The conformations of cholinergic agonists

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We have been determining the conformations of nicotinic and muscarinic agonists by X-ray diffraction analysis of crystals of the compounds. By correlating the observed conformations of agonists which selectively activate specific receptors, and by considering possible perturbations of the conformations observed in crystals, it is possible to determine a unique conformation for any specific class of compounds. A correlation of the crystal structures of the nicotinic agonists acetylcholine, 1,1-dimethyl-4-phenyl piperazinium, nicotine, lactoylcholine and acetyl-α-methylcholine allows specification of the conformation of such agonists at nicotinic receptors. It appears that the ganglionic receptor can accommodate a longer molecule than the motor end plate receptor. A similar correlation of the crystal structure analyses of the muscarinic agonists muscarine, 2-methyl-4-trimethylammoniummethyl-1,3-dioxolan, acetyl-β-methylcholine, acetyl-α-methylcholine and *trans*-acetoxy cyclopropyl trimethylammonium allows the active conformation at muscarinic receptors to be specified. The absolute configuration of potent muscarinic agonists whose stereoisomers have been separated and tested is entirely consistent. It appears the conformation of acetylcholine relevant to the nicotinic junction and to the muscarinic junction is the same, but the molecule fits on the receptors in different ways.

The conformations of muscarinic antagonists

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We have determined the conformations of hyoscine hydrobromide and hyoscyamine hydrobromide by X-ray diffraction analysis of crystals of the compound. The two observed conformations are almost identical though the crystal packing is completely different. A comparison of these conformations and that of the muscarinic antagonist quinuclidinyl benzilate analysed by Carlstrom and Meyerhöffer (1969) shows that the three muscarinic antagonists whose structures are known are very similar. By using this evidence on the preferred conformation of muscarinic antagonists and one rule about the preferred conformation of an organic functional group, it is possible to specify the required conformation of muscarinic antagonists and the chemical groups necessary for potent antagonistic activity. The conformations of many compounds in this class can be predicted in this way.

REFERENCE

CARLSTROM, D. & MEYERHÖFFER, A. (1969). The crystal structure of quinuclidinyl benzilate. *Acta Cryst.*, B25, **6**, 1119–1123.

Saturation effects in the uptake of decamethonium in skeletal muscle

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Decamethonium has been found to accumulate in the end-plate region of mice, but no evidence of saturation was found (Waser, 1965). In rats which have been injected with labelled decamethonium the compound enters muscle fibres in the