Review

Therapeutic targeting of the ceramide-to-sphingosine 1-phosphate pathway in pain

Daniela Salvemini[1], Timothy Doyle[1], Michaela Kress[2], and Grant Nicol[3]

[1] Department of Pharmacological and Physiological Sciences, St Louis University School of Medicine, 1402 S. Grand Blvd, St Louis, MO 63104, USA
[2] Department of Physiology and Medical Physics, Division of Physiology, Innsbruck Medical University, A-6020 Innsbruck, Austria
[3] Department of Pharmacology and Toxicology, School of Medicine, 635 Barnhill Drive, MS A402, Indianapolis, IN 46202, USA

Approximately 20% of the population in Western countries suffers from chronic pain syndromes for which treatments are frequently insufficient or non-existent. In particular, chronic pain management with opiate/narcotic analgesics is often hampered by the development of analgesic tolerance and hyperalgesia, necessitating escalating doses to achieve pain relief. There is a major need for renewed focus on novel targets that will be effective in both neuropathic and inflammatory pain. Compelling evidence implicates ceramide-to-sphingosine 1-phosphate (S1P) pathways as contributors to pain of diverse etiologies. Moreover, S1P and its receptors are emerging as important neuronal and immune cell regulators interacting at several sites in the pain pathway. It is therefore timely and important to critically evaluate the pharmacological basis for targeting the ceramide-to-S1P pathway as an approach to pain management.

Ceramide-to-S1P axis

Ceramide is a potent proinflammatory and proapoptotic sphingolipid generated by enzymatic hydrolysis of sphingomyelin (SM) by sphingomyelinases (SMases) and from *de novo* synthesis by serine palmitoyltransferase and ceramide synthase (*de novo* pathway) [1] (Figure 1). Ceramide serves as a second messenger to activate downstream effectors including ceramide-activated protein kinase and ceramide-activated protein phosphatase and as a precursor to other second messengers, such as S1P [1]. Ceramide can activate transcription factors [e.g., nuclear factor κB (NF-κB)] and mitogen-activated protein kinases (MAPKs) [e.g., extracellular signal-regulated kinase (ERK) and p38 kinase]; increase the formation of several proinflammatory cytokines [e.g., tumor necrosis factor-α (TNF-α)]; induce cyclooxygenase-2 (COX-2) expression to increase formation of prostaglandins (PGs) such as PGE_2 [2] and nitroxidative species [superoxide (SO, $O_2^{\cdot -}$), nitric oxide, and the product of their interaction peroxynitrite (PN, $ONOO^-$)] [3,4]. Thus, ceramide biosynthesis inhibitors exert beneficial antiapoptotic and anti-inflammatory effects [5]. Once generated, ceramide can be metabolized to sphingosine by ceramidases, and then sphingosine kinase 1 and 2 (SphK1 and SphK2) convert sphingosine to S1P (Figure 1) [6]. S1P levels are further regulated by its dephosphorylation by S1P phosphatases and lipid phosphate phosphatases or cleavage by S1P lyase [6]. The cleavage of S1P by S1P lyase leads to irreversible breakdown of the sphingosine backbone, making this pathway the major sphingolipid degradation pathway [6]. The enzymes and substrates for S1P production are found in most cells including endothelial cells, immune cells (e.g., thrombocytes, macrophages, and mast cells), and central and peripheral nervous system cells (e.g., neurons, glia, and Schwann cells) [6,7]. The tight regulation of S1P levels by these synthesis and degradation pathways are vitally important because the absence of S1P by deletion of both SphK1 and SphK2 causes lethal deficits during embryonic development; mice carrying null mutations for SphK1 and SphK2 exhibit severely disturbed neurogenesis, including neural tube closure and angiogenesis [8]. Presumably, cells release S1P via specific transporters. Although members of the multidrug resistance-associated protein ABC family are generally accepted to function as S1P transporters [6], a novel transport protein, spinster 2 (spsn2), has been identified in zebrafish and seems to be specific for S1P [9]. S1P is a multifaceted molecule implicated in many regulatory processes including immune surveillance [10–13]. The important and rapidly emerging role of S1P and the therapeutic value of targeting this sphingolipid as a novel approach in cardiovascular, pulmonary disorders, and chronic autoimmune disorders (e.g., colitis, arthritis), cancer, and neurodegenerative diseases such as multiple sclerosis has been recently reviewed [14–20].

