Synaptic failure and muscle weakness in anti-MuSK-Myasthenia gravis are exacerbated by cholinesterase inhibition

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In myasthenia gravis (MG) the neuromuscular junction is impaired by the antibody-mediated loss of postsynaptic acetylcholine receptors (AChRs). Muscle weakness can be improved upon treatment with pyridostigmine, a cholinesterase inhibitor, or with 3,4-diaminopyridine (3,4-DAP), which enhances presynaptic quantal release of acetylcholine. The clinical efficacy of pyridostigmine is in doubt for the Muscle Specific Kinase (MuSK) form of myasthenia. In this form of MG, patients develop antibodies against MuSK, a protein essential for assembling AChRs in the postsynaptic membrane. To investigate the role of the pyridostigmine and 3,4-DAP upon MuSK-MG we injected mice with anti-MuSK-positive patient IgG that depletes MuSK from the endplate and leads to muscle weakness over 14 days. Systemic delivery of pyridostigmine at therapeutically relevant levels for one week exacerbated the anti-MuSK-induced structural alterations and functional impairment at motor endplates in the diaphragm muscle. In a sub-clinical model of MG, 9 days of pyridostigmine treatment even precipitated generalised muscle weakness. In contrast, one week of treatment with 3,4-DAP enhanced neuromuscular transmission in the diaphragm muscle. Thus, while both drugs, pyridostigmine and 3,4-DAP, increase acetylcholine in the synaptic cleft, only pyridostigmine potentiated an anti-MuSK-induced decline in endplate AChR density. These results suggest that ongoing pyridostigmine treatment potentiates anti-MuSK-induced AChR loss, specifically by prolonging the activity of acetylcholine in the synaptic cleft.