

SUMMARY

- (1) In view of the controversial literature reports on the nature of antagonism exhibited by the nicotinic ganglion blockers and the interest evinced in the muscarinic ganglion receptors from time to time, it was decided to investigate the mode of action of several nicotinic ganglion blockers (hexamethonium, tetraethylammonium, mecamylamine, pempidine, chlorisondamine and pentolinium) and also of atropine (muscarinic ganglion blocker) in great detail employing a variety of test objects. The nicotinic ganglionic blockers were investigated with the intact dog nictitating membrane, isolated rabbit and guinea pig ileum and isolated hypogastric nerve vas deferens. The muscarinic ganglion blocker (atropine) was investigated with the intact cat nictitating membrane.
- (2) Contractions of dog nictitating membrane in situ were recorded by a frontal writing lever. Preganglionic fibres of the superior cervical ganglion were stimulated by supramaximal rectangular pulses of 2.5 msec duration at frequencies ranging from 1 to 250/sec for 30 sec every 10 min. The ganglion blocking agents were administered closely into the arterial blood supply of the ganglion. Analysis of the data according to the method of Arunlakshana & Schild (1959) revealed that hexamethonium, tetraethylammonium and lower doses of mecamylamine, pempidine, chlorisondamine and pentolinium acted competitively whereas the higher doses of the latter four blockers did not act competitively.

(3) Contractions of the isolated rabbit ileum were recorded by isotonic and auxotonic levers and those of the isolated guinea pig ileum were recorded by isotonic lever. Nicotine and DMPP were used as agonists.

(a) Isotonic lever : Analysis of the data according to the method of Arunlakshana & Schild (1959) revealed that hexamethonium and tetraethylammonium and lower doses of mecamlamine, pempidine, chlorisondamine and pentolinium acted competitively and the higher doses of the latter four blockers did not act competitively.

(b) Auxotonic lever : (i) Hexamethonium and tetraethylammonium and lower doses of mecamlamine, pempidine, chlorisondamine and pentolinium acted competitively and the higher doses of the latter four blockers did not act competitively (analysis of Arunlakshana & Schild, 1959). (ii) Recovery of the responses of isolated rabbit ileum to DMPP following exposure to hexamethonium (4.95×10^{-5} M) for 15 min occurred after 15 min while that following exposure to chlorisondamine (2.76×10^{-7} M) occurred after 75 min. (iii) The dose ratios of hexamethonium (4.95×10^{-5} M) and chlorisondamine (8.83×10^{-6} M) with DMPP as the agonist were 12.75 ± 0.36 and 8.36 ± 0.21 respectively. When the same doses of hexamethonium and chlorisondamine were added cumulatively in three divided doses each, the dose ratios were 11.69 ± 0.21 and 19.56 ± 0.36 respectively. (iv) Next, the data obtained with hexamethonium and chlorisondamine were subjected to analysis according to the method of Paton & Rang (1965). The dose ratios

of hexamethonium (4.95×10^{-5} M) and chlorisondamine (2.76×10^{-6} M) with DMPP as the agonist were 9.0 ± 0.6 and 4.0 ± 0.3 respectively. When both the antagonists were used together in the same concentrations the dose ratio was 38.0 ± 1.5 which is very close to the product of the individual dose ratios ($9 \times 4 = 36$). (v)

Hexamethonium (1.57×10^{-4} M) and chlorisondamine (8.83×10^{-7} M) or hexamethonium (1.57×10^{-4} M) and chlorisondamine (8.83×10^{-8} M) induced nonparallel shifts to the right of dose-response curves of DMPP and there was reduction of maximal responses. However, hexamethonium (1.57×10^{-4} M) and chlorisondamine (2.76×10^{-8} M) induced a parallel shift of the dose-response curve and there was no reduction of the maximal responses. This indicated that hexamethonium (1.57×10^{-5} M) could protect the specific receptors against the lower dose of chlorisondamine but not against the higher doses of chlorisondamine. The data under (ii), (iii), (iv) and (v) support the earlier conclusion that hexamethonium acted competitively and chlorisondamine did not act competitively.

(vi) Atropine antagonised responses to DMPP. The antagonism was not competitive (analysis of Arunlakshana & Schild, 1959). This supports the literature reports (van Rossum, 1962 a,b).

(4) Contractions of the isolated vas deferens were recorded by isotonic lever. Hypogastric nerve supplying the muscle was stimulated preganglionically with supramaximal rectangular pulses of 2.5 msec duration at frequencies ranging from 1 to 250/sec for 30 sec every 10 min. Lower doses of hexamethonium, tetraethylammonium, mecamylamine, pempidine, chlorisondamine and pentolinium

produced parallel shifts to the right of the frequency-response curves. This suggested competitive antagonism. With higher doses, the shifts were not parallel and the maximal responses were reduced. Analysis of the data according to Arunlakshana & Schild (1959) indicated that none of the blockers acted competitively.

(5) Contractions of the cat nictitating membrane in situ were recorded as described for the dog membrane. Muscarine and 4-(*m*-chlorophenyl-carbamoyloxy)-2-butyryl-trimethylammonium chloride (McN-A-343) were used as agonists and were injected by close intra-arterial injections into the blood supply of the superior cervical ganglion. Both the agonists elicited dose-related contractile responses of the nictitating membrane. The agonist dose-response curves were shifted to the right in a parallel manner (without suppression of the maximal responses and flattening of the curves) by atropine. Analysis of the data according to the method of Arunlakshana & Schild (1959) indicated that the antagonism was competitive.

(6) It is concluded that hexamethonium and tetraethylammonium acted as competitive antagonists at the superior cervical ganglion of dog and the ileum of rabbit and guinea pig. Hexamethonium, tetraethylammonium, mecamlamine, pempidine, chlorisondamine and pentolinium did not act competitively at the peripheral ganglia on hypogastric nerve innervating vas deferens. Mecamlamine, pempidine, chlorisondamine and pentolinium did not act competitively at the superior cervical ganglion of dog and the

ileum of rabbit and guinea pig. Atropine antagonised competitively the responses to the two "non-nicotinic" ganglionic stimulants, muscarine and McN-A-343 at the superior cervical ganglion of the cat.