

Na⁺ channel expression along axons in multiple sclerosis and its models

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Following the loss of myelin from axons in multiple sclerosis, some axons recover the ability to conduct impulses despite the absence of an insulating sheath, providing a basis for remission of clinical deficits. By contrast, other axons degenerate and contribute to non-remitting clinical deficits and, thus, disability. Investigations using laboratory models of multiple sclerosis indicate that altered expression of two distinct isoforms of Na⁺ channels underlies these two processes, and the study of human tissue reveals similar changes in multiple sclerosis.

Multiple sclerosis (MS), the most common neurological disorder to affect young adults, often displays a relapsing–remitting course, with patients experiencing remissions in which previously lost functions (e.g. vision and gait) are regained. In progressive forms of MS, however, clinical status inexorably worsens and there is acquisition of an increasing burden of non-remitting neurological deficits. Both of these processes – remission and progression – appear to involve voltage-gated Na⁺ channels within axons, and the expression of these molecules is therefore crucial in the pathophysiology of MS.

Inflammation, demyelination and axonal degeneration occur within white matter of the brain and spinal cord in MS. In normal myelinated axons within the white matter, Na⁺ channels are clustered at a high density in the axon membrane at the nodes of Ranvier, but are present in much lower densities (too low to support secure conduction) in the internodal and paranodal axon under the myelin. This is functionally important because dissipation of current through Na⁺ channel-poor portions of the axon membrane after demyelination can cause action potential conduction to fail, producing clinical deficits. Conduction failure in demyelinated axons is not, however, irreparable. Even before the molecular era (i.e. before the cloning of Na⁺ channels), it became clear that expression of Na⁺ channels along demyelinated (previously Na⁺ channel-poor) axon regions can lead to restoration of conduction, which underlies remission of clinical deficits, even in the absence of remyelination (Figure 1a–c) [1].

In addition to this adaptive role, Na⁺ channels can play a maladaptive role in disorders such as MS. Axonal degeneration occurs frequently in MS, and produces persistent neurological deficits [2,3]. It became clear

early in the molecular era that injury to CNS axons can be triggered by Na⁺ influx through persistently activated Na⁺ channels, which drives reverse Na⁺–Ca²⁺ exchange that imports damaging levels of Ca²⁺ into axons [4,5]. Consistent with a role for Na⁺ channels in axonal injury in MS, pharmacological block of Na⁺ channels prevents axonal degeneration within CNS white matter after a variety of insults [6–8], including injury produced by nitric oxide (NO) [9,10], which is present at increased concentrations within MS lesions [11]. Furthermore, recent studies have shown that the Na⁺ channel blockers phenytoin [12] and flecainide [13] have a protective effect in experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, where they prevent degeneration of CNS axons, maintain axonal conduction and improve clinical outcome.

As a result of molecular analysis it is now clear that at least nine different genes encode distinct voltage-gated Na⁺ channels (Na_v1.1–Na_v1.9), all sharing a common overall motif but with different amino acid sequences, voltage-dependencies and kinetics. Na_v1.1, Na_v1.2, Na_v1.3 and Na_v1.6 channels are expressed widely within the nervous system, Na_v1.7, Na_v1.8 and Na_v1.9 channels are expressed selectively within dorsal root ganglion and trigeminal ganglion neurons, and Na_v1.4 and Na_v1.5 channels are expressed within somatic and cardiac muscle, respectively [14].

Early cytochemical [15] and immunocytochemical [16,17] studies using pan-specific Na⁺ channel antibodies demonstrated higher than normal numbers of Na⁺ channels in chronically demyelinated axons in experimental model systems, and electrophysiological studies [18] indicated that these axons can support impulse conduction; however, these early studies did not distinguish between channel isoforms and thus did not reveal the molecular identity of the new axonal channels that restore conduction. A fourfold increase in binding sites for the Na⁺ channel blocker saxitoxin within demyelinated white matter from patients with MS, compared with controls, also suggested the expression of new Na⁺ channels [19] but provided no details about the channel isoform(s) that are expressed. Moreover, the identity of the Na⁺ channel isoforms in injured axons in MS has been enigmatic.

Recent studies have begun to identify the Na⁺ channel isoforms that are present along demyelinated axons in animal models of MS, and in human MS, and suggest that specific Na⁺ channel isoforms are associated

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Available online 17 September 2004

