The role of readthrough acetylcholinesterase in the pathophysiology of myasthenia gravis

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Abstract:

Alternative splicing induces, under abnormal cholinergic neurotransmission, overproduction of the rare "readthrough" acetylcholinesterase variant AChE-R. We explored the pathophysiological relevance of this phenomenon in patients with myasthenia gravis (MG) and rats with experimental autoimmune MG (EAMG), neuromuscular junction diseases with depleted acetylcholine receptors. In MG and EAMG, we detected serum AChE-R accumulation. In EAMG, we alleviated electromyographic abnormalities by nanomolar doses of EN101, an antisense oligonucleotide that selectively lowers AChE-R in blood and muscle yet leaves unaffected the synaptic variant AChE-S. Whereas animals treated with placebo or conventional anticholinesterases continued to deteriorate, a 4 wk daily oral administration of EN101 improved survival, neuromuscular strength and clinical status in moribund EAMG rats. The efficacy of targeting only one AChE splicing variant highlights potential advantages of mRNA-targeted therapeutics for chronic cholinergic malfunctioning.

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