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Involvement of sphingolipids in the cell metabolism and various pathologies

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Abstract. Being an essential component of plasma membrane, sphingolipids are bioactive lipids playing key roles in regulation of signaling. Compositions of sphingolipids, sphingolipid metabolism and its regulation in tissues, as well as involvement of sphingolipids in various pathological processes are analyzed in the review.

Keywords: sphingolipids, sphingomyelin, ceramide, sphingosine, acid sphingomyelinase, neutral sphingomyelinase, oxidative stress, cytokines, neurodegeneration

Introduction

Sphingolipids are a specific group of membrane lipids with the long-chain dehydroxyamine structure. They constitute an essential component of plasma membrane mainly locating on its outer surface. Sphingolipids are bioactive molecules crucial for the regulation of signaling. These lipids act not only as signal molecules but also as mediators in major cell processes [1, 2]. Occurring in many living organisms and almost in all types of tissues, sphingolipids take the second place among membranes lipids after phospholipids [3]. The sphingolipid family includes sphingomyelin and glycosphingolipids, to name cerebrosides, sulfatides, globosides and gangliosides [4, 5].

Involvement of sphingolipids in the cell metabolism

For many years, sphingolipids were thought to be membrane lipids. But in the course of the recent intensive studies, sphingolipids, to name sphingomyelin, ceramide, sphingosine, ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P), were

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found to play key roles in the regulation of various signaling pathways [6, 7]. As signaling molecules, the metabolites of sphingolipids regulate the processes taking place in the cell, such as cell proliferation and differentiation, growth, viability, senescence, apoptosis, cell-cell interactions, as well as vascular and endothelial integrity and inflammation [8, 9, 10, 11, 12, 13, 14]. Specific involvement of sphingolipids in the mechanisms underlying cell processes arouses increasing interest of researchers for search and study on their undiscovered aspects.

Sphingolipids are called “bioeffectors” to highlight their multifaceted involvement in the processes taking place in the cell. Sphingomyelin (SPH) and other sphingolipids together with cholesterol form the basis of essential membrane domains called “rafts” and “caveloae” playing significant roles in the cellular signal transduction pathways [15, 16, 17]. As the components of lipid bilayer, sphingolipids impart identity and fluidity to the membrane domains [18, 19]. The enzymes regulating formation and exchange of sphingolipids in cells, to name sphingomyelinases, ceramidases, sphingosine kinases and S1P-liasas are highly sensitive to a number of stimulating factors. Forming as the result of sphingomyelin’s hydrolysis in the presence of sphingomyelinase ceramide is the secondary messenger of the apoptotic receptors’ signaling pathways [20]. These interrelated metabolites are known to interact with the specific target proteins of phosphatases, kinases and G-protein coupled receptors (S1P-receptors) [21].

There are three pathways of sphingolipid metabolism: the *de novo* pathway formed by the saturated fatty acids, the salvage pathway and the SPH pathway; ceramide is the central molecule in sphingolipid metabolism as all the pathways converge at the ceramide focus (Fig.1).

