



REVIEW

Experimental autoimmune encephalomyelitis from a tissue energy perspective [version 1; referees: 2 approved]

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Abstract

Increasing evidence suggests a key role for tissue energy failure in the pathophysiology of multiple sclerosis (MS). Studies in experimental autoimmune encephalomyelitis (EAE), a commonly used model of MS, have been instrumental in illuminating the mechanisms that may be involved in compromising energy production. In this article, we review recent advances in EAE research focussing on factors that conspire to impair tissue energy metabolism, such as tissue hypoxia, mitochondrial dysfunction, production of reactive oxygen/nitrogen species, and sodium dysregulation, which are directly affected by energy insufficiency, and promote cellular damage. A greater understanding of how inflammation affects tissue energy balance may lead to novel and effective therapeutic strategies that ultimately will benefit not only people affected by MS but also people affected by the wide range of other neurological disorders in which neuroinflammation plays an important role.

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Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS), characterised by multifocal, perivenous inflammation and focal destruction of myelin, typically resulting in a relapsing-remitting pattern of neurological deficit and leading to a progressive, neurodegenerative pathology. MS is a heterogeneous disease, with a multifactorial aetiology¹⁻⁴ and a highly variable clinical course. It is therefore perhaps not surprising that the treatment of MS remains complex. The sequence of events in lesion genesis remains uncertain, particularly the genesis of the first lesion, and different patterns of lesion formation have been distinguished⁵, making modelling of the disease in animals difficult. Although no single model reflects the entire clinical and pathological spectrum of MS⁶, over the years autoimmune⁷, toxic^{8,9} and viral¹⁰ models have all been employed to understand different aspects of the disease. However, experimental autoimmune encephalomyelitis (EAE) has become the most widely used laboratory model of MS, and it has various factors in common with MS, including genetic susceptibility, age, and gender, influence the clinical course, and pathology of EAE, together with the type and preparation of antigen employed and the dose and route of administration^{7,11,12}. Though criticised as a model of MS^{13,14}, EAE remains a good model of CNS inflammation, and several treatments, including glatiramer acetate^{15,16}, fingolimod^{17,18} and natalizumab¹⁹, have been successfully translated from EAE to MS. Thus, if used wisely, EAE can be a valuable tool for better understanding not only the pathophysiology of acute MS-like lesions but also the mechanisms involved in dysfunction, damage and progression in MS in order to identify novel therapeutic targets.

In addition to implicating inflammation and demyelination, pathological studies have implicated neuronal and axonal damage and loss, which begin early in the course of the disease, as major causes of irreversible disability in patients with MS^{20,21}. Although the exact mechanisms associated with irreversible neuronal and axonal loss in MS and EAE are poorly understood and probably multifactorial, mitochondrial dysfunction²²⁻²⁸ and subsequent energy insufficiency are increasingly recognised as important contributing factors²⁹⁻³¹. In this review, we summarise the most recent advances in EAE research from an energy viewpoint, and focus on tissue hypoxia, mitochondrial dysfunction, reactive oxygen/nitrogen species (ROS/RNS) and sodium dysregulation.

Energy production in the central nervous system

The brain is a highly metabolic organ: whilst comprising only 2% of the body's mass, it requires 20% of the body's resting energy consumption³². Neurons have the highest energy demand³³, and it has been hypothesised that these energetic demands are met in part by energy production in neighbouring glia³⁴⁻³⁶. Glucose has often been considered the major metabolite used during oxidative phosphorylation for yielding energy in neurons and glia, but in fact different cell types can preferentially use different metabolic substrates and pathways to produce ATP under physiological conditions and, besides glucose, neurons and glial cells, can use lactate, pyruvate, glutamate and glutamine as metabolic substrates³⁷. Oxidative phosphorylation yields approximately 30 molecules of ATP per molecule of glucose, compared with

a meagre two molecules of ATP per molecule of glucose via glycolysis³⁸. Therefore, although ATP production by glycolysis is rapid, it is understandable why oxygen is essential to ensure an efficient energy metabolism, particularly in metabolically demanding cells such as neurons. Indeed, neurons demand a considerable supply of energy, and mitochondria, the key providers of this energy, must be distributed in appropriate numbers to meet demand.

Theoretical energy budgets have established that the majority of the energy consumed by the brain is used for restoration and maintenance of the resting membrane potential by the sodium-potassium (Na-K) ATPase^{33,39,40}, especially following electrical activity. However, a significant proportion of the brain's energy expenditure is associated with non-signalling or 'housekeeping' processes, including lipid turnover, proton leak across the mitochondrial membrane, cytoskeletal rearrangements, vesicle recycling, and protein synthesis^{40,41}. Therefore, it is easy to imagine how an impairment of energy metabolism can have significant consequences on CNS function. A number of factors, including nitric oxide (NO), other ROS/RNS and factors from immune cells, and tissue hypoxia, have been suggested to conspire to impair ATP production by compromising mitochondrial function in MS⁴²⁻⁴⁵. Deficiencies in mitochondrial transport and the mitochondrial respiratory chain enzymes, notably complex IV, will also impair ATP production, and the nature and importance of these deficiencies may well change during the different phases of the disease.

Consequences of energy failure

Energy failure due to mitochondrial dysfunction or damage is increasingly recognised to play a pivotal role in MS pathogenesis. Mitochondrial defects, which will certainly impair ATP production, have been demonstrated within acute⁴³ and chronic^{28,46,47} lesions and also in the normal appearing white matter²² of patients with MS. Indeed, metabolites produced as a probable consequence of ATP depletion are observed in the cerebrospinal fluid of patients with MS⁴⁸. Impaired ATP production can reduce sodium extrusion from the axoplasm into the extracellular space following electrical activity, and this deficit will be exaggerated in conducting demyelinated axons because of their increased expression and redistribution of sodium channels along the demyelinated axolemma⁴⁹ associated with the restoration of electrophysiological function⁵⁰⁻⁵². The excessive accumulation of intracellular sodium ions not only increases the energy demand to operate the Na-K ATPase, which is already one of the most significant ATP consumers in the CNS⁵³, but it also promotes the reverse operation of the sodium-calcium exchanger (NCX)^{54,55}, which imports calcium into the axoplasm. The energy-starved axon is unable to restore calcium homeostasis, resulting in calcium cytotoxicity and the initiation of cell death pathways. Such energy failure within axons further increases their susceptibility to excitotoxic injury⁵⁶. Small-diameter fibres, which preferentially degenerate in MS, may be more vulnerable to energy failure than their larger neighbours because of their lower mitochondrial number in relation to their surface area⁵⁷, although other mitochondrially mediated mechanisms may also play a role⁵⁸.

