Title: SITE ACTION OF BW33A AT THE RAT NEUROMUSCULAR JUNCTION

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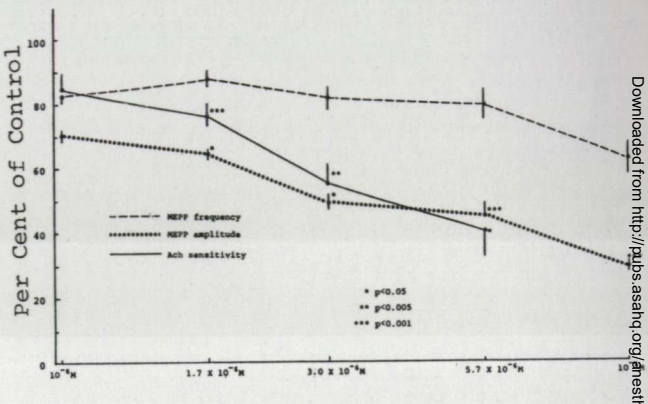
Introduction. Neuromuscular blocking agents of the non-depolarizing variety interact with the cholinergic receptors to produce muscle relaxation. Those receptors are thought to be present on the nerve terminal (presynaptic)[1] and on the motor endplate (postsynaptic). Currently available non-depolarizing agents have varying degrees of effects on both receptors. BW33A is a non-depolarizing muscle relaxant recently developed in the Burroughs-Wellcome Laboratories.[2] The purpose of this study is to elucidate the site of action of this drug at the neuromuscular junction.

Materials and Methods. The isolated rat phrenic nerve-diaphragm preparation was utilized. The preparation was mounted in a muscle bath containing rat Ringer's solution bubbled with 95% O_2 - 5% CO_2 gas mixture and maintained at room temperature (21∿23°C). Intracellular potentials were measured with glass capillary microelectrodes of 10 to 20Ω resistance filled with 3M KCL in a manner described previously.[3] Miniature endplate potentials (Mepps) were recorded and analysis of frequency and amplitude performed. Control observations were made for 3 minutes following which a solution containing the desired concentration of BW33A was added to the bath (10^{-8} - 10^{-5}M) for 15 minutes. Mepps were then again recorded for 3 minutes. Evaluation of the sensitivity of the endplate region to ionophorectically applied acetylcholine (Ach) was similar to that of Del Castillo and Katz.[3] The pipettes were filled with a 4M solution of Ach which was delivered by current pulses of 10 msec in duration. Maximal Ach sensitivity were obtained before and after application of the drug (10^{-6} - 5.7 x 10^{-6}M).

Results. There was significant and dose-dependent depression of Mepp amplitude with BW33A in the concentration range of 1.7 x 10^{-6}M to 10^{-5}M. There was also an equally significant depression of Ach sensitivity in the same dose range (Fig. I). There were no significant changes in Mepp frequency in the entire concentration range studied. Lesser concentrations of the drug had no significant effects on either Mepp amplitude or frequency. There was no change in muscle membrane input resistance or in the action potential generation evaluated by the threshold, rate of rise or spike amplitude.



Discussion. The dose-related decreases of both Mepp amplitude and Ach sensitivity suggest that BW33A has a postsynaptic site of action. The lack of changes in Mepp frequency may indicate the lack of a major presynaptic component of action.

Conclusion. BW33A is a non-depolarizing muscle relaxant with a predominant postsynaptic site of action.

References.

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3. Del Castillo J, Katz B: On the localization of acetylcholine receptors. J Physiol. 128:157-181, 1955.