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Review

Sphingolipid Signaling and Metabolism in Neuronal and Glial Cells: Implications for Cerebrovascular and Neurodegenerative Disorders

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ABSTRACT: Sphingolipids are essential bioactive lipids that play pivotal roles in maintaining the structural integrity of cellular membranes and regulating key signaling pathways in the central nervous system (CNS). In both neuronal and glial cells, sphingolipid metabolism regulates diverse processes, including cell survival, apoptosis, neuroinflammation, and myelination. Increasing evidence implicates dysregulation of sphingolipid pathways in the pathogenesis of various CNS disorders, notably cerebrovascular diseases such as small vessel disease and stroke, as well as neurodegenerative conditions including Alzheimer's disease, cerebral amyloid angiopathy, Parkinson's disease, and multiple sclerosis. This review summarizes the current advances in sphingolipid metabolism and signaling in the brain, with a focus on the functional interplay between neurons and glia, as well as the mechanisms by which disrupted sphingolipid homeostasis contributes to CNS pathology. Key sphingolipid metabolites such as ceramide, ceramide-1-phosphate, and sphingosine-1-phosphate emerge as critical mediators of neuroinflammation, blood-brain barrier disruption, and cognitive impairment. Furthermore, we explore emerging therapeutic strategies targeting sphingolipid pathways and their potential to slow disease progression and improve neurological outcomes. A deeper understanding of the roles of neuronal and glial sphingolipids in brain health and disease may advance the development of novel diagnostic tools and therapeutic strategies for cerebrovascular and neurodegenerative disorders.

Keywords: sphingolipid, ceramide, neurodegeneration, dementia, neuroinflammation

1. Introduction

Cerebrovascular diseases comprise a group of disorders that affect blood vessels and blood flow in the brain, leading to serious consequences such as reduced oxygen supply, brain damage, and neurological and cognitive impairment [1]. These disorders include stroke, carotid and vertebral stenosis, intracranial stenosis, aneurysms, and vascular contributions to cognitive impairment and dementia (VCID). Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), are marked by the progressive loss of neuronal structure and function in the brain and spinal cord. Despite their distinct etiologies, both cerebrovascular and neurodegenerative diseases lead to

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cognitive, motor, and behavioral impairments, resulting in a profound reduction in quality of life and a heavy societal and economic burden. The absence of effective disease-modifying treatments for these conditions underscores the urgent need for novel therapeutic approaches that target their shared pathogenic mechanisms.

Emerging evidence indicates that neurodegenerative and cerebrovascular disorders frequently coexist and interact in clinically significant ways [2, 3]. For example, vascular dysfunction can exacerbate the deposition of amyloid-beta and tau, accelerating the onset and progression of AD [4]. Although these disorders differ in their primary triggers, they share several overlapping pathological features, including abnormal protein aggregation, mitochondrial dysfunction, oxidative stress, synaptic loss, and chronic neuroinflammation. Neuroinflammation, a hallmark of central nervous system (CNS) disorders, reflects an intricate immune response mediated by resident glial cells (microglia and astrocytes) and, under pathological conditions, by infiltrating peripheral immune cells. The inflammatory milieu fosters oxidative stress and synaptic injury, aggravating both neuronal and white matter damage.

Microglia, the brain's resident immune cells, are the first responders to neuronal stress and injury. Upon activation, they undergo phenotypic changes and secrete a range of pro-inflammatory mediators, including cytokines (e.g., TNF-α, IL-1β, IL-6), chemokines, and reactive oxygen/nitrogen species (ROS/RNS). These factors synergistically contribute to oxidative stress, synaptic loss, and damage to both neurons and white matter. In parallel, reactive astrocytes play a critical role in initiating and perpetuating neuroinflammatory responses. Following CNS insults such as injury, infection, or neurodegeneration, astrocytes undergo extensive morphological and transcriptional changes, a process known as reactive astrogliosis [5]. Reactive astrocytes secrete pro-inflammatory cytokines (IL-1β and TNF-α), chemokines (CCL2 and CXCL10), ROS/RNS, and bioactive lipids, including sphingolipids such as ceramide [6, 7]. These molecules not only contribute to direct cellular and vascular damage but also amplify neuroinflammation by creating a self-perpetuating toxic environment. Additionally, reactive astrocytes upregulate cell surface proteins such as major histocompatibility complex class I and II proteins and intercellular adhesion molecules, thereby facilitating the recruitment and activation of microglia and peripheral immune cells [8, 9]. Through these concerted actions, astrocytes play a pivotal role in maintaining chronic neuroinflammation, which contributes to the pathogenesis and progression of both cerebrovascular and neurodegenerative disorders.

Within this complex neurovascular milieu, sphingolipids have emerged as critical regulators of neuronal and vascular homeostasis. These bioactive lipids, abundantly enriched in neuronal and glial membranes, govern key biological processes, including synaptic plasticity, myelination, cell survival, and neuroimmune communication [10]. Among the most prominent sphingolipid metabolites, ceramide, sphingosine, and S1P function within a tightly regulated metabolic balance that controls critical cellular processes, including apoptosis, autophagy, and inflammatory signaling. Disruptions in sphingolipid homeostasis marked by altered ceramide/S1P balance, coupled with dysregulated enzymatic activity or receptor signaling, have been implicated in several CNS disorders such as AD, PD, MS, and VCID [11].

Recent studies suggest that extracellular vesicles enriched with sphingolipids contribute to the propagation of neuroinflammation and the spread of misfolded proteins such as tau and α-synuclein, thereby facilitating disease progression [12, 13]. Insights from animal models with targeted deletions or overexpression of sphingolipid metabolic enzymes have further clarified their involvement in glial activation [14], neuronal cell death [15], and cellular proliferation [16].

Taken together, these findings position sphingolipids at the intersection of vascular and neurodegenerative pathology. This review provides a comprehensive synthesis of current knowledge on sphingolipid metabolism and signaling in the CNS, emphasizing the dynamic interplay between neurons and glia in cerebrovascular and neurodegenerative diseases. We explore how glial lipid signaling contributes to neuroinflammation, neuronal and white matter injury, and cerebrovascular dysfunction. Finally, we discuss emerging therapeutic opportunities that target sphingolipid pathways as promising strategies to mitigate neurodegeneration and cerebrovascular damage.

2. Sphingolipid Chemistry – Structural Features

Sphingolipids are an important, essential, but minor class of lipids, characterized by a shared structural backbone known as the sphingoid base, which is an aliphatic amino alcohol [17]. The sphingoid base, discovered in 1884 by German chemist J.L.W. Thudichum in brain tissue, was named after the enigmatic Sphinx due to its complex nature and unknown functions [18]. The sphingoid base typically contains one to three hydroxyl groups in the alkyl chain. It may also exist in saturated, monounsaturated, or di-unsaturated states, with the double bonds present in either cis or trans configurations, further contributing to the variation of sphingoid base. The most prevalent sphingoid base, sphingosine (Fig. 1), a monounsaturated amino alcohol with 2-amino-4-trans-octadecene-1,3-diol, was structurally identified in 1947

[19] . Modifications to the sphingoid base, such as the addition of fatty acyl chains of varying lengths (C14–C36) via an *N*-linked bond with the 2-amino group, generate the key component of sphingolipids, the ceramides (Fig. 1). Within the sphingolipid metabolic network, ceramide occupies a central position in both biosynthetic and degradative pathways. Ceramides can further be modified through the attachment of choline, phosphate, or sugar molecules through *O*-linked bonds at the C1 position, which contributes to the remarkable diversity of sphingolipids in eukaryotic cells. At present, 1,748 curated and 3,168 computationally predicted sphingolipid species have been identified [20], indicating the complexity of sphingolipids at the structural level. Sphingomyelin, the phosphocholine derivative of ceramide, is the most abundant subclass of sphingolipids in cellular membranes, indicating its significance in cellular structure and function. Structural diversity of sphingolipids places them in playing many functional roles in cellular membranes and in cellular signaling, including central regulators of membrane microdomain organization, receptor trafficking, cytoskeletal dynamics, and signaling for cell death and inflammation [21, 22].

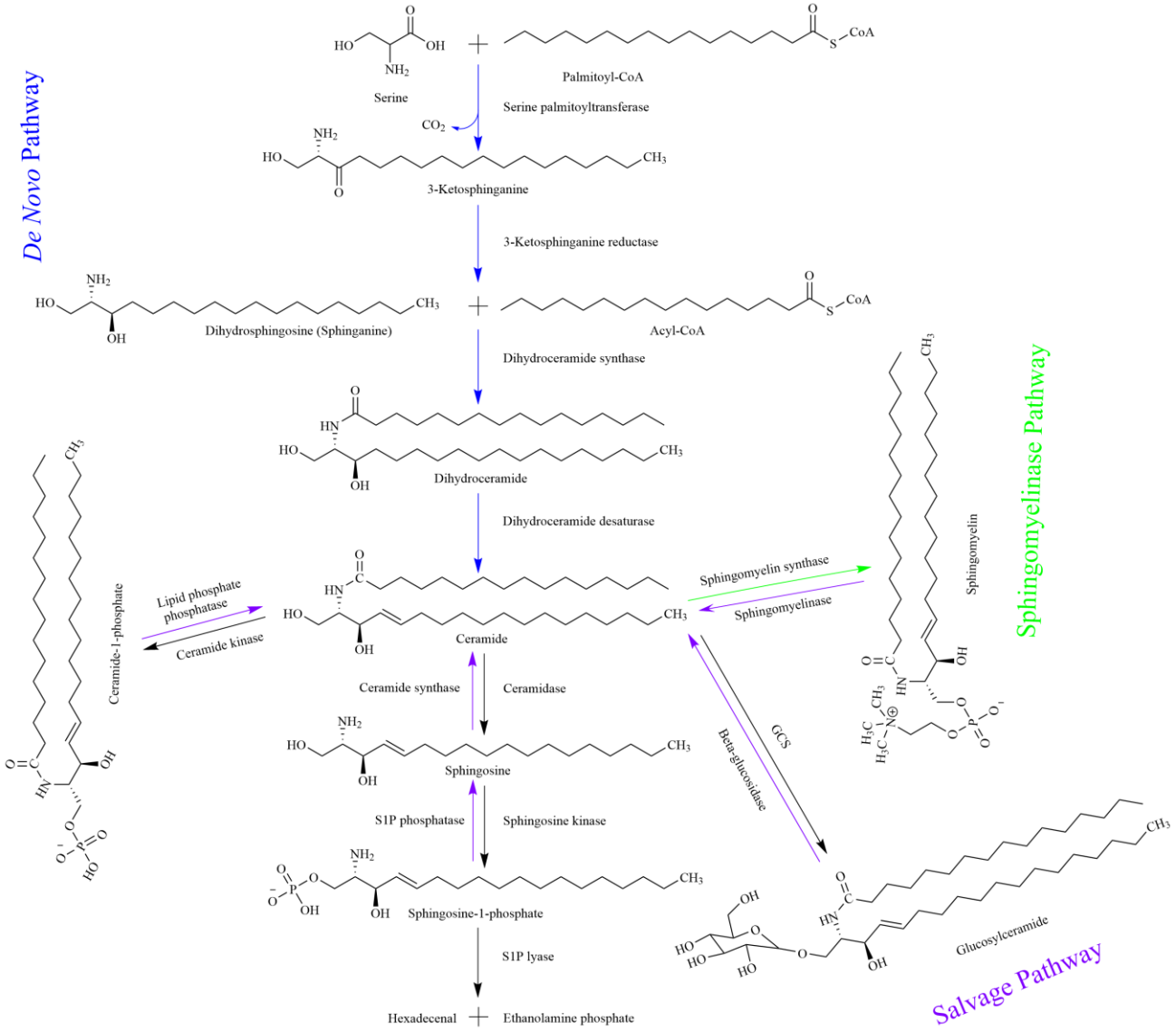

Figure 1. Basic structure of sphingolipids and sphingolipid metabolism. *De novo* synthesis of ceramide is initiated by the condensation of serine and palmitoyl-CoA by serine palmitoyl transferase (SPT) (blue). Ceramide is then generated through several steps and utilized for the biogenesis of other sphingolipids, including sphingomyelin (SM), glucosylceramide (GlcCer), sphingosine (Sph), sphingosine-1-phosphate (S1P), and ceramide-1-phosphate (C1P). On the other hand, ceramide is also produced from sources other than *de novo* synthetic pathway: hydrolysis of SM by sphingomyelinase (SMase) (red), and recycling from GlcCer or S1P through the salvage pathway (violet).

