OVERVIEW OF CONCEPTS OF THE SPHINGOLIPID METABOLISM

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Sphingolipids are important components of the cell involved in the processes of apoptosis, inflammation, oncogenesis, aging, proliferation, differentiation and growth of cells, as well as in the stress-induced response of cells.

The aim. To study research literature for summarizing the new concepts of sphingolipids biochemical role in the development of various pathological conditions.

Materials and methods. The open sources of scientific literature were analyzed.

Results and discussion. According to the analyzed data, the occurrence of pathologies is associated with the sphingolipid imbalance in cells, and excessive accumulation of ceramides, while by preventing the accumulation of ceramides in cells, it is possible to prevent the appearance of cardiac, neurological and metabolic pathologies, including insulin resistance, heart disease (atherosclerosis, heart failure), as well as hepatic steatosis. Therefore, it is promising to search for drugs that can inhibit individual components of the metabolism of sphingolipids and prevent the development of pathology.

Conclusions. Sphingolipids are involved in numerous processes in cells, and changes in the balance of individual members of this class of lipids can play a crucial role in the development of pathological conditions. At the same time, the accumulated data on disorders of the sphingolipid metabolism in various diseases contribute to the development of drugs based on inhibition of the corresponding components of the metabolism of these lipids.

Keywords: sphingolipids, ceramides, mitochondria, apoptosis, insulin resistance, viruses

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1. Introduction

Sphingolipids are important components of many biological processes in the cell. In recent years, the focus of research on these lipids has changed dramatically several times. Thus, for a long time sphingolipids were considered simply structural components of eukaryotic cell membranes. Then the results of research showed that some sphingolipids are crucial for many cellular processes as bioactive molecules and secondary messengers [1]. In addition, it was found that some representatives of this class of lipids have signalling properties, their role was determined in the stress-induced response of cells [2], apoptosis [3], processes of proliferation, differentiation and growth of cells, inflammation [4], oncogenesis [5, 6] and aging [7, 8]. The critical role in the regulation of cellular processes through the signalling sphingomyelin pathway belongs to ceramide, which as a secondary messenger has antiproliferative properties, regulates the phosphorylation of various proteins and is an inducer of apoptosis [2]. It is known that the level of ceramide in cells increases significantly under conditions of natural aging. Thus, a number of studies have shown the accumulation of ceramide and an increase in the ratio of ceramides / sphingomyelin in the cells of an aging organism [8, 9]. Recently, ceramides have been in the spotlight of scientists due to their role in various pathophysiological processes underlying cancer [10, 11], inflammation [4, 12], depression [13] and neurodegenerative disorders [14], given Alzheimer’s disease and dementia. In addition, later studies have highlighted their importance in obesity and diabetes [15, 16], as well as in cardiovascular disease [17]. It is suggested that the development of pathologies is associated with imbalance of sphingolipids in cells and excessive accumulation of ceramides, while preventing the accumulation of ceramides in cells may prevent the emergence of cardiac and metabolic pathologies, including insulin resistance, cardiovascular disease, atherosclerosis hepatic steatosis [18, 19]. At the same time, insufficient production of ceramide, known as Niemann-Pick syndrome, is caused by mutations in the acid lysosomal sphingomyelinase SMPD1 gene, which makes it impossible to convert sphingomyelin to ceramide [20]. It was also found that disorders of sphingolipid metabolism could directly or indirectly affect the functioning of mitochondria, provoking dysfunction of these organelles. In addition to the specific effects of ceramide outlined above, it is worth noting the central role of this lipid in the development of stress reactions in the cell. Ceramide is thought to coordinate the response to stress in a cell whose mechanism is universal for various eukaryotic organisms. However, sphingolipids perform various functions both at the level of the viral life cycle and in the regulation of antiviral immune responses [21, 22]. Such numerous and diverse
effects of sphingolipids lead to increased interest of scientists in this group of lipids and enzymes involved in their metabolism, as potential targets for the development of new therapeutic agents.

**The aim.** To investigate scientific literature sources to formulate the latest views on the biochemical role of sphingolipids in the development of various pathological conditions.

2. Materials and methods

The study is devoted to the analysis of open sources of scientific literature using the scientific base PubMed.

