104 Correlation between Metabolism and Behavioural Action of Psychotropic Tryptamine Derivatives. S. SZÁRA (U.S.A.).

N.N-dimethyltryptamine and its N.N-diethyl and N.N-dipropyl homologues produce autonomic symptoms, perceptual, emotional, and thinking disturbances in man (in doses of 1 mg/kg) similar to LSD_{25} or mescalin but for a much shorter period of time. The corresponding dibutyl derivative causes only very slight symptoms while the dihexyl compound is completely inactive in the same dose.

The psychotropic activity of these homologue derivatives was found to be dependent primarily upon the rate of their metabolism in the liver.

Besides MAO, for which these tertiary amines are poor substrates, they are attacked by two competing microsomal enzymes both requiring TPNH, and O_2.—6-hydroxylation produces psychotropically active metabolites, while dealkylation forms practically inactive compounds. 6-hydroxylation is inhibited, among others, by chlorpromazine, reserpine, and by the substrate itself at higher concentrations, while the dealkylation reaction follows the Michaelis–Menten law. The inhibition of 6-hydroxylation by substrate is more pronounced in the case of the higher homologues; the dibutyl derivative is hydroxylated very slowly and the dihexyl compound is not hydroxylated at all.

Thus a definite correlation exists between the ability of a derivative to serve as substrate for the 6-hydroxylation reaction and its behavioural and psychotropic activity. This points to the significance of the formation of a 6-hydroxylated metabolite in producing behavioural and psychological symptoms for which evidence from animal and human experiments will be presented.

The question will also be discussed how new drugs with direct and indirect psychotropic activity could be designed from metabolic considerations.

105 5-Hydroxytryptamine and 5-Hydroxytryptophan Decarboxylase Activity in the Developing Nervous System of Rats and Guinea-Pigs. S. E. SMITH, R. S. STACEY and I. M. YOUNG (United Kingdom).

The concentration of 5-hydroxytryptamine (5-HT) and 5-hydroxytryptophan decarboxylase activity has been examined in foetal, neonatal and adult rats and guinea-pigs. Only whole brains were used. 5-HT was assayed fluorimetrically and decarboxylase was estimated by the formation of 5-HT on incubation of whole homogenates at pH 8 with excess 5-hydroxytryptophan and pyridoxal-5-phosphate.

In both species the amount of decarboxylase activity at birth approached the adult figure. This was also true of the amount of 5-HT stored in the brains of guinea-pigs at the same stage of development. Even during the latter half of foetal life the 5-HT concentration was as much as half that of the adult and rose during the first few weeks of extra-uterine life. This finding contrasts strikingly with the very low concentrations of 5-HT found by Nachmias in the neonatal rat.[1]

In the brain there appears to be a dissociation of decarboxylase activity (which, unlike that in the kidney,[2] develops very early in foetal life) from 5-HT storage which increases much later. At birth, guinea-pigs are relatively well developed whereas rats are very immature. The results suggest a correlation between the amount of 5-HT in the brain and the degree of maturity.

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1. NACHMIAS, V. T. (1960), *J. Neurochem.*, **6,** 99.
2. HUANG, I., TANNENBAUM, S. and HSIA, D-Y. Y. (1960), *Nature (Lond.)*, **186,** 717.

106 Effect of Reserpine and the Metabolism of Serotonin in Tryptophan Deficient Rats. E. M. GAL, P. A. DREWES and C. A. BARRACLOUGH (U.S.A.).

Rats kept on tryptophan-free diet for 6 weeks showed about 70 per cent lower serotonin in the brain than their tryptophan fed controls. A single injection of 5 mg/kg of reserpine phosphate produced sedation and 80 per cent mortality in these chronically deficient rats. Mitochondrial monoamine oxidase activity was only increased in the liver after 4 weeks on deficient diet. When rats were given on the ninth day of dieting a single dose of 5 mg/kg of reserpine, the controls regained their normal serotonin and norepinephrine levels by the twenty-first day while those on the deficient diet remained serotonin depleted. By this method, serotonin-depleted rats could be produced well before the onset of chronic tryptophan deficiency with less than 5 per cent mortality. The serotonin levels were 75 per cent lower in the brain and the spleen, 70 per cent lower in the blood and 60 per cent lower in the small intestine than those of the controls. There was no meaningful difference in the norepinephrine content of the brain between the serotonin depleted and the control animals. A second injection of 1–2 mg/kg of reserpine on the twenty-third day produced sedation in both groups of rats. EEG studies failed to reveal any difference in the hypothalamic activity or in thresholds of arousal and recruiting in either control or in the depleted rats after administration of reserpine. It is concluded that the control nervous system action of reserpine does not require the presence of serotonin in rat brain.

107 Comparative Effects of α-Ethyltryptamine Isomers on Certain Systems in vitro and in vivo. M. E. GREIG, A. J. GIBBONS, J. P. DAVANZO and O. K. SEBEK (U.S.A.).