In tissue damage involving vascular lesions, significant sources of S1P include activated thrombocytes and erythrocytes [8,21]. Although S1P in blood plasma may reach micromolar concentrations, it remains largely bound to plasma proteins [8,21]. At inflammation sites, free S1P can reach high concentrations locally [8,21] and systemic S1P concentrations are elevated in patients with rheumatoid arthritis (RA) [18]. Proinflammatory cytokines such as TNF-α stimulate SphKs and upregulate intracellular S1P production in many cell types; and inhibitors of SphKs have beneficial anti-inflammatory effects in animal models of disease [20,22]. Upon activation, cells release S1P to

Corresponding author: Salvemini, D. (salvemd@slu.edu)
Keywords: FTY720; inflammation; multiple sclerosis; nociception.

 0165-6147/$ – see front matter © 2013 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tips.2012.12.001

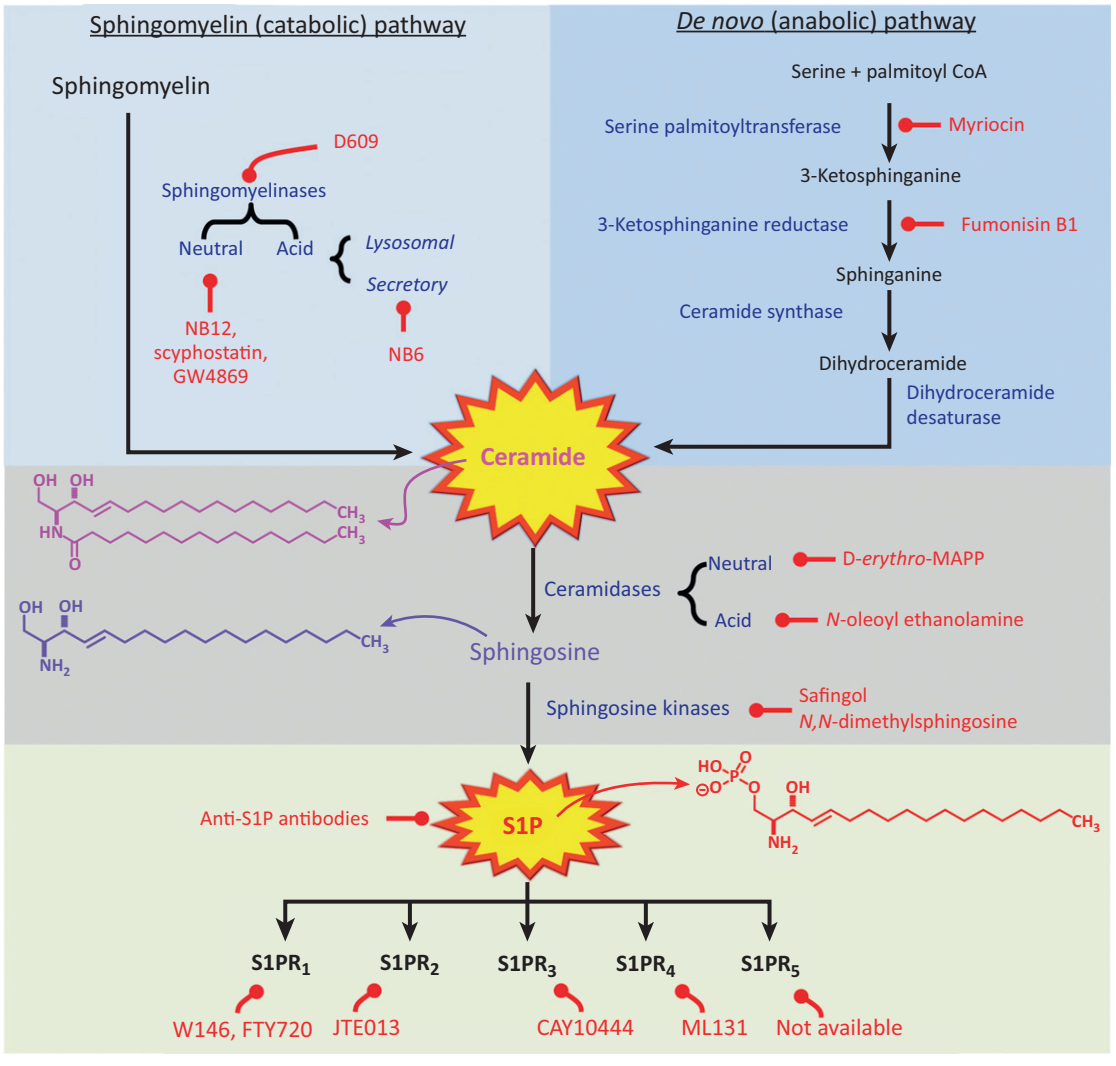

Figure 1. A simplified overview of the sphingolipid biosynthetic pathway leading to ceramide and sphingosine 1-phosphate (S1P) formation. Ceramide can be formed by either a catabolic or an anabolic pathway. In the catabolic pathway, ceramide is released by hydrolysis of membrane sphingomyelin by neutral or acid sphingomyelinases. The formation of ceramide by acid sphingomyelinase is sometimes referred to as the salvage pathway. In the *de novo* pathway, ceramide is formed by a series of reactions in the endoplasmic reticulum starting from serine and palmitoyl CoA. Ceramide may act as a second messenger in proinflammatory and proapoptotic signaling pathways or act as a substrate for the formation of additional sphingolipid mediators. If acted upon by ceramidases, ceramide is converted to sphingosine, which can be further phosphorylated by sphingosine kinases to form S1P. Once formed, S1P can act intracellularly or transported across the plasma membrane to act extracellularly on any of five cognate G-protein-coupled receptors. Each biosynthetic step is reversible by additional enzymes that provide counterregulatory mechanisms of ceramide and S1P formation. Blue, enzymes; red, enzymatic inhibitors or receptor antagonist.