3. Research results

3.1. Sphingolipids as components of cell membranes

Sphingolipids are important components of cell membranes, and sphingomyelin is a structural lipid of the membrane bilayer, and its metabolites and precursors perform both structural and signalling functions [2, 23]. Ceramide is a metabolite of sphingomyelin and not only structures membrane clusters around the transmembrane protein, forming shelves, but also acts as a secondary mediator of signalling cascades, primarily related to the regulation of viability [2]. Ceramides are essential to ensure the structural integrity of plasma and mitochondrial membranes. Moving the ceramide molecule between the outer and inner surfaces of the membrane (flip-flop transitions) can change the configuration of the membranes and the affinity of the proteins to the membrane, which in turn affects the activity of membrane enzymes. It was found that a sharp increase in ceramide content in cells during the action of various toxic substances causes the activation of a number of signalling pathways (ERK, p38) involved in the implementation of apoptosis, and precedes the development of inflammatory reactions and cell death in various tissues [11]. Thus, mitogen-activated protein kinase p38 is involved in ceramide-induced cardiomyocyte apoptosis [24]. Biologically active sphingolipids can inhibit a number of molecules involved in the transmission of hormonal signals in cells such as Akt / protein kinase B and phospholipase D. In addition, ceramides synthesized in the endoplasmic reticulum can penetrate the mitochondria through membrane contacts and increase membrane permeability to cytochrome-c and adenylate kinase [25].

Other sphingolipids, such as sphingosine and sphingamine, also function as proapoptotic factors, so it is believed that the balance between ceramide, sphingosine-1-phosphate and other proapoptotic sphingolipids is critical in the regulation of ceramide-induced programmed. Thus, sphingosine and ceramide induce cell cycle arrest and are involved in receptor-dependent apoptosis, whereas sphingosine-1-phosphate helps maintain cell viability during division by inhibiting differentiation [26].

In addition, different molecular species of ceramide differ in intracellular localization and biological effects [27]. Short-chain artificially synthesized ceramides (D-erythro-N-acetylphosphoglycerine and N-hexanoyl-D-phosphoglycerine) are thought to penetrate cells more easily and cause a greater toxic effect than long-chain natural analogues synthesized in the endoplasmic reticulum. These observations allow the use of short-chain ceramides in the treatment of some forms of cancer [9, 10].

3.2. The effect of sphingolipids on mitochondria

In most cell types, one of the key events in apoptosis is the release of proapoptotic proteins from the mitochondria into the cytoplasm. A detailed study of the mechanisms of apoptosis revealed that this process is facilitated by the formation of ceramide channels in the outer membrane of mitochondria [3]. It is known that ceramide, which is part of the plasma membrane, is important for its structural and functional organization. In addition to its structural function, ceramide can act as a secondary mediator in the transmission of various signals and has a high regulatory weight in apoptosis, inducing the release of proapoptotic proteins from mitochondria [3, 25].

Recently, many studies have emerged that suggest a strong relationship between ceramide metabolism, mitochondria, and separate mitochondria as a specialized compartment of sphingolipid metabolism with its own subpopulation of synthesizing and metabolizing ceramide enzymes. Thus, the detected content of various sphingolipids in mitochondria, taking into account sphingomyelin and ceramides [25], involves the creation of ceramide directly in these organelles. Subsequent studies of the sub mitochondrial activity of ceramide synthase have shown that ceramide can be synthesized on both the outer and inner membranes of mitochondria [28]. Recent studies characterize some isoforms of ceramides synthases (CerS1, CerS2, CerS4, and CerS6) in isolated mitochondria from mouse brains [29]. This also suggests that the synthesis of some ceramide-forming enzymes must be localized in the mitochondria. In addition, selective hydrolysis of the mitochondrial pool of sphingomyelin to form ceramide during the action of bacterial sphingomyelinase on the mitochondria causes apoptosis. Conversely, the generation of ceramides in the plasma membrane, endoplasmic reticulum, or Golgi apparatus during the action of sphingomyelinase on these cell compartments has no effect on cell viability. Undisputed evidence of the involvement of the mitochondrial pool of ceramide in apoptosis has been demonstrated in Caenorhabditis elegans nematode cells, where apoptosis induced by ionizing radiation was stopped by ceramide synthase inactivation and restored by microinjection of long-chain ceramides [30].