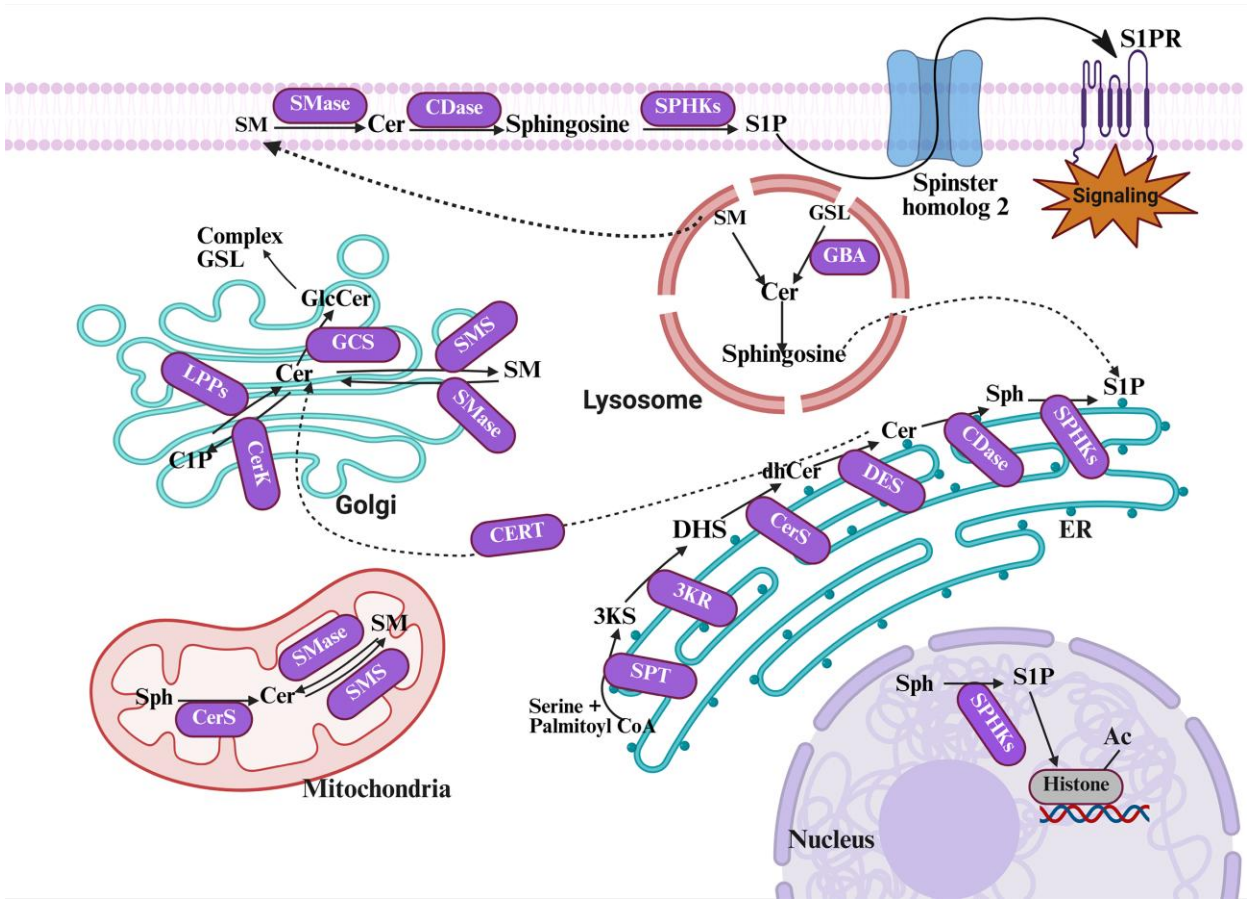

Figure 2. Sphingolipid metabolism in cellular organelles. The *de novo* synthesis pathway for ceramide (Cer) occurs on the cytosolic surface of the endoplasmic reticulum (ER). This process begins with the condensation of L-serine and palmitoyl-CoA to form 3-ketosphinganine (3kdhSph), which is then reduced by 3-ketosphinganine reductase to produce sphinganine. Ceramide synthase (CerS) *N*-acylates sphinganine to generate dihydroceramide (dhCer), which is converted to ceramide by dihydroceramide desaturase. Ceramide is transported to the Golgi apparatus by ceramide transport protein (CERT), where it serves as a substrate for sphingomyelin (SM) synthesis via SM synthase or for glucosylceramide (GlcCer) production, a precursor for glycosphingolipids (GSLs). Alternatively, ceramide can be phosphorylated into ceramide- 1-phosphate (C1P) by ceramide kinase. GSLs and SM undergo further metabolism through lysosomal degradation within the endosomal system.

3. Metabolism of Sphingolipids

The metabolic complexity of sphingolipids arises from multiple biosynthetic and degradative routes that interconnect dynamically to regulate cellular lipid homeostasis. Among these, three principal pathways (Fig. 2): (i) *de novo* synthesis- occurs in the endoplasmic reticulum using saturated fatty acids, (ii) sphingomyelinase (SMase) pathway- converts sphingomyelin in the cell membrane or in lysosome to ceramide using SMase, and (iii) salvage pathway- takes place in lysosomes, breaking down complex sphingolipids to generate sphingosine, operate in close coordination to maintain ceramide and sphingolipid balance across cellular compartments [23].

3.1 *De novo* synthetic pathway

De novo sphingolipid biosynthesis occurs on the cytosolic side of the endoplasmic reticulum membrane, where ceramide is produced through multiple enzymatic reactions (Fig. 2) [24, 25]. Initially, serine and palmitate react to form 3-keto-dihydrosphingosine. This reaction is catalyzed by serine palmitoyltransferase (SPT), an enzyme localized to the ER that controls the rate-limiting step in the *de novo* pathway [26-28]. SPT belongs to the alpha-oxoamine synthase family and facilitates the condensation of amino acids with acyl-CoA to generate alpha-amino ketone [29]. In this process, sphingoid bases are synthesized through the decarboxylation of serine, followed by its condensation reaction with palmitoyl-CoA (Fig. 2). These sphingoid bases are the structural backbone for all complex sphingolipids. Among them, sphingosine, sphinganine, and phytosphingosine are prominent precursors in the context of sphingolipid metabolism. Phytosphingosine is predominantly found in

plants, yeast, and certain specialized human tissues, such as the skin and intestine.

Additionally, SPT can utilize glycine and alanine as substrates, resulting in the formation of 1-deoxysphingolipids (Fig. 2) [30]. Although the function of these atypical sphingolipids is not fully understood, elevated levels of 1-deoxysphingolipids have been observed in the plasma of individuals with diabetes and non-alcoholic fatty liver disease [31]. These lipids are also associated with toxicity in beta cells and neurons, and other human genetic conditions with mutations in SPT genes [32-34].

The enzyme 3-ketosphinganine reductase (KDSR) facilitates the conversion of 3-ketosphinganine into sphinganine by reducing the ketone group. KDSR belongs to the short-chain dehydrogenase/reductase family, which is involved in diverse metabolic processes, including lipid and steroid metabolism [35]. Sphinganine then undergoes *N*-acylation, where a family of six ceramide synthase (CerS) enzymes adds fatty acids of varying chain lengths to produce dihydroceramides (Fig. 1 and 2) [36, 37]. These enzymes are localized to the cytosolic side of the ER, with six isoforms (CerS1-6) displaying tissue-specific expressions and distinct specificities for acyl-CoA chain lengths [38, 39].

In the final step of the *de novo* ceramide biosynthetic pathway, the enzyme dihydroceramide desaturase (DES) introduces a trans double bond at the C4 position of the sphingoid backbone, converting dihydroceramide into ceramide (Fig. 1 and 2) [40]. Humans express two isoforms of DES: DES1, which primarily exhibits Δ4-desaturase activity, and DES2, which also has C4 monooxygenase activity. DES2 is predominantly expressed in the intestine, kidney, and skin, where phytoceramide is notably abundant [41, 42].

Ceramide synthesized in the ER is subsequently transported to the Golgi apparatus for conversion into other sphingolipids (Fig. 2). This transport occurs through two mechanisms with distinct metabolic processes. The first involves ceramide transport protein (CERT), a well-characterized non-vesicular transporter that specifically transports ceramides containing C14–C20 fatty acids to the Golgi for sphingomyelin synthesis. The second mechanism is vesicular transport, which facilitates the transfer of long-chain ceramides (greater than C20) to the Golgi for glucosylceramide (GlcCer) synthesis. Unlike CERT, this vesicular transport system is dependent on phosphoinositide3-kinase (PI3K) activity and remains less characterized [43].

Ceramide is further metabolized into complex glycosphingolipids and sphingomyelin within the Golgi apparatus. Sphingomyelin synthases (SMS1 and SMS2) catalyze the transfer of a phosphorylcholine group from phosphatidylcholine to ceramide, resulting in the formation of sphingomyelin, the most abundant sphingolipid on cell membranes. Although the Golgi contains both enzymes, SMS2 also controls the amount of sphingomyelin at the plasma membrane [44]. Ceramide can be converted into glycosylphingolipids, including GlcCer in the Golgi and galactosylceramide in the endoplasmic reticulum. GlcCer serves as a precursor for gangliosides, while galactosylceramide is transformed into sulfatides [45]. The synthesis of GlcCer involves ceramide and uridine diphosphate (UDP)-glucose, catalyzed by glucosylceramide synthase (GCS) on the cis side of the Golgi [45]. Conversely, galactosylceramide synthesis occurs on the luminal surface of the ER under the regulation of galactosyltransferase [46]. Additionally, ceramides in the Golgi can be phosphorylated by ceramide kinase to form ceramide-1-phosphate (C1P). It plays a significant role in promoting cell growth, preventing apoptosis, and regulating inflammation across various cell types [22, 47]. While the *de novo* pathway primarily generates ceramides from basic precursors within the endoplasmic reticulum, additional flexibility in sphingolipid metabolism is achieved through the sphingomyelinase pathway. This route enables cells to rapidly produce ceramide in response to external stimuli such as oxidative stress, cytokine signaling, and apoptosis, linking sphingolipid metabolism directly to cellular stress responses and signaling cascades.

3.2 Sphingomyelinase pathway

The hydrolysis of sphingomyelin to generate ceramide is catalyzed by SMases, which cleave the phosphocholine head group from sphingomyelin [48]. SMases are classified based on their optimal pH activity profiles: acid SMase (aSMase) and neutral SMase (nSMase) are located in lysosomes and cell membranes, respectively, while alkaline SMase (alk-SMase) is found in the gastrointestinal tract [48]. alk-SMase is specifically expressed in the intestine and liver, where it plays a role in absorbing dietary sphingomyelin. In contrast, aSMase and nSMase are widely expressed across various tissues and are crucial for the catabolism of sphingomyelin in these tissues. These enzymes are involved in critical metabolic processes like apoptosis, inflammation, and immune responses, and their dysregulation is linked to pathological conditions such as Niemann-Pick disease and neurodegenerative disorders like AD [49].

aSMase, a lysosomal metalloenzyme, operates optimally at pH 4.5–5. It is divided into lysosomal SMase and secretory SMase [50]. Lysosomal SMase primarily hydrolyzes sphingomyelin in lysosomes, although it also functions at the plasma membrane through lysosomal membrane trafficking. This enzyme produces surface ceramide and is involved in ceramide signaling pathways,

including those that regulate apoptosis. A deficiency in lysosomal SMase disrupts these pathways, impairing cellular function [51]. In contrast, secretory aSMase is secreted by the Golgi apparatus and is implicated in physiological and pathological processes, including atherosclerosis, where it may promote lipoprotein aggregation. These roles underscore the enzyme's importance in maintaining cellular homeostasis and its connection to disease mechanisms [52].

nSMase, with an optimal activity at pH 7.4, is an enzyme activated by various physiologically significant molecules, including tumor necrosis factor-alpha (TNFα). Mammals express four distinct nSMase types: nSMase1, nSMase2, nSMase3, and mitochondria-associated nSMase [53]. nSMase1 is a membrane protein with two transmembrane domains at its C-terminal region. It plays a vital role in ceramide production under stress, which is crucial for T-cell receptor signaling. nSMase2, known to be palmitoylated at two cysteine clusters, is central to stress-induced ceramide generation. Additionally, several anti-cancer drugs inhibit its activity, highlighting its therapeutic relevance [54]. nSMase3 is a C-terminal-anchored integral membrane protein with an endoplasmic reticulum localization signal and an N-terminal proline-rich domain, likely involved in protein-protein interactions. These enzymes are implicated in the development of various diseases, including atherosclerosis, inflammation, and heart failure, underlining their significance in pathological processes [55, 56].

