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Review article

Sphingosine kinase 1/sphingosine-1-phosphate receptors dependent signalling in neurodegenerative diseases. The promising target for neuroprotection in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is one of the most common serious neurodegenerative disorders in the world. The incidence of PD appears to be growing and this illness has an unknown pathogenesis. PD is characterized by selective loss of dopaminergic (DA) neurons in the substantia nigra (SN), with an enigmatic cause in most individuals. Current pharmacotherapies and surgery provide symptomatic relief but their effects against the progressive degeneration of neuronal cells are strongly limited if present at all. Therefore, uncovering novel molecular mechanisms of DA cell death and new potentially disease-modifying pharmacological targets is an important task for basic research. Significant progress has been made in understanding the role of disturbed sphingolipid metabolism, particularly relating to ceramide and sphingosine-1-phosphate (S1P) in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative diseases. Additionally, the neuroprotective potential of an S1P receptors (S1PR) modulator, fingolimod (FTY720), in multiple sclerosis (MS) and numerous other diseases has been observed over the past decade. In this review, we briefly summarise recent achievements in defining intracellular S1PR-dependent actions, discuss their significance to therapeutic approaches, and explore their neuroprotective potential as a target in PD treatment.

Contents

Neuronal degeneration in Parkinson's disease

A major pathological hallmark of Parkinson's disease (PD) is the degeneration and death of dopamine (DA) neurons of the substantia nigra pars compacta (SNpc) and loss of their projections to the striatum, which results in a dramatic depletion of striatal DA levels. These alterations lead to disturbances in motor function, including bradykinesia, muscle rigidity, and resting tremor. Non-motor features such as sleep disturbances, depression, and anxiety

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are increasingly recognized as very early symptoms in PD patients. In addition to neuronal damage, an important pathological hallmark of PD is intracellular accumulation of alpha-synuclein (ASN) in the form of Lewy bodies (LB). Genetic studies of PD patients have identified several mutations in the gene *SNCA*, encoding ASN. Mutations in other genes, such as *LRRK2, GBA, Parkin, PINK1, and DJ-1* are associated with autosomal dominant or recessive inheritance of PD. Importantly, only 5–10% of PD patients exhibit monogenic forms of the disease and the majority of PD cases are sporadic, resulting from a combination of genetic and environmental risk factors [1]. It is well recognized that DA neurons of the SNpc are particularly vulnerable to oxidative damage and inflammatory attack. Several theories suggest that DA neurodegeneration in SN is associated with a high level of iron and neuromelanin in SN, which contribute to oxidative stress and decreased levels of the key endogenous antioxidant, reduced glutathione, within this brain structure. Epidemiological, *post-mortem* imaging, and animal model studies have highlighted the role of the neuroinflammatory process in PD, particularly the importance of microglial cells in SNpc. A primary insult, such as free radical (FR) generation, may activate glia. Reactive microglia may then be a source of nitric oxide, other FRs, neurotoxins, or cytokines that act in an autocrine/paracrine manner and subsequently stimulate other glial cells and suffering neurons, perpetuating DA cell death [2]. Substances released by degenerating neurons include ASN and other misfolded proteins. Progressive secretion of ASN, which may be responsible for prion-like cell-to-cell transmission of altered proteins, according to the 'pathogenic spread' hypothesis, can contribute to the cascade of events leading to the severe neurodegeneration [3].

Together, numerous studies emphasize that the pathological hallmarks of PD are coexistent and exacerbate one another's effects, leading to the extensive degeneration of brain structures. Disturbed homeostasis between bioactive sphingolipids, S1P, and ceramide may also result in a vicious circle of molecular events, leading to DA cells degeneration and death. S1P regulates proliferation, migration, and cell survival. Its effects are largely in opposition to the apoptosis and growth arrest mediated by ceramide, which is accumulated in AD. Several studies have demonstrated that the 'sphingolipid rheostat' regulating cellular fate has been significantly affected in AD. However, the role that S1P and ceramide plays in PD is not clear.

