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Review

Integrated sphingosine-1 phosphate signaling in the central nervous system: From physiological equilibrium to pathological damage

Rasoul Ghasemi[a,b], Leila Dargahi[c], Abolhassan Ahmadiani[d,*]

[a] Department of Physiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Neurophysiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] NeuroBiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Sphingosine-1 phosphate (S1P), a bioactive sphingolipid metabolite, plays an essential role in cellular homeostasis. It is well evidenced that enzymes responsible for S1P production, as well as S1P receptors are expressed in the central nervous system (CNS), implying that S1P may contribute to CNS physiology. In current review, we will present the current knowledge about developmental and neuromodulatory functions of S1P in the brain. Considering neuroprotective effects of S1P, we also review the relation between S1P and cellular autophagy, mitochondrial function, oxidative stress and apoptosis as well as molecular pathways underlying neuroprotective effects of S1P. Given these pivotal functions, in the last section, we will summarize latest findings about possible contribution of S1P dysregulation in neurological disorders like Alzheimer's disease and multiple sclerosis.

Contents

* Corresponding author. Fax: +98 2122432047.
E-mail address: aahmadiani@yahoo.com (A. Ahmadiani).

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1. Introduction

Sphingosine-1-phosphate (S1P) is a bioactive metabolite derived from sphingolipid, which is present in plasma membrane. It was originally thought to be an inactive end-product of sphingosine metabolism [1], however, over last 2 decades, it was discovered that S1P participates in various cellular functions such as in anti-apoptotic, proliferative, and inflammatory signaling pathways [2]. Since then numerous studies have shown that enzymes responsible for S1P production and S1P receptors are present in the brain, implying that S1P might be involved in the regulation of various physiological and pathophysiological processes in the brain [1]. Considering the expression of S1P in the brain, in current work we reviewed current state of knowledge about S1P metabolism and its cellular targets, and protective functions of S1P in the central nervous system (CNS), and addressed how S1P exert such functions. Furthermore, the recent evidences about the roles of S1P dysregulation in important neurological disorders and S1P targeted treatments will also be reviewed herein.

2. S1P metabolism

S1P is produced intracellularly through ATP dependent phosphorylation of sphingosine, this process is catalyzed by sphingosine kinase (SphK). Sphingosine is formed as a by-product of sphingolipid metabolism. Briefly, under the influence of sphingomyelinase enzyme, sphingomyelin is degraded to ceramide in the cell membrane, ceramide then is converted to sphingosine by ceramidase enzyme, and finally sphingosine is phosphorylated to generate S1P [3]. Sphingosine kinases (SphKs) as the main enzymes regulating S1P production are a class of evolutionarily conserved lipid kinases with five domains which are expressed widely in different species from yeast to humans [1,4]. The activity of SphKs and consecutive production of S1P is responsive to various cellular stimuli, a process that ultimately determine cell fate [5] . Until now, two isoforms of SphK have been characterized, namely SphK1 and SphK2. Despite high similarity in amino acid sequence, these two isoforms are derived from two distinct genes, have different patterns of developmental and tissue-specific expression and subcellular localization, as well as different kinetic properties [3]. For instance, while SphK1 is found in the cytosol of eukaryotic cells, and is activated upon recruitment to the plasma membrane, the membrane associated SphK2 is localized to cellular organelles like nucleus and endoplasmic reticulum [3]. These differences between SphK1 and SphK2 suggest that these two enzymes may participate in distinct physiological processes [5]. Expression of SphK1 is shown to protect cells from apoptosis and enhance proliferation/growth, and promotes tumor formation [6,7]. The effects of SphK2 however, seems to be more complicated; on one hand it has been reported that knockdown of SphK2 could sensitize cells to apoptotic stimuli [8,9], indicating pro- survival effects for SphK2 but on the other hand, evidences are also available suggesting that SphK2 could induce apoptosis independent of activation of S1P receptors [10]. Beside regulation of S1P synthesis, modulation of S1P degradation also is an essential factor in determining the cellular levels of S1P. Degradation of S1P is achieved mainly by S1P degrading enzyme, S1P-lyase (S1PL). In addition, S1P could also be dephosphorylated by S1P phosphatases (S1PP) or lipid phosphate phosphatases or converted back to ceramide by ceramide synthase [3,8]. As S1P precursors (sphingosine and ceramide) have opposing functions on cellular fate, keeping a dynamic balance between relative levels of pro-apoptotic ceramide and sphingosine and pro-survival S1P known as “sphingolipid rheostat”, eventually determines cell fate (Fig. 1). Accordingly agents and/or situations which induce conversion of ceramide-sphingosine to S1P would change the rheostat toward S1P and direct the cell towards survival and vice versa [8,11].

3. S1P receptors

Following the discovery of S1P, it was firstly assumed that cellular function of S1P is solely carried out via its intracellular second messenger properties. This notion was ruled out when it was revealed that some specific effects of S1P could be abrogated by pertussis toxin (a G-protein inhibitor), suggesting that these effects of S1P might be mediated through G-protein coupled receptors [12]. In contrast to sphingosine, S1P is not able to cross the lipid bilayer, this then raised the question how the generated S1P leaves the cells to reach these proposed receptors. It has been revealed that ATP-binding cassette family of transporters (ABC) and/or spinster-like family of transmembrane transporters are two main mechanisms which help S1P to leave cell and exert its G-protein coupled receptor mediated effects [13,14]. Until now, five family members of S1P receptors have been characterized designated as $S1P_1$–$S1P_5$. The genes encoding these receptors are shown by italicized names *S1PR1–S1PR5* (in human) and *S1pr1–S1pr5* (in non-humans) respectively [15]. These receptors show different tissue distribution, while $S1P_1$, $S1P_2$ and $S1P_3$ also known as endothelial differentiation gene or EDG-1, EDG-5 and EDG-3 respectively are ubiquitously expressed in most tissues, $S1P_4$ (EDG-6) is largely expressed in the lymphoid tissues and $S1P_5$ (EDG-8) is mostly restricted to brain, skin and natural killer cells [8,16]. Among S1P receptors $S1P_1$ is one of the first and most characterized receptors which Hanson et al. investigated its crystal structure and reported that $S1P_1$ receptor has structural properties which limit the access of extracellular ligands to the binding site of receptor. This limited accessibility of extracellular ligands to the binding pocket causes saturation rate of S1P to be lowered even in the presence of excess ligand. Accordingly, authors concluded that the way in which ligands (including S1P) gain access to the binding pocket of S1P receptor might be through a gap between helices I and VII in the membrane bilayer. In this way sphingolipid molecules bind to their receptors within the confine of the membrane rather than the extracellular milieu [17].

4. S1P functions

For several years S1P has been viewed as an inactive end-product of sphingosine metabolism, but arduous works during the last 2 decades, have unraveled several important roles for S1P. In present section, we briefly review the general functions of S1P