Sphingomyelin degradation is a major pathway for producing ceramide and its metabolites, including S1P, the last sphingolipid before full degradation. Ceramide undergoes deacylation by ceramidase (CDase) into sphingosine, with three isoforms: acid CDase (ASAH1) in lysosomes, neutral CDase (ASAH2) at the plasma membrane, and alkaline CDases (ACER) in various compartments, including the Golgi (Fig. 2) [57]. Sphingosine is then phosphorylated by sphingosine kinases (SphK1 and SphK2) into S1P. S1P can be degraded by lipid phosphate phosphohydrolases or S1P lyase (S1PL) [58]. S1P is a crucial mediator of cell survival and growth, playing a key role in regulating the balance between pro-survival and pro-apoptotic metabolites, known as the “sphingolipid rheostat” [23]. In addition to *de novo* synthesis and sphingomyelin hydrolysis, cells efficiently recycle sphingolipid intermediates through the salvage pathway. This process ensures the continuous regeneration of ceramide and other sphingolipid species from degraded membrane components, thereby integrating lysosomal catabolism with biosynthetic renewal and sustaining lipid signaling equilibrium.

3.3 Salvage pathway

The salvage pathway depicted in Figure 1 is a critical route in sphingolipid metabolism that facilitates the recycling of sphingolipid base, primarily sphingosine, derived from the lysosomal degradation of complex sphingolipids [59]. Several key enzymes, including SMases, glucocerebrosidase (acid- β-glucosidase), ceramidase, and ceramide synthases (Fig. 1), are involved in the salvage pathway, which significantly contributes to cellular ceramide levels and has been estimated to account for approximately 50-90% of total sphingolipid biosynthesis [60, 61]. Unlike *de novo* synthesis, which initiates in the endoplasmic reticulum from serine and palmitoyl-CoA, the salvage pathway regenerates ceramide through enzymatic breakdown of existing sphingolipids, ensuring efficient lipid turnover and signaling adaptability. The catabolic process begins in acidic compartments (late endosomes and lysosomes) (Fig. 2), where complex glycosphingolipids and sphingomyelin are hydrolyzed. Acid sphingomyelinase cleaves sphingomyelin into ceramide and phosphocholine, providing a major source of lysosomal ceramide [61-63]. Similarly, β-glucosidase removes the glucose moiety from GlcCer, another abundant glycosphingolipid, resulting in the liberation of ceramide. These reactions contribute to shared ceramide pools that can either act as a signaling molecule or undergo further catabolism [63].

Ceramide within lysosomes is hydrolyzed by acid ceramidase, releasing free sphingosine and fatty acid. Unlike ceramide, sphingosine is capable of exiting the lysosome and entering the cytosol, where it serves as a substrate for metabolic reutilization [64, 65]. In the cytosolic face of the ER or in ER-associated membranes, ceramide synthases acylate sphingosine as described in the *de novo* ceramide synthesis mechanism. Ceramide produced via the salvage pathway can activate cellular signaling via phosphorylation and dephosphorylation of key regulatory proteins, including p38 mitogen-activated protein kinase (MAPK) and protein kinaseC isoforms, thereby influencing apoptosis, cell cycle progression, and stress responses [66].

In summary, sphingolipid metabolism forms a tightly coordinated network linking biosynthetic and degradative pathways across cellular organelles. The *de novo,* sphingomyelinase, and salvage routes collectively regulate the levels of key bioactive lipids, ceramide, sphingosine, and S1P, that govern cell survival, differentiation, and stress responses. Disruption of this balance can shift the ceramide/S1P ratio, predisposing cells to inflammation, vascular dysfunction, and neurodegeneration.

4. Physiological Role of Sphingolipids

Beyond their metabolic complexity, sphingolipids serve not only as biochemical intermediates but also as fundamental structural elements of cellular membranes. Their unique molecular architecture confers both physical stability and dynamic functionality to lipid bilayers, providing the foundation for the specialized microdomains that orchestrate cellular signaling and communication.

4.1 Structural component and lipid raft

Sphingolipids are essential structural elements of eukaryotic membranes and play a foundational role in the formation of microdomains ("lipid rafts") [67]. Sphingolipids contain hydroxyl and amide groups that enable sphingolipids to participate simultaneously as both donors and acceptors in hydrogen bonding, facilitating the formation of a tightly packed hydrogen-bonded network [68, 69]. Glycosphingolipids contribute additional stability through inter-sugar residue interactions, while sphingomyelin engages in polar head group interactions. Furthermore, sphingolipids have a strong affinity for cholesterol due to favorable Van der Waals forces, promoting the segregation of lipids into specialized membrane regions [67, 70]. These interactions collectively drive the lateral assembly of sphingolipids into microdomains. These microdomains are not only structural but also functional, influencing critical cellular processes such as calcium regulation, endocytic trafficking, protein sorting, and signal transduction [67, 71]. The rafts are enriched in sphingolipids and cholesterol, creating tightly packed, ordered regions that differ from the more fluid surrounding membrane. Their formation depends on the unique biophysical properties of sphingolipids, including saturated hydrocarbon chains and the ability to form hydrogen bonds, which support membrane rigidity and organization [72]. Unlike other membrane lipids, sphingolipids are synthesized from two fundamental components: long-chain bases and fatty acids. Sphingolipids also utilize serine instead of glycerol as the backbone for acyl chain attachment. These defining structural elements, along with variable head-group modifications, grant sphingolipids a range of unique and vital functions within eukaryotic cells [28]. While their structural properties ensure membrane integrity and compartmentalization, sphingolipids also function as potent signaling molecules. The same molecular diversity that enables them to organize lipid rafts underlies their capacity to regulate vital cellular processes such as growth, differentiation, and programmed cell death.

4.2 Cellular processes: growth, proliferation, differentiation, and apoptosis

Sphingolipids, such as ceramide and S1P, are key regulators of fundamental cellular processes, including growth, proliferation, differentiation, and apoptosis [73]. Ceramide is known for its pro-apoptotic and anti-proliferative effects. It promotes programmed cell death by alteration of mitochondrial outer membrane permeability, resulting in the generation of ROS, the release of cytochrome C, and caspase activation [74]. Previous studies have shown that levels of ceramide increase prior to the mitochondrial phase of apoptosis, accompanied by ROS generation [75]. Various stress stimuli, including chemotherapeutic agents, oxidative stress, and radiation, increase intracellular ceramide levels, which in turn facilitate apoptosis and activation of many downstream signaling pathways [76].

In contrast, S1P supports cell survival and proliferation. It is generated by phosphorylation of sphingosine by sphingosine kinases, particularly SphK1 and SphK2 [77, 78]. Once formed, S1P can act intracellularly or be secreted to function as a ligand for five G-protein-coupled receptors (S1PR1–5), which modulate cell survival, proliferation, migration, vascular integrity, and immune cell trafficking [79]. Intracellularly, S1P inhibits histone deacetylases, enhancing gene transcription related to proliferation and survival [80]. Ceramide facilitates differentiation in multiple cell types, including oligodendrocyte lineage cells, neuronal progenitors, keratinocytes, and myoblasts in part through activation of protein phosphatase 2A and modulation of MAPK signaling pathways [81-85]. Ceramide accumulation is associated with neuronal differentiation, where it modulates the activity of protein phosphatases and kinases essential for neosynthesis [86]. Glycosphingolipids, such as ganglioside monosialic acid 1 and 3 (GM1 and GM3), which have a single sialic acid residue, contribute to cell differentiation by promoting receptor clustering and modulating downstream signaling pathways [87, 88]. Beyond their intracellular roles in proliferation and apoptosis, sphingolipids exert critical effects at the vascular level. Their signaling pathways, particularly those mediated by ceramide and S1P, extend to the regulation of endothelial integrity, vascular tone, and inflammatory responses, processes essential for maintaining cerebrovascular health.

4.3 Endothelial barrier function and maintenance of vascular health

Sphingolipids, particularly S1P, play a key role in maintaining endothelial barrier integrity and overall vascular homeostasis. Ceramide, on the other hand, tends

to promote vascular leak; therefore, a tight balance between these two is needed [89]. Among the five S1P receptors, S1PR1 is the primary receptor, which is ligated or activated by S1P, thereby strengthening cell-cell contact and enhancing endothelial integrity and barrier strength. Higher concentrations of S1P can activate S1PR2, which disrupts adherens junctions, leading to increased vascular leak and, consequently, increased vascular permeability. S1PR1 and S1PR2 have opposite effects on endothelial cell migration, which is thought to be due to the downstream signaling of S1PR2 binding to the Rho pathway [90]. These opposing effects of S1P receptor subtypes arise from distinct downstream signaling cascades: S1PR1 primarily signals through Rac1 to stabilize junctions, whereas S1PR2 activates Rho/ROCK, promoting cytoskeletal contraction and barrier disruption; the net effect therefore depends on local concentration, receptor expression balance, and inflammatory context [91]. Within the blood-brain barrier (BBB), S1P signaling through S1PR1 reorganizes the actin cytoskeleton and tight junction complexes, thereby reducing paracellular permeability and preserving barrier stability even under inflammatory conditions [92].

Disruption of this sphingolipid signaling axis can profoundly impair endothelial function. Reduced S1P availability or an altered ceramide/S1P ratio correlates with increased endothelial permeability, vascular leakage, and inflammation, hallmark features of many vascular and neuroinflammatory disorders [89, 92]. Beyond barrier stability, sphingolipids play a role in regulating vasomotor tone. S1P enhances endothelial nitric oxide synthase (eNOS) activity through S1PR1 activation, promoting nitric oxide (NO) production and facilitating vasodilation, while decreasing vascular stiffness [93]. Conversely, ceramide accumulation disrupts this process by increasing ROS, which impairs NO bioavailability and promotes vasoconstriction and endothelial dysfunction [94]. Sphingolipids also mediate cell and solute trafficking by regulating transcytosis and paracellular (tight-junction-dependent) permeability pathways [95]. Through its action on the cytoskeleton and tight junction complexes, S1P controls the passage of molecules across the endothelium, especially in the BBB [96].

Sphingolipid signaling also intersects with immune and inflammatory responses. Ceramide promotes pro-inflammatory signaling by activating pathways such as protein kinase B (Akt) and MAPK, inducing cell cycle arrest and cytokine production, and amplifying endothelial inflammation [97, 98]. Conversely, S1P exerts immunomodulatory effects through S1PR1, regulating leukocyte egress and trafficking while dampening inflammatory markers, thus conferring endothelial protection [96, 99]. This opposing relationship exemplifies the broader "sphingolipid rheostat," where the balance between ceramide and S1P determines cellular fate, shifting toward apoptosis and inflammation or survival and repair.

