WEDNESDAY, AUGUST 26 — 9:00 A.M.
Space Engineering Lecture Room
Chairman: Dr. B. Dubnick

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PHARMACOLOGICAL AND BIOCHEMICAL EFFECTS OF METHAMPHETAMINE (M), FENFLURAMINE (F) AND 1-1-N-BENZYL-β-METHOXY-3-TRIFLUOROMETHYL-PHENETHYLAMINE (1-SKF 39728). C. D. Morgan*, A. Groppetti*, A. Revuelta*, F. Cattabeni* and E. Costa, Laboratory of Preclinical Pharmacology, NIMH, St. Elizabeths Hospital, Washington, D. C. 20032

M is twice as active as F and SKF in eliciting anorexia but its effects are less persistent; M increases motor activity but F and SKF decrease motor activity. M causes a sustained depletion of brain norepinephrine (NE), F of brain serotonin (5-HT). These actions of M and F may depend on drug metabolites which bind to specific neurons; gas chromatographic and mass spectrometric investigations of these metabolites will be discussed. Brain amine depletion is unrelated to the anorexic effect because SKF causes anorexia without depleting brain monoamines. F analogues (like SKF) with a β-methoxy substituent neither deplete monoamine stores nor form brain metabolites, suggesting that β-hydroxylation may be a necessary step for drug metabolite binding to brain. From this and other data, we conclude that anorexia is due to a drug action on receptors other than presynaptic monoaminergic neurons. However, an action on the latter may be associated with other pharmacological responses: increase of motor activity by M is associated with accelerated brain DM turnover; decrease of motor activity with accelerated brain 5-HT turnover.

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MODIFICATION BY PSYCHOTROPIC DRUGS OF THE CYCLIC AMP RESPONSE TO NOREPINEPHRINE (NE) IN RAT BRAIN. G.C. Palmer*, G.A. Robison*, A.A. Manian and F. Sulser. Psychopharmacology Res. Ctr., Vanderbilt Univ. Sch. of Med., Nashville, Tenn. 37203 and Psychopharmacology Res. Branch, NIMH, Chevy Chase, Md. 20203.

Paired areas of rat hypothalamus and brain stem were prepared and incubated according to Kakiuchi and Rall (Mol. Pharm. 4: 367, 1968). NE (5×10^{-5}M) elicited a two- to five-fold increase in endogenous cyclic AMP (cAMP). Chlorpromazine (CPZ), prochlorperazine and 7-hydroxy-CPZ (all 10^{-5}M) antagonized the increase in cAMP in both hypothalamus and brain stem while the butyrophenone derivative, haloperidol, (10^{-5}M) was effective only in the brain stem. Pharmacologically inactive metabolites of CPZ, CPZ-sulfoxide, 7,8-dihydroxy-CPZ, 3,7-dihydroxy-CPZ and 7-methoxy-CPZ failed to modify the NE induced cAMP response. 8-Hydroxy-CPZ and the tricyclic antidepressant imipramine, a tertiary amine with CPZ-like properties, was effective in blocking the cAMP response in the hypothalamus while the tricyclic antidepressant protriptyline, a secondary amine, was without effect. None of the active drugs changed the basal levels of the cyclic nucleotide. The specificity observed in the present experiments suggests that CPZ could owe part of its pharmacological activity to its ability to inhibit the accumulation of cAMP in certain cells within the CNS. (Supported by USPHS Grants MH-11468, MH-08107 and AM-14240.)

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EFFECT OF LEVODOPA ON GLUCOSE, GLYCOGEN AND LACTATE IN SPECIFIC REGIONS OF MOUSE CNS. Richard L. Young*, Ronald F. Albano* and Annette M. Charnecki* (SPON: Herbert Sheppard). Hoffmann-La Roche Inc., Research Division, Department of Pharmacology, Nutley, New Jersey 07110

The implication of discrete structures of the CNS in the syndrome of Parkinsonism and the effectiveness of L-3,4-dihydroxyphenylalanine (levodopa) in the treatment of this disease has led to a search for a regional impact of levodopa on the intermediary metabolism of the CNS in vivo. Owing to the lability of substrates of glycolysis in subcortical structures of larger animals, the time-course of impact of levodopa (400 mg/kg, i.p.) on cerebral cortex, caudate nucleus, brain stem and spinal cord was studied in the mouse. Glycogen was lowered 30 minutes after injection in only the brain stem. At intermediate times an elevation of glycogen was noted in only this region which persisted at 6 hours and was accompanied by a slight increase of glycogen of spinal cord. Glucose was initially elevated and then lowered in plasma and all areas of the brain. Lactate was not altered in any region, and rectal temperature remained constant ± 1°. Levodopa, therefore, appears to alter glycogen in a regionally specific manner without affecting lactate, an index of aerobic glycolysis.

