

The Demyelinated Axon

The best known demyelinating diseases in clinical practice are multiple sclerosis (MS) and the demyelinating neuropathies, but axons can also be demyelinated by a variety of other immunological, viral, metabolic and traumatic insults. In recent years a great deal has been learned about the response of the axon to demyelination, particularly in response to an inflammatory insult, and this knowledge has led not only to a deeper understanding of how symptoms can arise in demyelinated axons, but also to the possibility of treatment to limit the disability resulting from demyelination and the associated damage to the axon itself. Thus, injury to myelin is followed by electrophysiological adaptation of the axonal membrane which can restore electrical conduction, but which may itself contribute to symptoms and make the axon vulnerable to degeneration.

Conduction block

The myelin sheath forms an insulating layer which decreases membrane capacitance and increases membrane resistance, allowing secure and rapid propagation of the action potential from one node of Ranvier to another. Acutely demyelinated internodes leak current, and conduction can be blocked because the nodal sodium current may be insufficient to depolarise the denuded axolemma. In clinically eloquent pathways this will lead to disability, for example during relapses of MS¹ or in demyelinating neuropathies. There is also evidence to suggest that products of inflammation interact adversely with axonal function and contribute to conduction block, and of particular importance may be nitric oxide, which has been shown to block conduction at concentrations comparable to those thought to occur in acute MS lesions² (see Figure 1).

Restoration of conduction

Conduction can recover as inflammation subsides, and inflammatory mediators such as nitric oxide are gradually depleted. Demyelination is also followed by a number of changes in the density and distribution of membrane channels which further help to restore conduction. In central axons the Na_v1.6 channels, normally aggregated at the nodes of Ranvier, are redistributed in a diffuse pattern along the axon,³ and this can enable the action potential to

propagate across the demyelinated internode. Many demyelinated axons also acquire a diffuse distribution of the Na_v1.2 channel subtype, which is usually seen in premyelinated axons during development³ (see Figure 2). Na_v1.2 populated axons seem to be resistant to injury, but may be more liable to conduction failure and ectopic activity. Finally, it is known that the N-type voltage-gated calcium channel can be expressed abnormally along the demyelinated axolemma in MS,⁴ and this may play a role in axonal injury.

Remyelination is another factor which aids the recovery of conduction. A nodal like clustering of sodium channels, along with other paranodal and juxtaparanodal proteins, is seen in a proportion of demyelinated axons and this may be a prerequisite for remyelination to occur.⁵ It is believed that oligodendrocyte contact could be responsible for triggering these changes in central axons. New central myelin internodes are shorter and thinner than normal, but conduction is restored nonetheless.⁶ Furthermore, remyelinated nodes have the normal Na_v1.6 aggregations, favouring the restoration of secure conduction.⁷ In MS, remyelination is seen particularly in younger patients early in the course of the illness, and the reasons why remyelination fails and is not a more ubiquitous process remain unclear.

Although these recovery mechanisms can restore conduction, it usually remains insecure, and leaves the demyelinated axon vulnerable to a temporary conduction block in certain circumstances, which include:

- Small rises in body temperature. These shorten the action potential by speeding the kinetics of sodium channels, hence reducing the current available to depolarise the axonal membrane to its firing threshold.
- Sustained electrical activity, which loads the axon with sodium and hyperpolarises its membrane away from the firing threshold through increased activity of the electrogenic Na/K ATPase pump.⁸
- Sodium channel blocking agents such as lidocaine can induce an iatrogenic conduction block by reducing the excitatory nodal current.⁹

The clinical consequence of these events is a temporary worsening of pre-existing disability with raised ambient temperatures or with activity, although silent lesions may also be unmasked.



Tom Hayton is a clinical research fellow in the Department of Neuroinflammation at the Institute of Neurology, London. He is currently working on quantitative MR imaging and neuroprotection in MS. He has worked in clinical neurology in Manchester and London. He did his undergraduate training at the University of Edinburgh.



Julian Furby, MRCP, is a clinical research fellow at the Institute of Neurology, London. His research interests are in multiple sclerosis, neuroprotection and MRI measures of neurodegeneration in this disease. He qualified from the University of Nottingham and has worked in clinical neurology in London and Oxford.



Dr Raj Kapoor is a Consultant Neurologist based at the National Hospital for Neurology and Neurosurgery. His research interests include the pathophysiology of demyelination and the development of treatment to prevent the progression of disability in MS. With colleagues in London, he is currently undertaking a trial of neuroprotection with lamotrigine in secondary progressive MS.

