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Sphingolipid abnormalities in psychiatric disorders: a missing link in pathology?

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1. ABSTRACT

Sphingolipids are biologically active lipids ubiquitously expressed in all vertebrate cells, especially those in the CNS. Aside from their essential roles as structural components of cell membranes, studies over the past two decades have shown that they play vital roles in cellular signaling, cell differentiation and proliferation, apoptosis and inflammation. Given these properties, it is not surprising that disruption of sphingolipid metabolism is strongly associated with several diseases that exhibit diverse neurological, psychiatric, and metabolic consequences. Here, we review the emerging roles of sphingolipids in disease pathogenesis in psychiatric disorders, including schizophrenia, bipolar disorder and major depression. Understanding sphingolipid metabolism and it dysregulation in human disease is significant for the development of new therapeutic approaches.

2. INTRODUCTION

Major advances in sphingolipid research over the past 20 years have transformed our understanding of this class of lipid molecules and have uncovered many roles for glycolipids in both the basic functioning of the brain under normal conditions and in disease states. In addition to their roles as structural components of cell membranes, sphingolipids are now known to play vital roles in cellular signaling, cell-to-cell interactions, apoptosis and inflammation, and have been found to modulate developmental processes, such as cell differentiation and proliferation. Many of these functions have been associated with the pathology of human diseases.

Genetic mutations in the genes encoding several of the enzymes of sphingolipid metabolism result in lysosomal storage diseases, including Fabry disease, Farber

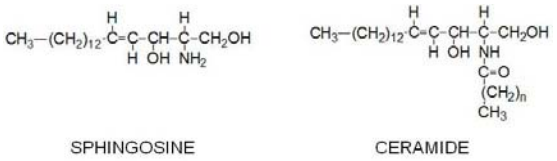

Figure 1. The structures of sphingosine and ceramide.

disease, Gaucher disease, Niemann-Pick disease, and metachromatic leukodystrophy and Krabbe disease (1). Significantly, many of these disorders involve neurological and psychiatric symptoms (2-11). Abnormal levels of sphingolipids have been implicated in several neurodegenerative disorders, including Alzheimer's, Huntington's disease and amyotrophic lateral sclerosis (12-16). Emerging studies have further implicated disrupted sphingolipid metabolism in psychiatric disorders, especially schizophrenia. Schizophrenia is a complex and severe brain disorder with poorly defined etiology and pathophysiology. It is associated with diverse systems dysfunction, many of which are related to the emerging functions of glycolipids. This review will summarize the evidence for involvement of sphingolipids in schizophrenia, bipolar disorder and major depression, and the pathways in common between sphingolipid metabolism and pathological features of these disorders.

3. WHAT ARE SPHINGOLIPIDS?

Sphingolipids are a major class of lipids that are ubiquitous constituents of eukaryotic membranes. They are composed of one polar head group and two nonpolar tails. At the core of all sphingolipids is the long-chain amino alcohol, sphingosine (Figure 1). Sphingolipids are synthesized in a pathway that begins in the endoplasmic reticulum and is completed in the Golgi apparatus. They are then transported via vesicles and monomeric transport to the plasma membrane and endosomes, where they perform many of their functions. On a broad scale, sphingolipids are typically classified as ceramides, sphingomyelins or glycosphingolipids. The addition of a long chain fatty acid, at the amine group at carbon 2 of sphingosine yields N-acylsphingosine, commonly known as ceramide (Figure 1). Depending on the attachment of a mono- or oligo-saccharide head group to the sphingosine base, different subclasses of glycosphingolipids are generated as described below. Detailed reviews of sphingolipid biosynthesis and metabolism have been previously published and will be reviewed only briefly here (17-19).

3.1. Ceramide (N-acylsphingosine)

De novo ceramide synthesis begins in the endoplasmic reticulum with a condensation reaction between palmitoyl-CoA and serine leading to the formation of 3-keto-dihydrosphingosine. This reaction is catalyzed by serine palmitoyltransferase (encoded by one of three *SPTLC* genes). 3-keto-dihydrosphingosine is then reduced to form sphinganine, which is acylated by a ceramide synthase (*LASS*2) to form dihydroceramide (Figure 2). Dihydroceramide is then converted into ceramide by dihydroceramide desaturase (encoded by *DEGS1*). Six individual ceramide synthases, LASS1-6, are known to catalyze the formation of dihydroceramides, or ceramides (depending on whether the substrate is dihydrosphingosine or sphingosine, respectively). Recently, a more complex mechanism of regulating ceramide levels has become appreciated involving the recycling or salvage pathway. In the salvage pathway, ceramide is hydrolyzed by ceramidases to sphingosine, which is then re-acylated via the action of ceramide synthases (LASS1) to regenerate ceramide (Figure 2).

