

Sphingolipid Catabolism

Subjects: **Cardiac & Cardiovascular Systems**

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In the plasma membrane and other cellular compartments (endosome/lysosome), sphingomyelin can be hydrolyzed to ceramide by sphingomyelinases. Ceramide generated by this pathway is further degraded into sphingosine by ceramidases. Sphingosine can also be phosphorylated by sphingosine kinases to sphingosine-1-phosphate. Changes in the profiles of sphingomyelin and its metabolites ceramide, sphingosine, and sphingosine-1-phosphate (S1P) can result in a pathological condition triggered by accumulation or by altering cell signaling.

diabetes

angiotensin II-induced hypertension

sphingomyelin

1. Introduction

1.1. Sphingolipid Metabolism

In the anabolic pathway, sphingolipids synthesis begins in the endoplasmic reticulum with the condensation of L-serine and palmitoyl coenzyme A (CoA) to form 3-ketosphinganine by serine palmitoyltransferase. Subsequently, 3-ketosphinganine reductase is responsible for reducing 3-ketosphinganine to sphinganine, which can be acylated to form dihydroceramide by ceramide synthase. Finally, dihydroceramide is oxidized by a desaturase, which results in ceramide formation ^{[1][2][3]}. Ceramide is transported from the endoplasmic reticulum to the Golgi apparatus and is converted into sphingomyelin by sphingomyelin synthase or glycosphingolipids by ceramide glucosyltransferase. Sphingomyelin and complex glycosphingolipids can be transported to the plasma membrane (**Figure 1**) ^{[3][4]}.