Indirect modulation of the functional state of mitochondria by ceramides may be mediated by a change in the ratio of pro- and antia apoptotic proteins of the Bcl-2 family on the outer surface of the mitochondrial membrane. The direct effect of ceramide on mitochondria is possible due to the formation of channels for the release of cytochrome-c in the outer membrane of mitochondria, the opening of mitochondrial pores in the inner membrane of these organelles in the presence of Ca²⁺, as well as due to the activation of Bax on the outer membrane of mitochondria or suppression of the respiratory chain with the subsequent accumulation of reactive oxygen species. It has now been shown that ceramide can directly or indirectly affect the respiratory chain [23, 25, 29], causing severe suppression of the initial stage of the respiratory chain. Inhibition of the main flow of electrons in the respiratory chain stimulates the formation of reactive oxy-
gen species, firstly, by increasing the lifetime of reduced electron transporters at the beginning of this chain and, secondly, by increasing intracellular oxygen concentration, which is no longer reduced by cytochrome oxidase. Stimulation of the formation of reactive oxygen species in the mitochondria causes the opening of the mitochondrial pore and the launch of a subsequent cascade of apoptosis.

3.3. Sphingolipid metabolism and insulin resistance

The role of ceramides in the pathogenesis is determined not only by their participation in apoptotic signaling, but also in the work of other regulatory signalling cascades in the cell. It is known that ceramide can act on various components of the insulin signalling cascade and lead to impaired insulin function [31]. When synthetic analogues of ceramide (C2-ceramide, C6-ceramide) are added to cell culture, insulin-stimulated glucose uptake, translocation of glucose transporters, and/or glycerogen synthesis are inhibited. In the culture of muscle cells, adipocytes and hepatocytes, synthetic C2 and C6-ceramides inhibit the activation of Akt / PKB, which underlies the rapid effects of glucose uptake and anabolic metabolism [32]. Ceramide suppresses this signalling step by two independent mechanisms. First, ceramide enhances dephosphorylation of Akt / PKB by direct activation of protein phosphatase 2A, which is responsible for dephosphorylation of protein kinase C. Second, ceramide inhibits the translocation and activation of Akt / PKB by activating PKCζ, which phosphorylates Akt / PKB by an inhibitory residue contained in the pH domain of the enzyme [33]. In addition, ceramide inhibits phospholipase D, an integral part of insulin-stimulated glucose metabolism. Thus, on human umbilical vein endothelial cells and human diploid fibroblasts, it was found that during the physiological aging of cells there is an increase in ceramide content, which is accompanied by impaired interaction of phospholipase D with PKCζ and/or ARF, as well as a significant decrease in phospholipase D activity [34].

Ceramide inhibits glycogen synthesis by inducing dephosphorylation and inhibition of Akt / PKB and preventing protein kinase translocation into the plasma membrane. Ceramide has been shown to enhance the phosphorylation of Thr-563/560-PKCζ / λ, thereby mimicking the action of insulin and phosphatidylinositol 3,4,5-triphosphate (a product of PI3 kinase) on aPKC in the liver of mice [35]. Moreover, C6-ceramide (but not its inactive analogue dihydro-C6-ceramide) induces PKCζ activity and also causes a selective enhancement of the association between Akt and PKCζ [36]. C6-ceramide, like C2-ceramide, does not alter Akt phosphorylation in unstimulated cells and in cells, expressing dominant negative PKCζ, and reduces Akt phosphorylation in platelet-stimulated cell growth cells. These data suggest that ceramide-mediated excess activation of PKCζ leads to a decrease in Akt phosphorylation.

Thus, given the data of numerous studies, increasing the level of ceramides in morphologically and functionally different types of cells and tissues is a universal process in the development of metabolic syndrome, diabetes, cardiovascular and neurodegenerative diseases. Ceramides are involved in regulating the activity of key molecules involved in the insulin-signalling cascade. At the same time, the question remains as to the role of ceramide in the regulation of changes in insulin-dependent activation of phospholipase D in old age, both in classical targets of the hormone and in new ones, such as nervous tissue.