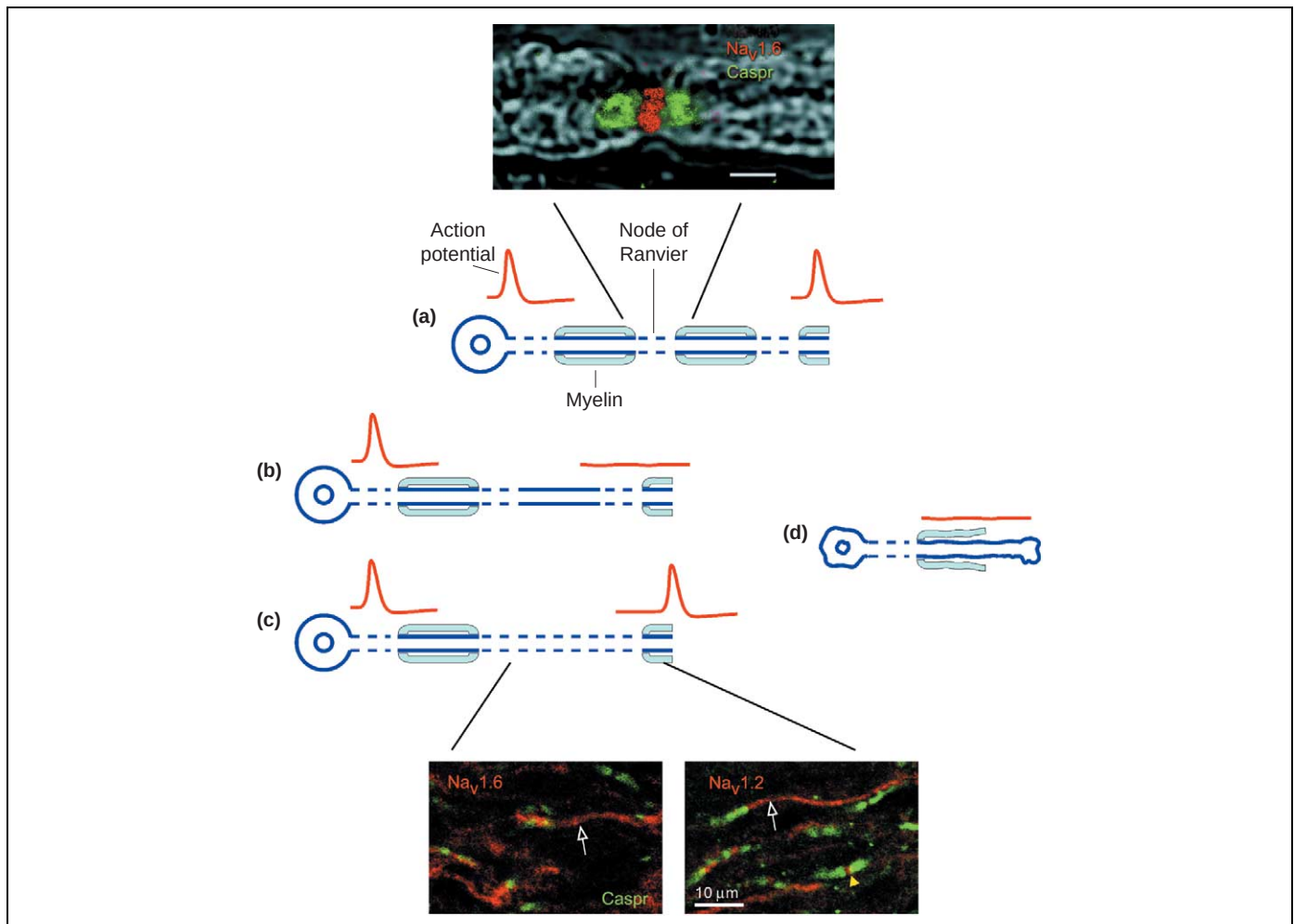


Figure 1. (a) Voltage-gated Na^+ channels, now known to be of the $\text{Na}_v1.6$ channel subtype, are clustered at a high density within the normal axon membrane at nodes of Ranvier but are sparse in the paranodal and internodal axon membrane under the myelin. Aggregation of $\text{Na}_v1.6$ channels (red) is shown at a node of Ranvier, bounded by Caspr (a constituent of the paranodal apparatus) in paranodal regions (green), in a normal myelinated axon. The fluorescence image of the node was merged with differential contrast image, which shows the myelin sheath. Scale bar = $5\ \mu\text{m}$. Image reproduced, with permission, from [52]. (b) Demyelination in multiple sclerosis (MS) initially exposes axon membrane with low Na^+ channel density that cannot support secure action potential conduction, and conduction block ensues. (c) Some demyelinated axons acquire higher than normal densities of Na^+ channels in demyelinated (formerly paranodal and/or internodal) regions, supporting the restoration of conduction that underlies clinical remissions. Changes in $\text{Na}_v1.6$ and $\text{Na}_v1.2$ channel expression are shown in optic nerve axons in experimental autoimmune encephalomyelitis (EAE). There is a loss of $\text{Na}_v1.6$ channel immunostaining (left) and an increase in $\text{Na}_v1.2$ channel immunostaining (right) at nodes (arrowhead). Demyelinated axonal profiles display diffuse $\text{Na}_v1.6$ channel (left) and $\text{Na}_v1.2$ channel (right) immunostaining (white arrows), which can extend for tens of microns along the fiber axis. Scale bar = $10\ \mu\text{m}$. Images reproduced, with permission, from Oxford University Press [28]. (d) Degeneration of axons also occurs in MS, and produces non-remitting, permanent loss of function. The steps that lead to axonal degeneration are only partially understood.

with restoration of conduction and axonal degeneration; these observations might have important therapeutic implications. In this article, recent progress in this rapidly evolving area will be reviewed.

$\text{Na}_v1.2$ and $\text{Na}_v1.6$ channels in normal and dysmyelinated axons

Within the normal nervous system at early stages before glial ensheathment, Na^+ channels are present at a low density along the entire length of pre-myelinated axons [20]. It is now known that $\text{Na}_v1.2$ channels are distributed diffusely along non-myelinated axons [21–23], and support action potential conduction that is known to occur in pre-myelinated axons [24,25]. By contrast, $\text{Na}_v1.6$ channels cluster at the nodes at Ranvier in myelinated axons (Figure 1) [26]. Isoform-specific studies have shown that after myelination, there is a loss of $\text{Na}_v1.2$ channels and an aggregation of $\text{Na}_v1.6$ channels at mature nodes of

Ranvier in normal axons [23,27]; $\text{Na}_v1.6$ channels are not detectable in the paranodal and internodal axon membrane under the myelin.

