Review

Nutritional roles and therapeutic potentials of dietary sphingomyelin in brain diseases

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(Received 11 October, 2023; Accepted 12 December, 2023; Released online in J-STAGE as advance publication 26 December, 2023)

Sphingolipids have recently gained interest as potential players in variety of diseases due to their import roles in human body particularly, the brain. As sphingomyelin is the most common type of sphingolipids, deficits in its distribution to brain cells may contribute to neurological anomalies. However, data is limited regarding the impact of different levels of dietary sphingomyelin intake on neural function especially if this approach can boost cognition and prevent neurological disorders. This review evaluates the effect of dietary sphingomyelin and its metabolites (ceramide and sphingosine-1-phosphate) in animal models and in humans, with a primary focus on its impact on brain health. Additionally, it proposes multiple neuroenhancing effects of sphingomyelin-rich diet. This presents an opportunity to stimulate further research that aims to determine the therapeutic value of dietary sphingomyelin in preventing, improving or slowing the progression of central nervous system disorders.

Key Words: **sphingomyelin, dietary supplementation, brain health, disorders of the CNS, neuroenhancing effects**

Sphingomyelin (SM) is the most abundant sphingolipid that plays a vital role as a structural component found in mammalian cell membrane. Structurally, SM composition consists of a fatty acid chain bonded to an amide group and a long chain sphingoid base (sphingosine) as a backbone with polar head group of phosphorylcholine.[1] Functionally, SM has numerous roles as it is involved in cell signaling during proliferation, cell growth, differentiation, motility, apoptosis, cell survival, migration, and angiogenesis in addition of being a receptor for toxins and microbes.[2] The degradation of SM is by initiated by the activation of sphingomyelinase (SMase) enzyme leading to the release of SM metabolites such as ceramide (Cer) and sphingosine 1-phosphate (Sph-1-P) which are also crucial for the cellular morphology and activity.[2] In particular, SM contributes to the brain functioning especially at early stages of life as it enhances cognitive maturation. Notably, it is a highly concentrated lipid in neural tissues (represents about 10% of brain lipids), especially in the membranous myelin sheath surrounding neuronal axons of the central nervous system (CNS).[2] Besides being a major component of myelin sheath, the other distinctive functions of SM in brain include its behavior as a driver of synaptogenesis and neurogenesis, as well as neuronal communication.[3] This emphasizes the pivotal role of SM in the development of the CNS and maintain of its hemostasis.

An increasing body of evidence is suggesting the implications of SM and its metabolites alterations in the pathogenesis of several brain disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) and stroke.[4–7] Additionally, low levels of SM were associated with psychiatric disorders such as schizophrenia (SCZ) and chronic stress related disorders.[8–10] On the other hand, previous data has shown that SM-enriched diet significantly enhanced neurocognitive development in neonates.[11] It was also found to enhance CNS myelination and myelin thickness in both animals and humans.[12,13] Furthermore, emerging evidence indicates the abilities of SM based supplementation in antagonizing features of AD-related proteopathy.[14]

Nevertheless, despite the increasing data that supports of the nutritional benefits of sphingolipids (SLs) particularly SM, in neurological disorders, a limited number of reviews have focused on attracting the attention regarding the possible roles of SM rich diet in improving neural function and cognitive development. This review discusses first the existing links between SM/Cer system perturbations and the major neuropsychiatric disorders particularly AD, PD, MS, stroke, and SCZ. Then, it sheds light on the potential positive effects of SM-based nutritional supplementation in CNS diseases and suggests several neuroenhancing mechanisms of this poorly explored diet.

Overview on Biochemical Characteristics of SM

Nutritional sources. Dietary sources of SM are distributed in a wide variety of plant and animal-based foods. However, animal-based foods such as milk, dairy products, and eggs are major sources of dietary SM due to their availability and relative low cost.[15] The SM concentrations in milk vary among species and stages of lactation. There is a lower amount of SM and Cer in infant formulas and commercial milks for adults than in human breast milk.[16] The SM content in human and animal milk supports its essentiality in neonatal development. Thus, milk contains 23.4–47.3 wet weight ratio (ww) of SM, while cheese and butter contain 24.3–365.7 ww and 29.2–44.4 ww, respectively. Chicken egg yolk offers 190.0 ww of SM. Other SM rich sources include almond [contains 304.3 dry weight ratio (dw) of SM], pecans (373.5 dw), pine nut (376.9 dw), walnut (612.9 dw), and microalgae (250–2,760 dw).[15] The concentration of the consumed SM varies depending on the dietary fat composition of meals consumed by a human. During lactation, the baby ingests only ~150 mg of SM per day. This amount increases in adulthood as an ordinary Western diet offers 0.3–0.4 g of SLs per day, with a large part represented by SM in meat, milk, egg products, and fish.[17] Table 1 summarizes the concentrations of SM in mg per 100 g of different nutritional sources.

Absorption, metabolism and brain distribution. The hydrolysis of dietary SM to Cer and phospho-choline occurs in the intestinal tract, specifically in the mid part of jejunum, where alkaline SMase (alk-SMase) the enzyme responsible for this reaction is abundant.[19] In humans, there are two sources of alk-SMase: the bile and the intestinal mucosa. Thus, following a meal rich in SM (western meal), the release of cholecystokinin

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doi: 10.3164/jcbn.23-97

Table 1. Content of sphingomyelin in food. Data obtained from Wang *et al.*[18]

Sphingolipid	Nutritional source	Amount (mg/100 g)
Sphingomyelin	Egg	82.0[b]
	Full-fat soy flakes	45.7[a,c]
	Chicken	41.8[b,c]
	Cheese	24.3–365.7[a,c]
	Milk	23.4–47.3[a,c]
	Butter (batch, continuous)	29.2–44.4[a,c]
	Yogourt	10.4[a,c]

[a]Represents dry weight. [b]Represents wet weight. [c]Estimation based on reported sphingolipid content (g/mol) using 751 as an average molecular weight for sphingomyelin.

