Biochimica et Biophysica Acta xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Book Review

Sphingosine 1-phosphate – A double edged sword in the brain☆

Indulekha Karunakaran, Gerhild van Echten-Deckert *

LIMES Institute, Membrane Biology & Lipid Biochemistry, University of Bonn, Bonn, Germany

ARTICLE INFO

Article history:
Received 15 December 2016
Received in revised form 28 February 2017
Accepted 13 March 2017
Available online xxxx

Keywords:
Sphingosine 1-phosphate
Synaptic transmission
Neuroinflammation
Neuronal autophagy
Phosphatidylethanolamine

ABSTRACT

The physiological functions of sphingosine 1-phosphate (S1P) and its pathological roles in various diseases are increasingly being elucidated. Particularly, a growing body of literature has implicated S1P in the pathogenesis of brain related disorders. With the deciphering of more intricate aspects of S1P signalling, there is also a need to reconsider the notion of S1P only as a determinant of cell survival and proliferation. Further the concept of 'S1P-ceramide' balance as the controlling switch of cellular fate and functions needs to be refined. In this review, we focus on the brain related functions of S1P with special focus on its role in synaptic transmission, neuronal autophagy and neuroinflammation. The review also attempts to bring out the multi-faceted nature of S1P signalling aspects that makes it a 'double edged sword'. This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo Escríba-Ruíz.

Contents

1. Introduction

After being discovered in 1876 and researched intensively for decades [1], sphingolipids have been accepted beyond doubt as crucial signalling molecules. While ceramide and sphingosine-1-phosphate (S1P) of the sphingolipid pathway were for years in the major focus, ceramide-1-phosphate (C1P) and dihydroceramide are more recent favourites [2] and the list is expected to grow. The notion of dynamic

☆ This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo Escríba-Ruíz.

* Corresponding author at: Kekulé-Institut, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany.
E-mail address: g.echten.deckert@uni-bonn.de (G. van Echten-Deckert).

http://dx.doi.org/10.1016/j.bbamem.2017.03.008
0005-2736/

balance between ceramide associated with apoptosis and S1P mediating cell survival, popularly known as 'sphingolipid rheostat' no longer holds true in all cell types and under all conditions and is considered to inadequately reflect the versatile cellular functions of these metabolites [3]. In this backdrop, this review tries to capture the intricacies surrounding S1P signalling in the brain in light of its emerging and previously unknown functions in synaptic transmission, autophagy and neuroinflammation.

2. Metabolism and occurrence of S1P

The *de novo* pathway for sphingolipid biosynthesis starts with serine and fatty acyl-CoA condensation catalysed by serine palmitoyltransferase. Other enzymes 3-ketodihydrosphingosine reductase, dihydroceramide synthases, and dihydroceramide desaturase act in a consecutive manner to yield ceramide which is acted upon by ceramidases and sphingosine kinases (SKs) to yield S1P [4,5]. Sphingomyelin (SM) is the most prevalent sphingolipid in cellular plasma membrane representing a source of bioactive sphingoids (Fig. 1). In the salvage pathway, breakdown of SM by means of a group of sphingomyelinases (SMases) leads to the formation of ceramide, another critical signalling molecule per se and an intermediate in the production of other bioactive active compounds including C1P, sphingosine and S1P. S1P is generated by means of two enzymatic reactions, deacylation of ceramide to sphingosine by means of ceramidases [6] and the phosphorylation of sphingoid base to S1P by sphingosine SKs (Fig. 1). SK1 and SK2 are two kinase isoforms involved in S1P production [7]. Intriguingly, SK1 and SK2 have different intracellular locations and biological functions [8]. There are multiple enzymes involved in the catabolism of S1P. The irreversible breakdown of S1P to phosphoethanolamine and hexadecenal is catalysed by the enzyme S1P lyase (S1PL) [9]. S1P phosphatases (SPPs) catalyse the removal of the phosphate group which yields sphingosine which in turn can be channelled to S1P production via phosphorylation or fed into the salvage pathway for the synthesis of ceramide [10]. Intricate regulation of the sphingolipid pathway has been discussed in detail in many reviews including the ones by Hannun and Obeid [5], and Huwiler et al. [11]. In an alternative pathway, ceramide can be channelled to produce glucosylceramide (GlcCer) by the catalytic action of GlcCer synthase which can be converted to lactosylceramide (LacCer) by the addition of a galactose residue. Subsequent addition of monosaccharides leads to the formation of various complex glycoshingolipids including sialic acid containing gangliosides that are integral components of membrane microdomains and crucial for many signal transduction events [12,13]. Also, ceramide can be phosphorylated selectively to produce C1P by ceramide kinase which has pro-inflammatory functions [14]. The balance between the levels of the two bioactive lipids, ceramide and S1P has been claimed to determine cell fate with increased ceramides initiating apoptosis and S1P promoting proliferation and cell survival [15]. S1P can bind to G-protein coupled receptors (GPCRs) designated as S1PR1, S1PR2, S1PR3, S1PR4 and S1PR5 which depending on the coupled G proteins elicit several effector functions [16]. The extracellular functions of S1P secreted by blood cells, endothelial cells and mast cells are well known [17]. Anelli et al. [18] were the first to show that also neural cells including primary cultured cerebellar granule cells and astrocytes release S1P as a result of exogenous stimulation. In a follow up report, the mitogenic effect of S1P released by primary cultured cerebellar astrocytes in response to basic fibroblast growth factor (bFGF) has been demonstrated [19]. Notably, intracellular receptor-independent actions of S1P are also documented in different cell types [20], including neurons [21].

