Myasthenia gravis

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction (NMJ), the connection between nerve and muscle. Patients suffer from fatigue and muscle weakness due to impaired communication between the nerve ending and the muscle fibre. In MG the immune system makes antibodies that attack the NMJ, disrupting its function. In approximately 80% of MG patients, the antibodies bind to and interfere with the acetylcholine receptor (AChR) through which the muscle receives chemical signals from the nerve ending. As many as half of the remaining MG patients instead have recently been shown to have autoantibodies against an important regulatory protein called Muscle Specific Kinase (MuSK). Another, small subset of patients instead have antibodies against low-density lipoprotein receptor-related protein 4 (LRP4), a protein that works together with MuSK to regulate the NMJ. Progression of the disease may be similar in patients with these three forms of autoimmune MG cases, but there are typically differences in age at onset, involvement of thymus and maximum severity. Muscles in different parts of the body may be differently affected.

In a healthy muscle, the nerve terminal releases the neurotransmitter acetylcholine which acts via the acetylcholine receptors (AChRs) on the muscle surface to initiate muscle contraction. Effective neurotransmission of this kind depends upon the tight packing of muscle AChRs into clusters immediately beneath the nerve terminal from which the acetylcholine is released. In MG the numbers of these AChR are often reduced. Patients then can suffer from fluctuating muscle weakness and fatigue.

Autontibodies against AChR (anti-AChR) can recruit the complement protein of the innate immune system to damage the muscle surface at the NMJ. By binding directly to the AChRs, these antibodies can also cause the more rapid destruction of the AChRs at the NMJ. Both these pathogenic mechanisms tend to reduce the ability of the muscle AChRs to respond to acetylcholine released from the nerve. Autoantibodies against MuSK (anti-MuSK) also seem to disrupt NMJ signalling by reducing the number of AChRs at the NMJ, but via a different pathogenic mechanisms. Recent studies in experimental animals suggest that anti-MuSK antibodies act to remove MuSK from the NMJ and that this leads to reduction in the number and density of AChRs without involving complement attack upon the NMJ. In both anti-AChR and anti-MuSK MG the deterioration in AChR numbers progresses so that the ability of the nerve to trigger contraction becomes marginal and often fails upon repeated activation, causing fatigue. The mechanism by which LRP4 antibodies cause impairment of the NMJ has so far not been described.

MuSK and LRP4 are both concentrated with AChRs and help to ensure they remain densely packed at the NMJ. The MuSK-LRP4 complex plays a central coordinating role in the formation of the NMJ during development. Recent work suggests that MuSK remains important in organising the NMJ throughout life. Thus if MuSK is reduced at the endplate (as occurs when anti-MuSK patient antibodies are injected into mice), loss of the organiser leads to loss of the AChRs that convey the contraction signal. Our recent findings suggest that this leads directly to failure of acetylcholine signalling and weakness. Findings over the last years have provided further knowledge about the MuSK-LRP4 protein complex and its important role in stabilising these AChRs at the healthy NMJ. This understanding of how the MuSK

complex supports the NMJ may allow further insight into the processes of AChR loss in disorders like MG, and may potentially reveal a way in which we can help prevent muscle weakness by preventing the loss of AChRs.

A treatment plan for MG may include drugs to enhance the function of the damaged NMJ as well as treatments aimed at reducing the harmful autoimmune antibodies in the blood. Symptomatic drugs, such as inhibitors like acetylcholinesterase (AChEIs), enhance the actions of acetylcholine at the NMJ and thereby increase the activation of the diminished number of AChRs that remain at the myasthenic NMJ. AChEIs are generally the first-line treatment for most patients. However, such AChEIs often become less effective when they are repeatedly used over weeks and months. Clinical observations suggest that AChEIs may not benefit the anti-MuSK form of MG while recent studies in mice raise the possibility that drugs like pyridostigmine might even be harmful in the anti-MuSK form of MG (but not to anti-AChR MG patients). In AChR-positive MG patients, thymectomy (removal of the thymus) may cause remission by reducing levels of anti-AChR antibodies in the blood. Individually tailored immunosuppressive therapy using a range of different drugs is so far still the most effective therapy and may be supplemented by plasma exchange (replacement of the antibody-containing fluid of the blood) in more severe cases of MG.