(CCK) by duodenum stimulates the contraction of gallbladder and liberation of bile alk-SMase together with bile salts in the intestine. At the same time, CCK stimulates the secretion of trypsin by pancreas leading to dissociation of both intestinal alk-SMase and neutral ceramidase from the mucosa into the lumen. The digestion of SM then occurs by alk-SMase and neutral ceramidase in the presence of bile salt producing sphingosine which is absorbed in the epithelial cells and converted to either to fatty acid or to Cer.[19] Previous results have showed that the liver has the highest neutral-SMase activity while the kidney and brain have high levels of both neutral-SMase and ceramidase activities, which indicates a high production of Cer in liver and Cer/sphingosine in the kidney and brain.[20] During development and aging, the activity of these enzymes increases significantly, likely, due to the correlation of SLs metabolism with maturation and neurodegeneration.[20] The aborted sphingosine is converted to chylomicron palmitic acid in enterocytes.[17] The *de novo* synthesis of SM occurs via SM synthase 1 (found in the trans Golgi cisterna) and SM synthase 1 (found in the localized at the plasma membrane as well as the Golgi) which catalyze the transfer of the phosphocholine (PCh) head group of phosphatidylcholine (PC) to Cer (Cer + PC → SM + diacylglycerol).[21] After SM has been absorbed and metabolized through the intestinal wall, it is transferred to the brain and other tissues based on the kinetics properties of the SLs transporters and blood-brain barrier (BBB).[22] In the brain, SM and its metabolites serve as a key actor for a variety of functions (Fig. 1).

Physiological Roles of SM for CNS Homeostasis

SM is an important element for different neurological functions including neurogenesis, synaptogenesis, synaptic transmission, myelin sheath formation, neuronal-glial connection, and neuron differentiation.[3] Milk SM is an important source of choline the precursor of acetylcholine which is a key neurotransmitter especially for neurodevelopment.[23] Dietary SM provided to children ideally by human breast milk enhances cognitive development by upregulating oligodendrocytes mitotic activity leading to increased axon myelination.[12] Membranous myelin sheath contains particularly highly amounts of hydroxySMs and long-chain SMs. [24] Due to their asymmetrical distribution, these lipids provide the biophysical properties for membrane curvature and myelin compaction.[3] Besides the structural roles, SM is also a bioactive element that when catabolized by either neutral or acidic SMase its primary metabolite Cer acts as a potential lipid second messenger or cellular signals transductor involved in a variety of cellular pathways such as those related to neuronal cell response to extracellular stimuli and to stress.[25] Hence, extracellular insult mediated by different stressors such as tumor necrosis factor (TNF), Fas ligands, and chemotherapeutic agents induces the activation the SMases-mediated conversion of membrane SM into Cer. The latter coordinates distinct cellular stress response pathways by regulating proteins phosphorylation as well as multiple downstream targets such as interleukin converting enzyme (ICE)-like proteases, stress-activated protein kinases, and the retinoblastoma gene product. These pathways can result in cell cycle arrest, apoptosis, and cell senescence.[26] The reason why an increase in Cer levels could be a more adequate indicator of CNS insults than elevated SM levels as Cer release from membranous SM is triggered by insulting stimuli of neural cells.

Implications of SM Deficit in Brain Disorders

Neurodegenerative diseases. The involvement of SM anomalies in AD development has been previously explored and

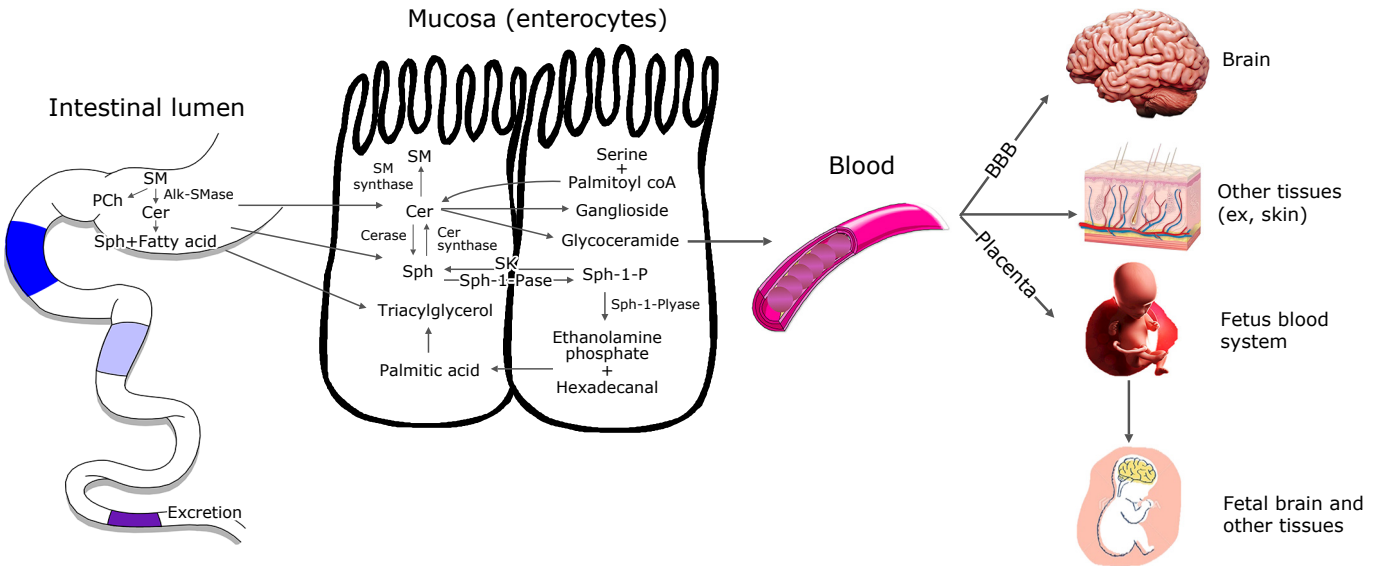

Fig. 1. SM absorption, metabolism, and distribution to the brain. Alk-SMase, alkaline sphingomyelinase; BBB, blood-brain barrier; Cer, ceramide; SM, sphingomyelin; Sph, sphingosine; Sph-1-P, sphingosine-1-phosphate; Sph-1-Pase, sphingosine-1-phosphatase; SK, sphingosine kinase; PCh, phosphocholine.

