THE PHARMACOLOGICAL ACTIVITY OF SOME CYCLIC ANALOGUES OF CHOLINE

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A number of choline analogues have been shown to interact at cholinergic synapses (Burgen et al, 1956; Bowman et al 1967; Barker & Mittag 1975). It has been demonstrated that many analogues inhibit the high affinity transport of choline into synaptosomes while some analogues are acetylated by choline acetyltransferase in vitro (Sollenberg et al 1979).

3-Hydroxy-N,N-dimethylpiperidinium (3-hydroxypiperidinium) and 2-hydroxymethyl-N,N-dimethylpiperidinium (2-hydroxymethylpiperidinium) are analogues in which a choline moiety is immobilized by being fixed in a ring structure (Borkhataria et al 1979). The choline moiety of hemicholinium-3 (HC-3), is fixed in a morpholinium ring in a similar way to the choline moiety of the 3-hydroxypiperidinium molecule. Apart from the hemicholinium analogues, there has been very little work conducted on cyclic choline analogues and it was therefore thought of interest to study these cyclic piperidinium compounds and investigate their actions at the cholinergic synapse.

Experiments were performed on nerve-muscle preparations to detect any action on cholinergic transmission. Both piperidinium analogues were found to have a blocking action on the rat phrenic nerve diaphragm preparation. 3-Hydroxypiperidinium, 5.4 μmol /ml, and 2-hydroxymethylpiperidinium, 3.6 μmol /ml, produced a block of muscle contractions in the rat diaphragm. This paralysis was shown to be prejunctional in nature by being reversed by choline 0.1 μmol /ml.

The two analogues had a direct depolarising action on the frog rectus abdominis muscle. 3-Hydroxypiperidinium, 1 μmol /ml, and 2-hydroxymethylpiperidinium, 0.7 μmol /ml enhanced the acetylcholine induced contractions of the frog rectus muscle and also independantly had a direct depolarising action on the muscle. Acetylcholine itself had an effect on the muscle at a concentration of 0.8 nmol /ml.

The two piperidinium analogues were shown to inhibit the transport of ^{3}H-choline into synaptosomal fractions of rat brain. 3-Hydroxypiperidinium was twice as effective as 2-hydroxymethylpiperidinium in this respect. A quantity of ^{14}C-3-hydroxypiperidinium was synthesized by a quaternisation procedure and this compound was itself shown to be incorporated into a preparation of synaptosomes in vitro. The synaptosomes were shown to acetylate 50% of the accumulated analogue to 3-acetoxy-N,N-dimethylpiperidinium (3-acetoxypiperidinium) indicating that 3-hydroxypiperidinium acts as a precursor of a false cholinergic transmitter.

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