

Neuroprotection on Multiple Sclerosis: A BDNF Perspective

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Multiple sclerosis (MS) is a progressive, chronic central nervous system (CNS) inflammatory demyelinating disease. It is the most common neurological disease in middle-aged adults, striking three times more women than men with diagnosis peaking at around 30 years of age, thus affecting people in their most productive years. It has a lifelong impact and its prevalence is increasing steadily over time. Investment in research that would delay or ideally prevent the progression could bring substantial rewards in terms of both reducing the financial burden and increasing quality of life.

The disease is thought to result from an inflammatory attack against myelin, which is produced by specialised glial cells in the CNS known as oligodendrocytes, and their death are commonly observed elements in MS lesions [1]. As a result, the efficient transmission of neuronal signals is disrupted, causing nervous system dysfunction. Once the disease presents, the condition is permanent and degenerative. An endogenous repair process often follows the death of these glial cells, which is effected by surviving oligodendrocytes in the lesion area and complemented by the recruitment of oligodendrocyte precursor cells (OPCs). This repair process is variable, but can result in the return to relatively normal CNS function. However over time and following successive demyelinating events, the myelin repair is ultimately insufficient, invariably leading to irreversible axonal damage and progressive and extensive disability [2,3]. Currently the failure of remyelination remains a major obstacle to recovery in MS patients and strategies aimed at improving and enhancing remyelination is critically important to complement the currently available immunomodulatory treatments. In this regard, studying molecules involved in oligodendrocyte myelination has the potential to identify novel therapeutic approaches and strategies to promote remyelination. Recently, increasing evidence suggest that Brain-Derived Neurotrophic Factor (BDNF) not only enhances CNS myelination during development [4-6], but also exerts neuroprotective roles following demyelination in animal models of MS [7,8].

BDNF is a member of the neurotrophin family of growth factors, and signals through two distinct classes of transmembrane receptors: the tropomyosin-related kinase B receptor (TrkB) and the structurally unrelated p75 neurotrophin receptor (p75NTR) [9,10]. Previous studies have shown that BDNF plays a key role in regulating CNS myelination, as evidenced by myelin deficits in both BDNF knockout as well as heterozygous mice [4-6]. *In vitro* studies have also suggested that BDNF can exert a number of effects upon the oligodendroglial lineage including proliferation, differentiation, maturation and myelination [6,11,12]. Recent studies have implicated that BDNF exerts functionally neuroprotective roles following CNS demyelination in animal models of demyelinating diseases including experimental autoimmune encephalomyelitis (EAE) and toxic models of demyelination such as cuprizone. In response to the cuprizone model of demyelination, BDNF heterozygote mice exhibit greater demyelination and reduced remyelination in the absence of change to the number of oligodendrocytes, microglia and astrocytes as well as the

extent of axonal injury [8]. A more severe course of EAE and increased axonal loss was observed in mice in which BDNF has been selectively deleted in GFAP positive cells such as oligodendrocytes, astrocytes and some neurons [7]. And it is more effective in reducing clinical severity and structural damage when the BDNF level is modulated at initial stages of EAE versus later stages [13]. Thus, this implicates there may be an early window of therapeutic opportunity for the modulation of BDNF levels, at least in EAE.

In the CNS, BDNF can be derived from both CNS resident cells and immune cells. In the normal CNS, BDNF is primarily derived from neurons [14]. However, following demyelination such as in MS and EAE, activated astrocytes express increased levels of endogenous BDNF [7,15,16]. In addition, BDNF can be produced by subtypes of immune-cells such as activated T cells, B-cells and monocytes [15,17]. Thus, BDNF is well placed to exert a modulatory effect upon myelination in this context [15,18]. However, CNS-derived BDNF appears to play a critical neuroprotective role in autoimmune demyelination. Mice deficient for BDNF in T-cells exhibited progressive disability and enhanced axonal loss in EAE and mice overexpressing BDNF in T-cells exhibited less severe EAE and axonal protection [7]. However, experiments utilising bone marrow chimeras reveal that immune cell-derived BDNF cannot influence disease severity following CNS deletion of BDNF [13]. This suggests that CNS resident cells are the major source of biologically relevant BDNF in autoimmune demyelination. Whether in this context BDNF exerts its influence directly on the myelinated axon / neuron-oligodendrocyte interface remains an open question.

The next would be to identify the molecular targets of BDNF in autoimmune demyelination. As the CNS myelination is normal in p75NTR knockout mice [6], BDNF receptor TrkB appears to be the key player in regulating the promyelinating effect of BDNF. *In vitro* studies have identified that BDNF exerts several influences upon oligodendroglial lineage such as proliferation, differentiation, maturation and myelination by activating oligodendroglial-expressed TrkB receptors [6,11,12]. In addition to oligodendroglial lineage cells, TrkB receptors are also present in neurons and astrocytes as well as infiltrating immune cells in the CNS [18,19]. Thus in this context, there is no shortage of potential BDNF targets. Interestingly, the activity of TrkB was increased in the neurons of EAE-diseased mice

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compared to the intact axons of control mice, suggesting BDNF is at least exerting a neuronal effect in this context [7]. In addition to significantly delay EAE onset and reduce clinical severity, treatment with BDNF engineered bone marrow stem cells also reduced the expression of pro-inflammatory cytokines and increased expression of anti-inflammatory cytokines [20]. Furthermore, immune cell expression of TrkB has been shown to play an important role in MS immunopathogenesis by modulating auto-reactive T cell survival and behaviour [18]. Collectively, these implicate that TrkB could be a key target of BDNF's neuroprotective role in autoimmune demyelinating diseases such as MS.

What is beyond dispute however is that regardless of the model or the strategy to manipulate BDNF expression, the effect it exerts is a uniformly promyelinating one. Given the difficulties inherent with using the recombinant neurotrophins themselves to treat demyelinating and other CNS disorders, increasing attention has turned to the development of alternative strategies to harness neurotrophic action for clinical use. One means of doing this is to use functional mimetics of neurotrophins. In the context of BDNF, the compounds that have the advantage of being able to selectively target TrkB receptors with appropriate pharmacokinetic properties could have a strong therapeutic potential for treating human demyelinating diseases such as MS in the future.

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