doi: 10.3164/jcbn.23-97

demonstrated.[7,27,28] This is believed to be mediated by both direct and indirect interactions between SM/cer system anomalies and Aβ formation, trafficking and clearance as reported by both laboratory and animal studies.[28] One *in vivo* study showed that the inhibition of acid SMase (the enzyme that degrades SM to Cer and phosphorylcholin) induced a decrease in reactive astrocyte secretion of mitotoxic extracellular vesicles and improved AD pathology in the 5xFAD mouse.[27] Qi *et al.*[29] also observed low levels of sphingosine, sphinganine, S1P, sphinganine-1-phosphate, and SM in $A\beta_{25-35}$-stimulated BV2 microglia. In another human study, He *et al.*[7] analyzed the levels of SLs and sphingolipid hydrolases in brain samples from AD patients and age-matched normal individuals. They found a meaningful increase of acid SMase and acid ceramidase (AC) activity in AD patients compared to controls, and this resulted in SM reduction and Cer elevation. Furthermore, Mielke *et al.*[28] included 120 probable AD patients to examine the link between their plasma levels of Cer, dihydroceramides (dhCer), SM, dihydrosphingomyelin (dhSM), and ratios of SM/Cer or dhSM/dhCer and their disease progression. The linear mixed effects models revealed that higher plasma levels of SM, dhSM, SM/Cer, and dhSM/dhCer ratios are negatively associated AD progression measured by the Mini-Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores.[28] Particularly, the dhSM/dhCer and SM/Cer ratios were the strongest predictors of clinical progression as higher values significantly declined MMSE and increased ADAS-Cog, thereby, predicting less progressed disease among AD patients. Additionally, there is an increasing body of evidence that supports the implications of lipid dyshomeostasis in PD development.[30] Particularly, it is suggested that SM and its metabolites play a role the pathophysiology of PD due to its involvement in the myelin sheath formation, nerve impulse transmission, presynaptic plasticity, and neurotransmitter receptor localization.[3] Abbott and her colleagues analyzed total Cer and SM levels in postmortem frozen brain gray matter and white matter samples from 9 sporadic PD cases and 10 control cases.[6] Remarkably, the levels of both SLs were lower in PD anterior cingulate cortex by 53% and 42% respectively compared to control levels. In contrast, the inhibition of Cer synthesis by myriocin (Myr) reduced intracellular aggregation of α-synuclein fibrils which promoted their sequestration into lysosomes in a cellular model of PD.[31] Furthermore, a decrease in SM levels, in particular those of the C22–C26 subspecies, was identified in post-mortem brain tissue of patients died from Huntington's disease, another neurodegenerative disease that affects primarily the caudate nuclei and putamen.[32]

Multiple sclerosis. Disruption of lipid profile of SM patients was previously evidenced suggesting a potential.[33] Moreover, current data supports the roles of sphingolipid as players in the MS pathogenesis. [34] Indeed, Chami *et al.*[5] analyzed the effects of acid SMase on myelin repair after acute and chronic demyelination and found positive results. Thus, they showed that acid SMase deficient mice had greater myelin recovery and oligodendrocytes count, in addition to lower detrimental astroglial reaction after 2 weeks remyelination in comparison to wild-type animals. This can be interpreted as the involvement of increased acid SMase induced SM degradation in exacerbating CNS demyelinating disorders as it may lead to decompaction and disruption of myelin sheath structure. Significantly higher levels of dhCer were identified in patients with active MS while lower levels of dhCer, Cer, and SM subspecies were found in patients with inactive MS.[35] This may suggest that decreased SM degradation is associated with less SM activity. Furthermore, the reduced consumption of essential lipids for SM biosynthesis was shown to increase demyelination and delay remyelination in humans after pathological neuronal damage. On the other hand, fish oil mixture (a nutritional source rich in SM) induced maturation of the human OPC ultimately leading to increase in myelin basic protein, myelin glycoprotein, and SM synthesis.[36]

Stroke. SLs are presumably involved in the pathogenesis of cardiovascular diseases including stroke.[37] Sui *et al.*[38] collected blood samples from 245 participants who were divided into healthy controls, pre-diabetes, and diagnosed diabetes. Then, they measured the levels of 8 major sphingolipid metabolites using high-performance liquid chromatography-tandem mass spectrometry and routine laboratory assays to determine blood values. Their findings reported a notable decrease in SM, S1P, sphinganine and sphingosine among pre-diabetic and diabetic patients compared to healthy controls. Additionally, reduced exogenous SM was found to favor atherosclerosis and hyperlipidemia in animal studies.[39–41] This suggests that low levels of SM and some particular SM subspecies is linked to worse cardiovascular risks, therefore, may increase the susceptibility to cerebral vascular events. This is supported by a recent observation of Zeng *et al.*[42] who conducted a quantification of endogenous sphingolipid content in stroke rats and identified a meaningful decrease in S1P in three biological samples including serum, brain tissue and HT22 cells from affected animals. An additional recent study by Lee *et al.*[4] revealed that compared to nonstroke controls, acute ischemic stroke (AIS) patients showed significantly lower levels of S1P and very-long-chain Cer. However, higher levels of long-chain Cer were found in AIS patients and were correlated with poor functional outcomes after adjusting for age, sex, hypertension, and National Institutes of Health Stroke Scale (NIHSS) score at admission.

