**Editorial**

**Double agents and breakdown of integrity at the neuromuscular junction in Miller–Fisher syndrome**

The neuromuscular junction lies beyond the protective security network of the blood–brain barrier and the connective tissue sheaths of peripheral nerves. This makes it vulnerable to attack by a variety of foreign agents such as the bacterial toxin that causes botulism and the paralytic components of animal venoms such as α-latrotoxin, produced by the black widow spider. In addition, homology between foreign antigens and extracellular components of ‘self’ proteins (‘molecular mimicry’) may result in autoantibodies of internal origin, arising during the normal defensive activity of the immune system, acting as double agents by binding to normal components of the neuromuscular junction. In the Miller–Fisher syndrome (MFS), a variant of Guillain–Barré syndrome characterized by ophthalmoplegia, areflexia and ataxia, it has been known for some time that antibodies against GQ1b gangliosides are generally present (reviewed in Willison and O’Hanlon, 1999) and that these antibodies can bind to motor nerve terminals and disrupt their function (Roberts et al., 1994; Buchwald et al., 1995). This has led to the suggestion that impairment of neuromuscular transmission may lie at the heart of some of the motor symptoms of MFS. In the present issue, O’Hanlon and colleagues take this evidence further with their report of overt structural breakdown of the nerve terminal associated with the disruption of neuromuscular transmission by anti-GQ1b antibodies in vitro (O’Hanlon et al., 2001).

There is good evidence that the anti-GQ1b antibodies present in MFS are often elaborated against LPS sequences on the bacterium *Campylobacter jejuni*, a common cause of enteritis. It is generally believed that the distinctive involvement of the extraocular muscles in MFS is a result of particularly high levels of GQ1b gangliosides in the cranial nerves that supply the eyes (Chiba et al., 1997), although it is by no means clear that this is the whole story. Neurophysiological studies have suggested that, while the functional defects in MFS are primarily sensory in the limbs, they are predominantly motor in the extraocular muscles (Fross and Daube, 1987). Immunolabelling studies have shown that anti-GQ1b antibodies bind both to nodes of Ranvier and to the neuromuscular junction. However, neither the identity of the cellular components of the neuromuscular junction to which the antibodies bind, nor the function of the molecular targets, is clearly established (Plomp et al., 1999; Bullens et al., 2000). These findings raise the question of how antibody binding might lead to the various symptoms of MFS.

In recent years, two groups have found that GQ1b antibodies can cause blockage of neuromuscular transmission, suggesting that this may account for some of the motor symptoms of MFS. Willison, in collaboration with Vincent and Newsom-Davis in Oxford and Plomp and Molenaar in Leiden, have found that addition of anti-GQ1b antibodies to the fluid bathing an isolated mouse muscle leads, in tens of minutes, to a massive increase in the frequency of spontaneous release of ACh quanta and eventual failure of evoked release, and thus of neuromuscular transmission. These effects are very reminiscent of those seen following application of α-latrotoxin (Roberts et al., 1994; Plomp et al., 1999). Their more recent studies provide evidence that this effect depends on calcium and involves complement, though apparently not by activation of the ‘classic pathway’ or the formation of a membrane attack complex. In this issue, they provide evidence of structural breakdown of the nerve terminal accompanying the loss of function (O’Hanlon et al., 2001). This breakdown involves disruption of neurofilaments and microtubules as well as envelopment of the degenerating nerve terminal by processes of Schwann cells. Their evidence suggests that this breakdown results from a complement-mediated increase in the calcium permeability of the nerve terminal and the subsequent activation of calcium-dependent lytic enzymes in the axoplasm. How much of the terminal axon degenerates is unclear, but a local breakdown, followed by rapid regeneration of the nerve, would be consistent with the known time course of reversal of some of the symptoms of MFS.

In contrast to the results from Willison and colleagues, Buchwald and colleagues have observed a rapid and reversible block of the evoked release of ACh quanta and a reduction in their postsynaptic effect. They have used rapid application of antibodies to a small part of the motor nerve terminal, observing significant effects within a few minutes (e.g. Buchwald et al., 1995, 2001). These effects were dose-dependent and were seen with purified IgG fractions that did not contain complement. The explanation for the differences in observations made by these two groups has not yet been resolved. One possibility is that by applying antibodies to a small region of the neuromuscular junction for a short time, Buchwald and her colleagues have been able to observe early, possibly transient effects which do not occur, or are harder to see, with diffuse bath application. There are several precedents for a dual action of agents that attack the nerve terminal. For example, α-latrotoxin itself is known to act by at least two different mechanisms, one dependent on calcium and one not (reviewed...
in Henkel and Sankaranarayanan, 1999). In addition, some β-neurotoxins with phospholipase activity appear to act in two stages: the first, associated with binding to the nerve terminal, leading to reduced transmitter release, and the second, associated with the phospholipase activity, leading to breakdown of the plasma membrane (Harris, 1991).

The overriding challenge for the immediate future is to determine the relevance of these observations on the action of anti-GQ1b antibodies at the neuromuscular junction in vitro to the pathogenesis of MFS. At present, there is no direct evidence of any impairment of neuromuscular transmission in typical MFS, much less of a particular mechanism of how such an impairment might occur. Detailed clinical neurophysiological studies of the status of neuromuscular transmission in MFS and further investigations of the nature of the accompanying areflexia and ataxia are certainly required. Ultimately, however, only investigation of motor point biopsy samples from patients with MFS can determine whether neuromuscular transmission is impaired and if so, at what level, and whether anti-GQ1b antibodies and complement are bound to neuromuscular junctions in MFS patients. In the absence of such samples, which will be very hard to come by, considerable ingenuity will be required if the role of immunological ‘double agents’ in the pathogenesis of MFS is to be better understood.

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References


