Neurological S1P Signaling as an Emerging Mechanism of Action of Oral FTY720 (Fingolimod) in Multiple Sclerosis

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FTY720 (fingolimod, Novartis) is a promising investigational drug for relapsing forms of multiple sclerosis (MS), an autoimmune and neurodegenerative disorder of the central nervous system. It is currently under FDA review in the United States, and could represent the first approved oral treatment for MS. Extensive, ongoing clinical trials in Phase II/III have supported both the efficacy and safety of FTY720. FTY720 itself is not bioactive, but when phosphorylated (FTY720-P) by sphingosine kinase 2, it becomes active through modulation of 4 of the 5 known G protein-coupled sphingosine 1-phosphate (S1P) receptors. The mechanism of action (MOA) is thought to be immunological, where FTY720 alters lymphocyte trafficking via S1P1. However, MOA for FTY720 in MS may also involve a direct, neurological action within the central nervous system in view of documented S1P receptor-mediated signaling influences in the brain, and this review considers observations that support an emerging neurological MOA.

Key words: FTY720, Fingolimod, Sphingosine 1-phosphate receptors, Multiple sclerosis, Central nervous system

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder that is best known for its effects on the white matter of the central nervous system (CNS). This autoimmune disorder represents one of the most common causes of disease-related demyelination (Steinman, 1996; Zamvil and Steinman, 2003; Frohman et al., 2006). MS affects up to 2.5 million people worldwide, with a 2:1 preponderance of females to males and with 70-80% of cases occurring in young adults (Bashir and Whitaker, 2002). The most common form of MS is characterized by “relapsing-remitting” neurological symptoms that can persist for many years, and which may be associated with severe neurodegenerative impairments, such as axonal damage and neuronal loss (Steinman, 1996; Chabas et al., 2001; Bashir and Whitaker, 2002; Frohman et al., 2006). The primary factors that initiate MS are still unknown. However, activation of the immune system is regarded as the key disease element in MS, resulting in the production of a variety of cytokines/other factors that have been associated with MS pathological features (Chabas et al., 2001; Filippini et al., 2003; Steinman, 2008). Recently, gene and protein array studies have provided molecular candidates for the potential development of MS therapies (Steinman, 2001; Lock et al., 2002; Steinman and Zamvil, 2003; Han et al., 2008). In addition to molecular targets, many cell types in different systems appear to be involved in MS: immune cells (T-cells, B-cells, natural killer cells, dendritic cells, and macrophages), CNS cells (neurons, astrocytes, and oligodendrocytes), and brain-resident cells (microglia and endothelial cells) (Zamvil and Steinman, 2003; Brinkmann, 2009; Chun and Hartung, 2010).

Currently available, disease-modifying therapies (DMTs) for MS aim to reduce immune response by targeting immunological pathways, but all are only partially effective: interferon beta-1α (Avonex, Rebif) and -1β (Betaseron), the synthetic peptide glatiramer...
acetate (Copaxone), the antineoplastic agent mitoxantrone (Novantrone), and the VLA4 blocker natalizumab (Tysabri) (Frohman et al., 2006; Gold et al., 2006; Chun and Hartung, 2010; Rammohan and Shoemaker, 2010). In addition, all DMTs are delivered by injection, requiring MS patients to tolerate the challenges of continual parenteral drug delivery, which is why many MS patients would prefer an oral treatment (Chun and Hartung, 2010; Rammohan and Shoemaker, 2010).

A new class of drug targets are the receptors for the signaling phospholipid known as sphingosine 1-phosphate (S1P) that interact with at least 5 cognate G protein-coupled receptors (GPCRs: S1P1-5) (Chun et al., 2002; Ishii et al., 2004). S1P, one of the most studied signaling phospholipids, was originally known as a metabolite that originated from cell membranes through metabolic pathways: sphingomyelin is cleaved to ceramide and sphingosine and then S1P is produced by phosphorylation of sphingosine via sphingosine kinases 1/2 (Sphk1/2) (Liu et al., 2002; Hla, 2004) (Fig. 1). Today, S1P is believed to be a potent signaling molecule with its 5 known receptors (S1P1-5) connecting to various downstream signaling pathways (Fig. 1), and which exert a variety of biological effects that have been extensively reviewed (Spiegel and Milstien, 2003; Ishii et al., 2004; Brinkmann, 2007; Herr and Chun, 2007; Choi et al., 2008b).

S1P receptors are expressed in a variety of cell types, including immune and CNS cells, and are thought to play a critical role in MS, indicating the possible link between S1P signaling and MS. In fact, S1P signaling via its receptors influences not only immune cells (Brinkmann et al., 2002; Graeler and Goetzl, 2002; Mandala et al., 2002), but also CNS cells (Rao et al., 2003; Gardell et al., 2007; Herr and Chun, 2007; Kimura et al., 2007; Miron et al., 2008c). Remarkably, S1P signaling has gained relevance to MS through FTY720 (known clinically as fingolimod, Novartis), an orally administered immunomodulatory agent current-

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**Fig. 1.** Phosphorylated FTY720 activates 4 of the 5 known S1P receptors. S1P and FTY720-P that are produced by sphingosine kinases activate S1P receptor-mediated signaling pathways. Activation of S1P signaling plays important biological roles in diverse systems. It is of note that FTY720-P activates 4 of the 5 S1P receptors (S1P1/3/4/5) with high affinity (binding affinity is shown except for S1P2; FTY720-P does not bind to S1P2 (> 10,000 nM)). Until now, FTY720 efficacy via S1P signaling was only shown in a few pathological systems, including MS and ischemia. In view of the diverse biological roles of S1P signaling, many more aspects of FTY720 efficacy remain to be evaluated.