Title: ANTAGONISM OF PRE- AND POSTSYNAPTIC NEUROMUSCULAR BLOCK BY METHYLGUANIDINE AND 4-AMINOPYRIDINE

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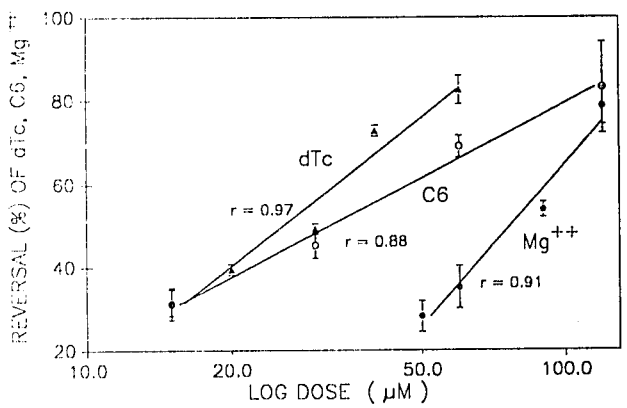
Introduction. It has been reported (1) that methylguanidine (MeG) prevents and antagonizes the neuromuscular (NM) block caused by nondepolarizing muscle relaxants (NDMR). NDMR inhibit NM transmission primarily by preventing the interaction of acetylcholine (ACh) with the cholinergic receptors of the postjunctional membrane and secondarily by antagonizing the positive nicotinic feedback mechanism of ACh mobilization from reserve depots (RES) to readily releasable sites (REL) (2). MeG also antagonizes the Mg^{++} induced NM block (1) caused by inhibition of release of ACh (3). In the present study we investigated the MeG antagonism of the NM block caused by hexamethonium (C6), a compound that causes NM block by inhibiting mobilization of ACh from RES to REL (2). We also compared the rates of development of the antagonist effect and the relative potencies of MeG and 4-aminopyridine (4-AP) for the reversal of the > 90% d-tubocurarine (d-Tc) block and the relative potencies of MeG for the reversal of > 90% d-Tc, Mg^{++} and C6 block.

Methods. Male Sprague-Dawley rats weighing 275 to 375 g were lightly anesthetized with ether and decapitated. Their phrenic nerve-hemidiaphragm preparations were suspended in modified Krebs' solution (4) having the same $[Ca^{++}]$ and $[Mg^{++}]$ as rat plasma. The bath was aerated with 95% O_2-5% CO_2 and its temperature was kept at 37°C; pH 7.38 to 7.42. The phrenic nerves were stimulated with supramaximal, square wave impulses of 0.2 ms duration at 0.1 Hz. The isometric force of contraction (P) of the muscles was quantitated by FT03 transducers and continuously recorded. After P became stable an about 90% neuromuscular (NM) block was produced by adding the appropriate concentrations of d-Tc, MG^{++} or C6. Subsequently the antagonist effect of MeG on the NM block produced by the 3 compounds was determined with the individual dose method. For the sake of comparison the antagonism of the d-Tc block by 4AP was also determined. In other experiments about 90% NM block was produced by d-Tc and 2 X EC90 of Meg or 4AP, determined in the first series of experiments, was added to the bath. In these experiments the time required for the recovery of P to 50% and 90% of control, the maximal recovery and the time to maximal recovery were observed. The effects of MeG and 4AP were compared with Student's t test; $p < 0.05$ was accepted as significant.

Results. The computer derived log dose-response regression lines for the antagonism of the d-Tc, Mg^{++} and C6 block indicate that MeG is a more potent antagonist of d-Tc (EC50=25.5 μM) than that of Mg^{++} (EC50=76.3 μM). The log dose-response regression lines of MeG and 4AP for the antagonism of the d-Tc block were found to be parallel. 4AP (EC50 = 1.9 μM) is about 12 times as potent as MeG (EC50 = 25.5 μM). After the addition of 2 X EC90 concentration P returned to 50 and 90% of control more rapidly with 4AP than with MeG. The maximal effect of 4AP on P (130.0 ± 7.5% of control) is greater than that of MeG (100.6 ± 5.0%); $p < 0.02$.

Discussion. The slopes of the dose-response regression lines of MeG (40.6) and 4AP (30.4), for the antagonism of d-Tc block, are similar. This indicates that the mechanism of their "anti-curare" effect is the same. In accordance with the different sites and mechanisms of the NM blocking effect of d-Tc, Mg^{++} and C6 the dose-response regression lines of these compounds are not parallel (see figure) and their antagonist potencies are also different. The 2 X EC90 dose of 4AP increased P, depressed by d-Tc, above control. The explanation of this finding is that in higher concentrations, than those necessary to antagonize block of NM transmission, 4AP penetrates into and increases the contractility of the muscle fiber (5). Thus for example, 40 μM 4AP increases P of the directly stimulated diaphragm to 170.0% of control. It appears that MeG does not penetrate easily into the muscle fiber and has no significant effect on its contractility.



LOG DOSE RESPONSE REGRESSION LINES OF MeG FOR THE ANTAGONISM OF dTc, C6, and Mg^{++} BLOCKS

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