3.4. Sphingolipids and viruses

In addition to their important role in various processes in the cell, sphingolipids and their metabolites are potential key regulators of the life cycle of intracellular pathogens such as viruses. The role of sphingolipids and glycosphingolipids has not been considered for many years in the presence of viral infection due to difficulties in detecting or measuring these lipids. However, with the advent of lipid mass spectrometry, it has become possible to accurately determine the level of sphingolipids and glycosphingolipids in virus-infected cells and virus particles. Thus, Martin-Acebes and colleagues [37] proved that the particles of West Nile virus were enriched in spongomyelin. At the same time, pharmacological inhibition of the activity of neutral sphingomyelinase (the enzyme that converts sphingomyelin to ceramide and phosphorylcholine) reduced the release of the virus from infected cells [37]. These data suggest that ceramide, which is formed due to catabolism of spongomyelin, is critical for the life cycle of West Nile virus. A number of studies have indicated that viruses can use sphingolipids and/or glycosphingolipids to penetrate target cells, replicate their genome, or form new virus particles enriched in these lipids [21, 22, 38–40].

Sphingolipids can affect virus replication in three ways: 1 – acting as receptors during virus penetration; 2 – modulating virus replication and 3 – forming an antiviral immune response. Several studies have shown that sphingosine kinases and their sphingosine-1-phosphate product enhance the replication of influenza, measles, and hepatitis B virus. In contrast, ceramides, sphingosine 1-phosphate, and sphingosine kinase-1 affect the expression of interferon and increasing the maturation, differentiation and location of dendritic cells in the tissue. It was also found that the synthetic molecule α-galactosylceramide stimulates the activation of natural killer cells and the secretion of interferon-γ [21, 22, 38]. Ceramide directly activates several enzymes and forms large, highly hydrophobic ceramide-enriched membrane domains that serve to reorganize receptors and signalling molecules [39, 40].

Thus, pharmacological inhibitors of the metabolic pathways of sphingolipids and glycosphingolipids have the potential to develop drugs with a broad spectrum of antiviral activity. Thus, it was found that pharmacological inhibition of acid sphingomyelinase by amitrityline, imipramine, fluoxetine, sertraline, escitalopram, maprotiline or genetic reduction of the activity of this enzyme prevents infection of cultured cells or isolated human nasal epithelial cells with SARS-CoV-2 coronavirus and vesicular stomatitis virus [39]. In addition, the administration of anti-ceramide antibodies or neutral ceramidase also shows a significant protective effect in the case of SARS-CoV-2 infection. Anticeramide antibodies and neutral ceramidase are not currently approved for clinical use, but the authors believe that after clinical trials, drugs based on these inhibitors can be used as a nasal spray to prevent infections [39].
4. Conclusions

1. Sphingolipids, in particular ceramides, are involved in numerous cellular processes, and changes in the balance of individual members of this class of lipids can be crucial for the development of pathological conditions.

2. Many studies indicate a strong relationship between the metabolism of ceramide, sphingomyelin and mitochondria. It has been established that ceramide can modulate the functional state of mitochondria directly and indirectly. Thus, ceramide can directly or indirectly affect the respiratory chain, causing severe depression of the initial stage of the respiratory chain. In addition, the accumulation of ceramide in cells promotes the formation of channels in the mitochondrial membrane and the release of pro-apoptotic proteins to the cytoplasm.

3. Sphingolipids affect various components of the insulin-signalling cascade, so it was found that ceramide inhibits insulin-stimulated glucose uptake, translocation of glucose transporters and glycogen synthesis. Ceramides exert their effects on glucose metabolism by inhibiting the activation of Akt/PKB and phospholipase D in insulin target cells.

4. The content of ceramide in the cells of various tissues is significantly affected by the activity of enzymes of the sphingomyelinase group, and a number of studies indicate the leading role of the lysosomal pool of sphingomyelinas, the so-called acid sphingomyelinas. Thus, an increase in the activity of acid sphingomyelinas in various tissues of the aging body and in the presence of pathologies. At the same time, inhibition of the activity of acid sphingomyelinas by their excessive activation can have a number of therapeutic effects in the treatment of some pathological conditions and prevent virus infection.

Conflict of interests

The authors declare that they have no conflicts of interest.

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