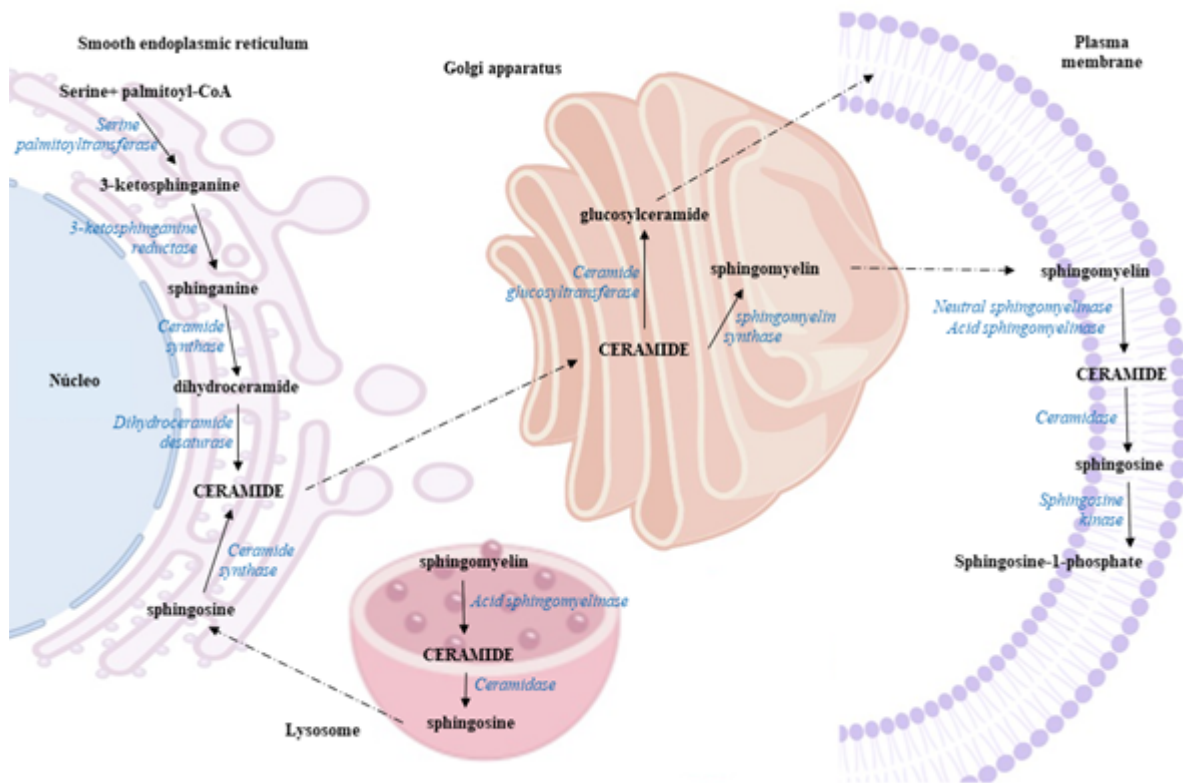


Figure 1: Sphingolipids metabolism in the cells

In the plasma membrane and other cell compartments, the sphingomyelin can be hydrolyzed by sphingomyelinases (SMases) and release ceramide. Ceramide can be hydrolyzed by ceramidases (CDases) to form sphingosine, which can be phosphorylated by sphingosine kinase (SK) to generate sphingosine-1-phosphate (S1P) (Figure 1) [3][5][6][7][8][9]. S1P can be cleaved by the S1P lyase to a fatty aldehyde and phosphoethanolamine [10]. Alternatively, S1P can be dephosphorylated back to sphingosine by phosphatases [11]. S1P can act as an intracellular second messenger or an extracellular ligand [12][13].

1.2. Classification of Sphingolipid Catabolism Enzymes

According to the optimal pH for their activity, SMases are classified into acid, neutral, and alkaline. aSMase can be subclassified based on their cellular location into lysosomal aSMase (L-SMase) and secretory aSMase (S-SMase) [5][6]. Ceramidases also have been classified according to their optimal pH in acid, neutral, and alkaline [7][8]. Two isoforms of sphingosine kinases (SKs) have been identified, sphingosine kinase-1 and sphingosine kinase-2 [9].

1.3. Genetic Diseases of Sphingolipid Catabolism Enzymes

Types A and B Niemann Pick disease is caused by aSMase deficiency, which leads to organ dysfunction due to the accumulation of sphingomyelin in various organs. Niemann Pick disease is inherited as recessive traits [14]. Farber disease is a lysosomal storage disorder, it is caused by mutations in the gene that encodes to aCDase, which lead to decreased aCDase activity and in turn, to ceramide accumulation and various pathological manifestations. Farber disease is inherited in an autosomal recessive manner [15].

1.4. Sphingolipid Catabolism Enzymes as Therapeutic Targets in Cardiovascular Diseases

Numerous human studies have shown that, in cardiovascular, renal, and metabolic diseases, the profiles of sphingomyelin [16][17][18][19] and its metabolites ceramide [20][21][22][23][24][25][26], sphingosine [27], and sphingosine-1-phosphate (S1P) [28][29] are altered (reduction or elevation) in the plasma, organs (liver and heart), and tissues (skeletal muscle and adipose). Most of these studies focused on the determination of ceramide in plasma. However, it is necessary to perform preclinical studies to determine the content of sphingomyelin and its bioactive metabolites in plasma and organs such as the brain, liver, heart, and kidney, because the sphingolipid metabolism imbalance can be affected directly or indirectly in various organs.

Changes in the expression or activity of the enzymes that participate in sphingolipid metabolism may explain the alterations in their profile. Concerning the expression at the mRNA level of the enzymes involved in the synthesis (serine palmitoyltransferase) and degradation of ceramide (SMase, CDase, and SK-1), the levels of these enzymes were increased in intra-abdominal adipose tissue and the myocardium of obese patients with or without type 2 diabetes [30][31]. Regarding enzyme activity, secretory SMase activity increased in the serum of patients with type 2 diabetes, chronic heart failure, or acute coronary syndromes [32][33][34]. In the adipose tissue of obese non-diabetic or diabetic patients, the activity of serine palmitoyltransferase, neutral and acid CDase (nCDase and aCDase) was increased, while the aSMase activity was decreased [22].

Changes in the profiles of sphingomyelin and its metabolites ceramide, sphingosine, and sphingosine-1-phosphate (S1P) can result in a pathological condition triggered by accumulation or by altering cell signaling. Therefore, drugs that modify the expression or activity of the enzymes involved in sphingolipid metabolism are attractive candidates for the treatment of cardiovascular, renal, and metabolic diseases.

Researchers evaluated the sphingomyelin content and its metabolites in two experimental models: diabetic and hypertensive rats. The results show that, in the plasma and liver of diabetic rats, sphingomyelin is increased; in the heart, ceramide; and in the kidney, S1P. Moreover, increased sphingomyelin was observed in the plasma and all evaluated organs of hypertensive rats, as well as increased ceramide and sphingosine in the heart, and increased S1P in the plasma, kidney, and heart (**Figure 2**).