Thus, there is good evidence that energy failure may play an important role in axonal degeneration in MS, and it follows that neuroprotective strategies aimed at protecting energy balance may be effective in MS. The animal model of MS, EAE, has been employed not only to study the role of energy deficits but also to explore strategies to achieve neuroprotection.

Tissue hypoxia in experimental autoimmune encephalomyelitis

Increasing evidence from neuropathological and magnetic resonance imaging (MRI) studies shows that MS lesions can experience low oxygen concentrations⁵⁹⁻⁶¹. Hypoxia can decrease mitochondrial oxygen consumption in cells (the respiratory rate)⁶² by initiating a decrease in ATP-using processes (metabolic demand) and also can have significant effects on mitochondrial movement, velocity and morphology; however, it is unclear from the human data alone whether the tissue hypoxia contributes to the pathogenesis of the disease. The presence of severe tissue hypoxia sufficient to compromise function was demonstrated by Davies *et al.*⁶³, who showed that the neurological deficits in a rat model of EAE quantitatively, spatially and temporally correlated with spinal white and grey matter hypoxia. Two independent methods were used to demonstrate hypoxia: an intravenous immunohistochemical⁶⁴ probe and a fine, oxygen-sensitive optical probe physically inserted into the spinal cord. The authors demonstrated the importance of hypoxia in the expression and progression of neurological deficits by showing that treatment with both acute (1 hour) and prolonged (7 continuous days) normobaric oxygen (~95%) reversed the hypoxia and partially restored function and attenuated disease severity, respectively. More recently, hypoxia was found to be a key factor in lesion formation in an animal model of the pattern III demyelinating lesion found in MS⁶⁵. This experimental lesion is induced by the intraspinal injection of the pro-inflammatory agent lipopolysaccharide into the dorsal white matter of adult rats⁶⁶, and the authors found that the demyelination was reduced, or even prevented, by breathing normobaric oxygen during the two-day period when the spinal cord otherwise would have been hypoxic⁶⁵. These findings may recommend the consideration of oxygen therapy for acute attacks in MS, but if extrapolation is considered to include progressive disease it is important to bear in mind that mitochondrial respiratory chain enzymes are deficient within neurons and that mitochondrial transport is also likely to be impaired, and these considerations may limit the therapeutic potential of oxygen therapy. Thus, the cause or causes of damage in progressive disease are not necessarily the same (and are not likely to be precisely the same) as those in the acute lesion.

A role for hypoxia in MS was further supported by Johnson *et al.*⁶⁷, who measured oxygenation in the cerebellum and cortex of awake, unrestrained mice with EAE and found that the grey matter was severely hypoxic. The same group also used susceptibility-weighted imaging (SWI) to assess deoxyhaemoglobin-based hypointensities in EAE mice *in vivo*⁶⁸. SWI is a protocol with MRI that is particularly sensitive to deoxyhaemoglobin and can visualise the venous vasculature^{69,70}, but it also detects parenchymal iron deposits and demyelination^{71,72}, which complicates the interpretation when imaging patients with MS

and animals with EAE. Given that the visibility of the venous vasculature is highly dependent on the partial pressure of oxygen, Nathoo *et al.*⁶⁸ modulated the inspired oxygen concentration during imaging, hypothesising that vascular hypointensities visible with normoxic conditions would disappear upon an increase in inspired oxygen. The authors concluded the presence of venous hypoxia due to the increased oxygen demand, arising from inflammation, outstripping supply⁶⁸.

Esen *et al.*⁷³ adopted a different approach, namely exposing mice to normobaric hypoxia for three weeks from the day of immunisation for EAE, to induce angioplasty and tissue survival. This strategy not only significantly delayed the onset of disease but also decreased inflammatory activity in the spinal cords of the mice. The authors attributed the beneficial effects to the induction of an anti-inflammatory milieu, but hypoxic pre-conditioning of the tissue to survive the hypoxic insult associated with EAE^{63,67} may also have played a role.

Reactive oxygen/nitrogen species in experimental autoimmune encephalomyelitis

ROS/RNS are routinely produced under physiological conditions; however, they normally pose very little threat because of a specialised set of endogenous defence and repair mechanisms. The CNS anti-oxidant defence system is composed of non-enzymatic (for example, glutathione [GSH] and uric acid) and enzymatic (for example, superoxide dismutases, GSH peroxidase, catalase, haeme-oxygenases, quinone oxidoreductases and peroxiredoxins) anti-oxidants^{74,75}. During pathological conditions, such as inflammation, the overproduction of ROS/RNS overwhelms this anti-oxidant system, resulting in oxidative/nitrative stress. ROS/RNS and the ensuing oxidative/nitrative stress have frequently been suggested to play an important early role in MS^{44,45} and EAE⁷⁶, mainly through their toxic actions on mitochondria^{76,77}, and therefore can indirectly contribute to a tissue energy deficit. ROS/RNS include superoxide, peroxynitrite and the hydroxyl radical. Superoxide, produced by a one-electron reduction of oxygen, is the precursor of most other forms of ROS. Dismutation of superoxide produces hydrogen peroxide, which in turn either can be fully reduced to water or, in the presence of ions of a suitable transition metal (for example, iron), can lead to the formation of the extremely toxic hydroxyl radical⁷⁸. Superoxide can also react with NO, in a reaction that is limited by the rate of diffusion of both radicals, to produce peroxynitrite. Mitochondria themselves produce low levels of superoxide under normal conditions; however, superoxide production can increase significantly under pathological conditions, particularly when mitochondria are damaged, or if the cytoplasmic oxygen concentration is abnormally high or low⁷⁹. Nevertheless, the most abundant source of superoxide is the respiratory burst, which is mediated by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases⁸⁰. Mossakowski *et al.*⁸¹, using intravitreal NADPH fluorescence lifetime imaging to detect functional NADPH oxidase (NOX) enzymes *in vivo*, recently reported a spatio-temporal correlation between the activated NOX enzymes and neuronal damage in mice with EAE. The authors identified activated macrophages/microglia as major cellular sources of activated NOX enzymes but showed for the first time that astrocytes are also major contributors of