Studies using isoform-specific antibodies in dysmyelinated mutants, in which myelin fails to form as a result of an abnormality within glial cells, have also provided information about the expression of Na^+ channels along axons where myelin is absent. These studies showed that $\text{Na}_v1.2$ channels continue to be expressed [21,23] whereas $\text{Na}_v1.6$ channels are not expressed [23] along dysmyelinated axons within *Shiverer* mutant tracts that have failed to form compact myelin. Together with the studies on developing axons, the observations from studies of dysmyelinated axons suggest that a relationship exists between myelin formation and the sequential expression of the $\text{Na}_v1.2$ and $\text{Na}_v1.6$ channel isoforms; however, these studies do not provide information about Na^+ channel expression in demyelinated axons.

Na_v1.2 channels in demyelinated axons: EAE

The Na⁺ channel isoforms expressed along demyelinated axons have been identified recently in studies that used subtype-specific immunocytochemical methods and *in situ* hybridization to examine white matter axons in mice with EAE [28,29]. Na_v1.1 and Na_v1.3 channels were not detectable along axons in control or EAE animals; this is notable because Na_v1.3 channels are upregulated and expressed within dorsal root ganglion cells and their axons [30], and in higher-order nociceptive neurons within the spinal cord dorsal horn, after peripheral nerve injury [31] and spinal cord injury [32]. Na_v1.8 channels are not detectable along CNS axons in control or EAE animals, although they are aberrantly expressed within cerebellar Purkinje neurons [33] and retinal ganglion cells (M.J. Craner *et al.*, unpublished) in EAE and MS, and appear to distort the firing pattern of these cells [34].

Both Na_v1.2 and Na_v1.6 channels are expressed along CNS axons in EAE where there is an increased frequency of Na_v1.2 channel-positive nodes and a reduction in the frequency of Na_v1.6 channel-positive nodes within white matter (Figure 1). An increase in the overall number of nodes in EAE suggests that some new myelin sheaths are formed, but it is not clear whether the Na_v1.2 channel-expressing nodes are formed along remyelinated (but possibly not yet fully mature) axons or by replacement of

Na_v1.6 channels with Na_v1.2 channels at preexisting nodes.

There is a large number of demyelinated axons in EAE. Diffuse Na⁺ channel immunostaining for Na_v1.2 and Na_v1.6 channels extends for tens of microns along demyelinated axons in EAE optic nerve (Figure 1); by contrast, diffuse Na⁺ channel immunostaining is very rare in control optic nerves (which do not contain unmyelinated axons) [28]. Similar changes are observed in the demyelinated spinal cord in EAE [29]. The increased expression of Na_v1.2 channels along demyelinated axons in EAE is accompanied by upregulated Na_v1.2 channel mRNA levels within retinal ganglion cells, which give rise to demyelinated optic nerve axons [28]. Thus, the emergence of increased numbers of nodes expressing Na_v1.2 channels, and of large regions of Na_v1.2 channel expression along extended regions of demyelinated fibers, appears to be associated with upregulated transcription of the gene encoding Na_v1.2 channels.

Na_v1.6 channels in injured axons: EAE

The activity of Na⁺ channels can trigger Ca²⁺-mediated injury of white matter axons, by providing a sustained Na⁺ influx that drives reverse (Ca²⁺-importing) activity of the Na⁺-Ca²⁺ exchanger [4]. The available evidence indicates that a persistent (non-inactivating) Na⁺