In addition to their roles in barrier function and inflammation, sphingolipids profoundly influence angiogenesis and vascular remodeling. S1P, acting through S1PR1, promotes endothelial proliferation, migration, and survival, processes essential for vessel formation and tissue repair under ischemic or inflammatory conditions [100]. In contrast, ceramide accumulation can impair angiogenic responses under shear stress, and there is evidence for microvascular endothelial dysfunction with chronic exposure to ceramides [101]. Sustained ceramide elevation further enhances the expression of endothelial adhesion molecules and activates neutrophils, fostering vascular inflammation and atherogenic remodeling [102]. At the same time, S1P signaling via S1PR1 inhibits NF-κB activation and cytokine release, exerting potent anti-inflammatory effects that protect vascular integrity [103].

Importantly, S1P signaling also supports vascular development and the maturation of new blood vessels, while dysregulation of this pathway contributes to pathological angiogenesis observed in cancer and chronic inflammatory diseases [94, 104]. Loss of SphK1 activity or reduced S1PR1 expression can impair vasodilatory signaling, leading to increased vascular tone and stiffness, and predisposing the endothelium to dysfunction [105]. Meanwhile, ceramide-driven oxidative stress and mitochondrial damage in endothelial cells further exacerbate vascular aging and smooth muscle cell dysfunction [94, 106].

Taken together, the dynamic interplay between S1P and ceramide orchestrates endothelial integrity, vascular tone, and the balance of inflammation. When this equilibrium is disrupted, whether by oxidative stress, enzymatic imbalance, or receptor dysregulation, it results in endothelial injury, impaired vasodilation, and chronic inflammation, and set the stage for the neurovascular dysfunctions explored in subsequent sections.

5. Sphingolipids in Neuronal and Glial Cells

The neuroimmune system plays a vital role in the development, maintenance, aging, and response to injury of the CNS. In the CNS, neuroinflammation represents a major pathological mechanism underlying the onset and progression of neurodegenerative diseases [107, 108]. Despite differences in the primary mechanisms of these disorders, chronic neuroinflammation is a predominant pathological feature during disease development [107-109]. Damage to CNS parenchyma often leads to the activation of glial cells, particularly microglia and astrocytes, which initiate a localized inflammatory

response [110]. These activated glial cells contribute to resolving inflammation by clearing apoptotic cells and suppressing pro-inflammatory signals, largely through the release of specialized pro-resolving mediators (SPMs) [111, 112]. However, when the resolution mechanisms fail or are dysregulated, it leads to sustained neuroinflammation. This chronic inflammatory state leads to the overexpression of inflammatory cytokines and progressive neuronal damage, ultimately driving the progression of neurodegenerative diseases [107-109].

Microglia, the primary immune cells of the CNS, perform three essential functions, including continuous surveillance of their microenvironment, support of neuronal health and homeostasis, and protection against harmful stimuli [113]. Depending on the brain region, microglia constitute approximately 5-12% of the CNS cell population and are integral to both homeostatic regulation and immune defense [110]. Disruption of ceramide homeostasis is implicated in both rare genetic conditions, such as Farber disease and autoimmune neuropathy type I (HSAN-I), as well as in common neurodegenerative diseases. Elevated ceramide levels have been observed in the plasma of PD patients, but a decrease has been noted in cortical areas. Several studies have reported that there is an increased ceramide concentration in AD patients. In the 5xFAD mouse model, ceramide levels are increased in serum exosomes, exposure to toxic amyloid elevates ceramide in astrocytes, and ceramide-rich exosomes activate the cell death pathway [13, 114]. Pharmacological inhibition of ceramide synthesis has demonstrated neuroprotective effects in a mouse model of AD (TgCRND8) [115]. Cell type-specific analysis using human iPSC-derived neurons, astrocytes, and microglia reveals significant differences in ceramide synthesis, composition, and metabolic response. Notably, glial cells showed elevated expression of genes involved in ceramide synthesis, higher rates of *de novo* ceramide production, and greater sensitivity to CerS inhibition [116]. RNA sequencing further demonstrates that CerS inhibition leads to significant transcriptomic change in glial cells, whereas neuronal gene expression remains unaffected, underscoring the greater metabolic plasticity of glia in sphingolipid metabolism [116]. In contrast, neurons exhibit a remarkably stable ceramide profile when compared to microglia and astrocytes [116]. Among glial cells, microglia and oligodendrocytes show enriched expression of genes directly linked to sphingolipid turnover and myelin-associated lipid processing [117]. For instance, microglia exhibit high transcript levels of UDP-galactose:ceramide galactosyltransferase 8 (UGCG) and sphingomyelin synthase 1, key enzymes involved in the synthesis of galactosyl ceramide and sphingomyelin, respectively. Astrocytes are especially associated with the production and release of harmful lipid species, which tend to have a greater detrimental impact on neurons and oligodendrocytes [118, 119]. Motor neurons predominantly accumulate C16:0 and C18:0 ceramides, both in the cytoplasm and nucleus. In contrast, astrocytes exhibit higher levels of long-chain ceramides, particularly C24:0, while microglia are enriched in C24:1 ceramide [116, 120]. These variations extend to the nuclear component, where glial cells contain more long-chain ceramides, specifically C22:0 and C24:0, compared to neurons, which retain elevated levels of nuclear C18:0 ceramide. *In vivo* studies show that CerS1 is predominantly expressed in neurons and is responsible for the synthesis of C18:0 ceramide [121]. Microglia exhibited notably low levels of CerS1 compared to other CerS. Inhibition of ceramide metabolism via Fumonisin B1 or GCS inhibitors leads to cell-type-specific alterations in ceramide levels. Astrocytes showed the most substantial reduction in ceramide levels particularly C14:0 and C16:0 species, reflecting their high CerS5/6 activity, while microglia exhibited more moderate changes, primarily in longer chain ceramides consistent with CerS2.

Beyond ceramide, downstream metabolites such as S1P also play an important role in cellular signaling. S1P functions both as an intracellular second messenger and as an extracellular ligand of G protein-coupled receptors (S1PR1- S1PR5), which are widely expressed in the CNS, including in microglia, astrocytes, and neurons [122]. These CNS cell types regulate S1P levels primarily through the activity of SphK1 and SphK2, which phosphorylate sphingosine to S1P. The role of S1P in neuroinflammation has been predominantly investigated in glial cells [123]. In astrocytes and microglia, S1P signaling is linked to processes such as proliferation, migration, and morphological changes that are often observed under inflammatory conditions [14, 124]. Lipopolysaccharide-induced activation of glial cells stimulates the S1P pathway, leading to increased SphK1 expression and enhanced S1P production. This cascade promotes glial proliferation and induces the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-17, as well as other neurotoxic molecules [125]. Research indicates that inhibiting SphK1 or S1PRs can attenuate these inflammatory responses, thereby reducing glial proliferation [126]. Treatment with the S1PR modulator FTY720 in TNF-α-simulated human astrocytes suppresses the secretion of monocyte chemotactic protein-1, highlighting the anti-inflammatory potential of targeting S1P signaling in glia [8]. While the pro-inflammatory role of glial S1P is well documented, recent studies have shown that S1P regulation differs in neurons. In AD, neuronal levels of SphK1 are significantly decreased, despite unchanged levels of S1P. Notably, the reduction in SphK1 expression and activity was more

prominent in AD neurons compared to wild type, whereas no such differential expression was observed in microglia and astrocytes. These emphasize a cell-type-specific regulation of S1P metabolism, where glia contribute to the amplification of inflammatory responses via increased S1P signaling, while neurons exhibit SphK1 function that may impair their ability to resolve inflammation effectively [127, 128]. However, SphK2 mRNA expression did not differ among the neurons, microglia, and astrocytes derived from wild type and AD mice. Sphingosine and S1P levels were also unchanged in these cells [128].

Bioactive sphingolipids have been shown to play crucial roles in the physiology and functions of glial cells under both healthy and diseased conditions, and emerging studies continue to expand our understanding of their impact. Recent evidence suggests that sphingolipids play a critical role in neuron-glia communication, serving as key modulators of cellular signaling, inflammatory responses, synaptic function, and neuroprotection. The balance of sphingolipid species, including ceramide, S1P, and glycosphingolipids, tightly regulates the neuroglial homeostasis, while dysregulation of these metabolic pathways contributes to the pathogenesis of numerous neurodegenerative and neuroinflammatory disorders [10, 129]. Neuron-glia signaling is essential for maintaining synaptic plasticity, metabolic support, and immune surveillance in the CNS. Astrocytes, microglia, and oligodendrocytes engage in dynamic crosstalk with neurons, and sphingolipids are increasingly recognized as crucial mediators in this interplay. Ceramide accumulation in astrocytes and neurons exacerbates neurotoxicity by enhancing oxidative stress and inflammation, hallmarks of AD, PD, MS, and ALS [130, 131]. In parallel, S1P signaling influences microglial motility and phagocytosis, processes essential for debris clearance and immune surveillance in neurodegenerative contexts [132]. Another emerging mechanism involves exosomal ceramide signaling, in which ceramide accumulation in glial membranes promotes exosome budding. These vesicles, enriched in bioactive lipids, enzymes, and regulatory RNAs, enable bidirectional neuron-glia communication, propagating inflammatory or stress signals and modulating synaptic function and neuronal survival [133]. For example, astrocyte-derived exosomes can transport misfolded pathogenic proteins and/or aberrantly expressed miRNAs into neurons, initiating or propagating neuroinflammation [114, 134], and contributing to neurodegeneration.

Additionally, S1P gradients in the perivascular space serve as spatial regulators of neurovascular interactions. While enriched in plasma, S1P is tightly controlled in brain parenchyma, establishing gradients that maintain BBB integrity, vascular tone, and leukocyte trafficking [91, 135]. Astrocytic endfeet and pericytes at the gliovascular interface are particularly sensitive to these S1P cues [136], linking systemic lipid metabolism and immune signaling to local neuronal support and glial reactivity. In summary, sphingolipids orchestrate essential signaling events in neuron-glia interactions, and their dysregulation serves as both a marker and mediator of CNS disease. Defining the spatial and temporal dynamics of sphingolipid signaling within the neuroglial unit may provide novel insights into disease mechanisms and opportunities for targeted therapeutic interventions.

6. Role of Sphingolipids in Neurodegenerative and Cerebrovascular Diseases

Sphingolipids play a pivotal role in regulating cellular processes implicated in the pathophysiology of neurodegenerative and cerebrovascular diseases such as AD, PD, Fabry disease, ALS, Niemann-Pick's disease, MS, and stroke [137-141]. Table 1 lists abnormalities in sphingolipid metabolism associated with neurodegenerative and cerebrovascular diseases.

Table 1. Sphingolipid metabolism abnormalities in neurodegenerative diseases.

