The Structure of the Metabolic Pathways Involved in the Metabolism of Neurotransmitters, with Emphasis on the γ -Aminobutyrate System

By C. J. VAN DEN BERG (*Study Group on Inborn Errors and Brain, Department of Biological Psychiatry, Faculty of Medicine, University of Groningen, Groningen, The Netherlands*)

The neurotransmitters acetylcholine, 5-hydroxytryptamine, dopamine, noradrenaline and γ -aminobutyrate are synthesized in the brain from precursors, entering the brain from the bloodstream. Schematically one can divide the metabolic pathways of these compounds into three broad categories, as follows.

(1) The neurotransmitter is part of a linear one-way pathway, in which the precursor is converted in a few steps into the transmitter and subsequently degraded to an end product leaving the brain. Apart from the initial precursor, none of the members of these pathways plays a significant role in other metabolic pathways in the brain. The interrelation of these pathways with other metabolic pathways consists only at the level of cofactors, ionic environment, pH etc.

(2) The transmitter is part of a similar system as to that in category (1), but some members of the pathway are utilized in other reactions and the degradation products of the neurotransmitter might be utilized again for the synthesis of the transmitter. The acetylcholine system is an example.

(3) The neurotransmitter is part of a complex set of metabolic reactions. Most of the members of these pathways are also members of other pathways. The γ -aminobutyrate system is an example. The part of the γ -aminobutyrate system that is specifically involved in the transmitter role of γ -aminobutyrate cannot be separated from other parts of the system.

The most important features of the γ -aminobutyrate system are (Van den Berg *et al.*, 1969; Van den Berg & Garfinkel, 1971) as follows.

(a) γ -Aminobutyrate is synthesized presynaptically from glutamate, originating from the tricarboxylic acid cycle.

(b) γ -Aminobutyrate is degraded 'postsynaptically' (neuronal cell bodies, dendrites and glia cells) to succinate, which enters the tricarboxylic acid cycle.

(c) The processes listed under (a) and (b) result in a transport of tricarboxylic acid-cycle intermediates from the presynaptic site to the 'postsynaptic' site. It can be argued that glutamine flows in the opposite direction, thereby compensating for the loss of intermediates in the presynaptic site.

Reuptake of γ -aminobutyrate into the nerve-endings from which it originates is probably quantitatively not very important unless the 'physiological'

turnover of γ -aminobutyrate is greater than the metabolic turnover ($0.14 \mu\text{mol/min per g}$).

The γ -aminobutyrate system is therefore not only part of a complex network of reactions, but it also couples the presynaptic and 'postsynaptic' structures together into one system. This type of metabolic coupling of the presynaptic and 'postsynaptic' structures does not occur in the systems classified under (1).

Van den Berg, C. J., & Garfinkel, D. (1971) *Biochem. J.* **123**, 211–218

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The Effect of Electrical Stimulation of the Locus Coeruleus on the Endogenous Concentration of 4-Hydroxy-3-methoxyphenylethylene Glycol in Rat Brain

By D. S. WALTER and D. ECCLESTON (*Medical Research Council Brain Metabolism Unit, Department of Pharmacology, University of Edinburgh, George Square, Edinburgh EH8 9JZ, U.K.*)

Free 4-hydroxy-3-methoxyphenylethylene glycol and its sulphate ester have been shown (Mannarino *et al.*, 1963; Schanberg *et al.*, 1968a), by the use of radioisotope techniques, to be the major metabolites of noradrenaline in brain. 4-Hydroxy-3-methoxyphenylethylene glycol has been demonstrated by g.l.c. to be present in the brain of a number of species (Schanberg *et al.*, 1968b; Sharman, 1969). Histochemical studies (Ungerstedt, 1971) have shown noradrenaline-containing neurons originate in the locus coeruleus, a bilateral structure innervating all parts of cortex. Because of the effects of psychotropic drugs on these neurons (Graham & Aghajanian, 1971) and of the behavioural effects on its stimulation (Arbuthnott *et al.*, 1970), increasing attention has also been focused on this nucleus.

Male albino Wistar rats (180–220 g) were anaesthetized with 1.6% Halothane in O_2 . A concentric bipolar electrode was placed stereotactically in the position of the left locus coeruleus, and electrical stimulation for 1 h was by 2 ms constant-current pulses, alternating in polarity at 0.2 mA and 10/s. Rats were then decapitated and the brains removed. Total 4-hydroxy-3-methoxyphenylethylene glycol was extracted from brain tissue by a method involving precipitation of brain protein with HClO_4 , overnight enzymic hydrolysis of conjugated 4-hydroxy-3-methoxyphenylethylene glycol, ethyl acetate extraction at pH 5.0 and chromatography on Bio-Rad AG1 resin (X4; Cl^- form). The eluate was acetylated (Sharman, 1969), trifluoroacetylated (Bond, 1972) and