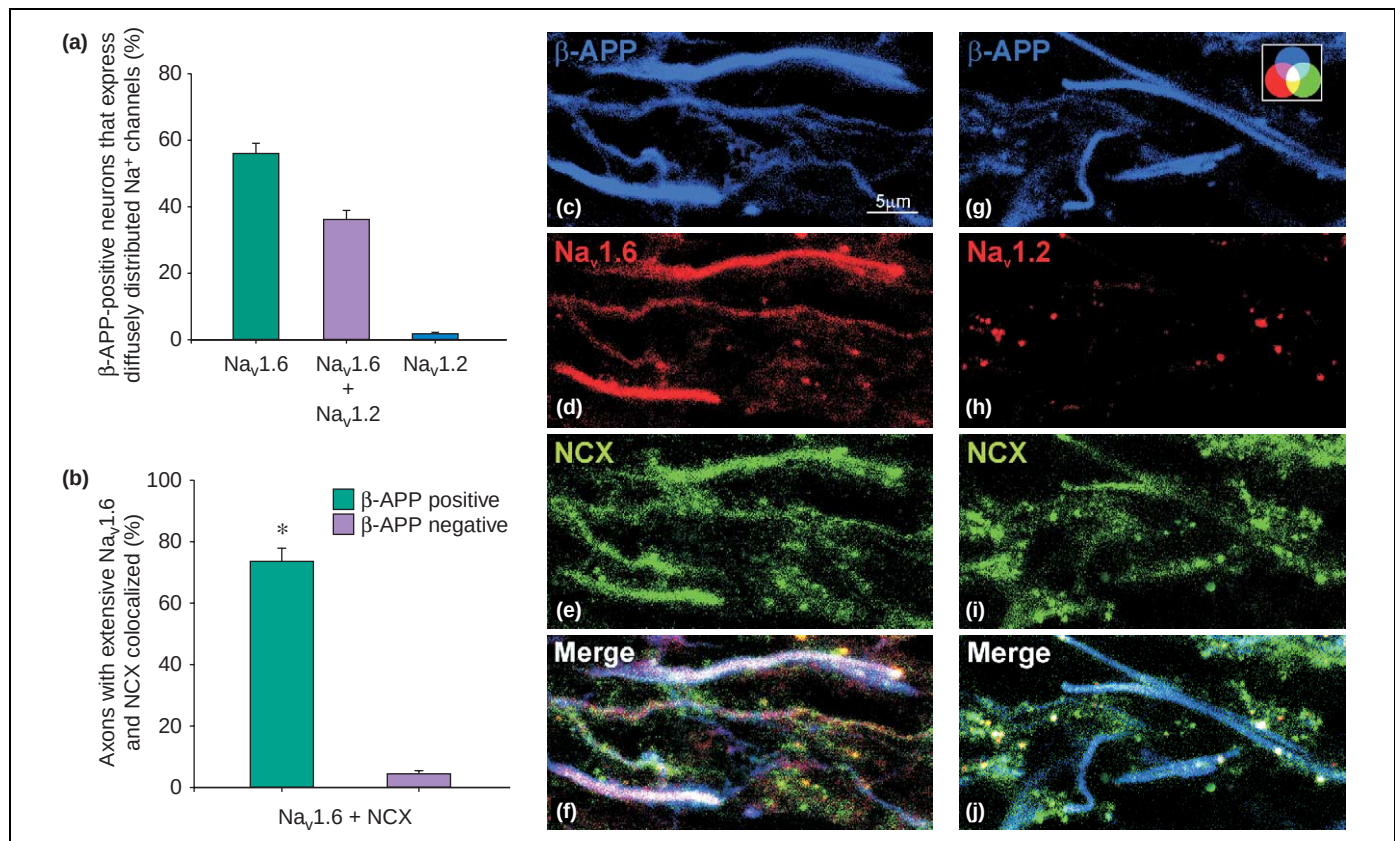


Figure 2. Coexpression of Na_v1.6 channels and the Na⁺-Ca²⁺ exchanger in degenerating spinal cord axons in experimental autoimmune encephalomyelitis (EAE). **(a)** The percentage of β-amyloid precursor protein (β-APP)-positive axons in EAE that express immunoreactivity for Na_v1.6 channels alone (green), both Na_v1.2 and Na_v1.6 channels (purple), and Na_v1.2 channels alone (blue) is shown. More than 90% of β-APP-positive axons express Na_v1.6 channels, either alone or together with Na_v1.2 channels. **(b)** Coexpression of the Na⁺-Ca²⁺ exchanger (NCX) and Na_v1.6 channels in β-APP-positive axons in EAE, determined by triple immunolabeling. The proportion of β-APP-positive axons that coexpress NCX and Na_v1.6 channels over extensive regions is significantly higher (green) than for β-APP-negative axons (purple). **P* < 0.001. Images: spinal cord axons in EAE immunostained for **(c,g)** β-APP (blue), **(d)** Na_v1.6 channels (red), **(h)** Na_v1.2 channels (red) and **(e,i)** the NCX (green) are shown. Panels **(f)** and **(j)** show merged images (white). Note the coexpression of Na_v1.6 channels, NCX and β-APP (a marker of axonal injury) **(e-f)**. Modified, with permission, from Oxford University Press [29].

conductance is involved [5]. Na_v1.6 channels are known to produce a persistent current in many cell types and this current is larger than the persistent current produced by Na_v1.2 channels [35–37]. Coexpression of Na_v1.6 channels and the Na⁺–Ca²⁺ exchanger within demyelinated axons might predispose these axons to injury and so Craner *et al.* [29] attempted to determine whether there is a correlation between the expression of Na_v1.6 channels, the Na⁺–Ca²⁺ exchanger and β-amyloid precursor protein (β-APP), a marker of axonal injury [2], in spinal cord axons from mice with EAE. Double-label immunocytochemistry demonstrated that 92% of β-APP-positive axons in EAE are Na_v1.6 channel immunopositive [either expressing Na_v1.6 channels alone (56%) or coexpressing Na_v1.6 and Na_v1.2 channels (36%)], whereas only 1.8% of β-APP-positive axons express only Na_v1.2 channels. Because these findings suggested that Na_v1.6 channels are preferentially associated with axonal injury, triple-labeling fluorescence immunohistochemistry was used to determine whether Na_v1.6 channels and the Na⁺–Ca²⁺

exchanger are colocalized in β-APP-positive axons in EAE [29]. Axon counts showed that 74% of β-APP-positive axons displayed extensive regions of coexpression of Na_v1.6 channels and the Na⁺–Ca²⁺ exchanger, whereas only 4% of β-APP-negative axons exhibited such coexpression (Figure 2). Thus, these data provide evidence for colocalization of Na_v1.6 channels and the Na⁺–Ca²⁺ exchanger within injured axons in a model of MS.