Disease	Samples / disease model	Sphingolipid species regulation	Implication in the disease	Ref.
AD (Alzheimer's disease)	Brain, postmortem human AD	Elevated levels of ceramide C16:0, C18:0, C20:0, and C24:0 in brains from patients with any of the tested neural defects.	Genes connected to ceramide metabolism (aSMase, nSMase2, GALC) were upregulated; linked to neuropathologic abnormalities.	[144]
	Brain, postmortem human AD with dementia	Ceramides were elevated more than three-fold in white matter and peaked at the stage of very mild dementia	A significant drop in sulfatides as observed by galactocerebroside sulfotransferase activities, linked to AD, even in people with very mild dementia	[143]
	Plasma, Human AD	Plasma ceramides (C16:0, C18:0, C20:0, C24:1) levels were elevated	Plasma ceramide C16:0, C18:0, C20:0, C24:1 associated with hippocampal atrophy, aging, cognition and AD development.	[145]

	Brain, postmortem human AD with capillary cerebral amyloid angiopathy (CAA)	Altered expression of ceramides, acid sphingomyelinase, and S1P receptors in reactive astrocytes and microglial cells	The increased levels of acid sphingomyelinase and ceramide in activated glia cells suggest that the sphingolipid pathway is involved in the neuroinflammatory response in pathogenesis of capillary cerebral amyloid-beta/tau accumulation.	[151]
	Plasma, human AD and age-matched non-AD controls; Brain, Mice with inhibition of acid sphingomyelinase ($ASM^{+/-}$) in a mouse model of familial AD (FAD; *amyloid precursor protein* [*APP*]*/presenilin 1* [*PS1*]) or, APP/PS1/$ASM^{+/-}$ triple mutant mice	Acid sphingomyelinase was elevated in fibroblasts, brain, and/or plasma from patients with AD and in AD mice	Lysosomal depletion, defective autophagy; promotes amyloid-beta accumulation and tau pathology.	[153]
PD (Parkinson's disease)	Cortex, 5xFAD transgenic mice model	S1P/ S1PR1, dysregulated	Dysregulated S1P and S1PR1 signaling via the Akt/mTOR/Tau pathway exacerbates development of AD-like pathology	[154]
	Plasma, human PD	In PD patients, levels of ceramide C16:0, C18:0, C20:0, C22:0, and C24:1 higher, monohexosylceramide C16:0, C20:0 and C24:0 also higher	Plasma ceramide and monohexosylceramide metabolism is also altered in sporadic PD (non-glucocerebrosidase mutation carriers) and higher levels associated with worse cognition	[170]
	Non-fasting plasma, human PD and normal control subjects	C14:0 and C24:1 levels significantly higher in PD. Verbal memory negatively correlated with ceramide C14:0 and C24:1 levels. C22:0, C20:0 and C18:0 associated with neuropsychiatric symptoms	In PD dementia, higher ceramide levels are linked to worse memory and a greater likelihood of multiple neuropsychiatric symptoms	[171]
	Substantia nigra, MPTP PD mice models	Ceramide C16:0 increased in the substantia nigra of mice in the PD preclinical-stage model. Total concentration of sphingomyelins in the striatum and substantia nigra increased in the preclinical-stage model	Elevated expression of sphingolipid metabolism genes linked to disease progression. Correlates intracellular accumulation of ceramides with neurodegeneration. Sphingomyelins are involved in reparative rather than neurodegenerative processes	[257]
	MPP^+ treated human neuronal dopaminergic neuroblastoma cell line SH-SY5Y	MPP+ induced significant alterations of Sphks and S1P lyase (S1PL) gene expression. Reduced activity of SphK1 and SphK2 in the cytosolic fraction and in the crude nuclear fraction, respectively	Inhibition of SphKs worsens alpha-synuclein buildup and Sphk1 inhibition plays an important role in caspase-dependent apoptotic neuronal death	[178]
	MPTP PD mice models and MPP^+ treated MN9D cells	Down regulation of SphK2 expression in the substantia nigra and cellular model	Exogenous S1P exhibits neuroprotective effects by activation of pCREB, PGC-1α and NRF-1 in the MN9D cells, and inhibiting ROS, highlighting S1P signaling has an important role in the survival of the dopaminergic neurons.	[177]
	Tissue from human Gaucher disease patients and glucocerebrosidase (GBA1) mutation carriers	Glucosylceramide accumulation	GBA mutations disrupt glucocerebrosidase function, leading to cellular stress, alpha-synuclein buildup, and increased risk for PD.	[160, 161]
	Tissue from human LRRK2mutation carriers	Significant alterations in sphingolipids in CSF	LRRK2 mutations disrupt neuronal homeostasis and promote neurodegeneration, linking hereditary PD to altered sphingolipid metabolism.	[173, 258]

HD (Huntington's disease)	Brain, R6/2 mice model	Significant decrease in the content of dihydrosphingosine, dihydrosphingosine-1-phospahte and dihydro ceramide [C18:0], mRNA expression of *Cers1* was markedly reduced, *Sptlc1* and *2* genes displayed an opposite expression profile	Early defects in *de novo* sphingolipid biosynthesis, including *Cers1, Sptlc1*, and *Sptlc2* mRNA. Highlights disrupted sphingolipid metabolism in HD, demonstrating the involvement of the *de novo* sphingolipid biosynthesis pathway as a key molecular mechanism underlying the increased cell-death susceptibility in HD	[181]
	Brain, postmortem human, R6/2 and YAC128 mice model. HD hiPSC cell lines, HD58-3	Up-regulation of S1PL protein was consistently paralleled by down-regulation of SPHK1 protein in human brain. S1P decreased in R6/2 mice	Imbalance in S1P-metabolizing enzymes leads to reduced S1P bioavailability and increased ceramide levels.	[182]
	Primary neurons BACHD transgenic mice model [FVB/N-Tg(HTT*97Q)IXwy/J]	Sphingosine kinase 2 (Sphk2) is hyperphophorylated in brain and promotes DNA double-strand breaks in cultured primary neurons	SphK2 promotes mutant huntingtin-mediated neurotoxicity and DNA damage.	[184]
ALS (Amyotrophic lateral sclerosis)	Spinal Cord and motor cortex, SOD1-G93A transgenic rats	Increased concentrations of two hydroxylated ceramides, the C24:0-OH and C24:1-OH	Spinal cord is more susceptible to lipid alterations during ALS disease progression than the motor cortex.	[194]
	Spinal Cord, FUS (1-359) ALS mice	The levels of sphingosine and sphinganine were dramatically increased in the spinal cord at the terminal stage of the disease. The ratio of the anti-apoptotic S1P to sphingosine and sphinganine sharply reduced	Altered enzyme expression linked to disrupted sphingolipid metabolism in the spinal cord more at the terminal stage of the disease. The decreased ratio of the S1P to sphingosine and sphinganine, indicates massive apoptosis of spinal cord cells.	[194]
MS (Multiple sclerosis)	CSF, lipidomic study	Ceramides (C16:0, C24:0) elevated,	Elevated ceramide causes bioenergetic mitochondrial dysfunction and axonal damage, contributing to disease pathogenesis through increased oxidative stress and reduced neuroprotective gene expression.	[201]
	Brain, postmortem human	In active MS, levels of sphingomyelin C20:0 (↓57%), C22:0 (↓70%), and ceramide C18:0 (↓64%) and C20:0 (↓69%) were significantly decreased. In both active and inactive MS, reductions were observed in sphingomyelin C16:0 and ceramides C20:0 and C22:0	The results suggest that during active-MS, the content of sphingomyelin and ceramide in normal appearing brain tissues are decreased and that during periods of disease inactivity, sphingolipid content of grey matter, but not white matter is similar to control brain	[202]
	Serum, relapsing-remitting MS	Antibodies for nonhydroxy fatty acid ceramide and brain D-erythrosphingosine present	Linked to progression markers and these antibodies may serve as biomarkers for monitoring disease pathology and progression.	[203]
	Formalin-fixed brain tissues from MS and periventricular leukomalacia patients; cuprizone-induced demyelination C57BL/6 mice model	Ceramides accumulated in reactive astrocytes, C18:0 ceramide was found to be significantly elevated in MS	Results suggest that disturbed sphingolipid pathways in reactive astrocytes may indirectly contribute to oligodendroglial injury in cerebral white matter disorders.	[205]
	EAE models of MS	Lactosylceramide (LacCer) increased	Enhances astrocyte activation, microglia/monocyte recruitment, and transcriptional programs.	[206, 207]
Stroke	Plasma from acute ischemic stroke (AIS) patients; MCAO mouse model	Long-chain ceramides (d18:1/14:0, d18:1/16:0, d18:1/18:0)	Associated with ischemic injury and poor functional outcomes.	[224, 225]
	Plasma from acute ischemic stroke (AIS) patients; MCAO mouse model	Sphingosine reduced and S1P increased	Increased S1P levels correlated with disease progression	[224]

MCAO mouse model	Increased aSMase activity along with ceramide C16:0, C18:0, C20:0, C22:0, C24:1 levels	Increased aSMase activity and ceramide levels associated with stroke injury	[259]
Rat model of chronic cerebral ischemia	Increased astroglial ceramide due to GCS downregulation and aSMase upregulation	Contributes to oligodendroglial apoptosis, myelin degradation, and ischemic white matter pathology.	[231]
MCAO mouse model	S1PR2 elevated	S1PR2 plays a critical role in controlling vascular damage, hemorrhage, and cerebrovascular permeability.	[228]

6.1 Alzheimer's disease

The hallmark pathological features of AD include amyloid plaques and neurofibrillary tangles, which are particularly prevalent in the cortex and hippocampus of the brain, leading to widespread cerebral atrophy and resulting in progressive memory loss, cognitive decline, and behavioral changes. It causes primarily a 'cortical' type of dementia. As the leading cause of dementia, AD has emerged as one of the most burdensome and costly diseases of the 21st century [142]. Recent studies indicate that sphingolipids, particularly ceramides, are critically involved in the progression of AD. Alterations in ceramide species, including variations in chain length and concentration, have been identified in both clinical samples and animal models of AD. Post-mortem analyses reveal elevated ceramide levels in the gray and white matter of AD brains, particularly in early disease stages [130, 143]. Elevated levels of ceramide subspecies (C16:0, C18:0, C20:0, C24:0) have been reported in the brains of AD patients, accompanied by upregulated expression of ceramide metabolism-related genes, such as aSMase, nSMase2, UGCG, and GALC [144]. Changes in plasma sphingolipid profiles, including increased ceramide C16:0, C18:0, and C24:1, along with decreased levels of phosphatidylcholines (e.g., PC36:5 and PC38:6), have been linked to hippocampal atrophy and AD progression [145]. Elevated ceramide levels in cerebrospinal fluid (CSF), possibly derived from astroglia, highlight its involvement in neuronal apoptosis and neurodegeneration [146, 147]. Microglia play a key role in early defense against AD by forming a barrier around amyloid deposits and clearing amyloid β through phagocytosis. Notably, most AD risk genes are expressed in microglia, many of which are specific to these cells [148, 149]. Amyloid-β (Aβ)-induced oxidative stress disrupts ceramide and cholesterol metabolism, further exacerbating neurodegeneration. Studies suggest that interventions targeting sphingomyelin synthesis or using antioxidants like α-tocopherol can mitigate these effects [129]. Additionally, increasing aSMase activity leads to decreased sphingomyelin levels but increased ceramide levels. Accordingly, heightened aSMase activity is associated with the accumulation of long-chain ceramides (e.g., C22:0, C24:0), which contributes to impaired membrane repair and Aβ aggregation, ultimately leading to synaptic dysfunction. These changes correlate with both Aβ and tau pathology [98, 99]. The ceramide/S1P rheostat emerges as a critical determinant of neuronal survival. While ceramides and sphingosine are pro-apoptotic, S1P supports cellular survival. Decreased S1P levels and an altered ceramide/ S1P ratio are associated with Aβ and tau accumulation in AD, presenting potential therapeutic and diagnostic implications [150, 151]. The Apolipoprotein E (ε) isoforms, especially ε4, is a major risk factor for AD [152]. The ApoE4 mutations were observed to disrupt sphingolipid homeostasis in CSF and circulation, thereby facilitating the progression of AD, especially during early stages such as mild cognitive impairment (MCI) [152]. Consistent with findings in animal studies, clinical research has shown that the ceramide system is crucial for memory impairment in AD. Increased aSMase in AD impairs lysosomal biogenesis, causing defective autophagy and promoting Aβ accumulation. Partial genetic or pharmacologic aSMase inhibition restores lysosomal function, improves autophagy, reduces amyloid pathology, and enhances memory, highlighting aSMase as a promising therapeutic target in AD [153]. Sphingosine and its derivatives, including S1P, contribute to AD pathology in 5xFAD transgenic mouse model by impairing mitochondrial function, increasing oxidative stress, and disrupting neuronal survival and vascular integrity [154]. Compared to non-transgenic wildtype littermates, significantly decreased levels of SphKs, increased S1PL, and increased S1PR1 were detected in 8- and 14-month-old 5xFAD mice, suggesting dysregulation of S1P and S1PR signaling may associate with the development of AD-like pathology [154]. S1PR agonist reduces infection-induced neuroinflammation, BBB permeability, and Aβ accumulation in APP/PS1 mice, likely by enhancing Aβ phagocytosis by astrocytes, thereby attenuating infection-related cognitive decline in AD without affecting baseline pathology [155]. In addition, the ceramide/S1P rheostat regulates cell fate, where ceramide accumulation increases free radical levels, reduces cell viability in SH-SY5Y neuroblastoma cells by inhibiting the PI3K/Akt pro-survival pathway, and promotes apoptosis through

decreased B-cell lymphoma 2 (Bcl-2) and increased Bcl-2 associated X protein and Hrk expression [156]. Fingolimod phosphate (FTY720-P), an S1PR agonist, protects neurons from oligomeric amyloid β-induced neurotoxicity in mouse neuronal culture by enhancing brain-derived neurotrophic factor (BDNF) expression and activating BDNF-tropomyosin receptor kinase B signaling [157]. The sphingolipid system affects numerous critical molecular pathways in AD, contributing to its pathogenesis. Since these interconnected pathways form a vicious cycle leading to significant brain damage in AD, identifying the primary initiating event remains challenging.

