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Neuroprotection in multiple sclerosis: A therapeutic challenge for the next decade

Anneke Van der Walt [a,c,*], Helmut Butzkueven [a,b,c,d], Scott Kolbe [b,d], Mark Marriott [a,b], Estella Alexandrou [d], Melissa Gresle [b], Gary Egan [b,c,d], Trevor Kilpatrick [a,b,c,d]

[a] The Royal Melbourne Hospital, Grattan St. Parkville, Melbourne, Australia
[b] Howard Florey Institute, Melbourne, Australia
[c] Centre for Neuroscience, University of Melbourne, Australia
[d] University of Melbourne, Australia

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ABSTRACT

Multiple sclerosis (MS) is the commonest cause of progressive neurological disability amongst young, Caucasian adults. MS is considered to be an auto-immune disease that results from an attack against myelin, the layer which surrounds axons. The pathophysiology of MS is complex, with both demyelination and axonal degeneration contributing to what is essentially an inflammatory neurodegenerative disease. Axonal loss is increasingly being accepted as the histopathological correlate of neurological disability. Currently, the underpinnings of neurodegeneration in MS, and how to promote neuroprotection are only partly understood. No established treatments that directly reduce nervous system damage or enhance its repair are currently available. Moreover, the ability of currently available immunomodulatory therapies used to treat MS, such as interferon-β, to prevent long-term disability is uncertain. Results from short-term randomized-controlled trials suggest a partial benefit with regards to disability outcomes, but this is yet to be established in long-term studies. Novel neuroprotective agents have been identified in preclinical studies but their development is being hampered by the absence of appropriate clinical platforms to test them. In this article, we will discuss some of the principal therapeutic candidates that could provide neuroprotection in MS and emerging methodologies by which to test them.

Contents

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS) that is characterized by multi-focal demyelination, oligodendrocyte loss, as well as axonal injury and neuronal loss (Lucchinetti et al., 2000). It is the commonest cause of neurological disability in young Caucasian adults. The initial presentation of MS is known as the first demyelinating event (FDE) or as a Clinically Isolated Syndrome (CIS). Subsequent disease activity, known as a relapse, develops in the great majority of people after a

Abbreviations: MS, Multiple sclerosis; CNS, Central nervous system; FDE, First demyelinating event; RRMS, Relapsing–remitting MS; SPMS, Secondary progressive MS; PPMS, Primary progressive MS; GluR, Glutamate receptors; NMDA, N-methyl-D-aspartate; AMPA, α-Amino-3-hydroxy-5-methil-4-isoxazol-propionic acid; NAWM, Normal appearing white matter; NO, Nitric oxide; NOS, Nitric oxide synthase; EAE, Experimental auto-immune encephalomyelitis; IGF-1, Insulin-like growth factor-type 1; EPO, Erythropoietin; LIF, Leukaemia-inhibitory factor; CNTF, Ciliary neurotrophic factor; LIFR-β, Leukaemia-inhibitory factor receptor-β; MRI, Magnetic Resonance Imaging; ON, Optic neuritis; mfVEP, multi-focal Visual Evoked Response; OCT, Ocular Coherence Tomography; EDSS, Expanded disability status scale.

* Corresponding author. Royal Melbourne Hospital, Department of Neurology, Grattan St. Parkville, VIC 3050, Australia. Tel.: +61 3 9342 8448; fax: +61 3 9439 5997.
E-mail address: Anneke.vanderwalt@mh.org.au (A. Van der Walt).

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CIS, at which time a diagnosis of clinically definite MS is made (Poser et al., 1983). More recently a new set of diagnostic criteria (Polman et al., 2005) allows for evidence of a second clinical attack to be substituted by MRI evidence of new inflammatory lesions subsequent to the initial clinical attack, resulting in earlier diagnosis. Although the clinical course of MS is heterogeneous, it most commonly follows a relapsing–remitting pattern (RRMS) that is characterized by the episodic development of neurological deficits, followed by complete or partial remission. Importantly, after a decade or more, MS frequently transforms into a progressive phase, secondary progressive MS (SPMS), in which disability levels increase inexorably, independent of relapses. Some 10–15% of patients present with progressive MS in the absence of relapses, a subtype of the disease known as primary progressive MS (PPMS) (C. Confavreux & Vukusic, 2006).

It was a long-held belief that relapsing–remitting MS represented episodic focal demyelination and remyelination, and that the pathological correlate of SPMS was eventual remyelination failure, producing axonal and neuronal degeneration. Permanent axonal loss was believed to occur due to loss of trophic support for axons, normally provided by oligodendrocytes (Compston, 1996; Scherer, 1999). However, it is now believed that progressive axonal loss occurs from the onset of the disease, and that the transition to SPMS simply represents a clinical threshold at which axonal loss exceeds the functional reserve provided by cortical plasticity and other compensatory mechanisms (C. Waxman, 1998; Bjartmar & Trapp, 2001). A number of observations over the last two decades support this notion. Firstly, a seminal paper by Trapp et al. drew renewed attention to the fact that significant axonal injury is observed in acute inflammatory lesions (Trapp et al., 1998), an observation described more than a century before by Charcot (1848). Secondly, serial MRI volumetric studies have shown that patients assessed after a CIS or in early RRMS lose cerebral, and particularly cortical volume, at twice the rate of age matched, healthy controls (De Stefano et al., 2003a,b; Filippi et al., 2003). Furthermore, there is evidence that the extent of axonal loss correlates with the reduction of the neuronal marker, N-acetylaspartate, on magnetic resonance spectroscopy and with T1-hypointensity on MRI (Bruck et al., 1997; van Walderveen et al., 1998a,b; Filippi et al., 2003). Several histopathological and imaging studies have also quantified axonal loss in normal appearing white matter (NAWM), and provide evidence of axonal loss early in the disease course (Evangelou et al., 2000; Bjartmar et al., 2001).

