

COMMENTARY

Targeting synaptic pathology in multiple sclerosis: fingolimod to the rescue?

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Multiple sclerosis (MS) is an inflammatory disorder affecting the brain and spinal cord. Major hallmarks of MS typically include inflammation, demyelination and axon degeneration, although recent studies have also implicated synaptic dysfunction and degeneration in disease pathogenesis. The discovery that treatment with the orally active immunomodulatory drug fingolimod (FTY720) confers benefits in animal models and human patients has opened up new avenues for the treatment of MS. In the present issue of the *BJP*, Rossi and colleagues used a mouse model of MS [experimental autoimmune encephalomyelitis (EAE)] to provide new evidence suggesting that fingolimod may target MS symptoms, at least in part, by ameliorating synaptic dysfunction. They demonstrated that fingolimod reversed modifications in glutamatergic transmission found in the striatum of EAE mice, accompanied by a reduction in the severity of dendritic spine loss. This report suggests that fingolimod treatment can have beneficial effects on synaptic pathology in MS, raising the intriguing possibility that fingolimod treatment may also be advantageous in other diseases of the nervous system where inflammation and synaptic pathology contribute to disease pathogenesis.

LINKED ARTICLE

This article is a commentary on Rossi *et al.*, pp. 861–869 of this issue. To view this paper visit <http://dx.doi.org/10.1111/j.1476-5381.2011.01579.x>

Abbreviations

EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis

Multiple sclerosis (MS) is classically characterized as an inflammatory disorder of the central nervous system, targeting regions of both the brain and spinal cord (Compston and Coles, 2008). The major pathological hallmarks to be found in MS patients typically include inflammation, demyelination and axon degeneration (Compston and Coles, 2008; Dutta and Trapp, 2011). The development of animal models of MS, such as mice with experimental autoimmune encephalomyelitis (EAE), has facilitated additional in-depth investigations into pathological changes occurring during the early stages of disease onset and progression. One notable result of such studies has been the demonstration of synaptic pathology occurring during the early stages of disease. For example, initial studies demonstrated that glutamate excitotoxicity is a significant event in EAE mice, and can be prevented with

AMPA/kainate antagonists (Pitt *et al.*, 2000; Smith *et al.*, 2000). Later studies revealed that synapses, known to be particularly vulnerable to excitotoxicity, become dysfunctional and undergo degeneration in EAE mice (Zhu *et al.*, 2003; Centonze *et al.*, 2009), potentially accounting for several of the clinical symptoms of MS, including cognitive deficits (Mandolesi *et al.*, 2010). However, the precise order and relationship of pathological events occurring in MS remains the subject of intense debate (Compston and Coles, 2008; Dutta and Trapp, 2011).

Given that inflammation is a key event in MS pathogenesis, a significant amount of research effort has been directed at developing immunomodulatory drugs as a treatment for human patients. Fingolimod (FTY720) is one such immunomodulatory drug, shown to be highly effective in clinical

trials for MS (Khatri *et al.*, 2011). As a result, in 2010 fingolimod was approved by the US Food and Drug Administration for use in patients with relapsing forms of MS. Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator that is capable of crossing the blood–brain barrier (for review, see Brinkmann, 2009). Its lipophilic nature and wide distribution following oral administration make it an ideal drug to target S1P receptors across a range of cell types in the nervous system (including neurons and glial cells), resulting in the prevention of lymphocyte invasion in MS (Brinkmann, 2009). However, the precise mechanism through which fingolimod confers neuroprotection in MS remains unclear (for review, see Cohen and Chun, 2011).