Collectively, in AD, it seems that ceramide accumulation drives neurodegeneration, oxidative stress, Aβ and tau pathology, and synaptic dysfunction, while elevated aSMase activity impairs autophagy, and disrupted S1P signaling exacerbates cognitive decline. These insights highlight the therapeutic potential of targeting sphingolipid metabolism in AD. While lipidomic and mechanistic studies of sphingolipid regulation are relatively well developed in AD, such investigations remain limited in other dementing disorders, including HD and MS, leaving a critical gap in our understanding of disease-specific lipid signaling pathways. Nevertheless, we have compiled the available studies on these disorders and expanded our discussion to highlight how sphingolipid alterations, particularly shifts in the ceramide/S1P rheostat, may contribute to neurodegeneration in these contexts.

6.2 Parkinson's and Gaucher disease

The progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the development of cytoplasmic inclusions comprising misfolded α-synuclein, known as Lewy bodies, are two principal neuropathological characteristics of PD, a movement disorder of the nervous system which impacts 2-3% of the elderly population [158]. Numerous investigations have shown that impaired sphingolipid metabolism could play a role in the etiology of PD [159]. Mutations of the GBA gene, which codes for the enzyme glucocerebrosidase (GCase), are a leading genetic risk factor for idiopathic PD. These mutations disrupt lysosomal autophagy, induce endoplasmic reticulum stress, mitochondrial dysfunction, and promote α-synuclein accumulation, thereby elevating the risk of sporadic PD by impairing the lysosomal enzyme glucocerebrosidase, which converts GlcCer into ceramide, leading to the buildup of glycosphingolipids [160, 161]. Gaucher disease (GD) is the most common lysosomal storage disorder or sphingolipidoses, caused by GBA1 mutations. GD is caused by deficient activity of the lysosomal enzyme glucocerebrosidase (GCase), leading to the intracellular accumulation of GlcCer and its deacylated form, psychosine [162]. The neuronopathic forms of GD (nGD), although rare, are characterized by severe neurological dysfunction and progressive neuronal loss. Experimental studies using mouse models of nGD have demonstrated that the loss of GBA1 leads to GlcCer accumulation, lysosomal and mitochondrial dysfunction, loss of dopaminergic neurons, motor deficits, and a reduced lifespan [163-165]. A notable link has emerged between GD and PD [166], as GBA1 mutations are more frequent in PD patients, although not all carriers develop Parkinsonism, indicating low penetrance. This connection highlights the role of sphingolipid dysfunction in PD. The condition is categorized into three types based on the degree and rate of progression in neurological involvement: type I (non-neuronopathic), and types II and III (neuronopathic), where macrophages and neurons are primarily affected, respectively. More recently, the accepted classification has been challenged by the association of type 1 GD and PD [167]. This lipid accumulation promotes inflammation through cytokine release and the buildup of neurotoxic glucosyl sphingosine, contributing to neurodegeneration and PD. Insights from this association have highlighted the role of ceramide pathways in Parkinson's disease. Another interesting observation is the presence of activated microglia, frequently observed in the brains of individuals with GD [168]. In a zebrafish model of GD, the buildup of glycosphingolipids triggered microglial activation and significant inflammation before neuron loss occurred [169], suggesting that impaired sphingolipid degradation drives neurodegeneration through microglial activation.

Postmortem brain tissues and plasma from individuals with sporadic PD show upregulated ceramide synthase gene expression and elevated levels of specific ceramide species, including long-chain (Cer14:0, Cer16:0, Cer20:0) and very long-chain ceramides (Cer24:1, Cer26:1) [170, 171]. Dominantly inherited genetic mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are recognized as the most common cause for hereditary type of PD and 2% of late-onset sporadic PD [172]. In a study, lipidomics performed on serum (n = 221) and CSF (n = 88), from a multi-ethnic population from the Michael J. Fox Foundation LRRK2 Clinical Cohort Consortium, revealed that predominant lipid species such as ceramides, triacylglycerols, and sphingomyelins were altered in PD patients and LRRK2 mutation carriers. Dysregulated pathways included sphingolipid metabolism, insulin signaling, and mitochondrial function, with similar patterns confirmed in an independent PD cohort (n = 315), supporting the potential of lipid-based biomarkers and therapeutic targets [173].

Recent studies have demonstrated elevated ceramide metabolism in animal models of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), and rotenone [174-176]. In PD, it is well established that SphK1 and SphK2, which are key enzymes in sphingolipid metabolism, regulate neuroinflammation and neuronal survival by modulating the balance between ceramide and S1P [128]. In MPTP-induced PD models, levels of SphK1 and SphK2 are significantly reduced in dopaminergic neurons of the substantia nigra. Consistent findings were observed in 1-Methyl-4-phenylpyridinium MPP+-treated mouse neuroblastoma cell line 9D (MN9D) cells, where inhibition of these isoforms by dimethyl-sphingosine triggers apoptosis, evidenced by elevated Caspase 3 levels. These results suggest that dysregulated S1P metabolism contributes to PD pathogenesis and may represent a novel therapeutic target [177]. Supporting this notion, another PD mouse model showed that exogenous S1P exerts neuroprotective effects, whereas inhibition of SphK1 and SphK2 enhances alpha-synuclein secretion, suppresses PI3K/Akt signaling, and promotes caspase-dependent neuronal death, further highlighting SphK1/S1P signaling as a promising therapeutic target in PD [178].

6.3 Huntington's disease

HD is an autosomal dominant neurodegenerative disorder characterized by chorea, dystonia, cognitive decline, and psychiatric symptoms. In HD, a CAG repeat expansion in the Huntingtin (HTT) gene causes striatal neuronal degeneration, primarily in the caudate nucleus, resulting in excitotoxicity [179, 180]. In Huntington's disease, the striatum shows distinct alterations in lipid composition and in the genes responsible for lipid metabolism, including those related to sphingolipids. The sphingolipid *de novo* biosynthesis pathway is also significantly affected in the disease [181]. Disruption of sphingolipid metabolism in HD manifests early, with notable effects observed in both human and animal models, where an imbalance in S1P-metabolizing enzymes leads to decreased S1P bioavailability and increased ceramide levels [182]. Reduced CerS1 expression and sphingolipid imbalances in the R6/2 mouse model provide the first evidence of altered *de novo* sphingolipid biosynthesis in HD. It also highlights early defects in sphingolipid-metabolizing enzymes CerS1, serine palmitoyltransferase long-chain base subunit 1 (SPTLC1), and serine palmitoyltransferase long-chain base subunit 2 (SPTLC2), indicating abnormal sphingolipid metabolism as a key pathogenic factor and a possible new target for treatment approaches in HD [181]. According to recent studies, the cytosolic S1P pathway, regulated by SphK1, promotes autophagic flux and influences neuronal autophagy. SphK1 relocates to autophagosomes upon activation, and its dysregulation is associated with neurodegenerative diseases. Pharmacological inhibition of S1PL demonstrates neuroprotective effects in a primary neuron model of HD [183]. SphK2 promotes DNA double-strand breaks in cultured primary neurons, and interestingly, SphK2 is hyperphosphorylated in the brain samples from a mouse model of HD, suggesting its pathogenic role in the disease. Importantly, the SphK2 inhibitor ABC294640 reduces DNA damage in neurons and increases survival in two neuron models of HD, highlighting SphK2 as a potential therapeutic target for HD [184]. Sphingolipid metabolism is disrupted in HD, resulting in abnormalities such as reduced expression of CerS1, SPTLC1/2, and an imbalance in S1P/ceramide levels. Neuroprotective benefits have been demonstrated with therapies targeting sphingolipid pathways, including SphK1 activation to promote autophagy, S1PL inhibition, and SphK2 inhibition. In summary, HD pathogenesis involves early and persistent disruption of sphingolipid metabolism, characterized by reduced CerS1 and SPTLC1/2 expression, increased aSMase activity, and impaired SphK1/2 signaling. This imbalance promotes ceramide accumulation, mitochondrial dysfunction, oxidative stress, and neuroinflammation, driving striatal neurodegeneration. Targeting sphingolipid-modifying enzymes, such as through S1PL or SphK2 inhibition, offers promising therapeutic avenues to restore lipid homeostasis and neuronal survival.

6.4 Farber disease

Farber lipogranulomatosis disease is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *ASAH1* gene, leading to acid ceramidase (aCDase) deficiency and ceramide accumulation. This buildup triggers widespread inflammation and lipid-laden macrophages, affecting both visceral organs and the brain. Symptoms vary but often include subcutaneous nodules, joint deformities, and neurological deficits, with severe cases resulting in early infant death [185]. In the brains of ASAH1-P361R/P361R mice, levels of ceramide, hydroxyceramides, dihydroceramides, sphingosine, dihexosylceramides, and GM3 ganglioside were elevated, with significant microglial and macrophage abnormalities identified as key pathological features [186]. While neurons also exhibited morphological changes, these alterations were less pronounced compared to those observed in microglia. These findings underscore the profound impact of aCDase deficiency on brain lipid metabolism and innate immune cell function in Farber disease. Unfortunately, there is currently no approved treatment for this devastating disorder. However,

therapeutic strategies aimed at correcting the underlying aCDase deficiency, such as enzyme replacement therapy (ERT) or gene therapy, are under investigation and hold promises for future intervention.

6.5 Amyotrophic lateral sclerosis

ALS, also known as "Lou Gehrig's disease," is a fatal neurodegenerative disorder characterized by the progressive loss of motor neurons, muscle atrophy, and paralysis, along with considerable disturbances in metabolic systems, especially lipid metabolism [187]. The hypermetabolism and dyslipidemia in ALS are clinically associated with the severity of symptoms [188, 189]. Specific SPTLC1 variants resulting in sphingolipid overproduction were identified as a cause for juvenile ALS [190]. In a pioneering study, Cutler and collaborators measured lipid levels in the spinal cords of ALS patients, revealing buildups of ceramides, sphingomyelin, and cholesterol esters, accompanied by heightened oxidative stress [191]. ALS patients and SOD1-G93A transgenic rat models of ALS exhibit numerous changes in their glycosphingolipid (GSL) metabolism. Key sphingolipid isoforms, including ceramide, cerebroside, galactosylceramide (GalCer), GlcCer, Lactosylceramide (LacCer), gangliosides (GM3, GM1), and SPMs, are found in higher amounts in the spinal cord tissues of ALS patients. Elevated levels of GlcCer and GM1 have been detected in the cerebrospinal fluid of individuals with ALS [192]. GCS inhibition accelerates the disease's progression, whereas GM3 administration slows it down [193]. It has been reported that there were alterations in sphingoid bases, sphingosine, sphinganine, S1P, and associated enzyme gene expression in FUS(1-359) ALS mice. In the terminal stage of the disease, levels of SPH were elevated, whereas S1P levels decreased. Altered gene expression, characterized by the activation of S1PL and the reduction of S1P phosphatase, indicates that sphingolipid metabolism may serve as a target for drug development in ALS [194]. Interestingly, Dodge et al. observed a reduction in sphingomyelin levels at the onset of paralysis, which returned to normal by the full-paralysis stage in the spinal cords of SOD1-G93A mice [193]. Importantly, Potenza et al. demonstrated that the S1PR1 agonist Fingolimod enhanced neurological function and prolonged survival in mSOD1G93A ALS mice by modulating neuroinflammatory and protective genes (CD11b, Foxp3, iNOS, IL-1β, IL-10, Arg1, and BDNF) in both the motor cortex and spinal cord [195]. Additionally, a phase IIa clinical trial of Fingolimod in ALS patients showed that it was safe, tolerable, and effective in reducing circulating lymphocytes and downregulating immune-related genes, such as CD40 ligand and forkhead box P3. This suggests that Fingolimod may be able to modify immune responses in ALS patients without impairing pulmonary function [196]. These findings underscore the critical role of altered sphingolipid metabolism in ALS pathogenesis, highlighting sphingolipid pathways as promising targets for therapeutic intervention.