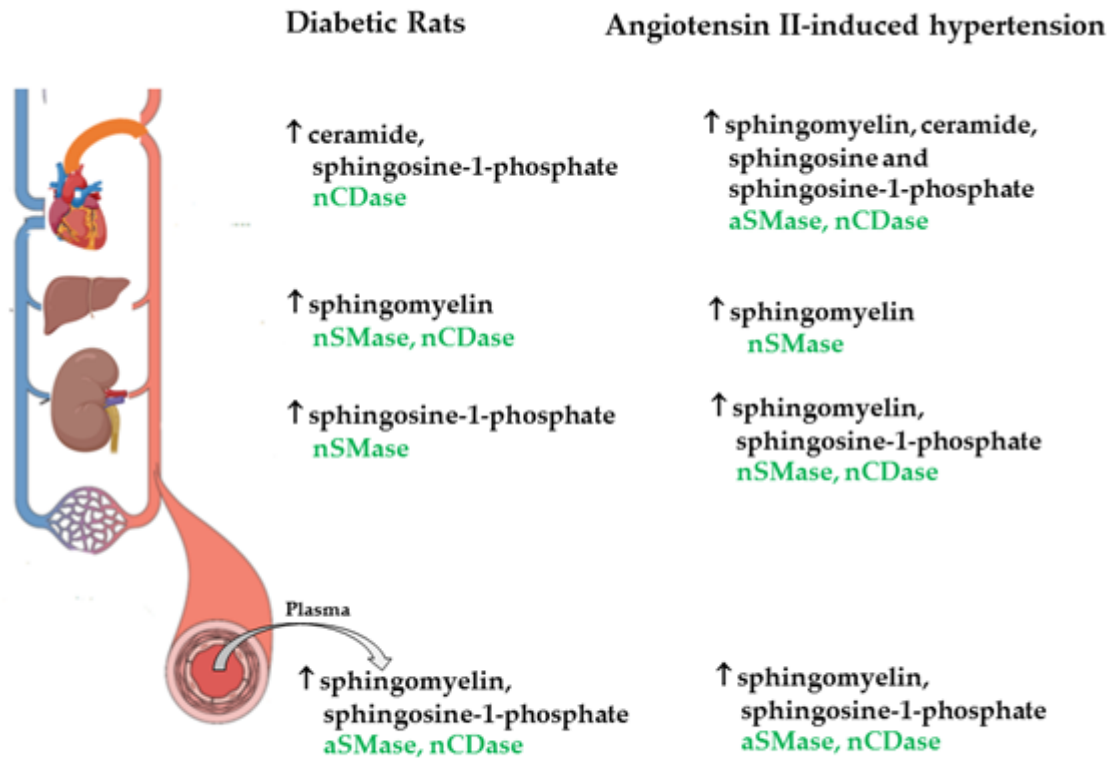


Figure 2: Sphingomyelin content and its metabolites as well as activity of the enzymes that participate in sphingolipid metabolism in two experimental models: diabetic and hypertensive rats.

The results suggest that empagliflozin downregulates the interaction of the de novo pathway and the catabolic pathway of sphingolipid metabolism in diabetes, whereas, in Ang II-dependent hypertension, it only downregulates the sphingolipid catabolic pathway (Figure 3).

