed by immersion in liquid nitrogen at either 60 or 120 sec. post injection. Assay of brain tissue showed presence of Bu and absence of AcBu at both times. In further experiments mice were administered i.v. various doses of AcBu or N,N-dimethyltryptamine (DMT) or 5-methoxy-N,N-dimethyltryptamine (5MeO-DMT) and their tremor activity in the period 30 to 120 sec. post injection was determined ballistographically. At 120 sec. the mice were killed and their brain assayed as above. Comparison of the tremorgenic activity of Bu, DMT and 5MeO-DMT at similar brain levels revealed Bu to be most active and DMT to be least active. (Supported in part by NIMH grant 14518 and UHF grant 9333-042331).

463

CORRELATIONS BETWEEN THE ACTIVITY OF DIMETHYLTRYPTAMINES AS 5-HYDROXYTRYPTAMINE ANTAGONISTS AND THEIR QUANTUM CHEMICAL PARAMETERS. Richard A. Glennon* and Peter K. Gessner. Dept. of Pharmacol., State Univ. of N.Y. at Buffalo, Buffalo, NY 14214.

A number of N-dimethyltryptamines (DMTs) possess hallucinogenic activity. It was of interest therefore to determine how these properties correlate with their quantum chemical parameters and their activity as 5-hydroxytryptamine (5HT) antagonists in a model system. The system used was the rat stomach fundus preparation. Previous work (Winter and Gessner, J.Pharmacol. 162, 286, 1968) showed DMTs act on two receptors in the rat stomach fundus: the 5HT receptor and a phenoxybenzamine resistant tryptamine (PRT) receptor, the net outcome being a contraction. In the present work the apparent intrinsic activity of the DMTs for the 5HT receptor in the rat stomach fundus was determined by obtaining dose response curves for 5HT in the presence of various bath concentrations of the DMTs and calculation therefrom of pA_2 values. Of the compounds investigated bufotenine had the highest pA_2 (7.41) followed by 5-methoxy-N-dimethyltryptamine (7.10). N-Dimethyltryptamine's pA_2 was 6.00. Electrophilic frontier electron densities were calculated using a PPP-SCF molecular orbital method. A correlation of .961 (N=8) was found between the pA_2 values and the electrophilic frontier electron density at position 4. (Supported by UHF grant FTF-6-UB-73 and NIMH grant F22 MH01671).

464

THE ROLE OF SEROTONIN AND CATECHOLAMINES IN THE SEXUAL DEVELOPMENT OF THE RAT. Vernon D. Parker,* Karam F. S. Soliman* and Charles A. Walker. The School of Pharmacy, Florida A and M University, Tallahassee, FL 32307, and Department of Pharmacology, Tuskegee Institute, Tuskegee Institute, AL 36088.

Serotonin (5-hydroxytryptamine, 5-HT), norepinephrine and dopamine levels were measured in different parts of the rat brain in order to determine the role of biogenic amines in sexual maturity. Pregnant mare serum gonadotropin (PMS) was injected into 25 days old immature rats for the induction of ovulation. Animals were sacrificed at 6 hours interval for 72 hours. The cortex, cerebellum, caudate nucleus and hypothalamus were separated and analyzed for their biogenic amine content using the method of Welch and Welch (1966). Levels of serotonin reached a maximum after 12 hours in all brain parts except the hypothalamus, which reach its peak 54 hours following PMS injection. Norepinephrine was found to reach its maximum value between 60 and 66 hours after PMS injection except for the cerebral cortex. Dopamine determinations revealed that maximum levels occur 12 hours after pretreatment in all parts except for the cerebellum. It was concluded from this study that PMS and central biogenic amines might be involved in sexual maturity and ovulation. (Supported by a grant from ONR).

465

BIOASSAY DETECTION OF ATROPINE-LIKE ACTIVITY IN TISSUE CULTURES OF DATURA STRAMONIUM. Ron C. Cooke* Harry R. Rasmussen* and Donald M. Pace* (SPON: M.H. Malone). Section of Physiology-Pharmacology, Univ. of the Pacific, Stockton, Calif. 95211

A rapid, dose-response assay for atropine-like activity was developed for crude plant material or extracts. Test materials (A: roots of D. stramonium var. tatula; B: roots grown in vitro in a chemically defined medium; C: callus tissue derived from stem sections grown similarly) were reduced to powders (> 200-mesh) and assayed vs. atropine SO_4. All substances were dissolved/suspended in 0.25% agar and injected I.P. in albino mice anesthetized with sodium pentobarbital using a log-dose increment of 0.301(2x). At +15,30,45 and +60 min. after injection, pupil diameter was measured using an ocular micrometer. Potency related to atropine SO_4 was: A = 0.00038x (95% C.L.=0.00024-0.00059; B = 0.0053 (95% C.L. = 0.0046-0.0088); chloroform extractive (0.27% w/v) from media of B = 0.013x (graphical); C = 0.000025(graphical). The calculated mean lambda for the assays = 0.29 (36 mice/assay; 3 dosage-levels for each standard and unknown).