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Autoregulation of acetylcholine release and micro-pharmacodynamic mechanisms at neuromuscular junction: Selective acetylcholinesterase inhibitors for therapy of myasthenic syndromes

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Abstract

© 2018 Petrov, Nikolsky and Masson. Neuromuscular junctions (NMJs) are directly involved into such indispensable to life processes as respiration and locomotion. However, motor nerve forms only one synaptic contact at each muscle fiber. This unique configuration requires specific properties and constrains to be effective. The very high density of acetylcholine receptors (AChRs) of muscle type in synaptic cleft and an excess of acetylcholine (ACh) released under physiological conditions make this synapse extremely reliable. Nevertheless, under pathological conditions such as myasthenia gravis and congenital myasthenic syndromes, the safety factor can be markedly reduced. Drugs used for short-term symptomatic therapy of these pathological states, cause partial inhibition of cholinesterases (ChEs). These enzymes catalyze the hydrolysis of ACh, thus terminate its action on AChRs. Extension of the lifetime of ACh molecules compensates muscular AChRs abnormalities and, consequently, rescues muscle contractions. In this mini review, we will first outline the functional organization of the NMJ, and then, consider the concept of the safety factor and how it may be changed. This will be followed by a look at autoregulation of ACh release that influences the safety factor of NMJs. Finally, we will consider the morphological features of NMJs as a putative reserve to increase effectiveness of pathological muscle weakness therapy by ChEs inhibitors due to opportunity to use micro-pharmacodynamic mechanisms.

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Keywords

Cholinesterases, Congenital myasthenic syndromes, Micro-pharmacodynamic mechanisms, Myasthenia gravis, Neuromuscular junction

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