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Journal of the Neurological Sciences 233 (2005) 27 – 35

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Sodium-mediated axonal degeneration in inflammatory demyelinating disease

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Available online 13 May 2005

Abstract

Axonal degeneration is a major cause of permanent neurological deficit in multiple sclerosis (MS). The mechanisms responsible for the degeneration remain unclear, but evidence suggests that a failure to maintain axonal sodium ion homeostasis may be a key step that underlies at least some of the degeneration. Sodium ions can accumulate within axons due to a series of events, including impulse activity and exposure to inflammatory factors such as nitric oxide. Recent findings have demonstrated that partial blockade of sodium channels can protect axons from nitric oxide-mediated degeneration in vitro, and from the effects of neuroinflammatory disease in vivo. This review describes some of the reasons why sodium ions might be expected to accumulate within axons in MS, and recent observations suggesting that it is possible to protect axons from degeneration in neuroinflammatory disease by partial sodium channel blockade.

Keywords: Sodium channel; Experimental autoimmune encephalomyelitis (EAE); Nitric oxide; Demyelination; Hypoxia; Energy depletion

1. Introduction

Axonal degeneration is now accepted to be a primary cause of permanent disability in a range of neuroinflammatory disorders, including multiple sclerosis (MS). Histological studies of MS lesions have shown that axonal degeneration can be substantial [1,2], and that its magnitude correlates with disability [3,4]. Furthermore, magnetic resonance imaging and spectroscopic (MRI and MRS) studies in patients with MS have demonstrated that disability correlates with cerebral, cerebellar, and spinal cord atrophy, and with measures of axonal injury [5–11]. Unfortunately, the mechanisms that underlie axonal degeneration in MS remain unclear. However, the magnitude of degeneration in some lesions correlates with the intensity of inflammation [1,12,13], implying that factor(s) associated with inflammation may be important in promoting at least some of the degeneration. In addition, less pronounced, yet progressive degeneration of axons occurs in the apparent absence of inflammation [14,15], possibly promoted by the effects of chronic demyelination. Evidence is accumulating that a common mechanism may contribute to both types of degeneration, namely the intra-axonal accumulation of sodium ions.

The first observations arose not from MS research, but from stroke-related research into the consequences of experimental anoxia in central axons. Studies conducted primarily by Peter Stys with Stephen Waxman and Bruce Ransom detailed a cascade in which sodium accumulation, promoted by an anoxia-associated depletion of axonal energy stores, leads to calcium-mediated degeneration [16–19] via reverse operation of the Na^+/Ca^{2+} exchanger (NCX). Our group, together with the Garthwaites', has demonstrated that exposure of axons to nitric oxide (NO), as will occur during neuroinflammatory disease, causes axons to degenerate, and that sodium accumulation is a key step in the degenerative pathway [20–22]. The involvement of sodium ions has also been implicated in a number of injury models, including anoxia [18,23,24], ischemia [25,26] and spinal cord injury [27,28], and it has recently also been explored in animal models of multiple sclerosis and Guillain-Barré syndrome (GBS), namely experimental auto-

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doi:10.1016/j.jns.2005.03.003

immune encephalomyelitis (EAE) [29,30] and experimental autoimmune neuritis (EAN) [31].

In this review we examine how potentially harmful levels of sodium could accumulate in axons in neuroinflammatory demyelinating lesions, such as those in MS. In particular, we discuss the potential roles of demyelination and inflammation, which are both features typical of MS lesions. Finally we summarise evidence that the partial blockade of sodium channels may provide a novel therapy for axonal protection in MS and GBS [29–31].

2. Demyelination

Demyelinating plaques are prominent in MS, and disruption of the myelin sheath is thought to be a major cause of the failure of axonal conduction. The pathophysiological properties of demyelinated axons are known in some detail (reviewed in Ref. [32]) and it is now clear that several of these properties render axons vulnerable to the accumulation of sodium ions.

First, axons respond to demyelination by increasing their expression of sodium channels along the axolemma formerly covered by the myelin sheath [33–35]. Indeed, de novo, diffuse labelling of sodium channels along demyelinated axons has been demonstrated histologically in models of genetic dysmyelination [37], chemically induced demyelination [33], EAE [35], and EAN [38]. The appearance of these channels is normally regarded as a beneficial development as it may enable the restoration of conduction along the demyelinated axons [39,40], thereby alleviating symptoms. However, the impulses cross the demyelinated segment using a continuous [39] or micro-saltatory [40] mode of conduction, meaning that sodium entry no longer occurs just at the nodes of Ranvier, but rather occurs along much of the length of the demyelinated axolemma. The number of sodium ions that enter the axon for each conducted impulse will therefore be considerably increased.

Demyelinated axons can also become hyperexcitable, generating continuous trains of impulses that arise ectopically at the site of demyelination, and conduct away from it in both directions. This type of ectopic activity is thought to underlie many of the positive symptoms experienced by patients with MS, such as tingling paraesthesiae [41,42]. Such activity can result in well over a hundred thousand additional action potentials an hour in individual axons [43,44], and this will dramatically amplify sodium entry into the affected axons. In addition, demyelinated axons can become mechanosensitive such that they generate bursts of impulse activity upon even minor physical deformation of the lesion [43]. This phenomenon manifests in patients in the form of Lhermitte's, and related symptoms and signs. Finally, axonal sodium loading may also be accentuated in demyelinated axons by impulse-triggered bursting, in which a single action potential triggers the formation of an ensuing short train of potentials upon passing through a demyelinated lesion [45].

3. Atypical sodium channel expression

Apart from an increased expression of sodium channels along demyelinated axons, there is now evidence that the type of sodium channel expressed in some neurons and axons may be altered during MS. For example, the expression of the $Na_v1.8$ channel, which is normally limited to the spinal sensory and trigeminal neurons in the adult nervous system, has been detected in Purkinje cells in both EAE and MS [46]. Furthermore, a shift in the expression of sodium channel subtypes at nodes of Ranvier, from $Na_v1.6$ towards $Na_v1.2$ has been reported in the optic nerve of mice with EAE [35]. It is known that at least some of these changes in channel expression can affect the electrophysiological behaviour of neurons [47], and it is therefore possible that altered sodium channel expression might predispose towards the accumulation of sodium ions in affected neurons and axons. In this regard it is known that $Na_v1.6$ can co-localise with the NCX along extended lengths of demyelinated axons in animals with EAE; this combination may be pathophysiologically significant as nearly 75% of axons that were immunopositive for β-amyloid precursor protein (β-APP), a marker of axonal injury, co-expressed $Na_v1.6$ and NCX, versus just 4% of β-APP negative axons [36].

4. Nitric oxide

The production of nitric oxide (NO) is increased within the CNS during MS [48–53], and nitrite and nitrate levels, indicating NO production, are often raised in the CSF of patients with MS (reviewed in Ref. [54]). It seems likely that the production of NO may have many important pathophysiological consequences for axons, including axonal degeneration. Certainly, as noted above, the severity of axonal injury in MS correlates with the degree of inflammation [1,12].

4.1. NO and mitochondrial inhibition

Exposure of axons to NO can result in conduction block. The block may be temporary, persisting only for the duration of exposure to NO [55,56], or it may be permanent due to the degeneration of the axons [57]. In fact, axons are particularly vulnerable to NO-mediated degeneration if they are electrically active while they are exposed to NO [57]. We have proposed that the degeneration is related to a depletion of energy, as NO is known to impair mitochondrial metabolism and limit ATP production [58,59]. The fact that electrically active axons are more vulnerable to the effects of NO [57] is in keeping with this possibility, on the basis that electrical activity increases metabolic demand.