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Invited review

Sphingosine-1-phosphate receptor therapies: Advances in clinical trials for CNS-related diseases

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ABSTRACT

The family of sphingosine-1-phosphate receptors (S1PRs) are G protein-coupled and comprise of five subtypes, $S1P_1$-$S1P_5$. These receptors are activated by the sphingolipid ligand, S1P, which is produced from the phosphorylation of sphingosine by sphingosine kinases. The activation of S1PRs modulates a host of cellular processes such as cell proliferation, migration and survival. These receptors are targeted by the drug fingolimod, a first in class oral therapy for multiple sclerosis. Importantly, S1PRs have also been implicated, in cellular experiments, pre-clinical studies and clinical trials in a range of other neurodegenerative diseases, neurological disorders and psychiatric illnesses, where S1PR drugs are proving beneficial. Overall, studies now highlight the importance of S1PRs as targets for modulating a variety of debilitating brain-related diseases. Here, we review the role of S1PRs in these illnesses.

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1. Introduction

The family of sphingosine-1-phosphate receptors (S1PRs) are G-protein coupled and are known drug targets for multiple sclerosis (MS) (Toman and Spiegel, 2002; Van Brocklyn et al., 1998; Brinkmann, 2007; Terada et al., 2004). The ligand of these receptors, namely S1P, is found at varying concentrations in different body fluids and tissues, where excessive levels of S1P at inflammatory sites is associated with pathology (Brinkmann, 2007). Erythrocytes, endothelial cells and thrombocytes are all sources of blood derived S1P (Bode et al., 2010; Pham et al., 2010; Tani et al., 2005), which is also generated by mast cells and macrophages (Jolly et al., 2005; Xiong et al., 2013). This blood cell borne source of S1P likely, thus, explains the relative high concentrations of S1P in the plasma and lymph tissue (Pham et al., 2010). The mechanism by which S1P is produced from these different cell types seems to be preserved (Thuy et al., 2014). In particular, a balancing act between the levels of ceramide, sphingosine (derived from ceramide) and S1P (a phosphorylated form of sphingosine) regulates the production of S1P. The phosphorylation of sphingosine to S1P is determined primarily by the high amounts of sphingosine kinase-1 (SphK1) and sphingosine kinase-2 (SphK2) along with low levels of both S1P phosphatase (which converts S1P to sphingosine) and S1P lyase (a S1P degrading enzyme which terminally cleaves the sphingolipid) (Fig. 1) (Pappu et al., 2007).

S1P acts as an extracellular ligand for cell surface S1PRs, through which the majority of S1P signalling occurs with reported additional intracellular second messenger functions (Van Brocklyn et al., 1998). Previously known as members of the endothelial differentiation gene (EDG) family, S1PRs are composed of five subtypes, $S1P_1$-$S1P_5$, each of which are approximately 400 amino acids in length (Toman and Spiegel, 2002). S1PRs are expressed ubiquitously and play important roles in cell survival, growth and differentiation in many cell types, including cells of the immune, cardiovascular and central nervous systems (Toman and Spiegel, 2002; Terada et al., 2004; Kono et al., 2008) (Fig. 2). These receptors also play important roles in embryonic development, often leading to embryonic lethality in S1PR-null animal models (Brinkmann, 2007; Yamagata et al., 2003). Four out of the five S1PRs are found in the CNS, these include $S1P_1$, $S1P_2$, $S1P_3$ and $S1P_5$, with all four receptors being expressed on neurons, astrocytes, oligodendrocytes and microglia. The level of expression of these receptors can vary depending on temporal, spatial and environmental conditions. For example, $S1P_1$ and $S1P_3$ expression has been shown to be important for the developing brain and are also up-regulated in the mature brain when exposed to pathological stimuli (Choi and Chun, 2013). In adult cells, S1PRs play a role in cytoskeletal rearrangements thus regulating immune cell trafficking, vascular homeostasis and cell communication in the CNS (Brinkmann, 2007). In the immune system it has been well-documented that internalisation of the $S1P_1$ prevents B and T cells from leaving the lymph nodes and entering the lymphatic circulation (Hla and Brinkmann, 2011). This in turn has important ramifications in many disease states where inflammation plays a destructive role.

