Inter-quaternary distance and ganglion-blocking activity in bis-quaternary compounds

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(*Communicated by H. R. Ing, F.R.S.—Received* 5 *August* 1958—*Revised* 6 *October* 1958)

(This paper has been published in full in *Proceedings* B, **150**, 381.)

Abstract

Ganglion-blocking agents of the bis-quaternary ammonium type fall into two classes: (1) those in which blocking activity depends upon the length of the chain connecting the two nitrogen atoms, and (2) those in which activity is relatively independent of the length of the linking chain. Members of the first class contain small quaternary groups, e.g. trimethylammonium; mono-quaternary ions containing such groups normally stimulate ganglia, but bis-quaternary ions of class (1) have a purely blocking action. Members of class (2) contain larger quaternary groups, e.g. triethylammonium, which also confer a purely blocking action upon mono-quaternary ions.

It is assumed that the blocking action of members of class (1) is due to their simultaneous combination with two receptor groups, as was originally suggested by Paton & Zaimis for the methonium series. Inter-quaternary distance/probability distributions are calculated for homologous polymethylene (4 to 8 carbon chains) and phenylalkane (2 to 4 carbon atoms in the alkane group) bis-quaternary compounds, taking into account the small number of atoms in the linking chains, the valency angle restriction, the energy barrier hindering free rotation about single bonds and the repulsion between the two terminal charges. The distributions so obtained can be satisfactorily correlated with ganglion-blocking activities in terms of the extent of overlap between them and an assumed distance, varying over the range 6 to 7·8 Å, between two receptors.

It is suggested that acetylcholine acts on ganglia by combining reversibly with an anionic group in a protein constituent of the synaptic membrane, and that this combination interferes with the interactions of neighbouring ionic groups in the protein, so causing a reversible rearrangement of the secondary or tertiary protein structure which allows depolarization of the membrane to occur. Bis-quaternary blocking agents of class (1) are assumed to combine similarly with an acetylcholine receptor, but the postulated protein rearrangement to be prevented by the simultaneous combination of the drug with an adjacent anionic group, so that the protein is temporarily 'locked' in its resting configuration.

Compounds of class (2), in virtue of their larger quaternary groups, are regarded as being unable to approach the acetylcholine receptors closely enough to cause the postulated protein rearrangement (although they hinder the close approach of acetylcholine), so that no locking mechanism need be invoked and activity is consequently independent of the length of the linking chain.

The inclusion of polymethylene bis-*N*-methylpyrrolidinium compounds in class (1) is explained by the discovery that certain members of the homologous series of *N*-alkyl-*N*-methylpyrrolidinium salts stimulate ganglia. The lack of ganglion-blocking activity among bis-quaternary compounds containing a rigid linking structure is also shown to be consistent with the basic hypothesis adopted in this paper.

BIOGRAPHICAL MEMOIRS OF FELLOWS OF THE ROYAL SOCIETY

VOLUME 4 NOVEMBER 1958 PRICE £1. 10s. (Post extra)

(Bound in blue buckram with 27 half-tone plates)

Published by the Royal Society, Burlington House, Piccadilly, London, W. 1

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PROCEEDINGS OF THE ROYAL SOCIETY, SERIES A

No 1265 26 May 1959 Vol 251

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PRINTED IN GREAT BRITAIN FOR THE ROYAL SOCIETY AT THE UNIVERSITY PRESS, CAMBRIDGE
(BROOKE CRUTCHLEY, UNIVERSITY PRINTER)