Na_v1.2 and Na_v1.6 channels in demyelinated axons: MS

Although EAE is the most commonly studied animal model of MS, there is no model that perfectly mimics all of the features of the human disorder, and the question ‘which Na⁺ channels are expressed along demyelinated axons in MS?’ therefore requires the examination of human tissue. Such a study [38] has been carried out recently on post-mortem spinal cord and optic nerve tissue from patients with disabling secondary progressive MS and from controls, acquired via a rapid autopsy protocol [39]; the study revealed a pattern of Na⁺ channel expression within acute MS lesions that is similar to the pattern observed in EAE. Control white matter, from patients with no neurological disease, displayed abundant myelin basic protein (MBP) and the expected pattern of focal expression of Na_v1.6 channels that was confined to nodes of Ranvier. Within acute MS plaques (which could be identified on the basis of attenuated MBP immunostaining and evidence of inflammation and recent phagocytosis of myelin), Na_v1.6 and Na_v1.2 channels were expressed along extensive regions running tens of microns along demyelinated axons (Figure 3). In some cases the region of Na_v1.6 or Na_v1.2 channel immunostaining was bounded by damaged myelin (Figure 3c,d) or Caspr (Figure 3e,f), a constituent of the paranodal apparatus [40,41], further confirming the identity of these profiles as previously myelinated axons.

To delineate the relationship between axonal injury and Na_v1.6 and Na_v1.2 channel expression within these MS lesions, colocalization of these channel isoforms with β-APP was examined. A large number of β-APP-positive axons were present within these MS plaques, suggesting the presence of ~7500 injured axons per mm³ of tissue within these acute lesions, similar to the value (11 000 per mm³) reported in earlier studies [2]. Almost all β-APP-immunopositive axons in these MS lesions expressed Na_v1.6 channels over extensive regions, whereas few β-APP-immunopositive axons expressed Na_v1.2 channel immunostaining [38]. Na_v1.6 channels and the Na⁺–Ca²⁺ exchanger tended to be colocalized within β-APP-positive axons within acute MS lesions. A majority of β-APP-positive axons displayed extensive regions where both Na_v1.6 channels and the Na⁺–Ca²⁺ exchanger were expressed (Figure 4). By contrast, Na_v1.2 channels and the Na⁺–Ca²⁺ exchanger tended to be expressed in β-APP-negative axons. Thus, similar to EAE, the majority of injured axons in acute MS lesions display extensive regions where both Na_v1.6 channels and Na⁺–Ca²⁺ exchanger are present, in contrast to apparently uninjured axons, which tend to express Na_v1.2 channels.

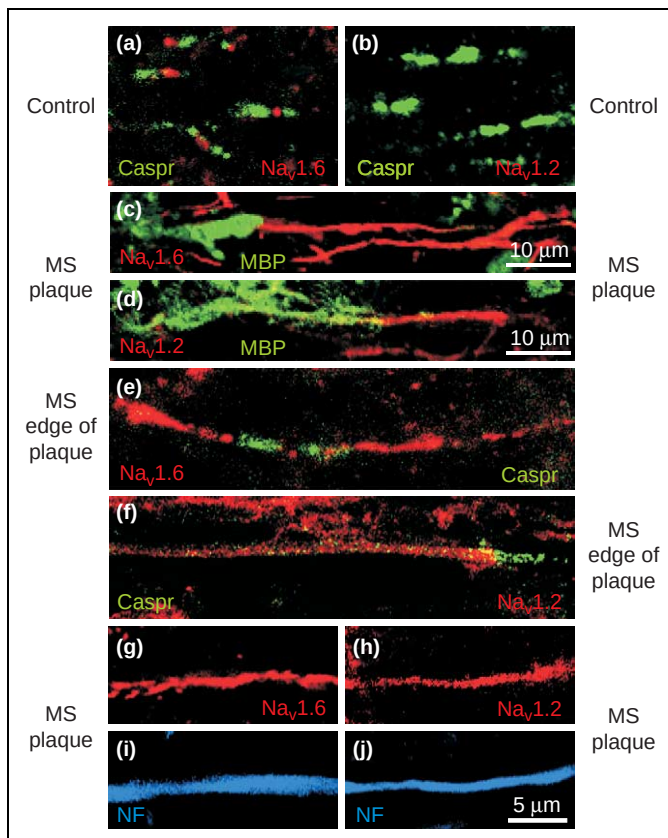


Figure 3. Changes in Na_v1.6 and Na_v1.2 channel expression along demyelinated axons within active lesions from patients with disabling secondary progressive multiple sclerosis (MS). Note the expression of (a) Na_v1.6 channels (red), bounded by Caspr (a constituent of the paranodal apparatus) (green), at nodes of Ranvier, whereas (b) Na_v1.2 channels (red) are not detectable at nodes within spinal cord from controls without neurological disease. Panels (c) and (d) show active MS lesions within spinal cord, where axons display residual damaged myelin (green) next to extensive regions of diffuse expression of Na_v1.6 channels (c) (red) and Na_v1.2 channels (d) (red), which establishes the identity of these profiles as axons. The presence of neurofilaments (NFs) (i,j) (blue) further confirms the diffuse distribution of Na_v1.6 channels (g) and Na_v1.2 channels (h) along axon regions that lack myelin. In some cases extensive regions of (e) Na_v1.6 channels (red) or (f) Na_v1.2 channels (red) are bounded by Caspr (green), without overlap, consistent with the expression of Na_v1.6 and Na_v1.2 channels within the demyelinated axon membrane. Abbreviation: MBP, myelin basic protein. Modified, with permission, from [38]. ©2004 National Academy of Sciences USA.