Schizophrenia and stress disorders. The exact pathogenesis of SCZ is still debated with different pathomechanistic models being proposed. Nonetheless, in a recent pioneer study Tessier *et al.*[8] performed a lipidomic analysis of 74 SCZ patients clinically stabilized by antipsychotic medication and 40 matched healthy subjects. Remarkably, SCZ patients with low SM membrane content (c/SM− SCZ) had significantly worse clinical profile assessed by positive and negative syndrome scale (PANSS) and more severe cognitive impairment as indicated by the Continuous Performance Test, Salience Attribution Test and Wisconsin Card Sorting Test compared to those with higher Sm membrane content (c/SM+ SCZ) patients. These findings agreed with previous observations by Schmitt *et al.*[10] which reported significantly lower quantities of SM in post-mortem brain tissues from patients with SCZ. Ponizovsky *et al.*[43] identified a correlation between decreased erythrocytic levels of SM and negative symptoms in patients with SCZ. Whereas Colón-Sáez and Yakel[44] showed that the enzymatic breakdown of SM by SMase leads to disruption of lipid rafts in rat primary hippocampal neurons which in turn results in significant alterations in the desensitization kinetics of native and expressed α7 nicotinic acetylcholine receptors (α7 nAChRs). Since, α7 nAChRs deficiency was demonstrated in SCZ patients, SM supplementation or acid SMase/Cer system targeting was suggested as a potential treatment to improve disrupted lipid rafts and α7nAchR function among SCZ patients.[44,45] Furthermore, Esaki *et al.*[46] reported a significant reduction in S1P levels in the corpus callosum of SCZ patients but not in those with major depressive or bipolar disorders in comparison with age- and sex-matched controls. This reduction shown in other studies was speculated to be the result of SCZ-associated upregulation in S1P-degrading enzymes genes.[45]

Abnormal SM levels may also be correlated with stress disorders. In an animal experiment, rats were exposed to chronic unpredictable stress and their lipidic changes in different brain areas were evaluated.[9] Thus, stress-induced alterations were mostly seen in the prefrontal cortex (PFC) where the SM and dhSM levels deceased profoundly while Cer levels increased. The authors attributed these anomalies in SLs metabolism to either dysregulated (increased) SMase activity leading to higher

hydrolysis of SM and dhSM into Cer and dhCer, respectively; or a decreased SM synthase activity causing lesser *de novo* synthesis of SM from its metabolites.

Potential Therapeutic Effects of SM Supplementation in Brain Disorders

SM-based dietary supplementation may be an interesting approach to treat brain diseases due to its multiple possible therapeutic mechanisms reported by previous studies. Although data is still highly limited, we speculate that the clinical benefits of SM diet are mediated by the following effects.

Direct neuroprotective and neuroenhancing effects. Natural nutritional products such as fruits, vegetables, coffee, green tea, soy products, nuts, and fermented-food have a well demonstrated neuroprotective action and their regular intake is associated with lower risks of neurological function decline.[47,48] SM-rich diets may also directly promote brain health by enhancing neuronal communication, neuronal survival (e.g., by upregulating cellular clearance of toxic elements), neurogenesis, oligodendrocytes mediated myelination and neuronal development. Hence, Yuyama *et al.*[14] used plant-derived and animal-derived SM to effectively promote the synthesis of extracellular vesicles (EVs) by neurons *in vitro*. In the same experiment, mice models of AD who were given oral doses of plant glucosylceramide (GlcCer) showed pronounced reduction in Aβ levels and plaque features in addition to notable improvement in cognition function. Furthermore, treatment with GlcCer was associated with a considerable increase in EVs including NCAM-1, L1CAM, and Aβ which suggested the SM- dependent enhancement of EVs release and Aβ clearance in both *in vitro* and *in vivo*.[14] In an experiment carried by Albi *et al.*[49] embryonic hippocampal cells (HN9.10) were cultured in the presence of human milk SM at concentrations ranging from 0.6% to 31%. Notably, the treated hippocampal cells showed growth in neurites supporting the roles of dietary SM in enhancing neurogenesis. In another study, Oshida *et al.*[13] tested the effects of dietary SM on CNS myelination in developing rates who were treated with SM biosynthesis inhibitor cycloserine (LCS). Thus, the SM-supplemented rats displayed significantly higher levels of the myelin dry weight and myelin total lipid content compared to SM non-supplemented rats. Consistently, Schneider *et al.*[12] analyzed the impact of dietary SM concentrations on the brain myelination and cognitive development during the first three months of life in 54 males and 34 females under the age of 2 years. Interestingly, they found a significantly positive association between higher nutritional SM levels and the verbal development in the first two years of life, the myelin composition in brain at 12–24 months, and the delayed onset and/or more prolonged myelination rates in different brain areas. They also explored the mechanisms of these findings using *in vitro* models and observed an SM diet-mediated increase in oligodendrocytes precursor cells (OPCs) proliferation, maturation and differentiation, in addition to amelioration in axonal myelination. Furthermore, in a randomized control trial including 24 very-low-birth-weight preterm infants admitted in the neonatal intensive care unit, nutritional intervention with SM-fortified milk (in which SM represents 20% of all phospholipids composition) had led to better neurobehavioral development (assessed by the Behaviour Rating Scale of the BSID-II, the Fagan test scores, the latency of VEP, and sustained attention test scores) at 18 months compared to supplementation with milk containing less SM (13% of all milk phospholipids).[11]