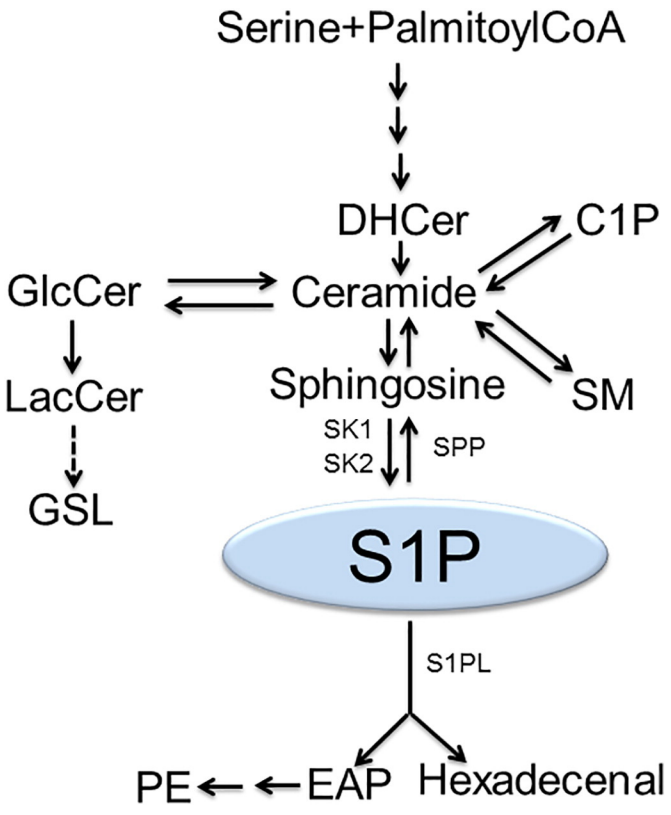

Fig. 1. Schematic of S1P metabolism. S1P is the catabolic intermediate of all sphingolipids. SK1, SK2, SPP and S1PL are the major enzymes that tightly regulate S1P levels. SM, sphingomyelin; C1P, ceramide 1-phosphate; DHCer, dihydroceramide; GlcCer, glucosylceramide; LacCer, lactosylceramide; GSL, glycosphingolipids; PE, phosphatidylethanolamine; EAP, ethanolamine phosphate; SK1, sphingosine kinase 1; SK2, sphingosine kinase 2; SPP, S1P phosphatase; S1PL, S1P lyase.

3. S1P in synaptic transmission

One of the important functions of S1P in the CNS is its role in neural development and survival [22,23]. Recently, its roles in synaptic transmission by modulating the release of neurotransmitters and membrane excitability are increasingly being recognized [24]. Studies in hippocampal slices revealed a role of S1P in regulation of synaptic strength and hence in memory formation [25]. On one hand exogenously added S1P increased AMPA receptor mediated miniature excitatory postsynaptic currents (mEPSCs) recorded from the CA3 region of the hippocampus. [25]. On the other hand, pharmacological inhibition or genetic ablation of SK1 led to an inhibition of long term potentiation (LTP) and affected spatial learning assessed by Morris water maze test [25]. There are additional studies that also point to a strong interconnection between SK1 and synaptic transmission. In SK1 deficient *C. elegans* mutants the release of neurotransmitter was impaired at neuromuscular junctions [26]. Furthermore, the importance of muscarinic signalling in recruiting SK1 to presynaptic terminals was demonstrated [26]. It appears that mechanisms that mediate SK1 translocation to synapses are critical for presynaptic plasticity. It was indeed shown that presynaptic calcium influx is involved in recruiting SK1 to synapses whereas in turn SK1 is essential for the recruitment of the priming protein Munc13 at synapses to mediate muscarinic signalling [27] Thus the question arises whether S1P acts intracellularly or via its receptors. On the one hand S1P was shown to operate via S1PR3 to regulate spontaneous release of glutamate from mossy fiber terminals [28]. The ability of S1P to augment glutamate secretion was further documented by Kajimoto et al. in hippocampal neurons [29]. The same group further went on to show that S1P acting through its receptors is involved in the regulation of exosomal multivesicular endosome (MVE) maturation. The autocrine action of S1P was found to be crucial for sorting of the cargo designated for release by exosomes [30]. On the other hand intracellular S1P was shown to affect synaptic transmission e.g. enhancing

Please cite this article as: I. Karunakaran, G. van Echten-Deckert, Sphingosine 1-phosphate – A double edged sword in the brain, Biochim. Biophys. Acta (2017), http://dx.doi.org/10.1016/j.bbamem.2017.03.008