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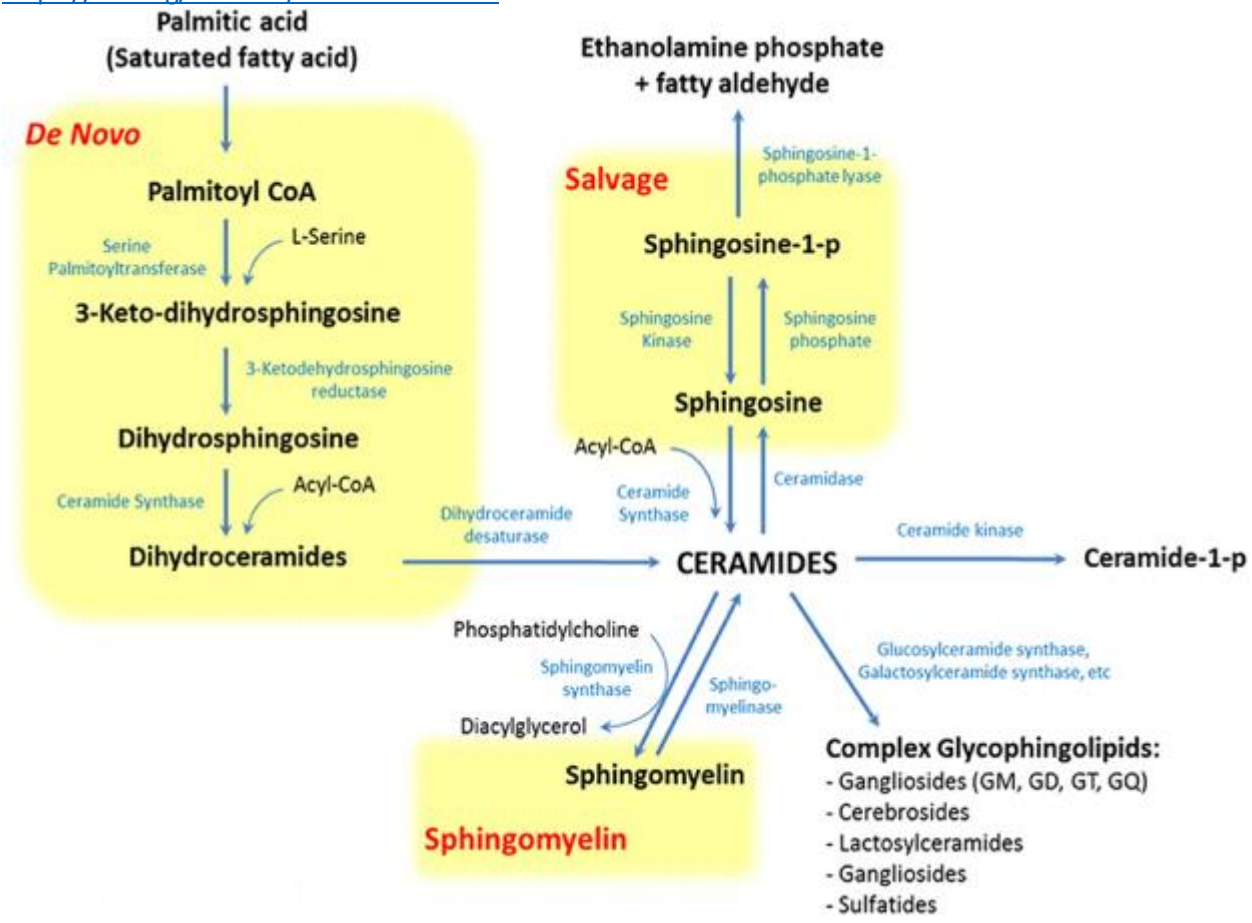

Figure 1. Essential metabolic pathways of sphingolipids [22].

Sphingomyelin (SPH) is a type of sphingolipid consisting of a phosphocholine head group, a sphingosine and a fatty acid. It is an essential plasma membrane component in the animal cells. The SPH hydrolysis in the plasma membrane catalyzed by sphingomyelinase is called sphingomyelin cycle triggering formation of ceramide in its turn converting into sphingosine. Ceramide is phosphorylated into ceramide-1-phosphate (Cer-1-P) by ceramide kinase (Cer-K) while a sphingosine is phosphorylated into sphingosine-1-phosphate (Sph-1-P) by sphingosine kinase (SK) [23]. As endogenous bioactive compounds, sphingolipids contain a backbone of sphingolipid bases, a set of aliphatic amino alcohols that includes sphingosine being a secondary messenger or a non-cellular modulator of cell proliferation and apoptosis [24]. In cells of the mammalians, SPH synthesis takes place in the Golgi complex

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where ceramide transported from the endoplasmic reticulum (ER) is modified by transfer of phosphocholine molecule from phosphatidylcholine to ceramide, the reaction is catalyzed by sphingomyelin synthase (SMS) [25]. Ceramide is formed upon SPH hydrolysis in the presence of sphingomyelinase (SMase) [26].

Ceramide (Cer) is a key molecule in the sphingolipid metabolism. Ceramides are formed by means of the SPH hydrolysis by SMase, as well as by the *de novo* synthesis in the endoplasmic reticulum initiated by serine-palmitoyltransferase (SPT) and the recirculization of sphingosine via ceramide synthase (CerS). SPH is a basic sphingolipid in the formation of ceramide, sphingosine, S1P and other sphingolipids. Some SPH metabolites act as the intracellular messengers, while others are the essential components of biomembranes.

Ceramide is a product forming as a result of interaction of sphingosine and fatty acids. Ceramide molecule consists of two fragments, to name sphingoid base with the amide bond and fatty acid residue [27]. Ceramide is a center of metabolic pathway of sphingolipids; it is synthetized *de novo* with involvement of L-serine and palmitoyl CoA by hydrolysis of sphingomyelin or glycosphingolipids and sulfatides. At the same time, ceramide can be synthetized from sphingomyelin under effect of sphingomyelinase or from ceramide-1-phosphate under effect of ceramide-1-phosphatase. Ceramide is catabolized to sphingosine, as well as to ethanolamine-1phosphate and C16 aldehydes of fatty acids [28].