Lipids-lowering effects. Several animal studies have demonstrated that dietary SM inhibits intestinal absorption of cholesterol and decreases the total hepatic lipid, hepatic triglycerides and cholesterol levels.[11,40,41] The dietary SM-mediated inhibition of cholesterol absorption is dose dependent[50] and is more effective with milk SM than egg SM.[51] In a randomized crossover study including healthy adult males and females, milk SM-enriched diet increased serum HDL cholesterol levels without affecting the serum triglycerides, total cholesterol, non-HDL cholesterol levels, as well as cholesterol absorption and fractional synthesis rate.[52] Nonetheless, the authors indicated several limitations such as the small sample size ($n = 10$), the possible insufficient dose of SM, solubilizing SM with olive oil which could have led to confounding findings, and the non-analysis of SMase activity. SM has high affinity to cholesterol which slows the rate of luminal hydrolysis, micellar solubilization, and micellar lipids uptake by enterocytes.[51] Thus, SM was found to inhibit cholesterol absorption and simulate cholesterol transport by downregulating the Niemann-Pick-Like Protein 1 (NPC1L1) mRNA, which is a key player in cholesterol absorption.[50] Additionally, dietary SM decreases the thermodynamic activity of cholesterol monomers lading to reduced uptake and esterification of cholesterol.[40] Whereas the triglycerides-lowering effects of dietary SM were found to be mediated by inactivation of the LXR-SREBP-1c pathway.[53] At the same time, imbalanced lipid homeostasis is a known factor that contributes to the development of different neurological diseases such as stroke, AD, PD, Huntington's disease, motor neuron diseases[54–56] as well as mental disease such as SCZ and autism spectrum disorders.[57,58] Therefore, the hypocholesterolemic and hypotriglyceridemic abilities of dietary SM may reduce the susceptibility to dyslipidemia-associated CNS damage.

Reduction in neuroinflammation. Dietary milk SM was found to exhibit antagonistic effects against systemic inflammation and LPS-mediated macrophage activation in mice.[59] Moreover, dietary SM was revealed to alleviate inflammation in rodents with experimentally induced colitis.[60] Milk SM was demonstrated by Norris *et al.*[61] to reduce inflammation and markers of macrophage infiltration in adipose tissue among high-fat-diet-induced obese mice. On the other hand, Cer and Cer 1-phosphate were reported to alter the inflammatory response to LPS through the inhibition of TNF-α and macrophage inflammatory protein-2 (MIP-2) release by macrophage.[62] Exogenous Cer down regulated the activity of macrophages by suppressing the TNF-α converting enzyme, the one responsible for pro-TNF maturation to soluble TNF.[63] Cer species were also recently involved in stimulating pro-apoptotic pathways in neutrophils in addition to modulating their migration, phagocytosis and superoxide production.[64] Microglia activity in the brain of LPS-exposed mice was inhibited by ceramide administration particularly C2 Cer which downregulated multiple signaling pathways including ROS, MAPKs, PI3K/Akt, Jak/STAT, and TLR4 signaling.[65] Inflammation is a key mechanism in the pathogenesis of CNS disorders.[66,67] Since exogenous Cer can across the BBB,[22] it may exert its anti-inflammatory effects on brain, thereby, reducing the immune-mediated neural cell loss and demyelination. Possible similar effects with dietary SM diet are not be excluded.

Decrease in brain uptake of neurotoxic elements. Disruption of BBB and intestinal permeability (gut-blood barrier dysfunction) is a key contributor of multiple neurological diseases.[68,69] This may due to the passage of neurotoxic elements such as gut microbiota-derived products and ingested metals/chemicals to CNS where they cause pathological changes. SM enriched diet may prevent this by restoring/maintaining the integrity of BBB and GBB. Thus, Milard *et al.*[70] found that milk SM induced an increase in tight junction expression (Occludin, ZO-1) possibly by favoring the expression of IL-8. This suggested the potential of SM to repair dysfunctional barriers including GBB and BBB. Indeed, chronic consumption of bovine milk (key source for SM) reversed the BBB hyperpermeability induced by long chain saturated fatty acids (LCSFA) enriched diet. Also, it is known that BBB and GBB permeability increases during local and systemic inflammation.[72,73] The fact that dietary

doi: 10.3164/jcbn.23-97

SM/Cer can reduce inflammation and perhaps neuroinflammation, supports its likelihood to improve BBB and GBB function, thereby, preventing the transfer of neurotoxic molecules to CNS.

Simultaneous consumption of other beneficial SL. SM rich foods (milk, dairy products, eggs, and nuts[15]) usually contain other nutritional elements such as gangliosides (found in egg yolk, and dairy products[74]) and omega-3 fatty acids (fortified dairy products and nuts[75,76]) which were shown to have therapeutic potentials in neurological diseases. Current evidence suggests that dietary gangliosides may have positive influence on cognitive functions.[77] In PD mice, daily administration of GM1 ganglioside for either 5 or 6 weeks reversed the loss of substantia nigra dopamine neurons, increased the levels of striatal dopamine, and decreased the accumulation of α-synuclein aggregates.[78] In line with this, treatment with GM1 ganglioside prevented the microglial activation and neuroinflammatory responses secondary to α-synuclein in mice models of PD.[79] Similarly, the beneficial effects of omega-3 fatty acids supplementation in reducing the susceptibility for neurological disease are increasingly recognized. Not only this, but treatment with omega-3 fatty acids was found to be effective in improving neurodegenerative diseases in their early stages.[80]

Other possible positive effects on brain health. Besides the previous suggested mechanisms, SM rich diet may also contribute on decreasing the risk of metabolic syndrome-related CNS diseases (i.e., stroke) by its possible anti-atherosclerotic effects. This is supported by a study conducted by Chung *et al.*[39] in which they reported a remarkable reduction in atherosclerotic lesion area in the aortic arch in apoE−/− mice treated with long-term dietary SM supplementation. Such effects may be due to the ability of exogenous SM to improve lipids metabolism (as shown above) which is a key element in the pathogenesis of atherosclerosis.[80] Moreover, exogenous dietary SM was found to exert attenuate tissular fat accumulation and obesity linked inflammation[61] which may lead to better cardiovascular health, ultimately, preventing pathological changes in cerebral vasculature. Additionally, it was revealed that SM supplementation resulted in regulation on the abundance of Lactobacillus, Faecalibacterium, Dubosiella, Turicibacter, and Parasutterella communities in the mice gut microbiota.[60] Hence, the regulation of gut flora abundance is another possible indirect neuroenhancing effect of SM rich diet as it may lead to modulation of gut dysbiosis which is involved in the pathogenesis of multiple neuropsychiatric conditions including AD, PD, MS, SCZ, ASD, anxiety, and mood disorders, etc.