function as either an autocrine or paracrine signaling molecule, leading to various cellular responses (Figure 2) through its activation of a family of five cognate G-protein-coupled receptors ($S1PR_{1–5}$) [13,23] (Figure 1). $S1PR_{1–3}$ are ubiquitously expressed, but $S1PR_{4/5}$ appear to be differentially expressed on various cells [2,21]. $S1PR_1$, $S1PR_4$, and $S1PR_5$ subtypes mainly couple to $G_{i/o}$, $S1PR_2$ and $S1PR_3$ subtypes couple to $G_{i/o}$, G_q, and $G_{12/13}$ [13,23]. S1P acts as a lipid growth factor that induces robust endothelial cell activation resulting in cellular locomotion, vascular maturation, angiogenesis, and antiapoptotic events [8,21]. In L929 fibroblasts and A549 lung carcinoma cells, TNF-α-induced COX-2 activity and subsequent PGE_2 production depends on SphK1-derived S1P [24,25]. Furthermore, TNF-α induced transcription of proinflammatory cytokines, chemokines, and adhesion molecules requires SphK1 activation [24]. Conversely, intraperitoneal administration of the SphK inhibitor, *N*,*N*-dimethylsphingosine (DMS) [5], or silencing ribonucleic acid (siRNA) knock-down of SphK1 significantly inhibits disease severity, reduces articular inflammation, and joint destruction in a murine collagen-induced arthritis model [20]. DMS treatment also downregulates serum levels of S1P, interleukin (IL)-6, TNF-α, interferon (IFN)-γ, and anticollagen immunoglobulin (Ig)G_1 and IgG_{2a}, suggesting that SphK-dependent overproduction of S1P is crucially involved in chronic autoimmune conditions and release of proinflammatory cytokines [20]. Mice with global S1P lyase deficiencies have highly elevated S1P levels and exhibit features of an inflammatory state with elevated levels of proinflammatory cytokines [26]. Intracellular roles for S1P have also been suggested and several targets recently identified [17].

In addition to their well-established roles in inflammation and cancer, ceramide [4,27–34] and S1P [28,29,34–42]

Download English Version:

https://daneshyari.com/en/article/2572776

Download Persian Version:

https://daneshyari.com/article/2572776

Daneshyari.com