Ceramide is the fundamental structural unit common to all sphingolipids. However, in addition to forming the basis for sphingolipid and sphingomyelin biosynthesis, it is now known that ceramide can act as a signaling molecule in its own right, being involved in signal transduction, cellular differentiation and proliferation, as well as apoptosis and degeneration of cells. These topics have been reviewed extensively previously (20-24). One of the most important reproducible findings for ceramide is its ability to elicit apoptosis. Apoptosis, while essential for the elimination of damaged cells, can lead to the development of several neurological disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and cerebral ischemia, all of which are characterized by the loss of specific populations of neurons (25). Ceramide can elicit apoptosis via several different downstream targets including death-associated protein kinase, kinase suppressor of Ras, protein kinase C, Rac, inducible nitric oxide synthase, ceramide-activated protein phosphatase, and c-Jun N-terminal kinase (26). At higher concentrations, ceramide has been shown to elicit its proapoptotic effects by increasing intracellular reactive oxygen species. In this context, ceramide and reactive oxygen species have been associated with mitochondrial dysfunction and release of proapoptotic cytochrome C (27). Given the multitude of cellular effects elicited by ceramide, it is not surprising that diverse and sometimes contradictory effects of ceramide have been reported. These may result from developmental, cell-type specific, compartment-specific or concentration-dependent effects of ceramide, as well as the unknown contribution of downstream sphingolipids.

More complex sphingolipids are formed by the addition of polar head groups at the 1-hydroxy position of ceramide. These include the sphingomyelins and glycosphingolipids (the cerebrosides, sulfatides, globosides and gangliosides).

3.2 . Sphingomyelin

Sphingomyelin, accounting for ~10% of mammalian cellular lipids, is the major representative of the class of phosphosphingolipids. The sphingomyelins are synthesized by the transfer of phosphorylcholine from

