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REVIEW

Sodium imaging as a marker of tissue injury in patients with multiple sclerosis

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Abstract
Recent studies have suggested that intra-axonal sodium accumulation contribute to axonal degeneration in patients with MS. Advances in MRI hardware and software allow acquisition of brain sodium signal in vivo. This review begins with a summary of the experimental evidence for impairment of sodium homeostasis in MS. Then, MRI methods for sodium acquisition are reviewed and the application of the techniques in patients with MS is discussed. Sodium imaging and ultra-high field MRI have the potential to provide tissue-specific markers of neurodegeneration in MS.

Contents

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1. Introduction

Although the importance of axonal damage in MS is well established, the causes and molecular mechanisms leading to neurodegeneration are still largely unknown.

Inflammation is a key contributor to neuro-axonal degeneration as suggested by positive correlations between inflammatory activity of MS lesions and axon damage (Trapp et al., 1998). Since inflammation contributes to neurodegeneration, and neurodegeneration is the best pathological correlate of clinical disability (Bjartmar and Trapp, 2001), the quantification of these two processes by means of Gadolinium (Gd)-enhanced MRI and measures of brain volume has been the focus of recent studies. The magnitude of the correlation between brain tissue loss and Gd-enhancement was found to be either absent or poor in most in vivo MRI studies (Coles et al., 1999; Li and Paty, 1999; Molyneux et al., 2000; Rice et al., 2000; Comi et al., 2001). This is consistent with the results of clinical trials of various therapeutic agents which failed to show a treatment effect on progression of brain atrophy, despite the presence of a dramatic effect on enhancement (Coles et al., 1999; Li and Paty, 1999; Filippi et al., 2000; Rice et al., 2000; Comi et al., 2001). Although the discrepancies between brain tissue loss and Gd enhancement can be related, in part, to methodological issues (Inglese et al., 2005), longitudinal studies consistently capture a partial and temporal disconnection between lesion activity and neurodegeneration suggesting that ongoing tissue loss is not exclusively and directly dependent on inflammation (Inglese et al., 2005). The aim of the present review is to describe abnormalities of sodium homeostasis as possible mechanisms of delayed axonal damage in MS and to highlight recent developments in MRI methods that allow measurement of the sodium signal in vivo at high and ultra-high field strength. Finally, the application of these new MRI techniques in patients with MS and their clinical impact is discussed.

2. Rationale for sodium MRI in MS

Experimental works have revealed several mechanisms of delayed neuroaxonal loss which include demyelination, altered glial biology, aberrant glutamate homeostasis, production of nitric oxide (NO), ion-channel alteration (Hohlfeld, 1997; Bjartmar et al., 2000; Werner et al., 2001; Smith and Lassmann, 2002; Waxman, 2006) and impairment of mitochondrial DNA and enzyme complexes of the electron transport chain (Dutta et al., 2006). These mechanisms are believed to be secondary to, and partially disconnected from inflammation.

Recent studies have suggested that intra-axonal sodium accumulation contribute to axonal degeneration by reversing the action of sodium/calcium exchanger and inducing a lethal rise in intra-axonal calcium (Ca) (Waxman, 2006) (Fig. 1). In demyelinated axons the loss of the myelin capacitative shield impairs the conduction of action potentials thus producing clinical symptoms. Early cytochemical studies showed that, after demyelination, the denuded axon membrane can develop higher-than-normal density of Na channels which can lead to restoration of impulse conduction, and contribute to clinical remission (Foster et al., 1980). While the expression of some Na channel

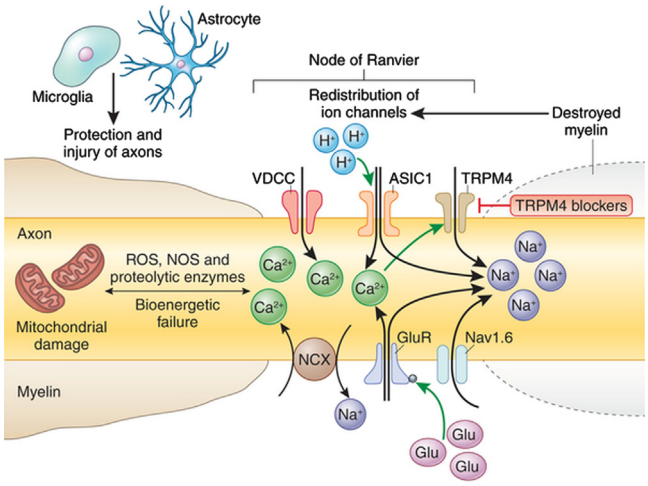

Fig. 1 Diagram showing accumulation of intra-axonal sodium and calcium in a chronically demyleinated axon. This leads to activation of proteolytic enzymes, production of reactive oxygen and nitrogen species, mitochondrial damage and energetic failure. Sodium influx is facilitated by several mechanisms including sodium channels (Nav1.6) overexpression, glutamate receptors (GluR), the reverse function of the sodium/calcium exchanger (NCX) (Hohlfeld, 2012). Published with permission.

isoforms may have an adaptive role restoring conduction, other isoforms may have a maladaptive role contributing to axonal degeneration (Smith and Lassmann, 2002). Immunocytochemical studies using panspecific Na channel antibodies subsequently confirmed the appearance of increased numbers of Na channels in experimentally demyelinated axons and in demyelinated lesions from MS patients (England et al., 1991; Moll et al., 1991).

It has been hypothesized that the molecular mechanisms of axonal/neuronal injury in inflammatory demyelinating diseases shares a final common pathway with those in hypoxia (Stys, 2004): under both pathophysiological conditions, a mismatch of the cellular demand and the production of energy can occur with subsequent depletion of adenosine tri-phosphate (ATP). After destruction of myelin, axons have a high demand of ATP and each action potential is accompanied by a higher sodium influx, resulting in an increased energy demand to keep the resting potential and the sodium concentration within the normal range. Additionally, ATP production is reduced by increased levels of nitric oxide produced in inflammatory lesions (Smith and Lassmann, 2002). ATP depletion, in turn, induces a failure of the Na/K-ATPase with additional increase of the intracellular sodium concentration. As a result, calcium is released from intracellular stores. Furthermore, the rising sodium concentration reverses the direction of the Na/Ca-exchanging ATPase, which additionally carries calcium into the neuron in order to reduce the concentration of sodium. Finally, the activation of various ionotropic and metabotropic glutamate receptors follows, resulting in a lethal increase of intracellular calcium which then activates a variety of calcium-dependent enzymes and further inhibits the energy production in mitochondria (Stys and Jiang, 2002, Stys, 2004)