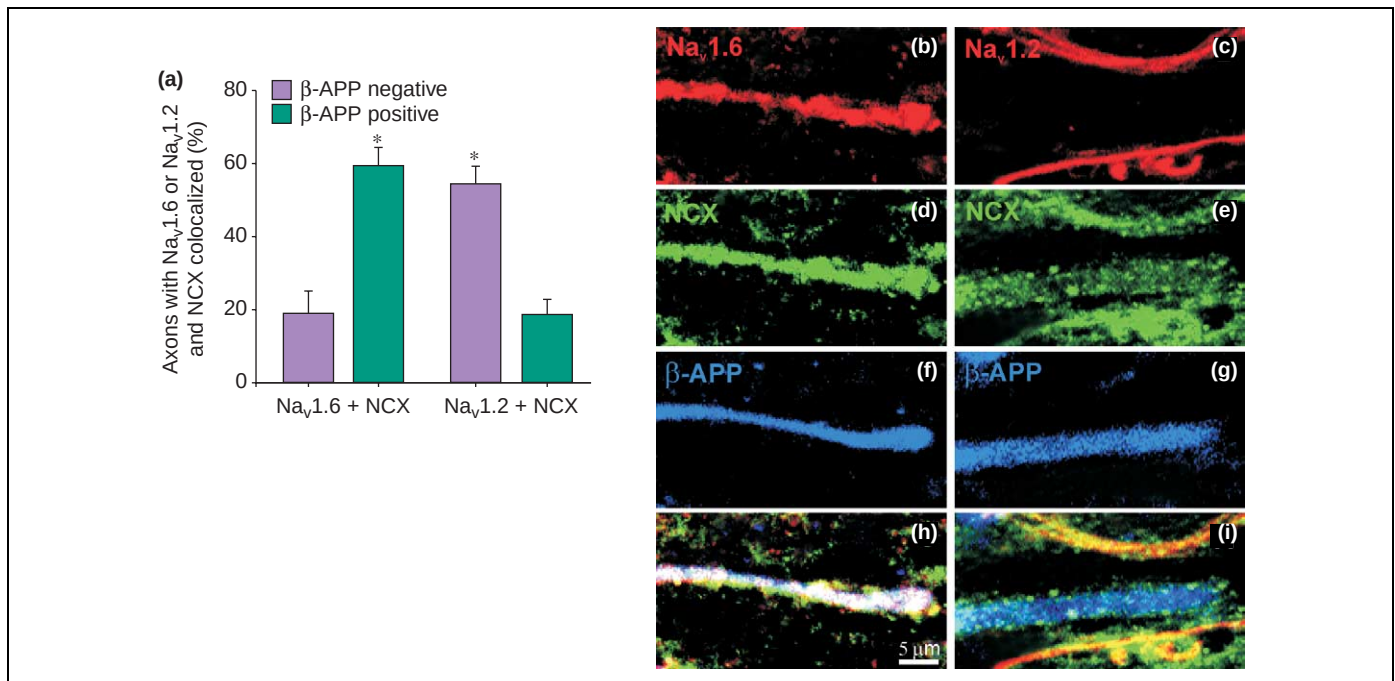


Figure 4. The Na⁺–Ca²⁺ exchanger and Na_v1.6 channels are coexpressed in β-amyloid precursor protein (β-APP)-positive axons in multiple sclerosis (MS). (a) The proportions of β-APP-positive axons (green) and β-APP-negative axons (purple) that coexpress the Na⁺–Ca²⁺ exchanger (NCX) and Na_v1.6 channels or the NCX and Na_v1.2 channels over extensive regions are shown. Coexpression of Na_v1.6 channels and the NCX is observed in a significantly higher proportion of β-APP-positive axons than in β-APP-negative axons. **P* < 0.005. The images show representative axons in MS spinal cord white matter immunostained for (b) Na_v1.6 channels (red) or (c) Na_v1.2 channels (red), (d,e) the NCX (green) and (f,g) β-APP (blue). Panels (h) and (i) show merged images (white). Panels (b,d,f,h) show coexpression of Na_v1.6 channels and the NCX within axons displaying β-APP. By contrast, panels (c,e,g,i) demonstrate NCX staining but an absence of Na_v1.2 channels within β-APP-positive axons, and coexpression of the NCX and Na_v1.2 channels within β-APP-negative axons. Modified, with permission, from [38]. © 2004 National Academy of Sciences USA.

What do Na_v1.2 channels do in demyelinated axons?

The widespread distribution of Na_v1.2 channels, extending for tens of microns along demyelinated but apparently uninjured axons in EAE and MS, is similar to the diffuse distribution of Na_v1.2 channels along pre-myelinated axons [23], in which action potential conduction is known to occur [24,25]. Na_v1.2 channels are also present along non-myelinated axons within the CNS [22,42,43] where they appear to support action potential conduction.

Na_v1.6 channels appear particularly well suited to support conduction at nodes, which can conduct high-frequency trains of impulses. Na_v1.2 and Na_v1.6 channels both produce rapidly activating and inactivating currents that can support action potential electrogenesis, but the rapid repriming kinetics of Na_v1.6 channels [37] can support sustained high-frequency opening whereas Na_v1.2 channels have slower repriming kinetics, and are more likely to generate activity in response to slow depolarizations [37,44]. The two isoforms also differ in terms of their ability to produce persistent currents, with Na_v1.2 channels producing significantly less persistent current than Na_v1.6 channels [35], a factor that might (see later) permit Na_v1.2 channels to be expressed along demyelinated axons without triggering reverse Na⁺–Ca²⁺ exchange. Thus, the deployment of Na_v1.2 channels along demyelinated axons might serve an adaptive function, supporting the conduction of action potentials. Evidence for a non-injurious role of diffusely distributed Na_v1.2 channels is provided by observations in *Shiverer* mice, which lack compact myelin and express Na_v1.2 channels along dysmyelinated CNS axons [21,23] but do not display evidence of ongoing axonal degeneration [45].

