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Synaptic Transmission and Excitability

P237.-Mimicking Human Myasthenic Syndromes in C. elegans: Evaluation of Function and Drug Modulation of Nicotinic Receptors

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In humans, gain-of-function mutations in the muscle nicotinic receptor (AChR) lead to slow-channel congenital myasthenic syndromes (SCCMS), characterized by slow decay of endplate currents, destabilization of the closed channel and prolonged activation episodes of AChR. Our goal is to use the free-living nematode C. elegans to generate models of these human syndromes. To this end, we first generated transgenic worms expressing mutant L-AChRs at 9' position of the M2 segment, which has been shown to form the gate of the ion channel in vertebrates. Electrophysiological recordings of L-AChRs from muscle cells of these transgenic worms show an increase of 11- to 14-fold of the open-channel lifetime and decreased desensitization rate with respect to wild-type, as expected for a gain-of-function mutation. We found that quinidine sulfate, a long-lived open-channel blocker of the human AChR used for the treatment of SCCMS, also reduces the open duration of the mutant C. elegans L-AChR. These results show that it is possible to mimic in C. elegans the molecular and functional changes observed in human AChRs as well as their responses to therapeutic drugs. We next generated mutant strains with L-AChRs mimicking gain-of-function mutations that lead to severe slow-channel CMS to be used as models of these human neuromuscular disorders for drug screening and development of therapeutic strategies.