Effects of 5,7-dihydroxytryptamine on transmission at serotoninergic synapses

5,7-Dihydroxytryptamine causes a long-lasting depletion of 5-hydroxytryptamine (5-HT), and also strongly inhibits the uptake of 5-HT, in the rat cns (Baumgarten, Björklund & others, 1973; Horn, Baumgarten & Schlossberger, 1973). This report describes the effect of the substance on 5-HT-mediated synaptic transmission from a specific 5-HT-containing neuron in the cns of the snail *Helix pomatia*. This neuron is known to synthesize and utilize 5-HT both as an excitatory and inhibitory transmitter (Cottrell & Macon, 1974; Cottrell, Berry & Macon, 1974). Because the 5-HT neuron and some of the neurons with which it makes monosynaptic connexions are readily identifiable (Cottrell & Macon, 1974), the system offers a unique opportunity to study the effect of drugs on serotoninergic transmission. Such studies are not yet possible in vertebrates because of the central localization of 5-HT-containing neurons.

When 5,7-dihydroxytryptamine (2×10^{-4} M) was tested on the excitatory post-synaptic responses (epsps) produced in the post-synaptic cells by stimulation of the 5-HT neuron, there was a rapid (less than 2 min) abolition of the response. The excitatory response to applied 5-HT was also abolished, but the excitatory response to applied acetylcholine (5×10^{-6} M) was unaffected (drugs were washed over the ganglion). There was a gradual and eventually complete recovery of epsps from the 5-HT neuron (approximately 1 h washing with saline), and a concomitant recovery of the response to 5-HT. 5,7-Dihydroxytryptamine also mimicked the effect of 5-HT applied to the follower neurons (i.e. caused a gradual and prolonged excitation). If following the application of 5,7-dihydroxytryptamine the preparation was briefly washed, the effect of applied 5-HT (2×10^{-5} M), but not acetylcholine (5×10^{-6} M), was abolished. Thus the effect of 5,7-dihydroxytryptamine is apparently due to a blockade of 5-HT receptors.

To test the specificity of the effect of 5,7-dihydroxytryptamine on the epsps elicited by the 5-HT neuron, different nerve trunks were stimulated to produce large epsps from a different source. Such epsps are thought to be cholinergic. They were not altered in amplitude by 5,7-dihydroxytryptamine. Furthermore, no appreciable reduction in membrane resistance due to 5,7-dihydroxytryptamine could be recorded in the follower neurons. The results thus indicate that in *Helix pomatia* 5,7-dihydroxytryptamine produces a relatively specific blockade of serotoninergic transmission by blocking 5-HT receptors.

Preliminary results have also shown that 5,7-dihydroxytryptamine lowers the 5-HT content of, reduces the uptake of 5-HT into, and influences 5-HT metabolism within the 5-HT neuron (Osborne, 1974). The substance does not, however, appear to cause changes in the ultrastructure of the cell. 5,7-Dihydroxytryptamine thus has many actions on 5-HT neurons and serotoninergic transmission.

We thank Dr. M. S. Berry for valuable advice. V. W. Pentreath was supported by a grant from the Medical Research Council to Dr. G. A. Cottrell.

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December 16, 1974

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A comparison between the solid state conformation of phenmetrazine and the α-sympathomimetic pharmacophore pattern

Some time ago one of us proposed phenmetrazine as a structure obeying the α-adrenergic pattern proposed by Pullman, Coubeils & others, (1972) and Coubeils, Courrière & Pullman (1972). This feature pattern derived from PCILO calculations on a number of phenethylamines is in agreement with that suggested by Kier (1969). The recent X-ray structural analysis of Carlstrom & Hacksell (1974) prompted us to compare in detail the crystal conformation of phenmetrazine with the predicted conformation.

Using a computer program (ROTRAN) developed in this laboratory we translated and rotated the molecule in such a way that the resulting orientation facilitates the inspection of the atomic coordinates with respect to a given molecular plane.

In Fig. 1 phenmetrazine is oriented so that the phenyl ring lies in the xy-plane and the N atom in the xz-plane. The torsion angles τ_1 and τ_2 as observed in the crystal are −105° and −175° respectively. This conformation is typical for many phenethylamines and is in agreement with one of the energy minima found in amphetamine by the PCILO calculations ($\tau_1 = -90°$ and $\tau_2 = 180°$). In fact, inspection of Fig. 1 shows a striking resemblance with the pharmacophore derived from the PCILO calculations. The distances between the O atom, the centre of the phenyl ring and the N atom are virtually identical to those of the suggested pharmacophore.

The slight departure of the distance from the N atom to the plane through the

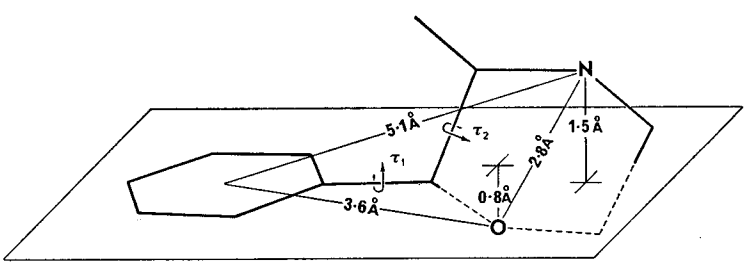

FIG. 1. Phenmetrazine as seen with the phenyl ring in the xy-plane and the N atom in the xz-plane.