Neither THC nor CBD in concentrations up to $1{\cdot}59\times10^{-5}$M had any effect on the rat phrenic nerve diaphragm preparation, or on acetylcholine induced contractions of the frog rectus abdominis muscle. THC ($1{\cdot}59\times10^{-5}$ mol/kg) was given intraperitoneally to the anaesthetized cat and had no effect on the pre- or post-ganglionically stimulated nictitating membrane.

THC and CBD would therefore appear to be inactive at the cholinergic sites investigated other than at the postganglionic parasympathetic nerve ending.

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An anticurare effect of hexamethonium at the mammalian neuromuscular junction

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The effect of hexamethonium on blocked or partly blocked neuromuscular transmission has been investigated using the rat diaphragm-phrenic nerve preparation immersed in a saline medium (Liley, 1956) at 36° C.

In preparations in which the contractile responses to nerve stimulation had been reduced to about 20% after the addition of (+)-tubocurarine chloride(8×10^{-7}M) following the addition of hexamethonium ($2{\cdot}8\times10^{-4}$M) the contractions increased to about 40% of the unblocked control within 8 minutes. This partial reversal of the block due to (+)-tubocurarine was maintained until the hexamethonium was washed out.

Endplate potentials (e.p.p.s) were recorded from curarized preparations with an insulated wire electrode placed extracellularly at the endplate region, the indifferent electrode being placed in the bath away from the preparation. Following the addition of hexamethonium, the amplitude of the e.p.p. was increased. The extent of the increase depended on the concentration of hexamethonium; the maximum increase was to 480% of the control size and was obtained with 8×10^{-4}M hexamethonium. When higher concentrations of hexamethonium were applied to the curarized preparation, the increase of the amplitude of the e.p.p. was less. The enhancement of the amplitude of the e.p.p. was seen only after (+)-tubocurarine had been used to produce neuromuscular block; in preparations blocked by gallamine or Mg^{++}, the addition of hexamethonium always resulted in a decreased size of the e.p.p.

In curarized preparations there was no prolongation of the e.p.p. after the addition of hexamethonium, which suggests that this drug had no anticholinesterase action. Hexamethonium had no effect on the velocity of hydrolysis of acetylcholine by erythrocyte acetylcholinesterase.

The mean quantal content of the e.p.p. elicited at 1 Hz was 178 ± 13 (thirty-one cells) in the presence of (+)-tubocurarine, and 149 ± 12 (thirty-four cells) after the addition of hexamethonium at $2{\cdot}8\times10^{-4}$ M.

It is concluded that hexamethonium exhibits an anticurare effect by some postsynaptic action on the muscle cells.

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Conformations and biological activities of cyclic analogues of choline aryl ethers

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In order to stimulate nicotinic receptors, Clark, Dawes & Williams (1968) suggested that choline phenyl ether must adopt a conformation in which the dihedral angle ('angle-of-twist') between the plane containing the benzene ring and the ether oxygen, and the plane containing the ether oxygen and the carbon atom situated β to the quaternary nitrogen must be 0°.

To look further into the problem of relating the conformations of choline aryl ethers with biological activity we have synthesized and studied (8-methyl-chroman-2-ylmethyl)trimethylammonium bromide (I), *cis* (II) and *trans* (III) isomers of N,N,N-trimethyl-2-phenoxycyclohexylammonium bromide, *cis*-N,N,N-trimethyl-2-(2,6-xylyloxy)cyclohexylammonium bromide (IV) and N,N-dimethyl-3-phenoxy-piperidinium bromide (V). The angles-of-twist about the phenyl oxygen bonds, determined using ultraviolet spectroscopy (Clark & Williams, 1967), are I—50°, II & III—48°, IV—75·5°, V—50·5°. The ring structures require a gauche conformation for the (O)C–C($\overset{+}{\text{N}}$) bond in compounds II, III & IV, and a fully staggered conformation in compound V.

On the pithed rat only compound V (300 μg i.v.) elicited appreciable ganglion stimulant activity producing a rise in blood pressure (inhibited by pentolinium, 0·5 mg i.v.) similar in magnitude to that produced by 20 μg of choline phenyl ether. On the guinea-pig isolated ileum, however, no compound elicited a nicotinic response. Examination of molecular models of compounds II, III and V shows that though free rotation about the phenyl-oxygen bond is restricted a conformation can be made in which the 'angle-of-twist' approaches 0° and the measured angles for these compounds are time averaged. If the assumption is made that a small degree of bond distortion occurs and allows compounds II, III and V to adopt a 0° 'angle-of-twist' about the phenyl-oxygen bond then our results suggest that a fully staggered conformation of the (O)C–C($\overset{+}{\text{N}}$) moiety is essential in order to stimulate the ganglionic receptors concerned in producing the pressor response in the rat.

All the test compounds blocked the ganglionic action potential in the rabbit isolated superior cervical ganglion preparation, the concentrations required to achieve a *ca* 50% blockade of the action potential being respectively II—1·1, III—1·3, V—1·6, IV—2·5, I—3·2 μg/ml. The concentration of choline phenyl ether required to achieve the same degree of blockade was, however, only 0·02 μg/ml. The possession of such low-level blocking activity by all the test compounds makes valid conclusions regarding the conformational requirements for blockade of the superior cervical ganglion difficult to draw.

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