What causes the signs and symptoms of multiple sclerosis (MS)? It is almost axiomatic to regard MS as a demyelinating disorder in which axonal conduction block, caused by loss of myelin, produces clinical deficits. In addition, during the past few years, increased attention has focused on axonal degeneration in MS. The available evidence suggests that demyelination provides a structural correlate for relapsing-remitting disease while axonal degeneration, which may be associated with atrophy of the brain and spinal cord, produces nonremitting deficits.

Neurons, of course, are the ultimate mediators of nervous system function and arbiters of neurologic status. Do surviving neurons in MS, nonatrophic and with intact axons, exhibit abnormalities at the molecular level, more subtle than axonal degeneration or neuronal atrophy? If so, are these abnormalities inconsequential molecular oddities or do they contribute to neuronal injury or perturb neuronal function? Among the molecules that make up neurons, ion channels are especially critical because they endow these cells with their signaling capabilities. Thus far, most studies on neuronal ion channels in demyelinating diseases have focused on their adaptive roles; restoration of impulse conduction can occur in chronically demyelinated axons as a result of the insertion of increased densities of sodium channels within the bared axon membrane. Emerging evidence, however, is also beginning to suggest that ion channels within neurons can be involved in maladaptive changes in MS.

Experimental studies in animal models of MS and molecular analysis of autopsy specimens from humans with MS have begun to raise the possibility that, in addition to demyelination and axonal degeneration, 2 distinct modes of dysregulated ion channel expression can injure neurons or interfere with neuronal signaling in MS. One abnormal mode of ion channel expression suggested by Kornek et al1 is the ectopic distribution of calcium channels, which they suggest are up-regulated within the axon membrane in experimental allergic encephalomyelitis (EAE) and in MS. They used immunocytochemical methods to examine the distribution of the α1n pore-forming subunit of the N-type voltage-gated calcium channel. Consistent with earlier reports, they observed a pattern of staining in the normal brain, which suggested the presence of substantial numbers of α1n subunits in presynaptic axon terminals (where they participate in synaptic transmission), but they observed only low levels of α1n within the plasma membrane of myelinated axons within normal white matter. In EAE and MS, they observed a different distribution of α1n immunoreactivity, which was present at higher levels in axons and axonal spheroids within demyelinating lesions, in a pattern similar to that of β-amyloid precursor protein (APP), a marker of acute axonal injury and possibly of impaired axonal transport. They interpret these results as indicating that α1n subunits (which in the normal brain are carried within axons by axoplasmic transport en route to the presynaptic terminal) are inserted into the demyelinated axon membrane in EAE and MS.
It is also now known that there are 10 different genes encoding molecularly distinct sodium channel subtypes, all sharing a common overall structural motif but with different amino acid sequences that under normal circumstances tend to produce non-functional channel proteins. However, in neurons with abnormal calcium channel activity, these proteins can be activated, leading to aberrant calcium ion fluxes that may contribute to axonal injury. Action potentials traveling along the axon or depolarization triggered by an initial insult, such as inflammation, could act to activate these channels. The hypothesis that calcium channel activity can contribute to axonal injury has been supported by the finding that blocking calcium channels can protect a subpopulation of myelinated axons from denervation and slow development of inactivation, and rapid recovery from inactivation.

A second type of molecular abnormality, termed transcriptional channelopathy, has been described in cerebellar Purkinje neurons and may perturb the ability of these cells to encode information in animal models of MS and in humans with MS. The timing of action potentials and the occurrence of complex bursts of action potentials within Purkinje neurons is critical for the proper functioning of the cerebellum in motor control and motor learning. It is well established that these aspects of Purkinje cell signaling depend in large part on current flowing through sodium channels. It is also now known that there are 10 different genes encoding molecularly distinct sodium channel subtypes, all sharing a common overall structural motif but with different amino acid sequences that under normal circumstances tend to produce non-functional channel proteins. However, in neurons with abnormal calcium channel activity, these proteins can be activated, leading to aberrant calcium ion fluxes that may contribute to axonal injury. Action potentials traveling along the axon or depolarization triggered by an initial insult, such as inflammation, could act to activate these channels. The hypothesis that calcium channel activity can contribute to axonal injury has been supported by the finding that blocking calcium channels can protect a subpopulation of myelinated axons from denervation and slow development of inactivation, and rapid recovery from inactivation.