oxidative stress in the CNS during chronic EAE. As NOX activation was not restricted to a specific cell type, Mossakowski *et al.* suggested that a locally acting soluble mediator, such as glutamate, may contribute to the activation seen, and they supported this by applying glutamate locally and measuring the increase in NOX enzyme activation in the brain stem of healthy mice. The authors observed excessive ROS production and a concomitant increase in neuronal calcium. Besides CNS NOX activity, NOX enzyme was overactivated in peripheral CD11b⁺ monocytes from mice with EAE and patients with relapsing-remitting MS, an effect that can be antagonized by systemic administration of epigallocatechin-3-gallate, the major polyphenolic compound of the green tea plant⁸¹. Recently, Radbruch *et al.*⁸² used the same technique to investigate whether NOX activity was evident during the remission phase of EAE. They found that during this phase of the disease, when neurological function in the mice is restored, astrocytes and microglia shift towards an activated phenotype, showing morphological changes and elevated levels of activated NOX enzymes, which correlated with subclinical neuronal dysfunction, characterised by elevated neuronal calcium.

Besides changes in NOX activity, alterations in other mediators of oxidative stress have been revealed in EAE. Two independent groups have reported reduced GSH levels in rodents with clinical EAE^{75,83}. Morales Pantoja *et al.*⁸³ found that this reduced GSH is a consequence of decreased levels of the enzymes and transporters that are required for *de novo* GSH synthesis because of diminished levels of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in EAE. Nrf2 is a transcription factor that regulates endogenous anti-oxidant systems. Under conditions of oxidative stress, Nrf2 translocates to the nucleus to promote the expression of Nrf2-regulated genes, including those that are involved in GSH synthesis. Nrf2 was low in both the cytoplasmic and nuclear fractions; however, the decrease in the latter was more severe, suggesting that the nuclear transport of Nrf2 is also affected in EAE⁸³. Interestingly, dimethyl fumarate, a current therapy for patients with MS, increases Nrf2⁸⁴, thus increasing GSH levels.

Mitochondrial dysfunction in experimental autoimmune encephalomyelitis

Several studies have reported significant mitochondrial abnormalities in both MS^{22,43,46,47} and EAE^{76,77,85}. Indeed, mitochondrial alterations such as mitochondrial vacuolisation, swelling and dissolution of cristae have been described to occur as early as three days post-immunisation of EAE⁷⁶. Early morphological alterations in mitochondria are associated with focal axonal damage in axons with intact myelin⁷⁷. Furthermore, whereas large-calibre axons recovered from such damage, thin-calibre axons had higher rates of progression⁷⁷.

Sadeghian *et al.*⁸⁵ recently showed that mitochondria in spinal cord axons of EAE mice are depolarised, often totally so, and fragmented, and have impaired trafficking. The mitochondrial deficits correlated with the neurological deficit, reversing during remission and re-occurring at relapse. The authors showed that this mitochondrial dysfunction was most severe within inflammatory foci but independent of demyelination or degeneration⁸⁵. The data implicate mitochondrial dysfunction and energy failure as major

causes of neurological deficits in the absence of overt structural damage.

Dysfunctional mitochondria usually generate more ROS, promoting increased oxidative stress. Accordingly, subtle decreases in mitochondrial membrane potential, coupled with increased oxidative stress, have been described prior to the onset of neurological deficit and immune cell infiltration in EAE⁸⁶. In addition to decreases in mitochondrial membrane potential, certain conditions such as oxidative stress, low adenine nucleotide concentrations, or increased calcium induce the formation of the mitochondrial permeability transition pore (mPTP)^{87,88}. Opening of this pore, as suggested by its name, increases the permeability of the mitochondrial membranes to low-molecular-weight solutes and some proteins, and it is one of the main causes of cell death. The peptidylprolyl *cis-trans*-isomerase cyclophilin D (CypD) is considered critical for opening the mPTP^{89,90}, and it was recently shown that a mitochondrially targeted CypD inhibitor significantly improved neurological deficit and protected axons, with minimal immunosuppression, in murine EAE⁹¹.

Sodium dysregulation in experimental autoimmune encephalomyelitis

One of the main consequences of energy failure is sodium dysregulation (that is, an excessive accumulation of sodium in axons) due to an inadequacy of sodium extrusion. A number of studies have implicated a role for voltage-gated sodium channels (VGSCs), and a rise in intra-axonal sodium ions, in promoting the degeneration of myelinated axons. A rise in internal sodium is not usually problematic if there is adequate ATP to restore sodium homeostasis via the Na-K ATPase (sodium pump), but energy insufficiency can allow sodium to rise sufficiently to cause reverse operation of the NCX and the importation of lethal quantities of calcium ions. This is particularly the case in demyelinated axons, which are more vulnerable to sodium dysregulation because of their adaptive re-expression of sodium channels along the denuded axolemma. Important early studies were performed in optic nerve axons with energy failure due to imposed anoxia (for example, 92), but the recognition that NO both was a potent inhibitor of mitochondrial function^{84,85} and was produced in abundance at sites of inflammation⁹³ suggested that sodium channels and raised internal sodium may also be responsible for degeneration of axons in inflammatory lesions^{55,94}. This reasoning suggested that axons may be rendered vulnerable to degeneration by impulse conduction because this would promote sodium influx, and the combination of electrical activity and NO exposure was found to be a potent cause of degeneration⁹⁵. It followed that axons may be protected from degeneration by partial blockade of their sodium channels using pharmacological agents^{96,97}, and the potency of this therapeutic approach was demonstrated in a number of investigations in EAE by using phenytoin⁹⁸, flecainide⁹⁹, lamotrigine¹⁰⁰, carbamazepine¹⁰¹, and safinamide¹⁰² and blockers of the NCX⁹⁷. Confidence that sodium channel blockade might provide an effective neuroprotective strategy in MS was enhanced by the discovery that the agents could also reduce the severity of inflammation and dampen microglial activation¹⁰²⁻¹⁰⁶, and two clinical trials have been performed. The first explored the value of lamotrigine in reducing