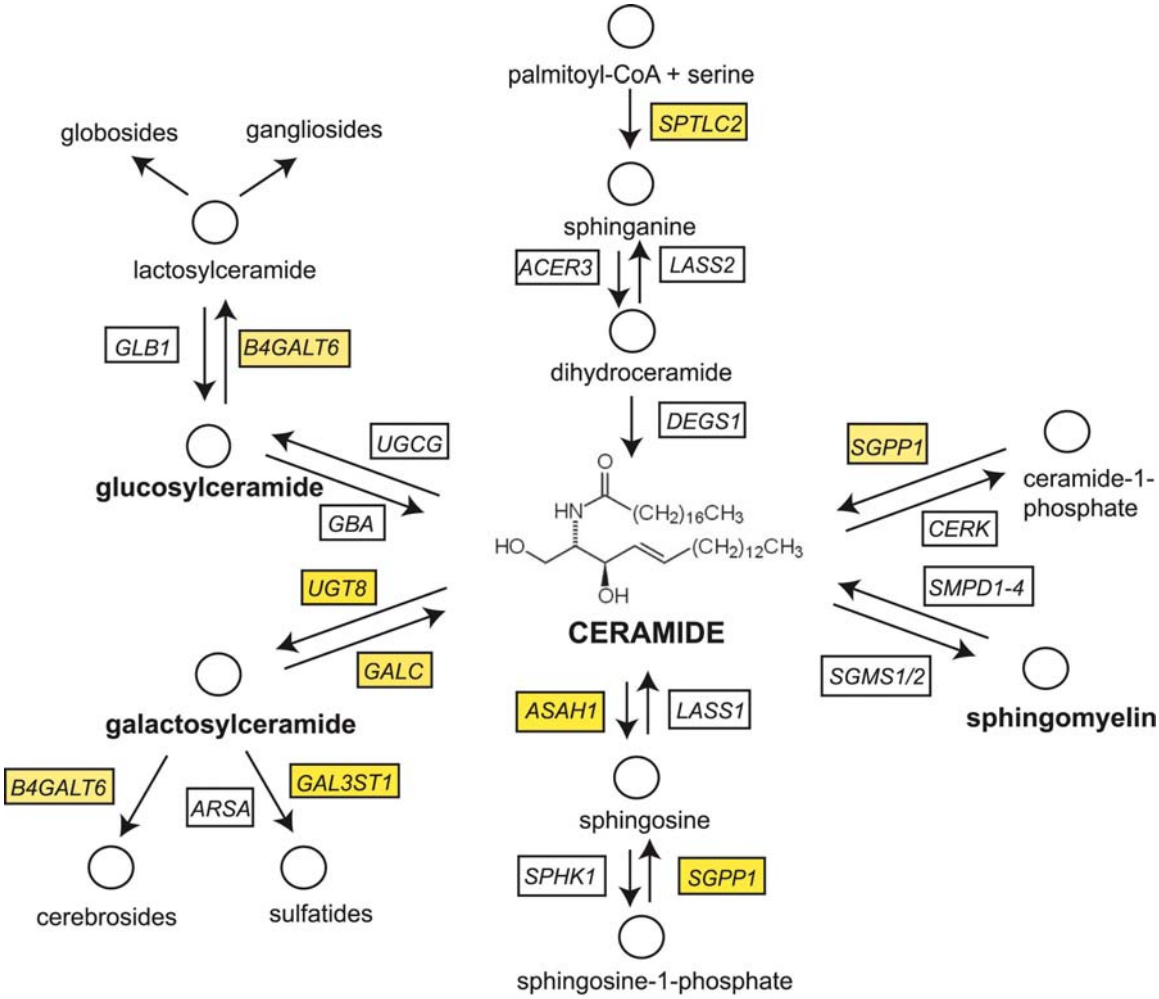

Figure 2. Schematic depiction of sphingolipid metabolism. Boxes indicate the genes encoding the enzymes responsible for the particular synthesis pathway. Shaded (yellow) boxes reflect those genes with altered expression patterns in brains of subjects with schizophrenia (from ref (43).

phosphatidylcholine to ceramide in a reaction catalyzed by sphingomyelin synthase (encoded by *SGMS1* or *2)* (Figure 2). They are important constituents of the cell membrane and are particularly enriched in the myelin sheath. In the hydrolytic pathway, sphingomyelin is cleaved by one of several sphingomyelinases (encoded by *SGMS1-4*), releasing phosphocholine and ceramide. These include lysosomal acid sphingomyelinases, zinc-dependent secretory sphingomyelinases, neutral magnesium-dependent sphingomyelinases, and alkaline sphingomyelinases and can be distinguished according to their pH optima and subcellular localization. Defects in the enzyme that degrades sphingomyelin, acid sphingomyelin phosphodiesterase (*SMPD1*), result in the lysosomal storage diseases such as the Niemann-Pick disease. Over 100 mutations in the *SMPD1* gene have been found to cause Niemann-Pick disease (28).

3.3. Glycosphingolipids

Glycosylation of ceramide forms a group of glycosphingolipids with diverse structures and a wide range of physiological and functional effects. The structural motif common to all glycosphingolipids is a monosaccharide, either glucose (the glucosylceramides) or galactose (galactosylceramides), bound directly to ceramide through a beta-glycosidic linkage (Figure 2). Glycosphingolipid composition varies depending on cell type, developmental stage and aging. With regards to the nervous system, the composition of glycosphingolipid in the CNS is very different from the PNS (29).

3.3.1. Glucosylceramides

Glucosylceramide is generated from ceramide by the action of ceramide glucosyltransferase (encoded by the gene *UGCG*). Stepwise elongation gives rise to either the gangliosides or the globosides. The gangliosides have at least three sugars at the 1-hydroxy position, one of which must be sialic acid (a.k.a. n-acetylneuraminic acid). The 60+ known gangliosides differ mainly in the position and number of sialic acid residues. The specific names for gangliosides are a key to their structure. The letter G refers to ganglioside, and the subscripts M, D, T and Q indicate