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multiple action potentials superimposed on a plateau depolarization. Figure 2 shows the effects of Nav1.8 channels on Purkinje cells in vitro, which are similar to the effects observed in dorsal root ganglion cells. When Nav1.8 sodium channels are experimentally expressed within Purkinje cells, the firing pattern changes markedly; Purkinje cells that express Nav1.8 produce larger action potentials compared with the responses in Purkinje cells that lack Nav1.8, and the secondary, tertiary, and subsequent action potentials that contribute to the bursts tend to be eliminated so that bursts are replaced by single action potentials (C). In response to a depolarizing stimulus (120 pA, 1 second), Purkinje cells expressing Nav1.8 produce sustained trains of action potentials (D) that are not seen in normal cells (B).

Figure 2. A-D, Expression of Na\textsubscript{\text{1.8}} sodium channels perturbs signalling in cultured Purkinje cells. These current-clamp recordings illustrate action potential activity in a control rat Purkinje cell (A, B) and in a Purkinje cell in which Na\textsubscript{\text{1.8}} sodium channels were biolistically expressed (C, D). Normal Purkinje cells spontaneously generate bursts of action potentials superimposed on a plateau depolarization (A). Following expression of Na\textsubscript{1.8} sodium channels, these bursts are replaced by single action potentials (C). In response to a depolarizing stimulus (120 pA, 1 second), Purkinje cells expressing Na\textsubscript{1.8} produce sustained trains of action potentials (D) that are not seen in normal cells (B).

Since biopsy of cerebellar tissue is not commonly performed in MS, it will not be easy to establish whether these physiologic changes occur in humans with MS. Clinical observations, however, provide some support for this suggestion. The not uncommon clinical observation of patients with MS having cerebellar deficits on examination but without apparent cerebellar lesions in neuroimaging studies is consistent with the hypothesis that molecular changes that are too subtle to be detected by currently available imaging techniques can lead to dysfunction within the cerebellum. In addition, paroxysmal ataxia has been well described in MS. The temporal profile of the sudden and brief attacks and the therapeutic response to carbamazepine are not easily explained by demyelination or axonal degeneration. However, the similarity of these attacks to the paroxysmal episodes that occur in the episodic ataxias, which are associated with inherited channelopathies, is consistent with the hypothesis that they are the result of a channelopathy.

Although more research will be needed to fully define the extent and to understand the causes and physiologic consequences of molecular changes within neurons in MS, the available information on ion channels may present some new molecular targets and some new therapeutic opportunities. For example, if N-type calcium channels are involved in the degeneration of axons in MS, pharmacologic blockade of these channels might be expected to ameliorate, at least partially, the loss of axons. This hypothesis could be readily examined in animal models.

Participation of Na\textsubscript{1.8} sodium channels in the production of cerebellar deficits in humans with MS, if con-
firmed by additional experiments, may also provide a new therapeutic target. In principle, blockade of Na,1.8 channels would be expected to restore normal electrogenesis in Purkinje cells, thus improving cerebellar function. Na,1.8-specific channel blocking drugs are not yet available, but this may change since the deployment of Na,1.8 channels within nociceptive spinal sensory neurons has made Na,1.8 an attractive molecular target.21 When Na,1.8-specific blocking drugs are developed, a next step will be to examine the effect of these drugs in animal models of MS, such as EAE.

Finally, are the transcription or deployment of other subtypes of calcium or sodium channels or channels selective for other ions altered in MS, and in how many types of neurons does this occur? There is some evidence for abnormal expression of the Na,1.2 sodium channel22 and of potassium channels23 in dysmyelinated axons in animal models. Axons and glial cells are intimately related in myelinated fibers, and both soluble factor-mediated and contact-mediated signaling from myelinating glial cells appear to modulate ion channel expression in axons.24,25 Thus, we may learn about other neuronal channels and receptors that are misexpressed in the demyelinating diseases. Far from being molecular oddities, these changes in the deployment of ion channels may be clinically important; although they do not detract from the importance of demyelination or axonal loss, they may suggest new molecular mechanisms and novel strategies for treating patients with MS and related disorders.

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