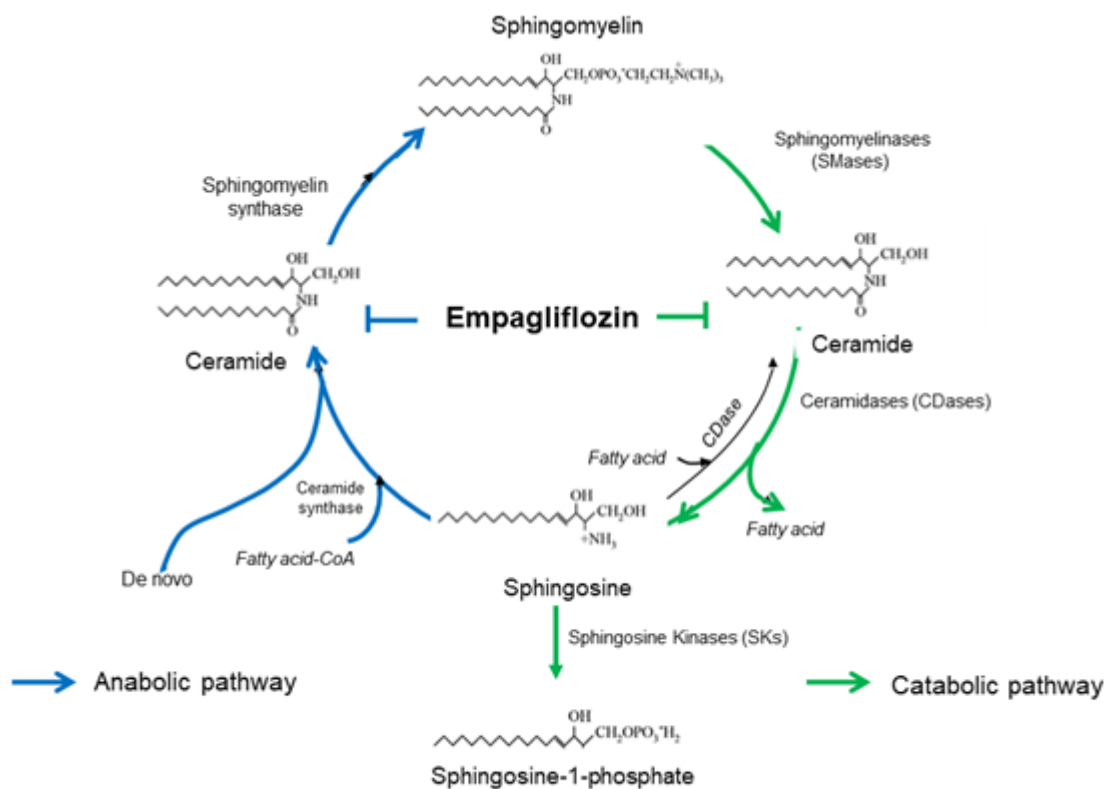


Figure 3: Sphingolipids metabolism in the model of diabetes and hypertension.

2. Applications

2.1. Pharmacologic Inhibitors of Sphingolipid Catabolism Enzymes

The use of pharmacologic inhibitors has been critical for the study of sphingolipid catabolism enzymes as a potential therapeutic approach in respiratory (chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis), neurodegenerative (Alzheimer’s disease), metabolic (obesity, diabetes), and cardiovascular disease (**Table 1**) [\[35\]](#) [\[36\]](#) [\[37\]](#) [\[38\]](#).

Table 1. Pharmacologic inhibitors of sphingolipid metabolism enzymes.

Enzyme	Pharmacologic inhibitors
aSMase	Tricyclic antidepressants (desipramine, imipramine, and amitriptyline), SMA-7, and siramesine.
nSMase	scyphostatin, GW4869, and G11AG

CDase	N-Oleoylethanolamide (NOE), D-e-MAPP, LCL84, LCL204, LCL464, SABRAC, DP24c, KPB70, KPB67, Ceranib-2, Carmofur, and 17a.
SK1	SKI-178, RB-005, PF-543, SLP7111228, Genzyme 51
SK2	(R)-FTY720-OMe, ABC294640, K145, SLP120701, SLR080811

2.2. Sphingosine 1-Phosphate and its Receptors as Drug Targets

One of the biological applications of S1P has emerged with the discovery of the immunosuppressant drug. FTY720 acts as an S1P agonist when it is phosphorylated to FTY720-P. FTY720 can be phosphorylated by both SK1 and SK2, but SK2 has more affinity for the drug than SK1 [39]. FTY720-P is a potent agonist of four S1P receptors: S1P₁, S1P₃₋₅ [40][41].

2.3. Sphingomyelin and its Metabolites as Potential Therapeutic Targets of COVID-19 Disease

In the serum of patients with COVID-19 increased the concentration of serine palmitoyltransferase and acid sphingomyelinase (aSMase). Also, increased the concentration of dihydrosphingosine, dihydroceramide, ceramide, and sphingosine, and decrease sphingosine-1-phosphate [42][43]. Symptomatic COVID-19 patients exhibited a decrease in their serum sphingosine levels compared to asymptomatic patients levels [44]. Interestingly, sphingosine binds to angiotensin-converting enzyme 2 (ACE2) and prevents its interaction with the viral spike protein of SARS CoV 2 in human nasal epithelial cells [45]. Infection of human epithelial cells and different human cell lines with SARS-CoV-2 is reduced by treatment with amitriptyline and other antidepressants. In addition, the administration of anticeramide antibodies or neutral ceramidase also protects against SARS-CoV-2 infections [46].

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