the rate of brain atrophy in secondary progressive MS¹⁰⁷. The trial failed its primary outcome measure, probably because the trial design did not allow for pseudoatrophy resulting from a reduction in inflammatory swelling (which was unexpected at the time), but there was a significant reduction in the deterioration of the secondary outcome measure of the 25-foot timed walk¹⁰⁷. Importantly, in the treated group, there was a significant reduction in circulating neurofilament, a marker of neuronal/axonal degeneration¹⁰⁸. The second trial examined whether phenytoin was effective in neuroprotection in acute optic neuritis¹⁰⁹, and the treated group showed a significant (30%) reduction in the loss of the retinal nerve fibre layer compared with placebo (the trial won the MS Research Prize for 2016).

Of the nine VGSC isoforms identified in mammals, Na_v1.2 and Na_v1.6 are predominantly expressed in the axolemma. In myelinated axons, the Na_v1.6 subtype of VGSCs, which produces both transient and persistent currents^{110–112}, is strategically located in high density at the nodes of Ranvier¹¹³ to allow fast propagation of action potentials. In contrast, Na_v1.2 VGSCs are preferentially located along the axolemma of unmyelinated axons¹¹⁴. During MS and EAE, the expression of these and other VGSC isoforms is dysregulated^{49,115–117}, contributing to ongoing damage and the expression of symptoms^{118,119}. Thus, it seems reasonable that further understanding the contribution of various VGSC isoforms to pathogenesis and progression in MS could facilitate more targeted therapy, thereby increasing efficacy while reducing any potential side effects. Recently, a non-CNS penetrant sodium channel blocking agent was successful in limiting damage in progressive EAE and a model of optic neuritis¹²⁰, and the drug gained selective access to inflamed regions of the CNS because of the associated breakdown of the blood-brain barrier. This therapeutic strategy could offer an opportunity to reduce side effects while retaining the beneficial effects of VGSC therapy.

An important adaptation of axons to demyelination in MS and EAE is the expression of both Na_v1.2 and Na_v1.6 isoforms along the denuded axolemma^{49,115}. Whilst these changes allow the restoration of conduction through the lesion^{50–52,121}, they may also add a vulnerability to degeneration through the mechanisms described above. The Na_v1.6 isoform, which is abundantly expressed, has been advanced as being the main mediator of axonal injury because it not only induces a larger persistent sodium current than Na_v1.2¹²² but also frequently co-localises with markers of axonal damage⁴⁹. More recently, Schattling *et al.*¹²³ showed that a mutation of Na_v1.2 that results in increased persistent sodium current can also increase degeneration in EAE. Furthermore, the authors showed that genetic manipulation of this isoform had no effect on the immune response in this model, implying that blocking Na_v1.2 activity may allow neuroprotection without the added immunomodulatory response seen with conventional pan-sodium channel blockers.

Na_v1.5 was recently reported to be upregulated in astrocytes in both monophasic and chronic-relapsing EAE, significantly

correlating with disease severity¹¹⁶. As with microglia, reactive astrocytes can be protective or detrimental; however, their pro-inflammatory effects have been suggested to contribute significantly to the inflammatory response in EAE¹²⁴, presumably through reactive astrogliosis and glial scar formation. It is noteworthy that Na_v1.5 has been shown to play an important role in astrogliosis via reverse operation of the NCX and a subsequent robust calcium response *in vitro*¹²⁵; thus, targeting Na_v1.5 may represent a therapeutic target for modulating reactive astrogliosis in MS and EAE.

Conclusions

In recent years, there has been a burgeoning of therapies for MS, most of which interfere with aspects of the acquired immune system. In this review, we have focussed rather on energy balance within the inflamed CNS, taking EAE as an animal model. We have identified tissue hypoxia and free radicals as important factors in the observed mitochondrial dysfunction, and discussed how this can result in neurological dysfunction, sodium dysregulation, calcium entry, and degeneration. Sodium channel inhibitors have unexpectedly emerged as neuroprotective agents, and these deserve more attention as they provide a safe, new therapeutic strategy that may help to redress an energy insufficiency by reducing neuronal energy demand. The other side of the 'energy coin', namely increasing energy supply, may be provided by increasing tissue oxygenation, and the first promising observations that this will provide an effective therapy are now emerging.

Abbreviations

CNS, central nervous system; CypD, cyclophilin D; EAE, experimental autoimmune encephalomyelitis; GSH, glutathione; mPTP, mitochondrial permeability transition pore; MRI, magnetic resonance imaging; MS, multiple sclerosis; NADPH, nicotinamide adenine dinucleotide phosphate; Na-K, sodium-potassium; NCX, sodium-calcium exchanger; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate oxidase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; ROS/RNS, reactive oxygen/nitrogen species; SWI, susceptibility-weighted imaging; VGSC, voltage-gated sodium channel.

Competing interests

Since 2010, Kenneth J Smith has received laboratory research support from Biogen Idec, Genzyme, Merck Serono, and UCB. Roshni A. Desai declares that she has no competing interests.