SM supplementation may confer protection against pathological alterations in brain health and improve different CNS conditions via several direct and indirect neuropromoting mechanisms. Nonetheless, current data is highly limited and doesn't allow to adequately determine the benefit of SM diet in the context of neurological disorders. Therefore, further studies are warranted to investigate how SM rich diet affects brain function and whether it could have therapeutic implications in the management of different neurological disorders of CNS.

Author Contributions

SA drafted, prepared, and reviewed the manuscript.

Acknowledgments

Author thanks the company Scientia Vallis (Paris, France) represented by Dr. Mohamed Amine Haireche, for their invaluable assistance in the editing of this review.

Abbreviations

alk-SMase	alkaline sphingomyelinase
BBB	blood-brain barrier
Cer	ceramide
CNS	central nervous system
PCh	phosphocholine
SK	sphingosine kinase
SLs	sphingolipids
SM	sphingomyelin
Sph-1-P	sphingosine-1-phosphate
Sph-1-Pase	sphingosine-1-phosphatase

Conflict of Interest

No potential conflicts of interest were disclosed.

References

1 Chakraborty M, Jiang XC. Sphingomyelin and its role in cellular signaling. *Adv Exp Med Biol* 2013; **991**: 1–14.
2 Bienias K, Fiedorowicz A, Sadowska A, Prokopiuk S, Car H. Regulation of sphingomyelin metabolism. *Pharmacol Rep* 2016; **68**: 570–581.
3 Signorelli P, Conte C, Albi E. The multiple roles of sphingomyelin in Parkinson's disease. *Biomolecules* 2021; **11**: 1311.
4 Lee TH, Cheng CN, Chao HC, *et al*. Plasma ceramides are associated with outcomes in acute ischemic stroke patients. *J Formos Med Assoc* 2022; **121 (1 Pt 1)**: 43–50.
5 Chami M, Halmer R, Schnoeder L, *et al*. Acid sphingomyelinase deficiency enhances myelin repair after acute and chronic demyelination. *PLoS One* 2017; **12**: e0178622.
6 Abbott SK, Li H, Muñoz SS, *et al*. Altered ceramide acyl chain length and ceramide synthase gene expression in Parkinson's disease. *Mov Disord* 2014; **29**: 518–526.
7 He X, Huang Y, Li B, Gong CX, Schuchman EH. Deregulation of sphingolipid metabolism in Alzheimer's disease. *Neurobiol Aging* 2010; **31**: 398–408.
8 Tessier C, Sweers K, Frajerman A, *et al*. Membrane lipidomics in schizophrenia patients: a correlational study with clinical and cognitive manifestations. *Translational Psychiatry* 2016; **6**: e906.
9 Oliveira TG, Chan RB, Bravo FV, *et al*. The impact of chronic stress on the rat brain lipidome. *Mol Psychiatry* 2016; **21**: 80–88.
10 Schmitt A, Wilczek K, Blennow K, *et al*. Altered thalamic membrane phospholipids in schizophrenia: a postmortem study. *Biol Psychiatry* 2004; **56**: 41–45.
11 Tanaka K, Hosozawa M, Kudo N, *et al*. The pilot study: sphingomyelin-fortified milk has a positive association with the neurobehavioural development of very low birth weight infants during infancy, randomized control trial. *Brain Dev* 2013; **35**: 45–52.
12 Schneider N, Hauser J, Oliveira M, *et al*. Sphingomyelin in brain and cognitive development: preliminary data. *eNeuro* 2019; **6**: ENEURO. 0421-18.2019.
13 Oshida K, Shimizu T, Takase M, Tamura Y, Shimizu T, Yamashiro Y. Effects of dietary sphingomyelin on central nervous system myelination in developing rats. *Pediatr Res* 2003; **53**: 589–593.
14 Yuyama K, Takahashi K, Usuki S, *et al*. Plant sphingolipids promote extracellular vesicle release and alleviate amyloid-β pathologies in a mouse model of Alzheimer's disease. *Sci Rep* 2019; **9**: 16827.
15 Yang F, Chen G. The nutritional functions of dietary sphingomyelin and its applications in food. *Front Nutr* 2022; **9**: 1002574.
16 Dei Cas M, Paroni R, Signorelli P, *et al*. Human breast milk as source of sphingolipids for newborns: comparison with infant formulas and commercial cow's milk. *J Transl Med* 2020; **18**: 481.
17 Nilsson Å, Duan RD. Absorption and lipoprotein transport of sphingomyelin. *J Lipid Res* 2006; **47**: 154–171.
18 Wang X, Wang Y, Xu J, Xue C. Sphingolipids in food and their critical roles in human health. *Crit Rev Food Sci Nutr* 2021; **61**: 462–491.