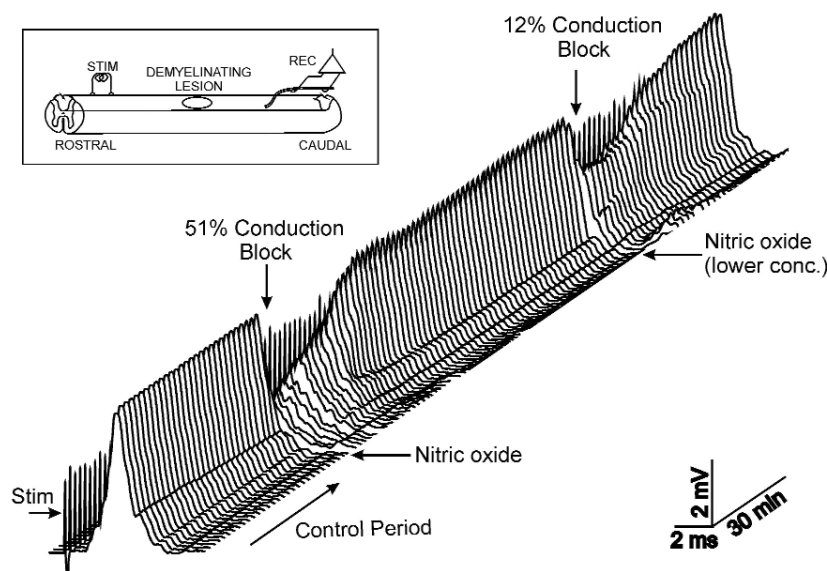


Figure 1: This figure shows a series of averaged compound action potentials propagating through an experimental demyelinating lesion in the spinal cord and recorded at two minute intervals. The injection of a nitric oxide donor into the lesion temporarily blocks conduction of a proportion of nerves, and this occurs in a dose dependent manner, with a second, lower dose of the donor producing a smaller degree of conduction block. Reprinted from reference 2.

Correspondence to:

Dr Raj Kapoor,
National Hospital for Neurology
and Neurosurgery,
Queen Square,
London,
WC1N 3BG, UK.
E. raj.kapoor@uclh.nhs.uk

Ectopic activity

Positive symptoms such as paraesthesiae, tonic spasms and paroxysmal ataxia or pain can sometimes occur because of ectopic impulse activity arising from demyelinated internodes.¹⁰ The depolarisations generating these discharges may sometimes be due to the slow inward sodium currents which arise from the adaptive changes to the demyelinated axonal membrane discussed earlier, or else to abnormal accumulation of extracellular potassium, which can lead to the axonal potassium currents reversing direction and becoming excitatory. Well over a hundred thousand extra action potentials can be generated from a single axon per hour.¹⁰ Mechanosensitive discharges may also occur in these axons, manifesting in MS most commonly as Lhermitte's phenomenon and visual phosphenes.

Axonal degeneration

In addition to acute and paroxysmal symptoms, demyelination leads to progressive disability. Disability may arise partly from a failure of the recovery mechanisms of remyelination and membrane adaptation, but there is a growing body of evidence that indicates that the inflammatory response can damage axons directly, and that chronically demyelinated axons are particularly vulnerable to degeneration.

In experimental models of inflammation, axons can degenerate when exposed to nitric oxide, particularly if they are electrically active.¹¹ Nitric oxide is known to be present in the plaques of MS, and may injure axons through a number of actions, among them an inhibition of mitochondrial respiration resulting in energy failure, a loss of ionic homeostasis, and a consequent intracellular accumulation of sodium ions. In models of ischaemia, axons loaded with sodium are at risk of degeneration because of the secondary influx of calcium ions through the reverse function of the membrane Na⁺/Ca²⁺ exchanger (NCX),^{12,13} and a similar mechanism may operate in the presence of nitric oxide, where axonal degeneration can be blocked by inhibition of sodium channels or of the NCX.¹⁴

Like the NCX, the sodium/glutamate transporter is also driven, in part, by the sodium gradient, though in this instance both sodium and glutamate are imported together in exchange for potassium. When the sodium gradient is reversed, so too is the direction of the exchange, resulting in a net release of glutamate and an increase in its extracellular concentration. In animal models glutamate-mediated white matter injury is thought to be mediated by 1) by α -amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptors¹⁵, and 2) via increased axonal expression of metabotropic glutamate receptors,¹⁶ both favouring intracellular calcium accumulation. AMPA antagonists have been shown to reduce axonal damage and disability in EAE.¹⁷