6.6 Multiple sclerosis

MS is a chronic, immune-mediated CNS disorder characterized by demyelination, immune cell infiltration, and neuroaxonal damage, influenced by both genetic and environmental factors, with significant societal and economic burdens [197]. Sphingolipids, including GalCer and sulfatides, are essential components of the myelin sheath and play a key role in oligodendrocyte differentiation and myelination. Disruption of sphingolipid metabolism compromises myelin integrity and is closely associated with demyelinating diseases such as MS. Evidence from MS brains shows altered sphingolipid profiles, including elevated ceramide levels around plaques [198], increased sphingosine in normal-appearing white matter [199], and higher hydroxylated sulfatide in white matter [200].

Sphingolipids exert their functions through direct signaling or by signaling via their specific receptors. A study using CSF samples from MS patients revealed elevated lipid signaling, decreased expression of neuroprotective genes, and increased oxidative stress. Lipidomic profiling indicated that ceramides C16:0 and C24:0 in MS CSF induce bioenergetic dysfunction and axonal damage in cultured neurons, highlighting their pathogenic role [201, 202]. Antibodies targeting sphingolipid have been identified in secondary progressive MS patients and are linked to disease progression [203]. Increased levels of CerS2 and ceramide C24:0 in CD11b(+) cells and leukocytes of MS patients facilitate pro-inflammatory actions. The genetic deletion of CerS2 diminishes immune cell infiltration into the CNS and postpones the onset of EAE symptoms in mice. CerS2 modulates Granulocyte colony-stimulating factor-induced C-X-C motif chemokine receptor 2 (CXCR2) expression, thereby facilitating neutrophil migration and contributing to the pathophysiology of MS [204]. Additionally, the accumulation of ceramides in reactive astrocytes impairs sphingolipid metabolism, leading to oligodendroglial apoptosis and demyelination in MS patients, as well as in animal models of demyelination [205]. LacCer, produced by β-1,4-galactosyltransferase 6 (B4GALT6), enhances astrocyte activation, transcriptional programs, and microglia/monocyte recruitment in EAE models of MS, positioning B4GALT6 as a potential therapeutic target for neuroinflammatory conditions, such as MS [206, 207].

Based on these findings, sphingolipid metabolism may be a promising therapeutic target for neurodegenerative diseases such as MS, where astrocyte activation exacerbates the condition. Fingolimod or FTY720 is the first oral disease-modifying therapy approved by the U.S. Food and Drug Administration (FDA) for relapsing forms of MS in 2010 [208]. Its mechanism of action involves the sequestration of lymphocytes in lymph nodes by downregulating S1PR1, thereby reducing their infiltration into the CNS and limiting neuroinflammation [209]. Clinical trials, including the FTY720 Research Evaluating Effects of Daily Oral therapy in MS (FREEDOMS) and Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting MS (TRANSFORMS) studies, demonstrated significant reductions in annualized relapse rates and MRI-detected disease activity compared to placebo and interferon β-1a, respectively [210, 211]. Fingolimod marked a major advancement in MS treatment by offering patients an effective oral alternative to injectable therapies [212, 213]. Despite its efficacy, the drug carries risks, including bradycardia, macular edema, and infections, necessitating close patient monitoring [214, 215]. Its success has also paved the way for the development of newer S1PR modulators with improved safety profiles.

In summary, dysregulation of sphingolipid metabolism plays a fundamental role in the pathogenesis of MS. Elevated ceramide promotes oligodendrocyte apoptosis, demyelination, mitochondrial dysfunction, and neuroinflammation through TNF-α/NF-κB signaling, whereas reduced S1P activity impairs oligodendrocyte precursor cell survival, migration, and remyelination [198, 216]. These metabolic disturbances cause oxidative stress and mitochondrial dysfunction, linking disrupted lipid homeostasis to progressive neurodegeneration in chronic MS lesions [217]. Therapeutic modulation of sphingolipid pathways using Fingolimod and next-generation S1PR modulators such as Siponimod has shown neuroprotective effects beyond immune regulation [218], underscoring the translational potential of targeting sphingolipid signaling in MS.

6.7 Stroke

Stroke, a leading cause of disability and death worldwide, is caused by an acute focal injury of the CNS by a vascular cause, such as cerebral infarction, intracerebral, or subarachnoid hemorrhage [219, 220]. Numerous preclinical and clinical studies have elucidated the mechanisms by which sphingolipid species affect stroke and demonstrated the therapeutic effects of regulating sphingolipids [221-223]. Sphingolipidomic analysis of plasma from patients with acute ischemic stroke revealed dynamic post-stroke alterations consistent with changes observed in the brain sphingolipid profile of a mouse stroke model (middle cerebral artery occlusion, MCAO). Specifically, at 3 hours post-MCAO, levels of long-chain ceramides (d18:1/14:0, d18:1/16:0, d18:1/18:0) increased, while very-long-chain ceramides (d18:1/20:0, d18:1/22:0, d18:1/24:0) decreased. By 24 hours, elevations in both long- and very-long-chain ceramides were observed, accompanied by reduced sphingosine and increased S1P levels. The atorvastatin (cholesterol-lowering drug) protects ischemic brain injury by restoring sphingolipid levels, including long-chain and very-long-chain ceramides and S1P, via modulation of *de novo* ceramide production, inflammation, and oxidative stress [224]. A similar study demonstrated dynamic sphingolipid changes in patients with acute ischemic stroke (AIS), characterized by reduced S1P and very-long-chain ceramides, and elevated long-chain ceramides. Higher ceramide levels were associated with poor functional outcomes, highlighting their potential as prognostic biomarkers for AIS [225-227]. Another study has demonstrated that S1PR2 controls vascular damage, hemorrhage, and cerebrovascular permeability in stroke, with its inhibition reducing matrix metalloproteinase 9 activity, highlighting its potential as a therapeutic target [228]. In contrast, Hasegawa et al. reported that FTY720 improved neurological outcomes, reduced infarct volume, and prevented neuronal death in a mouse model of transient ischemic stroke via S1PR1 activation; these effects were abolished by the S1PR1 antagonist VPC23019 [229]. Beyond acute ischemic stroke, the study found a significant correlation between post-stroke depression severity and serum ceramide levels, with elevated C16:0 and C18:0 levels serving as diagnostic markers and independent risk factors. This finding highlights stage-specific associations and warrants further investigation of the underlying pathophysiological mechanisms [230]. In a rat model of chronic cerebral ischemia, ceramide levels in white matter astrocytes were elevated due to the upregulation of aSMase activity and the downregulation of GCS expression, resulting in oligodendroglial apoptosis and myelin degradation [231]. These changes highlight the crucial role of ceramide in ischemic white matter pathology, particularly in the corpus callosum and internal capsule. Studies also show dynamic sphingolipid alterations post-stroke, with ceramide levels correlating with functional outcomes and post-stroke depression severity [232]. Subarachnoid hemorrhage involves early brain injury followed by delayed vessel constriction and ischemia. In a mouse model of SAH, it was observed that TNFα and S1P signaling in vascular smooth muscle cells increase cerebral arterial tone. Blocking these pathways preserved normal vascular function, reduced neuronal damage, improved brain perfusion, and enhanced neurobehavior in

mice [233]. Modulation of sphingolipid pathways demonstrates therapeutic potential, suggesting that sphingolipids may be promising biomarkers and targets for stroke treatment and recovery.

6.8 Fabry disease

Fabry disease is a pan-ethnic X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase A (GLA) gene. This enzymatic deficiency leads to the accumulation of globotriaosylceramide (Gb3) and its deacylated form globotriaosylsphingosine (Lyso-Gb3), resulting in widespread vascular and multisystem involvement [234, 235]. Clinical symptoms arise from the buildup of glycolipids in tissues, obstruction of blood vessels, or a combination of both factors. Cerebrovascular complications are particularly common, with ischemic stroke occurring nearly 12 times more often in young men (ages 25–44) and about 10 times more frequently in young women compared to the general population [236, 237]. Brain lesions are commonly seen on MRI in Fabry disease patients with stroke, potentially linked to inflammation, as genetic variations in pro-inflammatory markers are associated with an increased risk of small vessel-related brain pathology [238]. Advances in understanding sphingolipid metabolism dysregulation have led to the development of targeted therapies, such as ERT and pharmacological chaperone therapy, both of which aim to reduce substrate accumulation and slow disease progression.

7. Opportunities and Challenges in Clinical Translation

7.1 Current clinical trials and future directions

Table 2 summarizes compounds representing diverse classes of sphingolipid pathway modulators that target key enzymes and receptors, including SphK, SPT, GCS, and S1PR. SphK inhibitors (MP-A08/PF-543, ABC294640) reduce S1P-mediated inflammation and apoptosis. SPT inhibitors (myriocin, L-cycloserine) block *de novo* sphingolipid synthesis, lowering ceramide accumulation in ALS and AD models. GCS inhibitor PDMP decreases Aβ formation by reducing ceramide levels, while S1PR modulators (SEW2871, FTY720) enhance vascular integrity and neuroprotection in stroke and MS. Although most of these agents remain at the preclinical stage, FTY720 (Fingolimod), the first oral S1PR modulator approved by the FDA, demonstrates the translational potential of targeting sphingolipid signaling pathways in neurological disorders.

Since the FDA approval of Fingolimod (FTY720) for the treatment of MS in 2010, several new S1P modulators have been developed, including Siponimod, Ozanimod, and Ponesimod. These drugs were designed to provide precise target selectivity, greater potency, and safer adverse effect profiles. While Fingolimod targets S1PR 1, 3, 4, and 5, Siponimod and Ozanimod are more selective for receptors 1 and 5, and Ponesimod for only receptor 1 [239]. Given the early stage of these medications, multiple clinical trials are underway examining their pharmacokinetics, efficacy, and safety (NCT06408259; NCT06528665; NCT06396039; NCT06133049; NCT05828901; NCT05605782; NCT05516303; NCT05376579; NCT05335031; NCT05319093; NCT05123703; NCT04933552; NCT04926818; NCT04480853). These S1PR modulators are also being assessed for potential use in other neurodegenerative diseases (Table 2).

After discovering that aberrant S1P signaling might be implicated in the pathogenesis of AD, researchers looked towards FTY720 as a potential treatment for the disease [137, 240]. One ongoing phase II clinical trial aims to assess the safety of Siponimod in subjects with AD, its efficacy in slowing the rate of brain atrophy, and subsequent changes in cognition and CSF-derived inflammatory markers (NCT06639282). Another group is set to investigate the benefits of adding Ozanimod to approved AD treatments, including acetylcholinesterase inhibitors, memantine, or both, in a Phase II clinical trial (NCT06862960). One team is using a proprietary radioactive tracer, [11C]-CS1P1, which binds S1PR1, for PET imaging to test their hypothesis that S1PR1 is increased in the brains of subjects with AD and Related Dementia (ADRD) (NCT06129838).