A number of immunomodulatory and immunosuppressive drugs are approved for the treatment of RRMS in Australia. These agents have been shown to reduce relapse rate and, to a lesser extent, delay progression to SPMS (Trojano et al., 2007). However, disability progression still occurs in treated patients, albeit at a lower rate. Existing therapies also appear to be ineffective in slowing further disease progression in established SPMS with three of four studies being reported as negative (SPECTRIMS Study Group, 2001) and the fourth (Kappos et al., 2001) providing evidence of marginal benefit amongst a cohort with early SPMS, many of whom had ongoing relapses. Disease-modifying agents, targeted at episodic immune-mediated inflammation, presumably cannot sufficiently reduce the axonal injury component of MS pathology (Hemmer & Hartung, 2007) and hence, novel therapeutic strategies are required to reduce axonal degeneration in MS.

It is important to recognize that the term neuroprotection encompasses a number of processes essential to neuronal survival. MS is a complex, heterogeneous disease characterized by a fundamental breakdown in the symbiotic interactions that exist between neurons and oligodendrocytes, but also with microglia and astrocytes. As such, it is likely that there are bona fide molecular targets on each neural cell type that could ultimately be exploited to limit demyelination on the one hand or to reduce neuronal and/or axonal degeneration on the other. Consequently, the term cellular protection better encapsulates the complexity of the processes involved. Furthermore, disability in MS is contributed to by loss of neural cells whether they be oligodendrocytes or neurons and it is therefore clear that not only protective, but also regenerative strategies will be required in order to provide maximal benefit. Given the complex interactions between various neural cells, it is not surprising that it is often difficult to definitively determine the exact cellular target of a given therapeutic agent and in many instances it has become apparent that more than one cellular target is involved.

Animal models such as experimental auto-immune encephalomyelitis (EAE) and conditional knockout strategies in mice have substantially contributed to the unraveling of the complex disease processes involved in MS pathogenesis. Various models of EAE are in use and reflect different aspects of MS pathogenesis (Storch et al., 1998; Wujek et al., 2002). EAE is induced by the immunization of genetically susceptible mice with myelin proteins such as myelin basic protein, proteolipid protein or myelin oligodendrocyte glycoprotein (Wekerle, 2008). Brain inflammation and signs of neurological disease usually follows immunization according to a predictable schedule. In one of the most commonly used models, EAE is induced in C57BLG mice by a peptide derived from myelin oligodendrocyte glycoprotein with the animals experiencing a monophasic disease course characterized by a prodromal phase followed by paralytic disease that concludes in either spontaneous recovery or chronic disease. However, alternate models of EAE have also been created in rodents in order to better mimic MS disease course, including a chronic relapsing model (Zamvil et al., 1985) and an optic neuritis model (Bettelli et al., 2003). Although EAE differs from the human disease with regards to clinical course, the nature of the immune response as well as disease pathology (Sriram & Steiner, 2005) the model does share many overlapping histological, immunological, and genetic features with MS (Hauser & Oksenberg, 2006). Despite its limitations, the EAE model has contributed to our knowledge of MS disease pathogenesis and careful interpretation of results from experiments in animal models has aided in the development of anti-inflammatory treatments (Steinman & Zamvil, 2006). Furthermore, conditional knockout strategies in mice have aided in elucidating complex endogenous signalling pathways involved in axonal degeneration and regeneration. Nevertheless, development of new treatments for MS by direct application of one EAE model in isolation is fraught with potential difficulties given the differences between the human and murine immune systems, the complexity of MS pathogenesis and the limitations of the animal model itself. Understanding complex pathways does not necessarily predict the profile of activity of a potential therapeutic agent, particularly when it is given in pharmacological doses. New treatments will therefore always require a rigorous developmental process in human studies regardless of the results of exploratory work using animal models.

In this article, we provide an overview of the currently understood mechanisms of axonal injury, as well as potential neuroprotective therapeutic agents identified utilising in vitro and animal studies. It is beyond the scope of this review to comment on all of these studies and our focus is on what we believe to be the most feasible new therapies. A major stumbling block in the clinical development of new agents is the absence of reliable biomarkers specific to the different aspects of MS pathology. We briefly discuss possible outcome measures that could aid in the translation of laboratory tested therapeutic candidates to humans.

2. Mechanisms of axonal injury

We are starting to better understand the mechanisms underlying axonal injury in MS. The underlying disease pathophysiology is complex, with significant histopathological overlap between acute axonal injury and chronic injury processes. Axonal injury occurs at the time of acute inflammatory plaque formation as well as in inactive