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 British Journal of Pharmacology (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
Fingolimod and synaptic pathology in MS

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References