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References



1. Compston A: **Genetic epidemiology of multiple sclerosis.** *J Neurol Neurosurg Psychiatr.* 1997; **62**(6): 553–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Cook SD, Rohowsky-Kochan C, Bansil S, *et al.*: **Evidence for multiple sclerosis as an infectious disease.** *Acta Neurol Scand Suppl.* 1995; **161**: 34–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Weinshenker BG, Bass B, Rice GP, *et al.*: **The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability.** *Brain.* 1989; **112**(Pt 1): 133–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Herndon RM: **Herpesviruses in multiple sclerosis.** *Arch Neurol.* 1996; **53**(2): 123–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Lucchinetti C, Brück W, Parisi J, *et al.*: **Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination.** *Ann Neurol.* 2000; **47**(6): 707–17.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Schuh C, Wimmer I, Hametner S, *et al.*: **Oxidative tissue injury in multiple sclerosis is only partly reflected in experimental disease models.** *Acta Neuropathol.* 2014; **128**(2): 247–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Gold R, Linington C, Lassmann H: **Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research.** *Brain.* 2006; **129**(Pt 8): 1953–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Blakemore WF: **Observations on oligodendrocyte degeneration, the resolution of status spongiosus and remyelination in cuprizone intoxication in mice.** *J Neurocytol.* 1972; **1**(4): 413–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Ludwin SK: **Central nervous system demyelination and remyelination in the mouse: an ultrastructural study of cuprizone toxicity.** *Lab Invest.* 1978; **39**(6): 597–612.
[PubMed Abstract](#)
10. Miller SD, Vanderlugt CL, Begolka WS, *et al.*: **Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading.** *Nat Med.* 1997; **3**(10): 1133–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Teixeira SA, Varriano AA, Bolonheis SM, *et al.*: **Experimental autoimmune encephalomyelitis: A heterogeneous group of animal models to study human multiple sclerosis.** *Drug Discovery Today: Disease Models.* 2005; **2**(2): 127–34.
[Publisher Full Text](#)
12. Storch MK, Steffler A, Brehm U, *et al.*: **Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology.** *Brain Pathol.* 1998; **8**(4): 681–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. **F** Sriram S, Steiner I: **Experimental allergic encephalomyelitis: a misleading model of multiple sclerosis.** *Ann Neurol.* 2005; **58**(6): 939–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
14. Behan PO, Chaudhuri A: **EAE is not a useful model for demyelinating disease.** *Mult Scler Relat Disord.* 2014; **3**(5): 565–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Teitelbaum D, Webb C, Bree M, *et al.*: **Suppression of experimental allergic encephalomyelitis in Rhesus monkeys by a synthetic basic copolymer.** *Clin Immunol Immunopathol.* 1974; **3**(2): 256–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Keith AB, Arnon R, Teitelbaum D, *et al.*: **The effect of Cop 1, a synthetic polypeptide, on chronic relapsing experimental allergic encephalomyelitis in guinea pigs.** *J Neurol Sci.* 1979; **42**(2): 267–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Brinkmann V, Davis MD, Heise CE, *et al.*: **The immune modulator FTY720 targets sphingosine 1-phosphate receptors.** *J Biol Chem.* 2002; **277**(24): 21453–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Foster CA, Howard LM, Schweitzer A, *et al.*: **Brain penetration of the oral immunomodulatory drug FTY720 and its phosphorylation in the central nervous system during experimental autoimmune encephalomyelitis: consequences for mode of action in multiple sclerosis.** *J Pharmacol Exp Ther.* 2007; **323**(2): 469–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Yednock TA, Cannon C, Fritz LC, *et al.*: **Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin.** *Nature.* 1992; **356**(6364): 63–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Trapp BD, Peterson J, Ransohoff RM, *et al.*: **Axonal transection in the lesions of multiple sclerosis.** *N Engl J Med.* 1998; **338**(5): 278–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Ferguson B, Matyszak MK, Esiri MM, *et al.*: **Axonal damage in acute multiple sclerosis lesions.** *Brain.* 1997; **120**(Pt 3): 393–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Dutta R, McDonough J, Yin X, *et al.*: **Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients.** *Ann Neurol.* 2006; **59**(3): 478–89.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. **F** Campbell GR, Ziabreva I, Reeve AK, *et al.*: **Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis.** *Ann Neurol.* 2011; **69**(3): 481–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
24. Broadwater L, Pandit A, Clements R, *et al.*: **Analysis of the mitochondrial proteome in multiple sclerosis cortex.** *Biochim Biophys Acta.* 2011; **1812**(5): 630–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. Witte ME, Nijland PG, Drexhage JA, *et al.*: **Reduced expression of PGC-1 α partly underlies mitochondrial changes and correlates with neuronal loss in multiple sclerosis cortex.** *Acta Neuropathol.* 2013; **125**(2): 231–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. **F** Kim JY, Shen S, Dietz K, *et al.*: **HDAC1 nuclear export induced by pathological conditions is essential for the onset of axonal damage.** *Nat Neurosci.* 2010; **13**(2): 180–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. Hares K, Kemp K, Rice C, *et al.*: **Reduced axonal motor protein expression in non-lesional grey matter in multiple sclerosis.** *Mult Scler.* 2014; **20**(7): 812–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Haile Y, Deng X, Ortiz-Sandoval C, *et al.*: **Rab32 connects ER stress to mitochondrial defects in multiple sclerosis.** *J Neuroinflammation.* 2017; **14**(1): 19.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Waxman SG: **Ions, energy and axonal injury: towards a molecular neurology of multiple sclerosis.** *Trends Mol Med.* 2006; **12**(5): 192–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Trapp BD, Stys PK: **Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis.** *Lancet Neurol.* 2009; **8**(3): 280–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Campbell GR, Worrall JT, Mahad DJ: **The central role of mitochondria in axonal degeneration in multiple sclerosis.** *Mult Scler.* 2014; **20**(14): 1806–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Sokoloff L: **Metabolism of the central nervous system in vivo.** *Handb Physiol.* 1960; **3**: 1843–1864.
[Reference Source](#)
33. Howarth C, Peppiatt-Wildman CM, Attwell D: **The energy use associated with neural computation in the cerebellum.** *J Cereb Blood Flow Metab.* 2010; **30**(2): 403–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Pellerin L, Magistretti PJ: **Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization.** *Proc Natl Acad Sci U S A.* 1994; **91**(22): 10625–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Nave KA: **Myelination and support of axonal integrity by glia.** *Nature.* 2010; **468**(7321): 244–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. **F** Fünfschilling U, Supplie LM, Mahad D, *et al.*: **Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity.** *Nature.* 2012; **485**(7399): 517–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. Zielke HR, Zielke CL, Baab PJ: **Direct measurement of oxidative metabolism in the living brain by microdialysis: a review.** *J Neurochem.* 2009; **109** Suppl 1: 24–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Berg JM, Tymoczko JL, Stryer L: **The Regulation of Cellular Respiration Is Governed Primarily by the Need for ATP.** 2002.
[Reference Source](#)
39. Attwell D, Laughlin SB: **An energy budget for signaling in the grey matter of the brain.** *J Cereb Blood Flow Metab.* 2001; **21**(10): 1133–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. **F** Harris JJ, Attwell D: **The energetics of CNS white matter.** *J Neurosci.* 2012; **32**(1): 356–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
41. Engl E, Attwell D: **Non-signalling energy use in the brain.** *J Physiol.* 2015; **593**(16): 3417–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Aboul-Enein F, Lassmann H: **Mitochondrial damage and histotoxic hypoxia: a pathway of tissue injury in inflammatory brain disease?** *Acta Neuropathol.* 2005; **109**(1): 49–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Mahad D, Ziabreva I, Lassmann H, Turnbull D: **Mitochondrial defects in acute multiple sclerosis lesions.** *Brain.* 2008; **131**(Pt 7): 1722–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. **F** Fischer MT, Sharma R, Lim JL, *et al.*: **NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury.** *Brain.* 2012; **135**(Pt 3): 886–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

