Antibodies to ganglioside GM1 (anti-GM1 antibodies) have been implicated in the pathogenesis of Guillain–Barre syndrome (GBS), multifocal motor neuropathy (MMN) and motor neuron disease. Although the elevated titres of these antibodies have been amply documented in multifocal motor neuropathy and a motor axonal variant of GBS, or acute motor axonal neuropathy (AMAN), their exact role in the pathogenesis remains elusive. The GM1 epitope is present not only in motor neurons and their axons but also in the dorsal root ganglion cells and sensory axons. If anti-GM1 antibodies are pathogenic, what dictates the predilection for the motor system, and how do these antibodies affect the nervous system?

In an in vitro study, Takigawa and colleagues (Takigawa et al., 1995) showed an acute increase in the potassium current and, in the presence of complement, irreversible loss of the sodium current after topical application of the antibody to a mixed nerve, providing a rationale for the hypothesis that anti-GM1 antibodies block sodium channels, causing conduction block (Waxman, 1995). This finding also led to the contention that sodium channels may play a role in the pathophysiology of motor neuron disease (Gutmann et al., 1996).

In this issue of Brain, Paparounas and colleagues (Paparounas et al., 1999) report that anti-GM1 antibodies, bound to the nodes of Ranvier, activate the complement cascade without causing conduction block in vitro. This observation speaks against the role of anti-GM1 antibodies as a primary blocker of sodium channels. Using an in vivo model, we too failed to document sodium channel blocking even at rare sites of demyelinating conduction block (Hirota et al., 1997). Moreover, tetrodotoxin, a known sodium channel blocker, causes abnormalities quite unlike the findings seen in AMAN or MMN, namely marked slowing of conduction velocities and definite sensory involvement, as reported in a case of puffer fish poisoning (Oda et al., 1989). A recent study showed that sodium channels have no epitopes shared by GM1 (Sheikh et al., 1999).

Activation of the complement cascade as shown by Paparounas and colleagues (Paparounas et al., 1999) probably leads to axonal damage in vivo. If so, the irreversible drop of sodium current (Takigawa et al., 1995) may represent non-specific leakage as a result of axonal membrane disruption. This would explain the close association between the antibody and GBS with predominant axonal involvement or AMAN.

If anti-GM1 antibodies damage the membrane irreversibly, what accounts for the rapid clinical improvement after plasma exchange seen in some patients with ‘axonal’ GBS during the early stage. The markedly decreased amplitudes of compound muscle action potentials also recover quickly. Thus, we postulate reversal of the distal conduction block at the motor nerve terminal as one of the prevailing factors. Additional puzzles relate to the commonly increased threshold of excitation in the motor nerve trunk (inexcitable motor nerve). The depressed nerve excitability stands in contrast to the signs of increased excitability such as myokymia or fasciculations seen in some patients with GBS. Co-existing increase and decrease of nerve excitability may imply membrane depolarization, which often leads to depolarization block. This may be caused by extracellular potassium accumulation inadequately buffered by damaged Schwann cells. Alternatively, membrane hyperpolarization adjacent to the ischaemic segment may cause conduction block and fasciculations. In either case, a reversible state of abnormal excitability in motor nerve develops, probably as a prelude to axonal degeneration. MMN also has this paradoxical combination of hypo-excitability as represented by persistent conduction block and hyperexcitability manifested by fasciculations of the paretic muscles. Although the axonal excitability depends upon the integrity of various ionic conductances, the potassium channels play a key role in maintaining the normal membrane potentials. Their abnormalities were documented along the affected nerve segment in multifocal motor neuropathy (Kaji, 1997).

The other question centres on the sparing of the sensory fibres in AMAN and MMN. Nerve fibres develop membrane hyperpolarization after passage of impulse trains. This activity-dependent hyperpolarization, mediated by slow potassium channels and electrogenic sodium/potassium pumps, sufficiently increases the nodal threshold to cause conduction failure. As demonstrated by Vagg and colleagues (Vagg et al., 1998), motor axons are more prone to this type of conduction block than sensory axons, which tend to counter hyperpolarization by abundant inward rectifiers and non-inactivating sodium channels. Physiological as well as immunological characteristics probably predispose the motor axons for selective conduction block.

Among anti-GM1-positive cases, titres of immunoglobulin M (IgM) are high in multifocal motor neuropathy with persistent demyelination, whereas IgG antibodies are found.
in AMAN. The specific role of each class of immunoglobulins for these distinctive processes is unknown. IgM macromolecules bound to the axon may interfere with remyelination in MMN, thus causing persistent conduction block. IgGs are readily absorbed from the nerve terminals for retrograde transport to the soma and transneuronal uptake by the neuropils in the spinal grey (Engelhardt and Appel, 1990). Prompt internalization of IgGs may cause damage and dysfunction of not only the axon but also the soma.

Patients with multifocal motor neuropathy without overt conduction block, or the ‘lower motor neuron’ syndrome may have elevated titres of IgG anti-GM1 antibodies, and some benefit from intravenous immunoglobulins or immunosuppressants (Kornberg et al., 1994; Kaji, 1997). This clinical entity may be termed as chronic motor axonal neuropathy (CMAN), an axonal variant of motor-dominant chronic inflammatory demyelinating polyneuropathy (CIDP) or MMN, as opposed to AMAN as a subtype of GBS. It is of more than theoretical interest to differentiate this from motor neuron disease, lest we overlook therapeutic opportunities. Some patients with clinical features indistinguishable from those of juvenile segmental amyotrophy or Hirayama’s disease have elevated IgG anti-GM1 titres, and respond favourably to intravenous immunoglobulins. These cases, probably representing a focal form of CMAN, eventually develop spinal atrophy without long tract signs, indicating the damage of the spinal anterior horn cells and the neuropils, possibly through retrogradely transported IgGs.

A substantial number of patients with AMAN or MMN have no detectable elevation of anti-GM1 antibody titres. Antibodies to currently unrecognized epitopes may be identified in the future, disclosing additional subtypes of treatable ‘motor neuron disease’.

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References