It should be noted, nonetheless, that expression of Na_v1.2 channels along demyelinated axons might not fully restore the function of these axons because the ability of Na_v1.2 channels to sustain high-frequency conduction might be limited and the sensitivity of Na_v1.2 channels to slow depolarizations might contribute to ectopic firing or unstable patterns of firing after demyelination.

What do Na_v1.6 channels do in demyelinated axons?

Rapidly inactivating Na⁺ current would not be expected to produce the sustained influx of Na⁺ that is needed to drive reverse Na⁺–Ca²⁺ exchange and, as described earlier, a persistent Na⁺ conductance has been shown to have a prominent role in the triggering of reverse Na⁺–Ca²⁺ exchange and resultant Ca²⁺ entry that results in injury of myelinated axons [4,5]. Na_v1.6 channels produce a persistent Na⁺ current that becomes larger with depolarization [35,36]. Patch clamp studies on neurons expressing Na_v1.6 channels (using recombinant channels that were resistant to tetrodotoxin, permitting unequivocal identification of Na_v1.6 channel current) detected persistent Na_v1.6 channel currents in all cells that were studied [37]. Although Na_v1.2 channels might produce a persistent current when coexpressed with G-protein βγ-subunits [46], Na_v1.6 channels produce a much larger persistent current than Na_v1.2 channels [35], and in many cell types Na_v1.6 channels are responsible for the majority of persistent current [47]. Moreover, there is evidence that traumatic injury of axons can trigger Ca²⁺-induced proteolytic cleavage of Na_v1.6 channels at the III–IV linker that damages their inactivation mechanism, suggesting a feed-forward process that might further

increase $\text{Na}_v1.6$ channel current amplitude [48]. Calmodulin also increases the $\text{Na}_v1.6$ channel current amplitude in a Ca^{2+} -dependent manner [49]. These observations raise the possibility that persistent current through $\text{Na}_v1.6$ channels might be further increased by secondary changes in channel function triggered by an initial rise in intra-axonal Ca^{2+} levels early in the course of injury. Irrespective of this, the physiological data together with the immunocytochemical results are consistent with the proposal that $\text{Na}_v1.6$ channels, when coexpressed with the $\text{Na}^+/\text{Ca}^{2+}$ exchanger along demyelinated axons, can contribute to axonal injury.

Mapping the Na^+ channels in MS

The molecular identities and distribution of the Na^+ channels that are deployed in demyelinated and degenerating CNS axons are now being delineated both in animal models of MS and in MS itself. Interestingly, the two Na^+ channel isoforms that have been detected thus far, $\text{Na}_v1.2$ and $\text{Na}_v1.6$, show different patterns of distribution: $\text{Na}_v1.2$ channels tend to be present in axons that are β -APP-negative (i.e. in axons that do not display signs of injury), whereas $\text{Na}_v1.6$ channels tend to be expressed in axons that are β -APP-positive and thus

appear to be injured and, in these axons, this Na^+ channel isoform is often coexpressed with the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. This pattern of channel distribution suggests the model illustrated in Figure 5, in which the presence of $\text{Na}_v1.6$ channels, but not $\text{Na}_v1.2$ channels, might predispose axons to injury. Consistent with this proposal, dysmyelinated CNS axons, which express $\text{Na}_v1.2$ channels rather than $\text{Na}_v1.6$ channels [21,23], are substantially less sensitive than myelinated axons to injury triggered by activity of Na^+ channels [50]. Also consistent with this proposal is the observation that demyelinated axons are less sensitive than myelinated axons to injury triggered by activity of Na^+ channels [51], an observation that might be explained by the expression of $\text{Na}_v1.2$ channels along demyelinated axons that have not degenerated.

If, as proposed in this article, expression of $\text{Na}_v1.2$ channels along demyelinated axons serves to support conduction, strategies that induce expression of this channel might promote restoration of conduction, thereby encouraging remission in MS. It also might also be predicted that subtype-specific blockade of $\text{Na}_v1.6$ channels (or, preferably, of the persistent component of the current produced by $\text{Na}_v1.6$ channels) might have a

