Patient autoantibodies reveal the role of muscle specific kinase in maintaining the mature neuromuscular junction

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A subset of myasthenia gravis patients have autoantibodies against Muscle Specific Kinase (MuSK), a protein essential for assembling acetylcholine receptors (AChRs) at the developing muscle fibre membrane. To investigate the role of MuSK at the mature neuromuscular junction (NMJ) we injected mice with patient autoantibodies that deplete MuSK from the endplate and studied the time course of both structural and functional changes. C57B6/J mice, receiving daily injections of anti-MuSK patient IgG, lost weight from day 10 and demonstrated whole-body weakness at day 14. Electromyography showed synaptic impairment from day 6 in the *gastrocnemius* muscle and from day 10 in the hemidiaphragm muscle. During the 15 day injection series confocal microscopy revealed linear declines in the area and density of postsynaptic AChRs in the five muscles examined: *tibialis anterior*, diaphragm, sternomastoid, omohyoid and masseter (in each muscle 3-5% / day). Recordings from the diaphragm muscle demonstrated matching declines in the amplitudes of the spontaneous miniature endplate potentials, nerve-evoked endplate potentials and in the safety factor for neuromuscular transmission (all declined at 3% / day). A compensatory presynaptic mechanism became impaired from day 10, suggesting an ongoing role for MuSK in the homeostasis of the mature neuromuscular junction.

Together these results provide evidence that progressive and gradual loss of acetylcholine receptors from postsynaptic clusters is sufficient to cause synaptic failure and muscle weakness in this mouse model of anti-MuSK *myasthenia gravis*. It also highlights the role of MuSK throughout life in targeting and maintaining AChRs at the postsynaptic membrane of the NMJ.