Table 1. Lipid storage-related disorders showing psychiatric features

Disease	Deficient enzyme	Gene symbol	Reference # for psychiatric features
Gaucher disease	glucosyl ceramidase	*GBA*	8
Metachromatic Leukodystrophy	arylsulfatase	*ARSA*	5, 120
Niemann- Pick disease	sphingomyelinase	*SMPD1*	6, 9, 10, 11
Sandhoff disease	beta-hexosaminidase B	*HEXB*	2, 121
Tay-Sachs disease	beta-hexosaminidase A	*HEXA*	3, 4
Fabry disease	galactosidase	*GLA*	7

For each disease, the gene encoding the deficient enzyme is shown along with the references for the studies reporting psychiatric symptoms. Gene symbols shown are the official UniGene symbols from the National Center for Biotechnology Information.

that the molecule contains mono-, di-, tri and quatra(tetra)-sialic acid. The numerical subscripts 1, 2 and 3 refer to the carbohydrate sequence that is attached to ceramide. For example, GM2 has a single sialic acid residue on the second carbohydrate attached to the ceramide backbone. Gangliosides are particularly enriched in neuronal membranes of the CNS and errors in ganglioside metabolism and degradation often lead to severe neurological symptoms. Mutations in genes coding for enzymes of ganglioside metabolism cause lipid storage diseases called gangliosidoses, that comprise GM1 gangliosidosis and GM2 gangliosidosis (Tay-Sachs Disease and Sandhoff disease) (1).

Globosides represent cerebrosides that contain additional carbohydrates, predominantly galactose, glucose or N-Acetylgalactosamine. Different globosides are found in different organs outside of the brain. For example, lactosyl ceramide is a globoside found in erythrocyte plasma membranes. Globotriaosylceramide (also called ceramide trihexoside) contains glucose and two moles of galactose and accumulates primarily in the kidneys of patients suffering from Fabry disease.

3.3.2. Galactosylceramides

Galactosylceramides are the predominant glycosphingolipids in brain tissue and can constitute up to 2% of the dry weight of grey matter and 12% of white matter. They are major constituents of oligodendrocyte cell membranes, which form myelin. Cerebrosides constitute the predominant species of galactosylceramide: the glucocerebrosides (with an additional glucose) or the galactocerebrosides (containing an additional galactose). Galactocerebrosides are the most abundant type in cell membranes. In contrast, the glucocerebrosides represent intermediates in the synthesis or degradation of more complex glycosphingolipids and are not normally found in membranes. Excess lysosomal accumulation of glucocerebrosides is observed in Gaucher's disease (1).

The addition of a sulfate group to a cerebroside yields a sulfatide. Next to galactocerebrosides, sulfatides the second major lipid component of oligodendrocyte membranes and together, these two glycolipids comprise 27% of total myelin lipid (30). An accumulation of sulfatides is observed in the lipid storage disorder, metachromatic leukodystrophy (31).

4. SPHINGOLIPIDS AND LIPID RAFTS

Unlike phosphoglycerolipids, sphingolipids do not distribute homogeneously in the outer plasma membrane. Rather, it is postulated that sphingolipids, along with cholesterol, are highly enriched in specialized membrane microdomains, known as lipid rafts. The concept of lipid rafts was proposed over a decade ago (32), and while initial controversy over their existence persisted, the raft hypothesis is now widely accepted (32-35). These lipid domains show greater order and less fluidity than other parts of the membrane. It has been reported that membrane proteins with at least one transmembrane domain or with a hydrophobic modification are enriched in lipid rafts; these include G protein-coupled receptors, GPI-anchored proteins, flotillins, caveolins and other receptors, such as epidermal growth factor and insulin receptors. Hence, the general function of lipid rafts in association with signal transduction may be to concentrate receptors for interaction with ligands and effectors on both sides of the membrane, thus enhancing cell-to-cell communication and preventing inappropriate crosstalk between pathways.