Sphingosine is a primary component of other sphingolipids, including sphingomyelin. It is the most widely spread sphingoid base. Free sphingosine is formed as a product of ceramide hydrolysis by ceramidase involved in the cellular signaling [29]. Obtained from food, sphingolipids are hydrolyzed to ceramides and long-chain structures in the intestinal tract to be absorbed and participate in the metabolic process. A breakdown product of sphingomyelin, sphingosine easily penetrates lysosomal membrane. Non-lysosomal degradation of sphingomyelin can

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take place under effects of membrane-bound hydrolases in the neutral or basic conditions. Pivotal roles of sphingolipid metabolites can be seen in Figure 2.

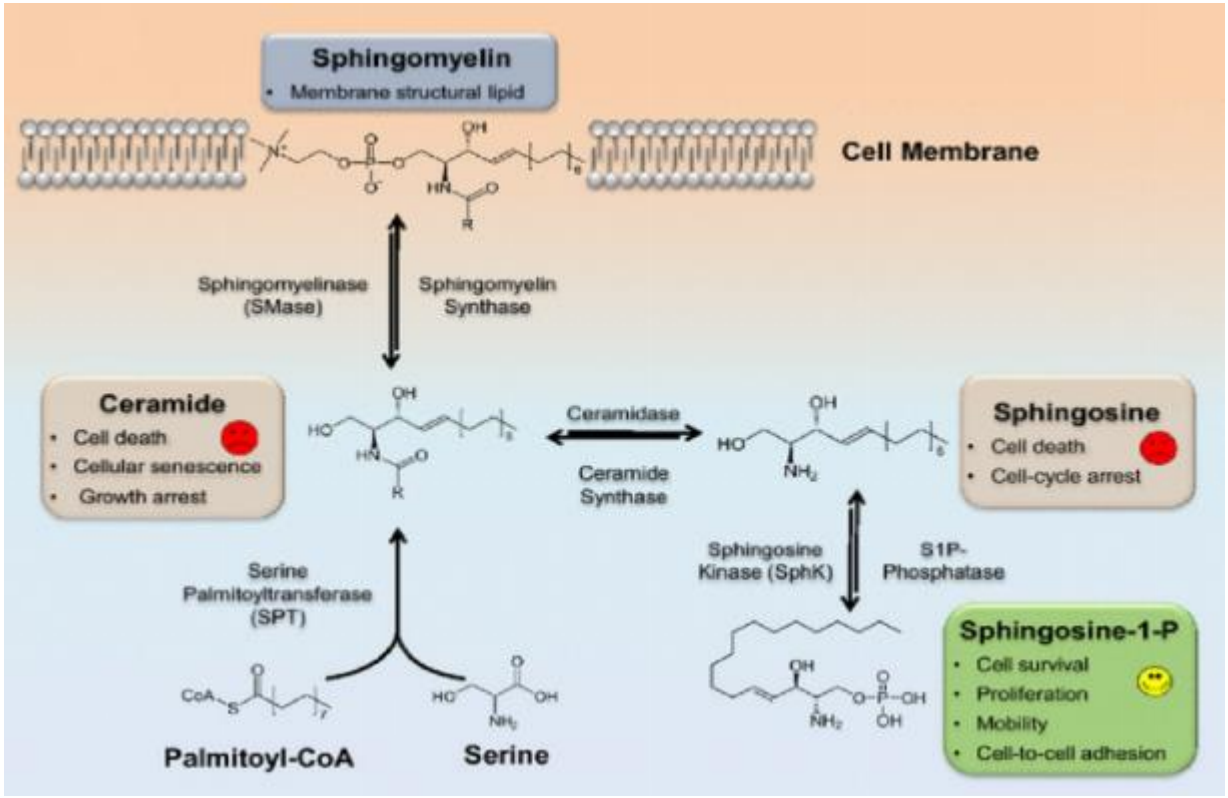

Figure 2. Metabolism and biological significance of sphingolipids [7].

