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Rapid relief of block by mecamylamine of neuronal nicotinic acetylcholine receptors of rat chromaffin cells in vitro: An electrophysiological and modeling study

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Abstract

The mechanism responsible for the blocking action of mecamylamine on neuronal nicotinic acetylcholine receptors (nAChRs) was studied on rat isolated chromaffin cells recorded under whole-cell patch clamp. Mecamylamine strongly depressed (IC50 = 0.34 μM) inward currents elicited by short pulses of nicotine, an effect slowly reversible on wash. The mecamylamine block was voltage-dependent and promptly relieved by a protocol combining membrane depolarization with a nicotine pulse. Either depolarization or nicotine pulses were insufficient per se to elicit block relief. Block relief was transient; response depression returned in a use-dependent manner. Exposure to mecamylamine failed to block nAChRs if they were not activated by nicotine or if they were activated at positive membrane potentials. These data suggest that mecamylamine could not interact with receptors either at rest or at depolarized level. Other nicotinic antagonists like dihydro-β-erythroidine or tubocurarine did not share this action of mecamylamine although proadifen partly mimicked it. Mecamylamine is suggested to penetrate and block open nAChRs that would subsequently close and trap this antagonist. Computer modeling indicated that the mechanism of mecamylamine blocking action could be described by assuming that 1) mecamylamine-blocked receptors possessed a much slower, voltage-dependent isomerization rate, 2) the rate constant for mecamylamine unbinding was large and poorly voltage dependent. Hence, channel reopening plus depolarization allowed mecamylamine escape and block relief. In the presence of mecamylamine, therefore, nAChRs acquire the new property of operating as coincidence detectors for concomitant changes in membrane potential and receptor occupancy.