45. Haider L, Fischer MT, Frischer JM, *et al.*: Oxidative damage in multiple sclerosis lesions. *Brain*. 2011; **134**(Pt 7): 1914–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Mahad DJ, Ziabreva I, Campbell G, *et al.*: Mitochondrial changes within axons in multiple sclerosis. *Brain*. 2009; **132**(Pt 5): 1161–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
47. Witte ME, Bo L, Rodenburg RJ, *et al.*: Enhanced number and activity of mitochondria in multiple sclerosis lesions. *J Pathol*. 2009; **219**(2): 193–204.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Lazzarino G, Amorini AM, Eikelenboom MJ, *et al.*: Cerebrospinal fluid ATP metabolites in multiple sclerosis. *Mult Scler*. 2010; **16**(5): 549–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Craner MJ, Newcombe J, Black JA, *et al.*: Molecular changes in neurons in multiple sclerosis: altered axonal expression of Na_v1.2 and Na_v1.6 sodium channels and Na⁺/Ca²⁺ exchanger. *Proc Natl Acad Sci U S A*. 2004; **101**(2): 8168–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Felts PA, Baker TA, Smith KJ: Conduction in segmentally demyelinated mammalian central axons. *J Neurosci*. 1997; **17**(19): 7267–77.
[PubMed Abstract](#)
51. Bostock H, Sears TA: Continuous conduction in demyelinated mammalian nerve fibers. *Nature*. 1976; **263**(5580): 786–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Smith KJ, Bostock H, Hall SM: Saltatory conduction precedes remyelination in axons demyelinated with lysophosphatidyl choline. *J Neuro Sci*. 1982; **54**(1): 13–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Ames A 3rd: CNS energy metabolism as related to function. *Brain Res Brain Res Rev*. 2000; **34**(1–2): 42–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Stys PK, Waxman SG, Ransom BR: Reverse operation of the Na⁺-Ca²⁺ exchanger mediates Ca²⁺ influx during anoxia in mammalian CNS white matter. *Ann N Y Acad Sci*. 1991; **639**: 328–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Bechtold DA, Smith KJ: Sodium-mediated axonal degeneration in inflammatory demyelinating disease. *J Neuro Sci*. 2005; **233**(1–2): 27–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Abramov AY, Duchon MR: Impaired mitochondrial bioenergetics determines glutamate-induced delayed calcium deregulation in neurons. *Biochim Biophys Acta*. 2010; **1800**(3): 297–304.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Stys PK: General mechanisms of axonal damage and its prevention. *J Neuro Sci*. 2005; **233**(1–2): 3–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Sajic M, Mastrolia V, Lee CY, *et al.*: Impulse conduction increases mitochondrial transport in adult mammalian peripheral nerves *in vivo*. *PLoS Biol*. 2013; **11**(12): e1001754.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Aboul-Enein F, Rauschka H, Komek B, *et al.*: Preferential loss of myelin-associated glycoprotein reflects hypoxia-like white matter damage in stroke and inflammatory brain diseases. *J Neuropathol Exp Neurol*. 2003; **62**(1): 25–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Graumann U, Reynolds R, Steck AJ, *et al.*: Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult. *Brain Pathol*. 2003; **13**(4): 554–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Yang R, Dunn JF: Reduced cortical microvascular oxygenation in multiple sclerosis: a blinded, case-controlled study using a novel quantitative near-infrared spectroscopy method. *Sci Rep*. 2015; **5**: 16477.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Papandreou I, Cairns RA, Fontana L, *et al.*: HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. *Cell Metab*. 2006; **3**(3): 187–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
63. Davies AL, Desai RA, Bloomfield PS, *et al.*: Neurological deficits caused by tissue hypoxia in neuroinflammatory disease. *Ann Neurol*. 2013; **74**(6): 815–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Zanelli SA, Trimmer PA, Solenski NJ: Nitric oxide impairs mitochondrial movement in cortical neurons during hypoxia. *J Neurochem*. 2006; **97**(3): 724–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Desai RA, Davies AL, Tachrount M, *et al.*: Cause and prevention of demyelination in a model multiple sclerosis lesion. *Ann Neurol*. 2016; **79**(4): 591–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Felts PA, Woolston AM, Fernando HB, *et al.*: Inflammation and primary demyelination induced by the intraspinal injection of lipopolysaccharide. *Brain*. 2005; **128**(Pt 7): 1649–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Johnson TW, Wu Y, Nathoo N, *et al.*: Gray Matter Hypoxia in the Brain of the Experimental Autoimmune Encephalomyelitis Model of Multiple Sclerosis. *PLoS One*. 2016; **11**(12): e0167196.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. Nathoo N, Rogers JA, Yong VW, *et al.