MUSCLE SPECIFIC KINASE AUTOANTIBODIES MODIFY POSTSYNAPTIC MEMBRANE DOMAINS AT THE MOUSE NEUROMUSCULAR SYNAPSE

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Muscle Specific Kinase (MuSK) is a transmembrane tyrosine kinase that functions to coordinate the clustering of acetylcholine receptors (AChR) in the postsynaptic membrane at the developing neuromuscular junction (endplate). Myasthenia gravis is a muscle weakness disease caused by failure of neuromuscular synaptic transmission. In a subset of myasthenia gravis patients, muscle weakness is thought to be caused by MuSK autoantibodies. The pathophysiological mechanisms for anti-MuSK myasthenia gravis remain to be fully described. We have studied the effects of injecting IgG from anti-MuSK-positive patients (AM IgG) into C57Bl6J mice. Mice receiving daily injections of AM IgG developed severe weakness over 15 days. In fibres of the diaphragm muscle, the amplitude of nerve-evoked endplate potentials declined progressively and this could be explained by a similar slow decline in postsynaptic AChRs density [1]. In cultured muscle cells the MuSK signalling pathway results in the assembly of large membrane domains rich in MuSK and AChR. Specifically, neural agrin triggers the activation of a tyrosine kinase cascade involving MuSK and Src kinase, the phosphorylation of the AChR (β-subunit-Y390) and the recruitment of the scaffolding protein, rapsyn, which cross-links the AChRs [2]. In the postsynaptic membrane of mice injected with AM IgG optical sections revealed reductions in the intensity of immunofluorescence for all of these components of the MuSK pathway, compared to control mice. The large AChR-rich postsynaptic membrane domains that are characteristic of healthy endplate disappeared, leaving behind constellations of tiny AChR microaggregates. There was also evidence of increased trafficking of intracellular AChRs beneath the postsynaptic membrane. We anaesthetized mice and used Alexa555-α-bungarotoxin to pulse-label endplate AChRs. AChR-turnover analysis showed that injections of AM IgG reduced the residency time for AChRs in the AChR-rich postsynaptic membrane domains. Our experiments suggest that MuSK autoantibodies cause MuSK to be depleted from the postsynaptic membrane with a consequent reduction in downstream tyrosine kinase signalling at the endplate. This leads to impaired retention of AChRs within the postsynaptic membrane scaffold, explaining the net rate of decline in junctional AChR density and synaptic potentials in our model of anti-MuSK myasthenia gravis.