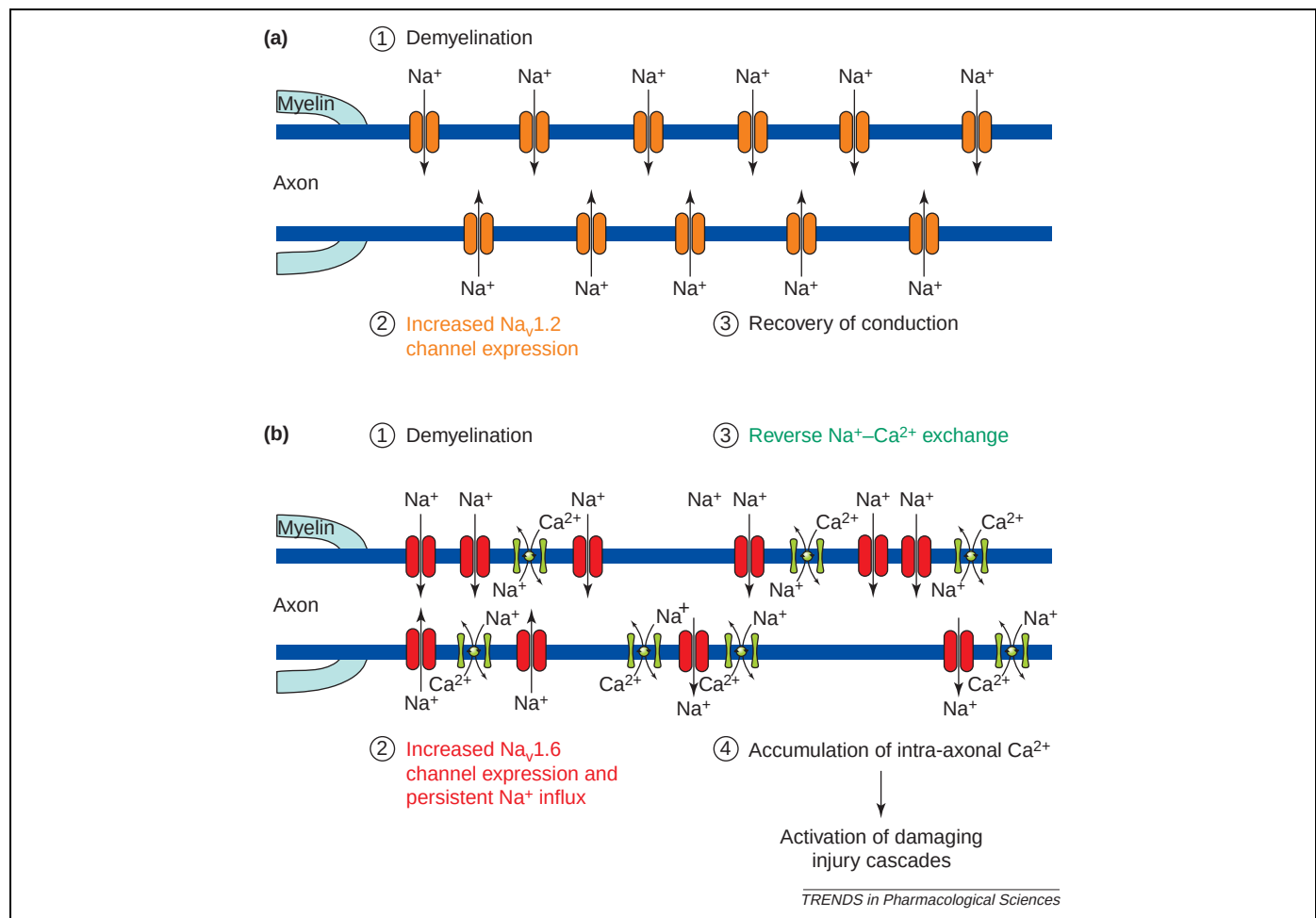


Figure 5. Different patterns of expression of $\text{Na}_v1.2$ and $\text{Na}_v1.6$ channels along demyelinated axons suggest different functions. **(a)** Following demyelination (1), $\text{Na}_v1.2$ channels are expressed diffusely (2) along some axons and support recovery of action potential conduction (3). **(b)** Expression of $\text{Na}_v1.6$ channels is upregulated in some axons following demyelination (1). In addition to producing a rapidly activating and inactivating current, these channels also produce a persistent Na^+ current (2) that can drive reverse $\text{Na}^+/\text{Ca}^{2+}$ exchange (3) and lead to accumulation of intra-axonal Ca^{2+} (4), triggering injurious secondary cascades and axonal injury. Modified, with permission, from [38]. ©2004 National Academy of Sciences USA.

protective effect, preventing axonal degeneration. The clinical efficacy of such an approach might depend, however, on the proportion of Na_v1.6 channels along demyelinated axons that require blockade for protection, and on the safety factor (i.e. the fraction of Na_v1.6 channels that are required to remain operable) at nodes along normal axons where this channel is required for saltatory conduction. It is encouraging, in this context, that the nonspecific Na⁺ channel blockers phenytoin [12] and flecainide [13] are protective in EAE, preventing axonal degeneration, maintaining axonal conduction and improving clinical outcome, without apparent negative side-effects in this animal model. Whether Na_v1.6 channel-specific blockade or nonspecific Na⁺ channel blockade will be useful clinically as a neuroprotective strategy in MS remains to be determined. The relatively safe side-effect profile of Na⁺ channel blockers that are already in clinical use might make it relatively straightforward to begin to answer these questions.

In addition to issues relating to protection of axons, several other questions remain unanswered. It would be interesting to correlate directly the changes in Na⁺ channel expression along demyelinated axons with clinical status. Comparison of patterns of Na⁺ channel expression within symptomatic versus asymptomatic (subclinical) lesions might, for example, demonstrate differences. There is, in addition, the possibility of lesion-to-lesion (acute versus chronic active versus chronic inactive) variability in Na⁺ channel expression.

In addressing these questions, it will be important to juxtapose observations in experimental models with results obtained in human tissue. As illustrated in this article, conclusions from the two are beginning to converge. We will undoubtedly soon understand more about the multiple roles of Na⁺ channels, not only in models of MS, but also in MS.

Acknowledgements

Research described in this article was supported, in part, by grants from the National Multiple Sclerosis Society and the Medical Research Service and Rehabilitation Research Service, Department of Veteran Affairs, and by gifts from Destination Cure and the Nancy Davis Foundation. The Neuroscience and Regeneration Research Center is a Collaboration of the Paralyzed Veterans of America and the United Spinal Association with Yale University. M.J.C. thanks Medical Director General, UK for support.

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