*: Detecting deoxyhemoglobin in spinal cord vasculature of the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis using susceptibility MRI and hyperoxygenation. *PLoS One*. 2015; **10**(5): e0127033.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Nair JR, Van Hecke W, De Belder F, *et al.*: High-resolution susceptibility-weighted imaging at 3 T with a 32-channel head coil: technique and clinical applications. *AJR Am J Roentgenol*. 2010; **195**(4): 1007–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Ishizaka K, Kudo K, Fujima N, *et al.*: Detection of normal spinal veins by using susceptibility-weighted imaging. *J Magn Reson Imaging*. 2010; **31**(1): 32–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Chavhan GB, Babyn PS, Thomas B, *et al.*: Principles, techniques, and applications of T2*-based MR imaging and its special applications. *Radiographics*. 2009; **29**(5): 1433–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Lee J, Shmueli K, Kang BT, *et al.*: The contribution of myelin to magnetic susceptibility-weighted contrasts in high-field MRI of the brain. *Neuroimage*. 2012; **59**(4): 3967–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Esen N, Katyshev V, Serkin Z, *et al.*: Endogenous adaptation to low oxygen modulates T-cell regulatory pathways in EAE. *J Neuroinflammation*. 2016; **13**: 13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. Schreiber G, van Horssen J, van Rossum S, *et al.*: Therapeutic potential and biological role of endogenous antioxidant enzymes in multiple sclerosis pathology. *Brain Res Rev*. 2007; **56**(2): 322–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Dimitrijević M, Kotur-Stevuljević J, Stojić-Vukanić Z, *et al.*: Sex Difference in Oxidative Stress Parameters in Spinal Cord of Rats with Experimental Autoimmune Encephalomyelitis: Relation to Neurological Deficit. *Neurochem Res*. 2017; **42**(2): 481–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
76. Qi X, Lewin AS, Sun L, *et al.*: Mitochondrial protein nitration primes neurodegeneration in experimental autoimmune encephalomyelitis. *J Biol Chem*. 2006; **281**(42): 31950–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
77. Nikić I, Merkle D, Sorbara C, *et al.*: A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. *Nat Med*. 2011; **17**(4): 495–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. Halliwell B, Hoult JR, Blake DR: Oxidants, inflammation, and anti-inflammatory drugs. *FASEB J*. 1988; **2**(13): 2867–73.
[PubMed Abstract](#)
79. Murphy MP: Mitochondria—a neglected drug target. *Curr Opin Investig Drugs*. 2009; **10**(10): 1022–4.
[PubMed Abstract](#)
80. Bedard K, Krause KH: The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiol Rev*. 2007; **87**(1): 245–313.
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Mossakowski AA, Pohlen J, Bremer D, *et al.*: Tracking CNS and systemic sources of oxidative stress during the course of chronic neuroinflammation. *Acta Neuropathol*. 2015; **130**(6): 799–814.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Radbruch H, Bremer D, Guenther R, *et al.*: Ongoing Oxidative Stress Causes Subclinical Neuronal Dysfunction in the Recovery Phase of EAE. *Front Immunol*. 2016; **7**: 92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Morales Pantoja IE, Hu CL, Perrone-Bizzozero NI, *et al.*: Nrf2-dysregulation correlates with reduced synthesis and low glutathione levels in experimental autoimmune encephalomyelitis. *J Neurochem*. 2016; **139**(4): 640–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Linker RA, Lee DH, Ryan S, *et al.*: Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain*. 2011; **134**(Pt 3): 678–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
85. Sadeghian M, Mastrolia V, Rezaei Haddad A, *et al.*: Mitochondrial dysfunction is an important cause of neurological deficits in an inflammatory model of multiple sclerosis. *Sci Rep*. 2016; **6**: 33249.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Hasseldam H, Rasmussen RS, Johansen FF: Oxidative damage and chemokine production dominate days before immune cell infiltration and EAE disease debut. *J Neuroinflammation*. 2016; **13**(1): 246.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Brustovetsky N, Brustovetsky T, Purl KJ, *et al.*: Increased susceptibility of striatal mitochondria to calcium-induced permeability transition. *J Neurosci*. 2003; **23**(12): 4858–67.
[PubMed Abstract](#)
88. Brustovetsky N, Brustovetsky T, Jemmerson R, *et al.*: Calcium-induced cytochrome c release from CNS mitochondria is associated with the permeability transition and rupture of the outer membrane. *J Neurochem*. 2002; **80**(2): 207–18.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Tanveer A, Virji S, Andreeva L, *et al.*: Involvement of cyclophilin D in the activation of a mitochondrial pore by Ca²⁺ and oxidant stress. *Eur J Biochem*.

