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GLYCOPYRRONIUM BROMIDE, AN ULTRAPOTENT M_1-SELECTIVE MUSCARINIC RECEPTOR ANTAGONIST *IN VITRO*.

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Glycopyrrolate is a muscarinic receptor antagonist widely used in anesthesia instead of atropine, but little is known about its selective blockade of muscarinic receptor subtypes. We therefore determined equilibrium dissociation constants of glycopyrronium bromide under *in vitro* conditions for M_1 (inhibition of twitch response on rabbit vas deferens), M_2 (inhibition of force of contraction of paced rat left atria), and M_3 (contraction of guinea pig ileum), and an atypical muscarinic receptor (contraction of rabbit iris sphincter; see Bognar et al. Naunyn-Schmiedeberg's Arch. Pharmacol. 1992, 345:611-618) which neither corresponds to M_1-M_3 nor to M_4 or m_5. (±)-Methacholine served as agonist in all models except in rabbit vas deferens where McN-A-343 was used. The affinity of glycopyrronium bromide was high for the M_1 receptor (apparent -log K_B value of 11.4±0.08, n=14). The drug blocked M_2 receptors in rat atria (n=14) with considerably lower affinity (-log K_B 9.1±0.08) compared to M_1 and M_3, and the atypical receptors, and possessed about equal potencies at the M_3 (-log K_B 10.3±0.03, n=10) and at the iris receptor (-log K_B 10.2 ±0.08, n=10). It is concluded that glycopyrronium bromide is *in vitro* an M_1-selective antimuscarinic drug with an about 100 or 10 fold higher affinity for M_1 or M_3 and iris receptors, respectively, compared to atropine. In contrast, at the M_2 receptor it is equipotent with atropine. Supported by DFG.

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ON THE OVER-ADDITIVE ANTIMUSCARINIC ACTION WITH ATROPINE OF POTENT ALLOSTERIC STABILIZERS OF ANTAGONIST BINDING TO M_2-RECEPTORS

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W84 (hexamethylene-bis-[dimethyl-{3-phthalimidopropyl} ammonium bromide]) stabilizes antagonist binding to M_2-receptors by an allosteric mechanism and acts in combination with atropine over-additively antimuscarinic.
Two derivatives of W84 were synthesized in which the phthalimide groups were replaced by 2-phenyl-2,3-dihydro-1H-quinazolin-4-one (Chin3/6) and in which the central bisquaternary moiety was changed to give 4,4'-bis-(phthalimidomethoxyiminomethyl)-1,1'-propane-1,3-diyl-bis-pyridinium dibromide (W-DUO). The stabilizing effect on [^{3}H]N-methylscopolamine binding was studied in guinea pig cardiac membranes (3mM $MgHPO_4$, 50mM Tris, pH 7.3, 37°C) and in intact left atria (3Hz, Tyrode's solution). The antimuscarinic action of the compounds was measured in left atria with oxotremorine as agonist. In cardiac membranes, the [^{3}H]N-methylscopolamine dissociation rate was reduced to half of the control value by the three compounds at EC_{50}~1μM. In intact atria, the allosteric activity was less pronounced (EC_{50}~10μM). The compounds had similar antimuscarinic potencies (pA_2~6). When combined with 1μM atropine, W84 and W-DUO exhibited (≥10μM) an over-additive antimuscarinic action. In contrast, Chin3/6 did not induce an overadditive effect. Thus, the structural modifications did not attenuate allosteric activity. However, the over-additive effect was lost when the phthalimide group was replaced by the quinazolinone moiety.