As it can be seen, sphingomyelin and its metabolites participate in the pivotal biological functions of the cell. Thus, ceramide causes cell death, as well as cellular senescence and arrest of growth. Similar to ceramide, sphingosine causes cell death and cell cycle arrest. In contrast to ceramide and sphingosine, sphingosine-1-phosphate (S1P) is essential for cell survival, proliferation, mobility and cell-to-cell adhesion. In addition to its crucial role in cell proliferation and viability, S1P is of special significant for chemotaxes, adhesion, angiogenesis, intracellular calcium homeostasis and formation of cytoskeleton [30].

Regulation of sphingolipid metabolism in tissues

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Regulation of sphingolipid metabolism depends on multiple factors having impacts on the activity of sphingomyelinases (SMases) increasing under effect of various cytokines, irradiation, apoptosis and cancer treatment [31]. In organisms of the mammalians, three classes of sphingomyelinases, to name acid, neutral and alkaline ones, were identified. These enzymes differ by pH values and places of distribution [32, 33]. Sphingomyelin breakdown in the plasma membrane proceeds with participation of neutral and acid SMAses to result in the formation of ceramide and phosphocholine [34, 35, 12]. The process is catalyzed by a group of SMAses; ceramide and phosphocholine form due to the destruction of the phosphodiester bond [36].

Acid sphingomyelinase (aSMase) is a lysosomal enzyme, a glycoprotein with pH of 5.0 catalyzing hydrolysis of sphingomyelin into ceramide and phosphocholine, participating in the sphingolipid metabolism and playing a significant role in the maintenance of normal levels of sphingomyelin and ceramides [37, 38, 39, 40]. Mg2+-dependent neutral sphingomyelinase (nSMase) is a mediator of the stress-induced production of ceramides [41]. The involvement of nSMase in the intracellular signaling and in pathogenesis of some neurological diseases has been proved [42]. SMases are active in lysosomes, cytosol, mitochondria, plasma membrane, the nuclei and nuclear matrix, the Golgi complex and organelles, to name endoplasmic reticulum. As the result of the SMases activation in the lipid rafts, SPH and its metabolites are transferred from the cell membrane to the lysosome. The higher expression of the alkaline and acid ceramidases and serine-palmitoyltransferase (SPT) could be seen *in vivo* in *ob/ob* mice with hereditary obesity and diabetes. This was observed to result in the accumulation of ceramide and spinhgosine-1-phosphate in the samples of adipose tissue as compared with those taken from the lean animals [43].

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Sphingolipids are the mediators of biological effects produced by a number of cytokines, particularly, of the tumor necrosis factor- α (TNF-α) and interleukins (ILs). These processes are based on the involvement of sphingolipids in the transduction and transformation of the cell signal [4]. Direct effect of the inflammatory cytokines, such as TNF-α and IL-1 on the cell lines of hepatocellular carcinoma was found to stimulate the expression of SPT providing direct mechanistic association between inflammation and sphingolipid synthesis [44]. The platelet growth factors and inflammatory cytokines, such as TNF-α activate sphingosine kinase and accelerate formation of S1P which in its turn provides cell viability and inflammatory responses [45]. In addition, TNF-α was established to accelerate *de novo* ceramide synthesis due to fast increase of aSMase overnight [46, 47]. Studies on the cultured myocytes demonstrated that even the slight increase in the ceramide concentrations in the culture medium resulted in the suppression of signaling and action of insulin [48, 49]. It can be concluded that even slight changes in the sphingolipid concentrations could result in the onset and progression of severe complications. The oxidative stress, cytokines and various pathogens activate aSMse and nSMase in some compartments to result in the production of ceramides [21]. Ceramide, phytosphingosine, sphingosine, sphinganine and their appropriate phosphates are the regulatory molecules at the same time determining functional activity of the cell in the normal and pathological conditions [50].

Involvement of sphingolipids in various pathological processes

Impaired catabolism of sphingolipids underlies many human diseases. Sphingolipidoses or disorders of sphingolipid metabolism are the diseases considered as the hereditary ones causing accumulation of some lipids in some tissues or organs and having a particular impact on neural tissues [51]. Consequently, the significance of sphingolipids as the predicative biomarkers in the pathogenesis of various diseases is intensively studied [52].

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Gaucher's disease results from the deficiency of acid β-glucosidase, a lysosomal enzyme responsible for the intralysosomal catabolism of its natural substrate, glucosyl-ceramide. The changes take place in special micro-domains of membranes called lipid rafts due to accumulation of glucosyl ceramide. Lipid rafts are crucial for adequate transduction of insulin signaling; the imbalance results in the onset of insulin resistance in patients with Gaucher's disease due to disorders in the insulin signaling [53].