In the current issue of the *British Journal of Pharmacology*, Rossi *et al.* (2011) have provided us with potentially important new insights into the mechanisms through which fingolimod attenuates neurodegenerative events in an established EAE mouse model of MS. Several studies have demonstrated that fingolimod can confer neuroprotective properties in EAE mice (for review, see Cohen and Chun, 2011). The new study builds on this previous knowledge by showing that fingolimod can significantly ameliorate synaptic dysfunction in EAE mice *in vivo*. Rossi *et al.* (2011) used established electrophysiological techniques (e.g. whole-cell patch clamp recordings) to demonstrate that oral administration ($0.3 \text{ mg}\cdot\text{kg}^{-1}$) of fingolimod reversed the increased duration and frequency of glutamate-mediated spontaneous excitatory postsynaptic currents observed in EAE mice. However, abnormal functioning of the axonal $\text{Na}^+/\text{Ca}^{2+}$ exchanger in EAE mice appeared to be unaltered by fingolimod treatment, suggesting a synapse-specific element to fingolimod-related neuroprotection. Importantly, fingolimod did not alter any of the major physiological parameters of basal synaptic transmission in healthy intact synapses, demonstrating that it only has effects on synapses undergoing pathological changes.

Alongside the reversal of functional synaptic deficits in EAE mice, Rossi *et al.* (2011) demonstrated morphological preservation of dendritic spines on striatal neurons when treated with fingolimod, indicating structural, as well as functional, preservation of synapses. Rossi *et al.* (2011) did not perform any morphological studies of presynaptic markers in their treated and untreated EAE mice (e.g. immunohistochemical labelling of a synaptic vesicle marker such as synaptobrevin or an active zone protein such as bassoon, or electron microscopy). Thus, it remains to be firmly established whether degeneration and loss of pre-synaptic nerve terminals previously reported in EAE mice (Zhu *et al.*, 2003) were also attenuated by fingolimod. The Rossi *et al.* (2011) study was confined to synapses in the striatum of EAE mice. However, the potentially exciting nature of their findings suggests that a more widespread spatial and temporal study of synaptic pathology in other regions of the brain and spinal cord is now warranted, in order to establish the extent of synaptic protection conferred. Such studies will demonstrate the extent to which amelioration of gross neurodegenerative changes in EAE mice correlates directly with prevention of synaptic pathology *in vivo*. Unfortunately, it is not technically feasible at present to reliably and sensitively measure synaptic integrity, function and/or density in the CNS of humans using imaging techniques, so it is not possible to validate the

current findings from EAE mice in early- and mid-symptomatic human MS patients treated with fingolimod. Given that animal EAE models are thought to differ in some aspects from MS in humans (Sriram and Steiner, 2005), such studies in human patients may ultimately be required to confirm the contribution of synaptic pathology to the pathogenesis of MS and the potential for fingolimod to delay disease progression by targeting synapses.

Perhaps most excitingly, from the wider perspective, the current study potentially opens up new therapeutic avenues for neurodegenerative conditions other than MS: it is conceivable that fingolimod may be capable of conferring neuroprotection in other diseases of the nervous system where inflammation and synaptic pathology contribute to disease pathogenesis. Synaptic pathology is an important and early event in many neurodegenerative conditions affecting both the central and peripheral nervous systems (for review, see Wishart *et al.*, 2006). For example, synaptic dysfunction and loss is widely considered to contribute directly to the pathogenesis of Alzheimer's disease, and is one of the best pathological correlates of cognitive decline in human patients (Coleman *et al.*, 2004). Similarly, synaptic degeneration at the neuromuscular junction is an early pathological hallmark in many motor neuron diseases, including amyotrophic lateral sclerosis and spinal muscular atrophy (Fischer *et al.*, 2004; Murray *et al.*, 2008). The ability to directly target neuroprotective strategies to the synapse during early stages of neurodegeneration is therefore much sought after, with the Rossi *et al.* (2011) study demonstrating that it can be achieved, at least in mouse models, through oral drug delivery. Increased levels of neuroinflammation have also been reported to occur in all three of the diseases detailed above (Hensley, 2010; Papadimitriou *et al.*, 2010). Thus, whether fingolimod protects synapses directly (as may be suggested by the axonal $\text{Na}^+/\text{Ca}^{2+}$ exchanger data in the Rossi study), or as a secondary consequence of an effect on levels of inflammation, may not be important. The findings of the Rossi *et al.* (2011) study are therefore likely to be sufficient to encourage others to investigate whether fingolimod has the capability to ameliorate synaptic pathology across a range of different neurodegenerative conditions.

Conflict of interest

The author has no conflicts of interest to declare.

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