Scientific Commentary

Sodium channel blockers and axonal protection in neuroinflammatory disease

Although demyelination is a cardinal feature of neuroinflammatory conditions such as Guillain–Barré syndrome (GBS) and multiple sclerosis, axonal degeneration also occurs in these disorders. Because loss of axons causes permanent, non-remitting loss of neurological function, there is substantial interest in protection of axons in these situations. Protection of axons within white matter and peripheral nerves, however, is likely to require strategies different from those that might be expected to be protective in grey matter of the nervous system; the higher surface-to-volume ratio and different complement of molecules that are expressed in axons compared with neuronal cell bodies imply that the molecular mechanisms underlying axonal degeneration are different from those that cause neurons to die. Studies over the past decade have demonstrated that a sustained sodium influx through voltage-gated sodium channels can trigger reverse sodium–calcium exchange which imports damaging levels of calcium into axons after they are exposed to insults such as anoxia, thereby activating injurious calcium-mediated processes (Stys et al., 1992a). Persistent sodium currents have, in fact, been demonstrated along the trunks of axons within the CNS (Stys et al., 1993) and PNS (Tokuno et al., 2003), and sodium channel blockers have been shown to have a protective effect, preventing axonal degeneration when axons are exposed to anoxia (Stys et al., 1992b). A link to neuro-inflammation was provided by Smith and colleagues, who demonstrated that nitric oxide (NO, which is present at high concentrations within the lesions of GBS and multiple sclerosis; see Smith and Lassmann 2002) can, possibly via mitochondrial injury which leads in turn to energy deficiency, trigger axonal degeneration (Smith et al., 2001). These investigators further showed that NO-induced axonal degeneration can be prevented by pharmacological blockade of sodium channels (Kapoor et al., 2003). Still another link between sodium channels and axonal degeneration in neuroinflammatory disorders was provided by the demonstration that the Na\textsubscript{v}1.6 sodium channel, which produces a persistent as well as a transient sodium current (Herzog et al., 2003), is co-localized together with the sodium–calcium exchanger, along extensive regions of degenerating axons in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (Cranner et al., 2004a), and in multiple sclerosis itself (Cranner et al., 2004b). Based on these observations, it was predicted that sodium channel blockade might protect axons in neuroinflammatory disorders. Indeed, it has been demonstrated that the sodium channel blockers phenytoin (Lo et al., 2002, 2003) and flecainide (Bechtold et al., 2004) have protective effects in EAE where they reduce the frequency of axonal degeneration, maintain the ability of the remaining axons to conduct impulses and improve clinical outcome. Building upon these results, it would seem logical to ask whether sodium channel blockers have a similar protective effect in models of GBS. In an article in this issue, Bechtold et al. (2005) demonstrate that flecainide protects axons in experimental autoimmune neuritis (EAN), again improving clinical outcome.

The observations summarized above are consistent with the idea that a direct therapeutic effect on axons, via the blockade of axonal sodium channels, is responsible for the protective effect of sodium channel blockers in these models of neuroinflammatory disease. Supporting this suggestion, a protective effect of sodium channel blockade was observed even when administration of phenytoin and flecainide was delayed until 7–10 days after disease induction in EAE (Lo et al., 2002, 2003; Bechtold et al., 2004) or until onset of disease in EAN (Bechtold et al., 2005).

It is also possible, however, that sodium channel blockade has other effects on other cellular targets which can ameliorate the disease process in multiple sclerosis and GBS and their models. It is well established that the expression of sodium channels is not confined to ‘excitable’ cells. Although perhaps not intuitive, since the role of sodium channels has classically been thought to be electrogenesis, sodium channels are present and functional within the membranes of Schwann cells and astrocytes (Sontheimer et al., 1996), raising the possibility that sodium channel blockade may alter the function of these cells in some way. Na\textsubscript{v}1.6 sodium channels are also present on immune cells, and recent studies indicate that these channels contribute to activation and phagocytic function of microglia and macrophages in EAE and multiple sclerosis (Cranner et al., 2004c). These observations raise the possibility that sodium channel blockade may attenuate the inflammatory response in neuroinflammatory disorders such as GBS. It is interesting, in this respect, that Bechtold et al. (2005) observed significantly fewer macrophages within the nerves of flecainide-treated rats with EAE.

Complicating the story still further, the expression of sodium channels is not static. On the contrary, it is highly dynamic, and recent studies have demonstrated that inflammation and inflammatory mediators can upregulate the
expression of sodium channels. Thus, the expression of Na\textsubscript{v}1.6 sodium channels is substantially increased in activated microglia and macrophages in both EAE and MS (Cranner et al., 2004c). Moreover, expression of the Na\textsubscript{v}1.9 sodium channel, which is expressed along small diameter axons within the PNS (Dib-Hajj et al., 1998; Fang et al., 2002), where it provides a route for a persistent sodium current (Cummins et al., 1999), is upregulated by inflammatory mediators such as the prostaglandin PGE\textsubscript{2} (Rush and Waxman, 2004). These latter results suggest the possibility that inflammation may trigger increases in the number of sodium channels that are deployed within immune cells and/or along axons, where they could contribute to the pathophysiology of inflammatory damage.

Despite the converging evidence for a protective effect of sodium channel blockers in neuroinflammatory disorders, important questions remain to be answered. Paramount among these questions is whether, and how, sodium channel blockers affect lymphocytes and other immune cells. Delineation of the mechanisms underlying the therapeutic effect of sodium channel blockers (neuroprotection versus immunomodulation) is especially important, since, if these drugs act predominantly by the first mechanism, the effects might be therapeutically additive to those of currently used immunomodulatory drugs. The precise nature of the immunomodulatory effect of sodium channel blockers (if any) also deserves study, and may be relevant to the question of whether these drugs can be used together with other immunomodulatory or immunosuppressive agents. Irrespective of the underlying molecular mechanisms, the new results in EAN, when juxtaposed to earlier results in EAE and other models, support the idea that sodium channels participate in the molecular cascade(s) leading to axonal degeneration in multiple sclerosis and GBS, and indicate that sodium channel blockers deserve further study as potential protective agents in neuroinflammatory disorders.

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