The archetypal S1PR drug, FTY720 (Gilenya/fingolimod) is a structural analogue of sphingosine, of which its phosphorylated form, FTY720p, binds S1PRs and thereby modulates the function of several cell types (Brinkmann, 2007; Aki and Kahan, 2003; Miron et al., 2008). As well as FTY720p, a number of more selective S1PR agonists and antagonists have been developed, helping to improve our understanding of the roles of specific S1PR subtypes in both healthy and diseased brains (Sim-Selley et al., 2009). When phosphorylated by sphingosine kinases (SphK) to its active form, FTY720p modulate all S1PRs except $S1P_2$ (Brinkmann, 2007; Terada et al., 2004), although whether or not FTY720p modulates $S1P_2$ remains controversial (Sobel et al., 2015). FTY720p causes internalisation of $S1P_1$, acting as a functional antagonist, thus attenuating lymphocyte egress from peripheral lymph nodes and preventing T cell infiltration and inflammation in the CNS (Billich et al., 2013; Brinkmann et al., 2010). It has been suggested that FTY720p ameliorates the symptoms of MS, primarily *via* limiting T cell mediated responses (Hla and Brinkmann, 2011; Sheridan and Dev, 2012). It is likely, however, that FTY720p also achieves part of this efficacy by enhances endothelial barrier function and influencing glial repair that helps restore nerve function (Foster et al., 2009; Hiestand et al., 2008).

The therapeutic potential of S1PR modulation has been rapidly gaining attention over the past number of years. Fingolimod, in particular, has been used in numerous clinical trials and animal experiments for a variety of diseases (Fu et al., 2014; Deogracias et al., 2012; Asle-Rousta et al., 2013). Given that it is well documented already that S1PRs are drug targets for MS (Brinkmann et al., 2010; Pritchard et al., 2014; Sheridan and Dev, 2014; Dev et al., 2008), here we focussed to review additional brain related diseases for which S1PRs have been proposed as potential drug targets. We outline the use of S1PR drugs in clinical trials, animal models and *in vitro* studies.

2. Biological functions of S1PRs in the CNS

Four of the five S1PRs are found in the CNS ($S1P_1$, $S1P_2$, $S1P_3$ and $S1P_5$) with all four receptors being expressed at varying degrees on neurons, astrocytes, oligodendrocytes and microglia **(**Fig. 3**)**. The level of expression of these receptors can vary depending on temporal and spatial factors as well as stimuli surrounding the cell. The role of S1PRs in the CNS has also been reviewed extensively (Choi and Chun, 2013; Hla and Brinkmann, 2011; Dev et al., 2008; Martin and Sospedra, 2014) and we therefore provide below only a brief overview of their role in neuronal and glial cells (Table 1).

In neurons, *in vitro* experiments reveal that S1P signalling mainly elicits morphological changes related to growth cone formation and neurite extension and retraction (Ishii et al., 2004). As in other cell types, differential expression of S1PRs can have opposing functions. For example, stimulation of neurons with nerve growth factor (NGF) activates sphingosine kinase 1 (SphK1), which converts sphingosine to sphingosine-1-phosphate. The resulting transactivation of $S1P_1$ promotes neurite extension. Overexpression and application of antisense probes to down-regulate S1PRs have demonstrated that $S1P_1$ promotes neurite extension, while $S1P_2$ and $S1P_5$ signalling inhibits this process (Toman et al., 2004; MacLennan et al., 2000). In addition, neurons lacking $S1P_2$ have been shown to elicit hyper-excitability, suggesting this S1PR subtype may play a role in neuronal activity (MacLennan et al., 2001). Synaptic activity is another function regulated in part by