S1P receptor signalling within the central nervous system

S1P levels are primarily regulated by two lipid kinases, the sphingosine kinases SPHK1 and SPHK2 (EC: 2.7.1.91), and S1P-degrading enzymes, such as S1P phosphatases (SPPs) that convert S1P to sphingosine and S1P lyase (SPL), which terminally cleaves this sphingolipid (Fig. 1). SPHK1 and SPHK2 sequence differences arise from alternate splicing, which affects their differential subcellular localization and biochemical properties. As a consequence, the S1P pools synthesized by individual kinases could play a different roles in cells. S1P synthesized by SPHK1 localised in the cytoplasm and endoplasmic reticulum can be transported out of the cell and exert mitogenic and anti-apoptotic effects in an autocrine, i.e 'Inside-Out signalling', or paracrine manner, affecting other cell types. Transport of these bioactive sphingolipids is carried out by spinster protein 2 (Spns2) and the ATP-binding cassette (ABC) family of transport proteins (ABC1, ABCG2, ABCA1). S1P is a ligand of five S1P-specific G protein-coupled cell plasma membrane receptors, called S1PR1-5. [4].

Four of the five S1PRs (S1PR1, S1PR2, S1PR3, and S1PR5) are located in both neurons and glial cells within the CNS. S1PR-mediated signalling is essential for development of the neural tube and vascular system during embryogenesis [5]. In the mature CNS, S1P regulates the activation of neuronal progenitor cells and their migration to affected regions. S1P-dependent signalling influences the synthesis of neurotrophic factors and pro-inflammatory cytokines, as well as cellular communication. S1PR1 is the most abundant S1PR receptor in the CNS. The level of expression of S1PR1 and S1PR3 changes over a lifespan, under pathological conditions, and depends on the environmental milieu. The key effector protein of S1PR1 and S1PR3 is phosphatidylinositol-3 kinase (PI3 K) conjugated to Akt kinase, which is responsible for phosphorylation of proteins associated with regulation of cell proliferation, migration, and survival. Mice with a S1PR1 receptor deletion are characterized by abnormal formation of the neural

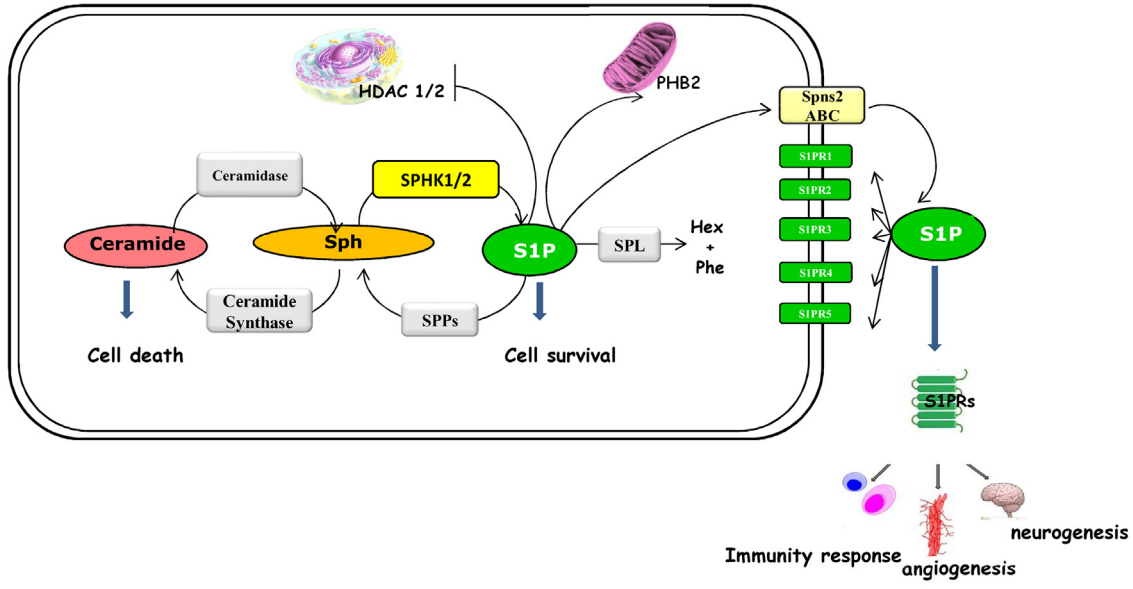

Fig. 1. Metabolism and mechanism of S1P action.
Abbreviations: S1P – sphingosine-1-phosphate, SPHK1/2 – sphingosine kinase 1 and sphingosine kinase 2, Sph – sphingosine, SPPs – S1P phosphatases, SPL – S1P lyase, Spns2 – spinster 2, transporter S1P, S1PR1-5–receptors for S1P, Phe – phosphoethanolamine, Hex – hexadecenal, HDAC1/2–histone deacetylases, enzymes with repressive influence on transcription, PHB2- prohibitin 2, protein regulating functional integrity of mitochondria. HDAC1/2 and PHB2 are intracellular S1P effector proteins.