Neuroprotection with sodium channel blockers

Based on the possibility that intracellular sodium accumulation can damage axons, the neuroprotective potential of drugs which block voltage gated sodium channels has been examined in various animal models. In experimental allergic encephalitis (EAE), the rodent model of MS, several sodium channel blockers have been shown to prevent axonal loss and to reduce disability.¹⁸ This work has led to a phase II clinical trial of neuroprotection with lamotrigine in people with secondary progressive MS at the Institute of Neurology in London. The result of this trial should be available in early 2009.

Other possible neuroprotective agents

Cannabinoids have also been identified as possible neuroprotective agents. By acting on the CB1 receptor an endogenous cannabinoid

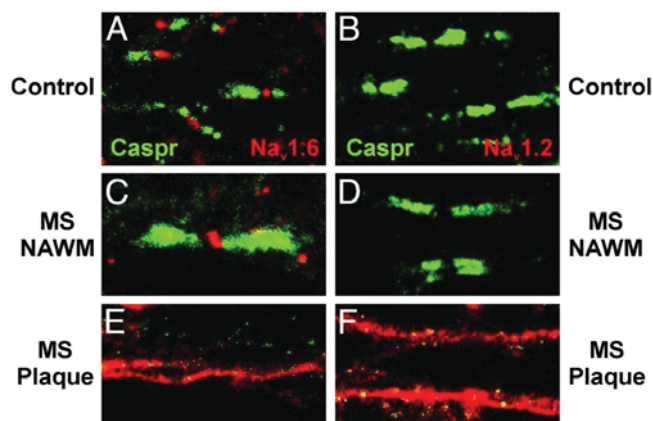


Figure 2: Immunostaining of post-mortem white matter from controls and MS patients. Nodes of Ranvier are indicated by immunostaining of paranodal contactin-associated protein (Caspr, green). Na_v1.6 (left, red) is aggregated at nodes in control CNS and MS normal appearing white matter (NAWM). In contrast a diffuse distribution along the demyelinated axon is seen within plaque tissue (E). Na_v1.2 (right, red) is found only in plaque tissue where it is distributed in a diffuse pattern (F). Reprinted from reference 3.

compound, 2 arachidonyl glycerol, is thought to modulate glutamate release and thereby reduce the impact of glutamate induced toxicity. Evidence from EAE and knockout mouse models supports this hypothesis¹⁹ and a clinical trial of neuroprotection with cannabinoids in progressive MS is currently under way in the UK.

Some calcium channel blockers, administered with or shortly after induction of EAE, improve clinical recovery after relapse and may also limit axonal degeneration.²⁰ It is possible that calcium channels may also be future targets for neuroprotection.

Imaging demyelination

Magnetic resonance imaging (MRI) is widely used in the diagnosis of MS. However, the T2-weighted high signal white matter lesion load correlates only modestly with disability.²¹ It is now thought that not all of these T2 high signal lesions represent areas of demyelination.²²

Newer, quantitative MRI techniques may be more specific for demyelination. Of note is the magnetization transfer ratio (MTR). This technique exploits the transfer of energy from protons bound to large molecules, such as those found in myelin or axons, to free protons in surrounding water. The higher the MTR, the greater the number of large molecules present in a tissue. Recent studies in MS²³ and EAE²⁴ have indicated that low MTR may be more specific for demyelination than other techniques, while studies in other central demyelinating disorders, such as adrenoleucodystrophy, suggest that it may also be more sensitive.²⁵

Conclusion

Acute inflammatory demyelination gives rise to disability from conduction block. As the inflammation resolves and recovery processes set in, the level of disability may improve. However, because conduction remains insecure, the axon is still vulnerable to temporary conduction block, giving rise to brief exacerbations of disability. Positive symptoms also occur as a consequence of ectopic impulse