- 1996; **238**(1): 166–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Nicoll A, Basso E, Petronilli V, *et al.*: Interactions of cyclophilin with the mitochondrial inner membrane and regulation of the permeability transition pore, and cyclosporin A-sensitive channel. *J Biol Chem.* 1996; **271**(4): 2185–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
91. Warne J, Pryce G, Hill JM, *et al.*: Selective Inhibition of the Mitochondrial Permeability Transition Pore Protects against Neurodegeneration in Experimental Multiple Sclerosis. *J Biol Chem.* 2016; **291**(9): 4356–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
92. Stys PK, Waxman SG, Ransom BR: Ionic mechanisms of anoxic injury in mammalian CNS white matter: role of Na⁺ channels and Na⁺-Ca²⁺ exchanger. *J Neurosci.* 1992; **12**(2): 430–9.
[PubMed Abstract](#)
93. Smith KJ, Lassmann H: The role of nitric oxide in multiple sclerosis. *Lancet Neurol.* 2002; **1**(4): 232–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Waxman SG: Sodium channel blockers and axonal protection in neuroinflammatory disease. *Brain.* 2005; **128**(Pt 1): 5–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Smith KJ, Kapoor R, Hall SM, *et al.*: Electrically active axons degenerate when exposed to nitric oxide. *Ann Neurol.* 2001; **49**(4): 470–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. Garthwaite G, Goodwin DA, Batchelor AM, *et al.*: Nitric oxide toxicity in CNS white matter: an *in vitro* study using rat optic nerve. *Neuroscience.* 2002; **109**(1): 145–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
97. Kapoor R, Davies M, Blaker PA, *et al.*: Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration. *Ann Neurol.* 2003; **53**(2): 174–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Lo AC, Saab CY, Black JA, *et al.*: Phenytoin protects spinal cord axons and preserves axonal conduction and neurological function in a model of neuroinflammation *in vivo*. *J Neurophysiol.* 2003; **90**(5): 3566–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
99. Bechtold DA, Kapoor R, Smith KJ: Axonal protection using flecainide in experimental autoimmune encephalomyelitis. *Ann Neurol.* 2004; **55**(5): 607–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Bechtold DA, Miller SJ, Dawson AC, *et al.*: Axonal protection achieved in a model of multiple sclerosis using lamotrigine. *J Neurol.* 2006; **253**(12): 1542–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
101. Lidster K, Jackson SJ, Ahmed Z, *et al.*: Neuroprotection in a novel mouse model of multiple sclerosis. *PLoS One.* 2013; **8**(11): e79188.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
102. Morsali D, Bechtold D, Lee W, *et al.*: Safinamide and flecainide protect axons and reduce microglial activation in models of multiple sclerosis. *Brain.* 2013; **136**(Pt 4): 1067–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
103. Craner MJ, Damarjian TG, Liu S, *et al.*: Sodium channels contribute to microglial macrophage activation and function in EAE and MS. *Glia.* 2005; **49**(2): 220–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
104. Carrithers MD, Dib-Hajj S, Carrithers LM, *et al.*: Expression of the voltage-gated sodium channel NaV1.5 in the macrophage late endosome regulates endosomal acidification. *J Immunol.* 2007; **178**(12): 7822–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
105. Black JA, Liu S, Waxman SG: Sodium channel activity modulates multiple functions in microglia. *Glia.* 2009; **57**(10): 1072–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Black JA, Waxman SG: Sodium channels and microglial function. *Exp Neurol.* 2012; **234**(2): 302–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
107. Kapoor R, Furby J, Hayton T, *et al.*: Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Neurol.* 2010; **9**(7): 681–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
108. Gnanapavan S, Grant D, Morant S, *et al.*: Biomarker report from the phase II lamotrigine trial in secondary progressive MS - neurofilament as a surrogate of disease progression. *PLoS One.* 2013; **8**(8): e70019.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
109. Raftopoulos R, Hickman SJ, Toosy A, *et al.*: Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016; **15**(3): 259–69.
[PubMed Abstract](#) | [Publisher Full Text](#)
110. Raman IM, Bean BP: Resurgent sodium current and action potential formation in dissociated cerebellar Purkinje neurons. *J Neurosci.* 1997; **17**(12): 4517–26.
[PubMed Abstract](#)
111. Tanaka M, Cummins TR, Ishikawa K, *et al.*: Molecular and functional remodeling of electrogenic membrane of hypothalamic neurons in response to changes in their input. *Proc Natl Acad Sci U S A.* 1999; **96**(3): 1088–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
112. Herzog RI, Cummins TR, Ghassemi F, *et al.*: Distinct repriming and closed-state inactivation kinetics of Nav1.6 and Nav1.7 sodium channels in mouse spinal sensory neurons. *J Physiol.* 2003; **551**(Pt 3): 741–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
113. Caldwell JH, Schaller KL, Lasher RS, *et al.*: Sodium channel Na_v1.6 is localized at nodes of Ranvier, dendrites, and synapses. *Proc Natl Acad Sci U S A.* 2000; **97**(10): 5616–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
114. Westenbroek RE, Merrick DK, Catterall WA, *et al.*: Differential subcellular localization of the R₁ and R₂ Na⁺ channel subtypes in central neurons. *Neuron.* 1989; **3**(6): 695–704.
[PubMed Abstract](#) | [Publisher Full Text](#)
115. Craner MJ, Lo AC, Black JA, *et al.*: Abnormal sodium channel distribution in optic nerve axons in a model of inflammatory demyelination. *Brain.* 2003; **126**(Pt 7): 1552–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
116. Pappalardo LW, Liu S, Black JA, *et al.*: Dynamics of sodium channel Na_v1.5 expression in astrocytes in mouse models of multiple sclerosis. *Neuroreport.* 2014; **25**(15): 1208–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
117. Black JA, Dib-Hajj S, Baker D, *et al.*: Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis. *Proc Natl Acad Sci U S A.* 2000; **97**(21): 11598–602.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
118. Felts PA, Kapoor R, Smith KJ: A mechanism for ectopic firing in central demyelinated axons. *Brain.* 1995; **118**(Pt 5): 1225–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
119. Kapoor R, Li YG, Smith KJ: Slow sodium-dependent potential oscillations contribute to ectopic firing in mammalian demyelinated axons. *Brain.* 1997; **120**(Pt 4): 647–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
120. Al-Izki S, Pryce G, Hankey DJ, *et al.*: Lesional-targeting of neuroprotection to the inflammatory penumbra in experimental multiple sclerosis. *Brain.* 2014; **137**(Pt 1): 92–108.
[PubMed Abstract](#) | [Publisher Full Text](#)
121. Bostock H, Sears TA: The internodal axon membrane: electrical excitability and continuous conduction in segmental demyelination. *J Physiol.* 1978; **280**(1): 273–301.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
122. Rush AM, Dib-Hajj SD, Waxman SG: Electrophysiological properties of two axonal sodium channels, Na_v1.2 and Na_v1.6, expressed in mouse spinal sensory neurones. *J Physiol.* 2005; **564**(Pt 3): 803–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. Schattling B, Fazeli W, Engeland B, *et al.*: Activity of Na_v1.2 promotes neurodegeneration in an animal model of multiple sclerosis. *JCI Insight.* 2016; **1**(19): e89810.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
124. Brambilla R, Morton PD, Ashbaugh JJ, *et al.*: Astrocytes play a key role in EAE pathophysiology by orchestrating in the CNS the inflammatory response of resident and peripheral immune cells and by suppressing remyelination. *Glia.* 2014; **62**(3): 452–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
125. Pappalardo LW, Samad OA, Black JA, *et al.*: Voltage-gated sodium channel Na_v1.5 contributes to astrogliosis in an *in vitro* model of glial injury via reverse Na⁺/Ca²⁺ exchange. *Glia.* 2014; **62**(7): 1162–75.
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