19 Duan RD. Alkaline sphingomyelinase: an old enzyme with novel implications. *Biochim Biophys Acta* 2006; **1761**: 281–291.
20 Sacket SJ, Chung HY, Okajima F, Im DS. Increase in sphingolipid catabolic enzyme activity during aging. *Acta Pharmacol Sin* 2009; **30**: 1454–1461.
21 Yamaji T, Hanada K. Sphingolipid metabolism and interorganellar transport: localization of sphingolipid enzymes and lipid transfer proteins. *Traffic* 2015; **16**: 101–122.
22 Eguchi K, Mikami D, Sun H, *et al*. Blood-brain barrier permeability analysis of plant ceramides. *PLoS One* 2020; **15**: e0241640.
23 Nilsson Å. Role of sphingolipids in infant gut health and immunity. *J Pediatr* 2016; **173**: S53–S59.
24 Staellberg-Stenhagen S, Svennerholm L. Fatty acid composition of human brain sphingomyelins: normal variation with age and changes during myelin disorders. *J Lipid Res* 1965; **6**: 146–155.
25 Jana A, Pahan K. Sphingolipids in multiple sclerosis. *Neuromolecular Med* 2010; **12**: 351–361.
26 Hannun YA. Functions of ceramide in coordinating cellular responses to stress. *Science* 1996; **274**: 1855–1859.
27 Crivelli SM, Quadri Z, Vekaria HJ, *et al*. Inhibition of acid sphingomyelinase reduces reactive astrocyte secretion of mitotoxic extracellular vesicles and improves Alzheimer's disease pathology in the 5xFAD mouse. *Acta Neuropathol Commun* 2023; **11**: 135.
28 Mielke MM, Haughey NJ, Bandaru VV, *et al*. Plasma sphingomyelins are associated with cognitive progression in Alzheimer's disease. *J Alzheimers Dis* 2011; **27**: 259–269.
29 Qi YY, Heng X, Yao ZY, *et al*. Involvement of Huanglian Jiedu decoction on microglia with abnormal sphingolipid metabolism in Alzheimer's disease. *Drug Des Devel Ther* 2022; **16**: 931–950.
30 Fanning S, Selkoe D, Dettmer U. Parkinson's disease: proteinopathy or lipidopathy? *NPJ Parkinsons Dis* 2020; **6**: 3.
31 Mingione A, Pivari F, Plotegher N, *et al*. Inhibition of ceramide synthesis reduces α-synuclein proteinopathy in a cellular model of Parkinson's disease. *Int J Mol Sci* 2021; **22**: 6469.
32 Phillips GR, Saville JT, Hancock SE, *et al*. The long and the short of Huntington's disease: how the sphingolipid profile is shifted in the caudate of advanced clinical cases. *Brain Commun* 2021; **4**: fcab303.
33 Nogueras L, Gonzalo H, Jové M, *et al*. Lipid profile of cerebrospinal fluid in multiple sclerosis patients: a potential tool for diagnosis. *Sci Rep* 2019; **9**: 11313.
34 Podbielska M, Ariga T, Pokryszko-Dragan A. Sphingolipid players in multiple sclerosis: their influence on the initiation and course of the disease. *Int J Mol Sci* 2022; **23**: 5330.
35 Podbielska M, Szulc ZM, Ariga T, *et al*. Distinctive sphingolipid patterns in chronic multiple sclerosis lesions. *J Lipid Res* 2020; **61**: 1464–1479.
36 Lewkowicz N, Piątek P, Namiecińska M, *et al*. Naturally occurring nervonic acid ester improves myelin synthesis by human oligodendrocytes. *Cells* 2019; **8**: 786.
37 Borodzicz S, Czarzasta K, Kuch M, Cudnoch-Jedrzejewska A. Sphingolipids in cardiovascular diseases and metabolic disorders. *Lipids Health Dis* 2015; **14**: 55.
38 Sui J, He M, Wang Y, Zhao X, He Y, Shi B. Sphingolipid metabolism in type 2 diabetes and associated cardiovascular complications. *Exp Ther Med* 2019; **18**: 3603–3614.
39 Chung RWS, Wang Z, Bursill CA, Wu BJ, Barter PJ, Rye KA. Effect of long-term dietary sphingomyelin supplementation on atherosclerosis in mice. *PLoS One* 2017; **12**: e0189523.
40 Eckhardt ER, Wang DQ, Donovan JM, Carey MC. Dietary sphingomyelin suppresses intestinal cholesterol absorption by decreasing thermodynamic activity of cholesterol monomers. *Gastroenterology* 2002; **122**: 948–956.
41 Nyberg L, Duan RD, Nilsson A. A mutual inhibitory effect on absorption of sphingomyelin and cholesterol. *J Nutr Biochem* 2000; **11**: 244–249.
42 Zeng K, Zhou X, Liu W, Nie C, Zhang Y. Determination of endogenous sphingolipid content in stroke rats and HT22 cells subjected to oxygen-glucose deprivation by LC–MS/MS. *Lipids Health Dis* 2023; **22**: 13.
43 Ponizovsky AM, Modai I, Nechamkin Y, *et al*. Phospholipid patterns of erythrocytes in schizophrenia: relationships to symptomatology. *Schizophr Res* 2001; **52**: 121–126.
44 Colón-Sáez JO, Yakel JL. The α7 nicotinic acetylcholine receptor function in hippocampal neurons is regulated by the lipid composition of the plasma membrane. *J Physiol* 2011; **589 (Pt 13)**: 3163–3174.
45 Zhuo C, Zhao F, Tian H, *et al*. Acid sphingomyelinase/ceramide system in schizophrenia: implications for therapeutic intervention as a potential novel target. *Trans Psychiatry* 2022; **12**: 260.
46 Esaki K, Balan S, Iwayama Y, *et al*. Evidence for altered metabolism of sphingosine-1-phosphate in the corpus callosum of patients with schizophrenia. *Schizophr Bull* 2020; **46**: 1172–1181.
47 Porras-García E, Fernández-Espada Calderón I, Gavala-González J, Fernández-García JC. Potential neuroprotective effects of fermented foods and beverages in old age: a systematic review. *Front Nutr* 2023; **10**: 1170841.
48 Rajaram S, Jones J, Lee GJ. Plant-based dietary patterns, plant foods, and age-related cognitive decline. *Adv Nutr* 2019; **10 (Suppl_4)**: S422–S436.
49 Albi E, Arcuri C, Kobayashi T, *et al*. Sphingomyelin in human breast milk might be essential for the hippocampus maturation. *Front Biosci (Landmark Ed)* 2022; **27**: 247.
50 Yang F, Chen G, Ma M, Qiu N, Zhu L, Li J. Egg-yolk sphingomyelin and phosphatidylcholine attenuate cholesterol absorption in caco-2 cells. *Lipids* 2018; **53**: 217–233.
51 Noh SK, Koo SI. Milk sphingomyelin is more effective than egg sphingomyelin in inhibiting intestinal absorption of cholesterol and fat in rats. *J Nutr* 2004; **134**: 2611–2616.
52 Ramprasath VR, Jones PJ, Buckley DD, Woollett LA, Heubi JE. Effect of dietary sphingomyelin on absorption and fractional synthetic rate of cholesterol and serum lipid profile in humans. *Lipids Health Dis* 2013; **12**: 125.
53 Chung RW, Kamili A, Tandy S, *et al*. Dietary sphingomyelin lowers hepatic lipid levels and inhibits intestinal cholesterol absorption in high-fat-fed mice. *PLoS One* 2013; **8**: e55949.
54 Menet R, Bernard M, ElAli A. Hyperlipidemia in stroke pathobiology and therapy: insights and perspectives. *Front Physiol* 2018; **9**: 488.
55 Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. *EMBO Rep* 2014; **15**: 1036–1052.
56 Björkhem I, Meaney S. Brain cholesterol: long secret life behind a barrier. *Arterioscler Thromb Vasc Biol* 2004; **24**: 806–815.
57 Esposito CM, Buoli M, Ciappolino V, Agostoni C, Brambilla P. The role of cholesterol and fatty acids in the etiology and diagnosis of autism spectrum disorders. *Int J Mol Sci* 2021; **22**: 3550.
58 Solberg DK, Bentsen H, Refsum H, Andreassen OA. Lipid profiles in schizophrenia associated with clinical traits: a five year follow-up study. *BMC Psychiatry* 2016; **16**: 299.
59 Norris GH, Porter CM, Jiang C, Blesso CN. Dietary milk sphingomyelin reduces systemic inflammation in diet-induced obese mice and inhibits LPS activity in macrophages. *Beverages* 2017; **3**: 37.
60 Li Q, Chen G, Zhu D, *et al*. Effects of dietary phosphatidylcholine and sphingomyelin on DSS-induced colitis by regulating metabolism and gut microbiota in mice. *J Nutr Biochem* 2022; **105**: 109004.
61 Norris GH, Porter CM, Jiang C, Millar CL, Blesso CN. Dietary sphingomyelin attenuates hepatic steatosis and adipose tissue inflammation in high-fat-diet-induced obese mice. *J Nutr Biochem* 2017; **40**: 36–43.
62 Józefowski S, Czerkies M, Łukasik A, *et al*. Ceramide and ceramide 1-phosphate are negative regulators of TNF-α production induced by lipopolysaccharide. *J Immunol* 2010; **185**: 6960–6973.
63 Rozenova KA, Deevska GM, Karakashian AA, Nikolova-Karakashian MN. Studies on the role of acid sphingomyelinase and ceramide in the regulation of tumor necrosis factor α (TNFα)-converting enzyme activity and TNFα secretion in macrophages. *J Biol Chem* 2010; **285**: 21103–21113.
64 Albeituni S, Stiban J. Roles of ceramides and other sphingolipids in immune cell function and inflammation. *Adv Exp Med Biol* 2019; **1161**: 169–191.
65 Jung JS, Shin KO, Lee YM, *et al*. Anti-inflammatory mechanism of exogenous C2 ceramide in lipopolysaccharide-stimulated microglia. *Biochim Biophys Acta* 2013; **1831**; 1016–1026.
66 Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener* 2020; **9**: 42.
67 Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation* 2013; **10**: 43.
68 Xiao M, Xiao ZJ, Yang B, Lan Z, Fang F. Blood-brain barrier: more contributor to disruption of central nervous system homeostasis than victim in neurological disorders. *Front Neurosci* 2020; **14**: 764.
69 Wasiak J, Gawlik-Kotelnicka O. Intestinal permeability and its significance in psychiatric disorders—A narrative review and future perspectives. *Behav Brain Res* 2023; **448**: 114459.
70 Milard M, Penhoat A, Durand A, *et al*. Acute effects of milk polar lipids on