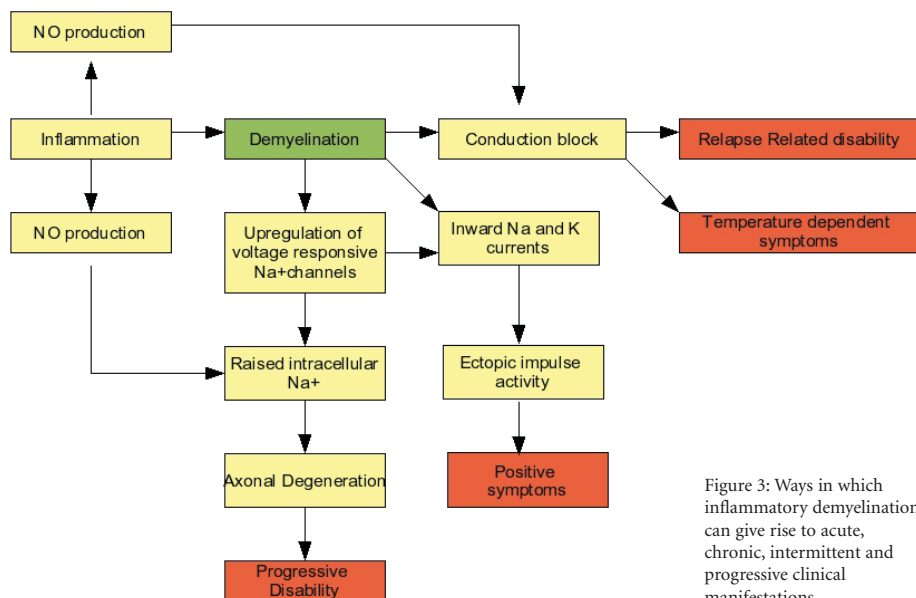


Figure 3: Ways in which inflammatory demyelination can give rise to acute, chronic, intermittent and progressive clinical manifestations.

activity due to changes in sodium and potassium currents.

With time a proportion of axons undergo remyelination, and this, together with adaptive changes in the expression and distribution of sodium and other membrane channels, may help to restore conduction. However these same adaptive changes may favour the accumulation of intracellular sodium and calcium ions and, as a consequence, promote gradual axonal degeneration and hence lead to progressive disability. It may be possible to slow down the progression of axonal degeneration using sodium channel blockers, and a phase II placebo-controlled trial of lamotrigine is currently under way to test this hypothesis.