Within the last decade, relatively simple sphingolipids, to name ceramide, sphingosine, sphingosine-1-phosphate and glucosyl ceramide were found significantly involved in the functions of neurons, regulating the neurons' growth and differentiation. Homeostasis of membrane sphingolipids in neurons and myelin is essential for prevention of synaptic plasticity loss, cell death and neurodenegeration [54]. Sphingolipids are the integral component of the brain cell membranes necessary for normal homeostasis and functioning of neurons. Neuronal transduction of signals with involvement of ceramide is mainly associated with inflammation, formation of free radicals and oxidative stress, as well as with dysregulation of calcium and damage of lysosomes [55, 56]. Products of ceramide metabolism, such as glucosyl- and lactosyl ceramides, stimulate cell proliferation inhibiting apoptosis [57]. Even slight changes in the balance of sphingolipids are significant for the onset of neurodegenerative diseases, particularly, of Alzheimer disease [58]. In Alzheimer disease, sphingomyelinase induces apoptosis in the neuronal cells triggering formation of pro-apoptotic molecule of ceramide [59].

Consequently, a number of studies were conducted to reveal alterations in sphingolipid metabolism in the brain cells in Alzheimer disease [58, 60, 26]. In Alzheimer disease, expression and activity of enzymes involved in S1P metabolism resulting in the decrease of the S1P concentrations can be seen [61, 62].

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Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system mainly affecting the motor system. It affects 1-2% of people older than 65 years and 5% of people older than 85 years of age [63]. Sphingolipids were found to be involved in the onset and progression of the disease. Higher concentrations of mono- hexosyl ceramide, lactosyl ceramide and sphingomyelin were found in the samples of postmortem brain tissues [64]. A group of researchers suggested that Imipramine, a tricyclic antidepressant mainly used in the treatment of depression and anxiety, could reduce the death of neurons in the hippocampus by inhibition of activity of aSMase [55]. The findings from the study demonstrated that activity of aSMase could be inhibited by reduction in concentrations of ceramide. The increase in the concentrations of ceramide causes dysfunction of endothelial barrier [65]. S1P is a barrier-protective agent responsible for integrity of the vascular barrier [66, 67]. With aging, the sensitivity of the liver cells to insulin sharply declines. Ceramides with the increase of their concentrations in a human organism with aging are essential in progression of hepatocytes' resistance to the effects of hormones. Activation of the *de novo* process of ceramide synthesis was demonstrated to be one of the causes for decline of cells' sensitivity to insulin [68]. With aging, products of metabolism were established to accumulate in the cell gradually destroying it.

Ratio of ceramides, cholesterol and long-chain aliphatic fatty acids (2:1:0.75) is the most significant normative indicator of the skin's health [69, 70]. Violation of the ratio triggers pathological processes in the skin.

In addition, in sclerosis inflammatory cytokines and oxidative stress are the potent activators of sphingomyelin cycle in oligodendrocytes. Increase in the concentrations of ceramides causes suppression of the signal pathways responsible for transduction of hormonal signals sometimes resulting in the onset of insulin resistance [71]. In addition, proliferation of aortic smooth muscle cells (ASMCs) under effect of lactosyl ceramide may cause exacerbation of atherosclerosis. On the

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other hand, cell apoptosis with involvement of the inflammatory cytokines, TNFα, interleukin-1 and low density lipoproteins (LDL) may occur by means of activation of membrane-coupled nSMase. Antibodies to nSMase may block apoptosis induced by LDL and TNFα and, thus, be instrumental in studies of apoptosis *in vivo* in experimental animals [72]. Ceramide was established to significantly reduce levels of resynthesized lipids in hepatocytes, as well as synthesis of phosphatidylcholine and phosphatidylethanolamine from major phospholipids of biological membranes [73]. Ceramide inhibits transduction of insulin signals and destroys pancreatic β-cells to finely result in the onset of diabetes mellitus.

Conclusion

Presently, there is a clear understanding of significance the sphingolipid synthesis pathways and mechanisms of control for their metabolism have. Worldwide, a lot of studies center on significance of sphingolipids in pathogenesis of various diseases, including obesity, insulin resistance, metabolic syndrome, diabetes mellitus and neurodegenerative disorders.

Further studies on molecular mechanisms underlying sphingolipid metabolism impairment in human organism in various pathologies are promising in view of search for new ways of correction of these pathological processes and generation of novel medications.

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