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DOPA DECARBOXYLASE IN HUMAN BRAIN. Kenneth G. Lloyd* and Oleh Hornykiewicz. Univ. of Toronto, Toronto, Ont., Canada.

Previous attempts at determining DOPA/5-HTP decarboxylase in human brain (post mortem) had but little success. In the present study we have used a very sensitive radioisotope assay for this enzyme, utilizing the trapping, in hyamine hydroxide, of the $14\text{-}CO_2$ produced from DOPA-14-COOH. Brain areas were homogenized in ice-cold isotonic dextrose. With this technique we found substantial pyridoxal phosphate dependent decarboxylation of L-DOPA in several areas in the normal human brain (4 brains examined). The values (in cpm/100 mg protein/2 hrs, minus blank) were as follows: Caudate nucleus (right side = r): 19,000 - 120,000; putamen(r): 52,000 - 230,000; hypothalamus: 12,000 - 50,000; cerebral cortex(r): 1700 - 7000; cerebellar cortex(r): 2000 - 5500; cerebellar white matter: 0 - 2700. Blanks (= incubates plus p-bromo-hydroxybenzyloxyamine, 2.5×10^{-3}M) ranged between 1500 and 3000 cpm/100 mg protein/2 hrs. In 3 cases with Parkinson's disease the values for the DOPA decarboxylase in the caudate nucleus(r) and putamen(r) were consistently lower than normal, between 2500 and 8500 cpm/100 mg protein/2 hrs. It remains to be determined whether the lower enzyme activities in the parkinsonian striatum can account for the severe dopamine deficiency in these brain areas. (Supported by the Clarke Inst. of Psychiatry and Eaton Labs.)

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EFFECTS OF HALLUCINOGENS ON RAT BRAIN MONOAMINE OXIDASE ACTIVITY. Barbara J. Collins*, Richard A. Lovell*, William O. Boggan*, and Daniel X. Freedman. Dept. of Psychiatry, Univ. of Chicago, 950 E. 59th St., Chicago, Ill. 60637.

Certain psychotomimetics have been shown to raise serotonin and lower 5-hydroxyindoleacetic acid in the rat brain, which may be interpreted as a monoamine oxidase inhibiting action. The experiments reported here investigate the MAO-inhibiting capacity of psilocin and LSD. C^{14}-tryptamine, C^{14}-tyramine, and C^{14}-serotonin were each incubated with a brain mitochondrial MAO preparation and presumptive inhibitors psilocin and LSD for various times at 37°C. Unchanged amine was separated from metabolite on an Amberlite CG column after the method of Robinson et al. (Biochem. Pharmacol. 17, 109, 1968), and radioactivity of the acid metabolite was measured as an index of MAO activity. Both psilocin and LSD inhibited MAO, but at the same concentration psilocin was a more potent inhibitor than LSD. We observed inhibition with LSD only at a high concentration (10^{-4} M) and could demonstrate only 30% inhibition under optimal conditions. Of the three substances, inhibition was greatest for either drug when serotonin was used as substrate, less so when tyramine was substrate, and least when tryptamine was used as substrate. Similar studies are in progress using enzyme from animals previously injected with these drugs. (Supported by USPHS, NIMH Grant MH 13,186-04 and by a research fellowship from The Schweppe Foundation to R.A.L.)

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SEPARATION OF AMINE AND AMINO ACID CONTAINING SYNAPTOSOMES FROM RAT BRAIN. Michael J. Kuhar*, Kenneth M. Taylor* Alan R. Wofsey* and Solomon H. Snyder. Depts. of Pharmacology and Psychiat., Johns Hopkins Univ. Sch. Med., Balto., Md. 21205.

We have extended our work on the separation of synaptosomes (pinched off nerve endings) containing various suspected neurotransmitters in continuous linear sucrose density gradients. Populations of synaptosomes containing serotonin, gamma-aminobutyric acid and norepinephrine were separable in gradients after short-time centrifugations (Fed. Proc., 29: 1383, 1970). Under these conditions we have examined the sedimentation characteristics of histamine containing synaptosomes and synaptosomes labeled with various radioactive amino acids. Substantial portions of histaminergic synaptosomes from rat hypothalamus were found in much lighter parts of the gradients than were the other aminergic synaptosomes. Synaptosomes from hypothalamic slices incubated in the presence of ^{3}H-histamine were sedimented in gradients and the distribution of exogenous and endogenous histamine was compared. It appears that some exogenous histamine may enter non-histaminergic compartments. Synaptic vesicles were isolated by osmotically shocking synaptosomes and the sedimentation of histamine vesicles were compared to the sedimentation of other amine containing vesicles. Synaptosomes labeled with various radioactive amino acids were also discriminable. (Supported by NIH grants 1-RO-1NB-07275 and 1-PO1-GM-16492.)