Several clinical trials are also underway examining the efficacy of S1PR modulators in the treatment of acute ischemic stroke. FTY720 has been shown to decrease brain inflammation and infarct expansion while improving neurologic function in individuals recovering from acute stroke [241, 242]. A Phase II clinical trial is underway to investigate the addition of Fingolimod to traditional treatment, including alteplase and mechanical thrombectomy, in subjects with anterior circulation acute ischemic stroke (NCT04675762). Another group is investigating the efficacy and safety of Fingolimod in treating intracerebral hemorrhage, with the hypothesis that the immunomodulatory effects of Fingolimod will protect against the neuroinflammatory damage that occurs after hemorrhage (NCT06087965).

Although multiple active clinical trials are exploring S1PR modulators in neurodegenerative and cerebrovascular diseases, there are no ongoing clinical trials employing sphingosine kinase inhibitors or ceramide synthesis inhibitors for this purpose registered with ClinicalTrials.gov. Research in animal models of HD and ischemia/reperfusion injury has shown that sphingosine kinase inhibitors could be promising

interventions. Selective inhibition of SphK2 in a mouse model of HD mitigates neurodegeneration, while inhibition of SphK1 in a rat model of ischemia/reperfusion injury decreased infarction area [184, 243]. Interestingly, SphK1 inhibition worsens the pathology of AD, and SphK2 downregulation contributes to the pathology of PD [177, 244]. In fact, FTY720, an S1PR modulator, has been shown to promote dopaminergic neuron survival in mouse models of PD [245]. This highlights the necessity of developing enzyme and/or cell-specific precision therapeutics for these conditions. In animal models of AD, inhibitors of ceramide synthesis have demonstrated potential for therapeutic benefits [153, 246, 247]. Further research should be dedicated to understanding the pharmacokinetics of these sphingolipid-altering drugs for their potential application in the treatment of neurodegenerative and cerebrovascular diseases.

Table 2. Potential therapeutic drugs targeting sphingolipid signaling in cerebrovascular and neurodegenerative disease

Drug name	Drug class / Targets	Associated disease model(s)	Pharmacological action	Development stage	Ref.
MP-A08/PF-543	Inhibits Sphingosine kinase (SphK) activity	Ischemia/reperfusion Injury	Alleviates neurological impairments, reduces brain infarction size, lowers brain water content, and decreases neuronal apoptosis.	Preclinical	[260]
ABC294640	Selective SphK2 inhibitor	Huntington's Disease (HD)	Reduces DNA damage, enhances neuronal survival, mitigates neurotoxicity from mutant huntingtin in BACHD transgenic mice models.	Preclinical	[184]
Exogenous S1P	Activates S1PR1	Parkinson's Disease (PD)	Promotes dopaminergic neuron survival in Parkinson's disease by enhancing mitochondrial function, upregulating PGC-1α/NRF-1/TFAM and maintaining ATP levels.	Preclinical	[177]
Myriocin	Inhibits sphingolipid synthesis (via SPT)	Amyotrophic Lateral Sclerosis (ALS)	Inhibits sphingolipid synthesis via SPT, reducing cytotoxic sphingoid bases, improving motor function, survival, and neuropathology, and correcting lysosomal protein sorting in neurodegeneration.	Preclinical	[261]
L-cycloserine	Inhibits ceramide synthesis (via SPT)	Alzheimer's Disease (AD)	Inhibits serine palmitoyltransferase (SPT), reducing ceramide synthesis, which decreases cortical Aβ42 and hyperphosphorylated tau levels in AD models.	Preclinical	[115]
PDMP	Inhibits glucosylceramide synthase	AD	Reduces amyloid β-peptide (Aβ) production by decreasing ceramide levels, without altering ganglioside composition.	Preclinical	[262]
FTY720 (Fingolimod)	S1PR1 agonist / modulator	Multiple Sclerosis	Modulates S1P receptors, sequestering lymphocytes in lymph nodes and reducing neuroinflammation.	FDA Approved (1st oral drug)	[208]
SEW2871	S1P receptor modulator	Stroke	Promotes collateral vessel growth, angiogenesis, and blood–brain barrier integrity after ischemic stroke through eNOS activation, thereby reducing infarct volume and improving neurological outcomes.	Preclinical	[263]
FTY720 (Fingolimod)	Activation of S1PR1	Stroke	Exerts neuroprotection after transient MCAO by activating S1P1 receptors, enhancing pro-survival Akt/ERK/Bcl-2 signaling, and suppressing caspase-3–mediated neuronal apoptosis	Preclinical	[229]

While the development or repurposing of drugs to target sphingolipid metabolism presents a promising therapeutic avenue, ongoing research is also devoted to leveraging specific sphingolipid species as biomarkers for diagnosing diseases, monitoring their progression, and predicting outcomes. The PRIORITY study is investigating potential biomarkers for cerebral amyloid angiopathy (CAA) using lipidomic analysis of cerebrospinal fluid and plasma samples. By collecting longitudinal samples from individuals with CAA over a 24-month period, the study aims to build a comprehensive clinical and biological dataset to inform the creation of a machine learning-based predictive model. This model

could ultimately support clinical diagnosis and guide therapeutic decision-making (NCT06960538).

7.2 Challenges in clinical translation

Targeting sphingolipid metabolism represents a promising approach for treating neurodegenerative and cerebrovascular diseases. However, translating this potential into effective clinical therapies remains a significant challenge. Sphingolipid signaling involves a tightly interconnected intracellular and extracellular network that varies across tissues and cell types. Because sphingolipids regulate essential processes such as proliferation, differentiation, and apoptosis, perturbing a single enzymatic or receptor node can produce unpredictable downstream effects. This biological complexity partly explains why several agents showing efficacy in preclinical models have failed to replicate success in clinical trials. Drugs with broad receptor activity, such as Fingolimod, have demonstrated translational feasibility, whereas compounds with narrow receptor selectivity often face safety or efficacy limitations.

A major hurdle is drug delivery across the BBB. Compounds that are sufficiently lipophilic to diffuse into the CNS risk accumulating in peripheral tissues and causing off-target effects. Conversely, molecules with limited lipid solubility may fail to achieve therapeutic concentrations in the brain. Yet, BBB integrity itself changes dynamically during disease progression, sometimes becoming leaky in later stages, which can unpredictably alter CNS drug levels and toxicity profiles. These variations must be considered when optimizing dosage and safety. Evidently, many sphingolipid targeted drug can cross BBB, such as, S1P receptor modulators, including Fingolimod, Siponimod, and Ozanimod, are highly lipophilic and demonstrate central pharmacodynamic effects, confirming their BBB permeability and direct CNS activity [248]; GCS inhibitors exhibit variable CNS access: miglustat readily penetrates the BBB and is used in neuronopathic lysosomal disorders [249], whereas eliglustat shows limited brain distribution; venglustat is CNS-penetrant but has produced mixed efficacy in recent clinical trials [250]. Recent advances in nanocarrier formulations, receptor-mediated transport systems, and prodrug designs are beginning to overcome these barriers.

Another translational challenge lies in the disease stage and timing of intervention. Conditions such as Alzheimer's and Parkinson's disease are typically diagnosed only after extensive and irreversible neurodegeneration has occurred. Consequently, most sphingolipid-modulating strategies aim to slow rather than prevent disease progression. This underscores the urgent need for reliable, early-stage biomarkers capable of identifying at-risk individuals before neuronal loss becomes irreversible.

Progress in lipidomic technologies has revealed distinct alterations in sphingolipid composition and enzyme activity across various neurological diseases; however, many findings are cell-type specific and derived primarily from post-mortem analyses. Peripheral lipidomics from plasma or cerebrospinal fluid (CSF) provides valuable systemic and CNS-specific information, respectively, while lipid profiling of brain-derived extracellular vesicles offers a minimally invasive window into neuronal and glial sphingolipid states. Integrating these complementary approaches could enable more precise disease monitoring and facilitate patient stratification for clinical trials.

Ultimately, addressing these challenges will require a multidisciplinary effort that unites advances in lipidomics, biomarker discovery, precision medicine, and next-generation drug-delivery systems. As understanding deepens regarding how specific sphingolipid species and pathways contribute to neurodegenerative and vascular pathology, opportunities will expand for developing targeted, personalized therapies that restore lipid balance, protect neural integrity, and improve patient outcomes.

8. Conclusions and Future Perspectives

Over the past three decades, sphingolipids have emerged from being viewed solely as structural membrane components to being recognized as dynamic regulators of neuronal, glial, and vascular signaling. Despite remarkable advances in defining their metabolic pathways and receptor-mediated functions, several critical questions remain unresolved, and major challenges continue to limit the successful translation of sphingolipid-targeted therapies into clinical practice.

A primary unresolved issue concerns the cell-type and context specificity of sphingolipid actions within the CNS. While the opposing effects of ceramide and S1P are well described, their precise spatial and temporal dynamics in distinct neural cell populations remain poorly defined. The heterogeneity among neuronal subtypes, astrocyte states, microglial activation phenotypes, and vascular endothelial cells complicates the interpretation of bulk lipidomic data. Moreover, the subcellular localization of sphingolipid pools, within mitochondria, lysosomes, or the plasma membrane, appears to dictate distinct signaling outcomes, yet current methods rarely achieve this level of resolution. These complexities underscore the need for cell-type-resolved and compartment-specific lipidomic profiling, ideally integrated with single-cell and spatial transcriptomic approaches.

From a translational perspective, therapeutic modulation of sphingolipid metabolism faces multiple barriers. Many key enzymes and receptors involved in sphingolipid pathways are ubiquitously expressed, raising concerns about systemic side effects when targeted pharmacologically. Although several S1P receptor modulators, such as Fingolimod, Siponimod, and Ozanimod, have demonstrated clinical efficacy in multiple sclerosis and other inflammatory disorders, their off-target effects and immunosuppressive properties limit their broader applicability [251]. Furthermore, challenges in BBB penetration, variable lipid solubility, and species-specific pharmacokinetics complicate the translation of preclinical findings. The development of CNS-selective modulators, prodrug formulations, or nanocarrier-based delivery systems could help overcome these limitations, but their safety and long-term metabolic consequences remain uncertain. Another major challenge lies in identifying robust, disease-specific sphingolipid biomarkers that can reliably distinguish between physiological fluctuations and pathological remodeling.

Methodologically, lipidomic quantification is technically demanding, requiring stringent control of pre-analytical variables, and the lack of standardized protocols across laboratories hinders data reproducibility and cross-study comparison. *In vivo* imaging of sphingolipid metabolism and turnover is still in its infancy, representing another frontier that could transform our mechanistic understanding.

Despite these challenges, the field is advancing toward a more integrative and systems-level understanding of sphingolipid biology. Emerging multi-omics approaches that combine lipidomics, metabolomics, and proteomics, with high-resolution imaging and computational modeling are redefining how sphingolipid signaling is mapped in space and time. These strategies will be crucial for mapping the spatiotemporal dynamics of sphingolipid signaling and identifying actionable molecular nodes. Moving forward, progress will depend on delineating cell-type-specific lipid signaling networks, developing BBB-permeable and selective modulators, and validating clinically robust sphingolipid biomarkers that serve diagnostic, prognostic, and pharmacodynamic functions. The expanding recognition of sphingolipids as measurable biomarkers [252-256] for metabolic and neurological disorders holds particular promise, enabling earlier diagnosis, personalized intervention, and real-time therapeutic monitoring. Collectively, these advances position sphingolipid research at the forefront of precision neurotherapeutics and open new opportunities for translating mechanistic insights into meaningful clinical outcomes.

In conclusion, sphingolipid research stands at an exciting yet challenging frontier. Bridging the gap between mechanistic insight and clinical application will require not only technological innovation but also conceptual shifts toward cell-type specificity, systems-level integration, and precision therapeutic design. The coming years promise to clarify how the manipulation of sphingolipid metabolism can move from theoretical potential to tangible impact in human neurological health.

Author contributions

The initial idea for this review was conceived by MNI, NM, and MIHB, and the manuscript was written and revised by MNI, NM, MIHB, NIK, LA, AJ, TA, and RI. In addition, NIK, and TA, contributed to the preparation of the illustrations and tables; MNI, NM, and MIHB read, reviewed, and approved the final manuscript. The final version of the manuscript was approved by all the authors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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