The D- and L-isomers of α-ethyltryptamine (α-ET) are monamine oxidase inhibitors of the competitive type. When tested *in vitro*, both forms were equally effective in suppressing the oxidation of

serotonin (5-hydroxytryptamine). Acute experiments *in vivo* in rats showed that D,L-α-ET alone caused an approximately 30 per cent increase of the brain serotonin in 1 hr. When the administration of D,L-α-ET was followed by 5-hydroxytryptophan (5-HTP) much higher levels of the brain serotonin were found. These were dependent on the doses of both α-ET and 5-HTP. When D,L-α-ET was followed by tryptophan (TP) the levels of brain serotonin also increased, but in this case higher doses of the inhibitor tended either to lower or to cause no further increase of brain serotonin. Since α-ET caused a maximum level of serotonin accumulation only when administered with 5-HTP, but not with TP, it was postulated that larger doses of α-ET inhibited 5-hydroxylation of TP. Support for this hypothesis was provided by determining the effect of α-ET on the synthesis of violacein, a bacterial (*Chromobacterium violaceum*) pigment, the development of which is dependent on 5-hydroxylation of TP. The amount of pigment formed was inversely proportional to the amount of either α-ET isomer, the D-form being more inhibitory. In chronic experiments with rats D,L-α-ET caused increases of brain norepinephrine. Polydipsia of unknown origin was caused only by the L-isomer. In dogs the D-form caused a greater stimulation of the central nervous system than the L-isomer. Additional testing is necessary before the significance of these observation can be determined.

108 Interactions of Serotonin and Other Indoles with Pyridine Coenzymes and Related Structures. S. G. A. ALIVISATOS (U.S.A.).

Diphosphopyridine nucleotide (Coenzyme I) and other "onium" bearing structures interact non-enzymically with various indoles including serotonin and tryptophan (charge-transfer complexes). When these phenomena were first observed in our laboratory,[1] they became apparent by the visual appearance of a yellow-greenish coloration. The spectroscopic counterpart of the visual impression was a broad, featureless absorption band extending from beyond 400 mμ to at least 300 mμ (transfer-spectrum).[2] The high absorption of both DPN and the indoles at the concentrations required for *in vitro* interactions prevented extension of the curves below 300 mμ. Kinetic and equilibria considerations[3] led to the conclusion that at least in the pH range 2·0 to 8·0 these interactions occur between one coenzyme molecule and one molecule of the indole. It was also shown that in this pH range there is not much difference in the intensity of the colour developed upon admixture of the reactants. However, at pH values above 8·0 the colour intensity increased rapidly. The equilibrium constants of these associations have been determined. Also, the dependence of the associations on various other groupings present in the interacting species, like the ethylamine residue of serotonin and the 6-aminopurine of coenzyme I, have been studied. The coenzyme I–tryptamine complex was isolated in relatively pure form and its properties were studied. The mechanism of these phenomena and their possible relation to *in vivo* interactions will be discussed.

1. *S.G.A. Alivisatos in* SHAFFER, J. H. *et al.* (1958), *Mechanisms of Hypersensitivity*, p. 259.
2. *Nature (Lond.)*, **186,** 718 (1960); **187,** 374 (1960).
3. *Biochim. Biophys. Acta.*, In press.

109 The Influence of Some Indole Derivatives on the Activity of Choline Acetylase and CoA. B. BOŠKOVIĆ and R. PRŽIĆ (Yugoslavia).

We have investigated the influence of the following substances on the activity of choline acetylase and CoA: *o*-phosphoryl-4-hydroxy-N-dimethyl tryptamine (Psilocybin); 5-hydroxytryptamine (5-HT); D-lysergic acid diethylamide (LSD_{25}); 2 - methyl - 3 - ethyl - 5 - dimethylaminoindole (Medmain); 2-brom-lysergic acid diethylamide (BOL); 7-methoxy-1-methyl-9 pyrid (3:4-β)-indole and adrenochrome.

We have found that Psilocybin, harmine and LSD_{25} in the concentration of 1×10^{-7} M do not have any effect on the activity of choline acetylase. 1×10^{-6} M in the system potentiates the action of the enzyme. BOL, 5-HT and Medmain are without effect on the activity of choline acetylase in the conc. of 1×10^{-7} M, 5×10^{-7} M and 1×10^{-6} M adenochrome (5×10^{-7} M) shows some inhibitory effect.

Psilocybin, LSD_{25} and Medmain in the concentrations of 1×10^{-7} and 1×10^{-6} M in the system have no effect on the activity of CoA. 5-HT in the concentrations of 1×10^{-7} M, 5×10^{-7} M and 1×10^{-6} M inhibits CoA, the percentage of inhibition depending on the concentrations used. BOL, 1×10^{-7} M, has no effect on the activity of CoA, but at the conc. of 1×10^{-6} M shows some inhibitory effect. Adrenochrome, 1×10^{-6} M, also shows some inhibitory to determine by the method used because of chemical interference by harmine with the other reagents.

110 Reserpine and Cardio-Vascular Centres. C. HEYMANS, A. F. DE SCHAEPDRYVER, G. R. DE VLEESCHHOUWER, A. C. TAQUINI, JR., and J. B. VAN DER SCHOOT (Belgium).

Pharmacological effects of reserpine on cardiovascular centres have been studied in 35 mongrel dogs, anaesthetized with morphine-chloralosane.

Intracisternal injections of reserpine (0·1 mg/kg) induce, in most cases, a moderate increase of the general arterial blood pressure and a marked sensitization of the carotid sinus vasomotor reflexes.

Injections of reserpine (20 mg) into the arterial circulation of the isolated perfused head, connected with the body by the vagi only, provoke a pronounced sensitization of the cardio-inhibitory centre to both reflex and direct stimulations.

Injections of reserpine (20 mg) into the arterial