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Review

Sphingolipids in apoptosis, survival and regeneration in the nervous system

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Abstract

Simple sphingolipids such as ceramide, sphingosine and sphingosine 1-phosphate are key regulators of diverse cellular functions. Their roles in the nervous system are supported by extensive evidence derived primarily from studies in cultured cells. More recently animal studies and studies with human samples have revealed the importance of ceramide and its metabolites in the development and progression of neurodegenerative disorders. The roles of sphingolipids in neurons and glial cells are complex, cell dependent, and many times contradictory. In this review I will summarize the effects elicited by ceramide and ceramide metabolites in cells of the nervous system, in particular those effects related to cell survival and death, emphasizing the molecular mechanisms involved. I also discuss recent evidence for the implication of sphingolipids in the development and progression of certain dementias.

Keywords: Sphingolipid; Ceramide; Apoptosis; Neuron; Sphingosine 1-phosphate; Alzheimer's disease

Contents

Abbreviations: Aβ, amyloid β peptide; A-SMase, acid sphingomyelinase; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DAPK, death associated protein kinase; DIV, days *in vitro*; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GlcCer, glucosylceramide; GSH, glutathione; GSK3, glycogen synthase kinase-3; JNK, c-Jun amino terminal kinase; MAPK, mitogen-activated protein kinase; NGF, nerve growth factor; NOE, N-oleoyl ethanolamine; N-SMase, neutral sphingomyelinase; PNS, peripheral nervous system; PI3K, phosphatidylinositide-3-kinase; PKC, protein kinase C; RA, retinoic acid; ROS, reactive oxygen species; SM, sphingomyelin; SMase, sphingomyelinase; SPh, sphingosine; SPhK, sphingosine kinase; S1P, sphingosine-1-phosphate; $S1P_{1-5}$, sphingosine-1-P receptor 1–5; STP, serine palmitoyltransferase

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1. Introduction

In the past decades major findings have emphasized the significance of sphingolipids as bioactive molecules that control diverse cellular processes such as proliferation, differentiation, growth, senescence, migration and apoptosis. Several lines of evidence, derived mainly from studies using cultured cells, suggest that sphingolipids are also essential mediators of cell growth and stress response in the nervous system.

Ceramide is at the centre of sphingolipid metabolism and has been recognized as a critical second messenger [1]. Ceramide accumulation is a common cellular response to various stimuli such as cytokines, ionizing radiation, heat shock, chemotherapeutic agents, exposure to receptor-specific ligands (TNFα, Fas ligand, 1,25-dihydroxyvitamin D3), and environmental factors such as stress, hypoxia/reperfusion, etc.

This review focuses on the role of ceramide and its immediate metabolites in the regulation of neuronal functions, particularly survival, death and neurite extension. I also discuss the evidence directly implicating these sphingolipids in some neurodegenerative diseases and other disorders of the nervous system. A brief introduction of ceramide synthesis and metabolism is presented although a more detailed discussion is provided by other reviews in this issue.

2. Ceramide metabolism

Ceramides are cellular precursors of more complex sphingolipids namely phosphosphingolipids, glucosphingolipids and galactosphingolipids. With exception of epidermis where ceramides form a barrier for water loss [3], most cells contain very low levels of ceramides under resting conditions. Our observations however indicate that ceramide mass in sympathetic neurons is exceptionally high [2], as it is in cerebellar granule cells (CGC) [4,5]. The implications of high levels of ceramide in neurons are unknown; but neuronal ceramide levels are still susceptible to augment. Numerous cellular stimuli induce transient, or sustained increase in ceramide with variable kinetics. Ceramide levels can reach up to 10 mol% of the total phospholipids [6] emphasizing the bioactive role of ceramide as a signaling molecule. Furthermore, since the formation of ceramide upon stimulation occurs in restricted cellular sites, the local concentration of ceramide could reach and exceed 25 mol % [7].

Ceramide is produced *de novo,* or by hydrolysis of sphingomyelin (SM) (Fig. 1). The pool of ceramide generated from the agonist-induced activation of sphingomyelinases (SMases) has long been involved in the signaling functions of ceramide. This pathway provides rapid increase of cellular ceramide levels in response to diverse stimuli. Comprehensive and extensive reviews of the different SMases and their role in cell signaling have been published [12,14–16]. The role of different SMases in the generation of ceramide in cells of neural origin is discussed below. On the other hand, ceramide generated from the *de novo* pathway has been recognized much later as a second messenger [8–11]. The discovery that many enzymes involved in the metabolism of sphingolipids are regulated in response to cellular stimuli has led to the concept of integrative signaling to explain the contribution of sphingolipid metabolic pathways in cell regulation [12].

Breakdown of ceramide occurs by the action of ceramidases (Fig. 1) [17,18]. Interestingly, some ceramidases can catalyze the reverse reaction and function as a ceramide synthase [19], therefore they can potentially increase ceramide concentration. Sphingosine (SPh) is converted to sphingosine 1-phosphate (S1P) by a family of sphingosine kinases (SPhKs), which are activated in response to stimulation by diverse agonists (see [20–22] for review). S1P is itself a very important bioactive lipid, implicated in several biological processes, often with effects opposed to those of ceramide.

3. Origin of ceramide in neurons and glia

The involvement of the *de novo* or the SM breakdown pathway for ceramide generation in cells from the nervous system depends both on the stimulus and the cell type. The use of specific enzyme inhibitors (Fig. 1) has proven very helpful to discriminate between the two pathways of ceramide production.