doi: 10.3164/jcbn.23-97

intestinal tight junction expression: towards an impact of sphingomyelin through the regulation of IL-8 secretion? *J Nutr Biochem* 2019; **65**: 128–138.
71 D'Alonzo Z, Lam V, Nesbit M, Graneri L, Takechi R, Mamo JCL. Chronic consumption of bovine dairy milk attenuates dietary saturated fatty acid-induced blood-brain barrier dysfunction. *Front Nutr* 2020; **7**: 58.
72 Galea I. The blood-brain barrier in systemic infection and inflammation. *Cell Mol Immunol* 2021; **18**: 2489–2501.
73 Michielan A, D'Incà R. Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. *Mediators Inflamm* 2015; **2015**: 628157.
74 Okuda T. Dietary control of ganglioside expression in mammalian tissues. *Int J Mol Sci* 2019; **21**: 177.
75 Tur JA, Bibiloni MM, Sureda A, Pons A. Dietary sources of omega 3 fatty acids: public health risks and benefits. *Br J Nutr* 2012; **107 Suppl 2**: S23–S52.
76 Ros E, Mataix J. Fatty acid composition of nuts—implications for cardiovascular health. *Br J Nutr* 2006; **96 Suppl 2**: S29–S35.
77 Palmano K, Rowan A, Guillermo R, Guan J, McJarrow P. The role of gangliosides in neurodevelopment. *Nutrients* 2015; **7**: 3891–3913.
78 Schneider JS, Aras R, Williams CK, Koprich JB, Brotchie JM, Singh V. GM1 ganglioside modifies α-synuclein toxicity and is neuroprotective in a rat α-synuclein model of Parkinson's disease. *Sci Rep* 2019; **9**: 8362.
79 Schneider JS, Singh G, Williams CK, Singh V. GM1 ganglioside modifies microglial and neuroinflammatory responses to α-synuclein in the rat AAV-A53T α-synuclein model of Parkinson's disease. *Mol Cell Neurosci* 2022; **120**: 103729.
80 Linton MF, Yancey PG, Davies SS, *et al*. The role of lipids and lipoproteins in atherosclerosis. In: Feingold KR, Anawalt B, Blackman MR, *et al*., eds. *Endotext*. South Dartmouth (MA), 2000.
81 Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation* 2019; **16**: 53.
82 Anand N, Gorantla VR, Chidambaram SB. The role of gut dysbiosis in the pathophysiology of neuropsychiatric disorders. *Cells* 2022; **12**: 54.