References

- McDonald WI. *Mechanisms of functional loss and recovery in spinal cord damage*. Ciba Found. Symp. 1975;34:23-33.
- Redford EJ, Kapoor R, Smith KJ. *Nitric oxide donors reversibly block axonal conduction: demyelinated axons are especially susceptible*. Brain 1997;120:2149-57.
- Craner M, Newcombe J, Black JA, Hartle C, Cuzner ML, Waxman SG. *Molecular changes in neurons in multiple sclerosis: Altered axonal expression of Nav 1.2 and Nav 1.6 sodium channels and Na/Ca exchanger*. PNAS 2004;101:8168-73.
- Kornek B, Storch MK, Bauer J, Djamshidian A, Weissert R, Wallstroem A, Stefferl A, Zimprich F, Olsson T, Linington C, Schmidbauer M, Lassman H. *Distribution of a calcium channel subunit in dystrophic axons in multiple sclerosis and experimental autoimmune encephalomyelitis*. Brain 2001;124:1114-24.
- Coman I, Aigrot MS, Seilhean D, Reynolds R, Girault JA, Zalc B, Lubetzki C. *Nodal, paranodal and juxtaparanodal axonal proteins during demyelination and remyelination in multiple sclerosis*. Brain 2006;129:3186-95.
- Felts PA, Smith KJ. *Conduction properties of central nerve fibers remyelinated by Schwann cells*. Brain Res 1992;574:178-92.
- Black JA, Waxman SG, Smith KJ. *Remyelination of dorsal column axons by endogenous Schwann cells restores the normal pattern of Nav 1.6 and Kv 1.2 at nodes of Ranvier*. Brain 2006;129:1319-29.
- Bostock H, Grafe P. *Activity-dependent excitability changes in normal and demyelinated rat spinal root axons*. J Physiol (Lond) 1985;365:239-57.
- Sakurai M, Mannen T, Kanazawa I, Tanabe H. *Lidocaine unmasks silent demyelinating lesions in multiple sclerosis*. Neurology 1992;42:2088-93.
- Smith KJ, McDonald WI. *Spontaneous and evoked electrical discharges from a central demyelinating lesion*. J Neurol Sci 1982;55:39-47.
- Smith KJ, Kapoor R, Hall SM, Davies M. *Electrically active axons degenerate when exposed to nitric oxide*. Ann. Neurol. 2001;49:470-6.
- 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 Neuroscience 1992;12:430-9.
- Bechtold DA & Smith KJ. *Sodium-mediated axonal degeneration in inflammatory demyelinating disease*. J Neurol Sci 2005;233:27-35.
- Kapoor R, Davies M, Blaker PA, Hall SM, Smith KJ. *Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration*. Ann Neurol 2003;53:174-80.
- Fowler JH, McCracken E, Dewar D, McCulloch. *Intracerebral injection of AMPA causes axonal damage in vivo*. Brain Res. 2003;991:104-12.
- Guerts JJC, Wolswijk G, Bo I et al. *Altered expression patterns of group I and II metabotropic glutamate receptors in multiple sclerosis*. Brain. 2003;126:1755-66.
- Smith T, Groom A, Zhu B, Turski L. *Autoimmune encephalomyelitis ameliorated by AMPA antagonists*. Nat. Med. 2000;6:62-66.
- Bechtold DA, Miller SA, Dawson AC, Sun Y, Kapoor R, Berry D, Smith KJ. *Axonal protection achieved in a model of multiple sclerosis using lamotrigine*. J Neurol 2006 253:1542-51.
- Pryce G, Ahmed Z, Hankey DJR, Jackson SJ, Croxford JL, Pocock JM, Ledent C, Petzold A, Thompson AJ, Giovannoni G, Cuzner ML, Baker D. *Cannabinoids inhibit neurodegeneration in models of multiple sclerosis*. Brain. 2003;26:2191-2202.
- Brand-Schieber E, Werner P. *Calcium channel blockers ameliorate disease in a mouse model of multiple sclerosis*. Exp Neurol 2004;189:5-9.
- Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. *A longitudinal study of abnormalities on MRI and disability from multiple sclerosis*. N Eng J Med 2002; 246:158-164.
- Fisher E, Chang A, Fox RJ, Tkach JA, Svarovsky T, Nakamura K, Rudick RA, Trapp BD. *Imaging correlates of axonal swelling in chronic multiple sclerosis brains*. Ann Neurol 2007 Advanced online publication.
- Schmierer K, Scaravilli F, Altmann DR, Barker GJ, Miller DH. *Magnetization transfer ratio and myelin in post-mortem multiple sclerosis brain*. Ann Neurol 2004;56:407-415
- Dousset V, Grossman RI, Ramer KN, Schnall MD, Young LH, Gonzalez-Scarano, Lavi E, Cohen JA. *Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging* [published erratum appears in Radiology 1992 Jun;183(3):878] Radiology 1992;182:483.
- Fatemi A, Smith A, Dube P, Zackowski KM, Bastian AJ, van Zijl PC, Moser HW, Raymond GV, Golay X. *Magnetization transfer MRI demonstrates spinal cord abnormalities in adrenomyeloneuropathy*. Neurology 2005;64:1739-1.

The Encephalitis Society action for Support, Awareness and Research
Invites you to

Encephalitis - the Broader Spectrum

featuring rare types of encephalitis

Presented by: the Encephalitis Society

Date: Tuesday 22 January 2008

Time: 13.00 – 18.00

Venue: The Resource Centre, 356 Holloway Road, London N7 6PA

Type of event: Seminar with Evening Wine Reception

Speaker(s): Professor Tom Solomon, Dr Ian Hart, Professor Gavin Giovannoni, Dr Sarosh R Irani

Admission: £50 normal rate, £35 student rate

Contact: Elaine Dowell • 01653 604366 • elaine@encephalitis.info

CPD applied for

Seminar Programme

13.00 Welcome Professor Clive Hawkins, Chair of the Encephalitis Society Advisory Panel • **13.10** Keynote Address: Global Infectious Encephalitis Professor Tom Solomon, Chair of Neurological Science, University of Liverpool • **13.50** Voltage Gated Potassium Channel Antibody Encephalitis. Dr Sarosh R Irani, Clinical Research Fellow Neurosciences Group, John Radcliffe Hospital, Oxford • **14.20** Fungal encephalitis: diagnostic and therapeutic challenges Dr William Hope, Infectious Diseases Physician and Senior Research Fellow, The University of Manchester • **14.50** Refreshments • **15.20** Keynote Address: Autoimmune Encephalitis Dr Ian Hart, Consultant in Neurology and Neuroimmunology, The Walton Centre for Neurology and Neurosurgery • **16.00** Encephalitis Lethargica Professor Gavin Giovannoni, Head of Neurology The Royal London Hospital • **16.30** Discussion • **17.00** Wine Reception