5. EVIDENCE FOR INVOLVMENT OF SPHINGOLIPID ABNORMALITIES IN PSYCHIATRIC DISORDERS

5.1. Glycolipid storage disorders with psychiatric features

Dysfunctional sphingolipid metabolism has been linked to a number of neurological disorders including Alzheimer's disease (13-15); Huntington's disease (12), multiple sclerosis (36) and amyotrophic lateral sclerosis (16). The first associations between glycan biology and psychiatric disorders arose from accounts that several lysosomal storage disorders presented with psychiatric manifestations (Table 1). Case study reports found that several patients with Niemann-Pick type C had initially been treated for schizophrenia for many years prior to their true diagnosis of Niemann-Pick type C (9, 11). In Tay-Sachs disorder, psychosis is reported in 30% to 50% of adult-onset patients and many are misdiagnosed with schizophrenia (37). Furthermore, mood disorders are present in more than 25% and cognitive impairment in more than 20% of Tay-Sachs disease patients (37). Two distinct clinical patterns of adult metachromatic leukodystrophy are observed: one presents with predominantly motor manifestations similar to those found in infantile cases, while the other presents as a schizophrenia-like psychosis, with prominent negative signs (38). These findings illustrate not only the importance of performing neurologic and radiological examinations on all psychiatric patients with chronic illnesses, but also the close relationship between impaired glycolipid function and psychiatric symptoms.

5.2. Studies on schizophrenia

The first report of altered sphingolipids in human brain dates back to 1969. Classical biochemical studies found decreases in the levels of galactocerebrosides, total cerebrosides and sulfatides, in post mortem brains of subjects with schizophrenia and other neurological disorders (39). However this finding in schizophrenia was based only on a single subject. Later studies during the 1980s implicated peripheral sphingolipid abnormalities in patients with schizophrenia. In one study, the metabolism of glycoproteins and glycosaminoglycans was found to be abnormal in schizophrenic patients, based on the levels of sphingolipids excreted in the urine (40). Another report demonstrated altered levels of GM3 and GD3 gangliosides, the primary glycolipids in neuronal membranes, in erythrocyte membranes of schizophrenic patients (41).

Although studies on membrane phospholipids and fatty acids in psychiatric disorders continued from this time, the specific involvement of sphingolipids in this context received little attention. It was not until 30 years after the initial report in human brain by Cherayil and colleagues that a second study reporting abnormalities in sphingolipid levels in human post-mortem brain from subjects with schizophrenia was published. Gattaz and coworkers measured the lipid composition in membranes from thalamus obtained post-mortem from 18 chronic schizophrenic patients and 23 healthy controls (42). Their results revealed decreases in the major myelin membrane components, sphingomyelin and galactocerebrosides in brains from subjects with schizophrenia compared to controls, consistent with the early study from 1969. In addition, they reported altered levels of membrane phospholipids, including phosphatidylcholine and phosphatidylserine (42).

Studies from our own laboratory have used custom microarrays to investigate the expression of genes encoding enzymes and proteins related to sphingolipid metabolism in post-mortem prefrontal cortex from subjects with schizophrenia at different stages of illness (n=30 subjects with schizophrenia and n=30 matched controls). Our results revealed significant widespread changes in gene expression of multiple enzymes that regulate sphingolipid metabolism pathways, primarily at early stages of the disorder (within 5 years from initial diagnosis). In particular, significant decreases in the expression for seven sphingolipid-related genes were validated in subjects with schizophrenia (43). Figure 2 highlights those genes showing altered expression in schizophrenia in our studies (shaded boxes). These changes were not found to be associated with antipsychotic drug treatment (43).

Given the complexity of the sphingolipid pathway, it is not explicitly clear how decreases in the expression of the genes detected in our study (43) specifically translate into alterations in the levels of the various glycolipid intermediates and end products. Decreases in the expression of *ASAH1*, which converts ceramide to sphingosine, or *UGT8*, the first step in the synthesis of galactosyl-ceramides would lead to increased levels of ceramide, consistent with other studies on post mortem brain (see below). Increased ceramide mass can be further utilized via sphingomyelin and glycosphingolipid synthesis pathways. However, it is possible that the decreased expression levels of *SPTLC2, GALC* and *SGPP1* might represent an attempt at compensation, leading to lower levels of ceramide. Decreased expression of *UGT8* and *GAL3ST1,* which encode enzymes responsible for the biosynthesis of galactocerebrosides and sulfatides could lead to the lowered levels of these myelin glycolipids observed previously (39, 42). A reduction in galactocerebrosides and sulfatides levels is a hallmark of decreased myelination and oligodendrocyte dysfunction, which has been widely observed in schizophrenia (44, 45).

5.3. Studies on schizophrenia and bipolar disorder

Major advances in lipid profiling methodology have facilitated the study of detailed lipid levels in various cell types and tissues. In a recent study, a high-throughput ultra performance liquid chromatography−mass spectrometry strategy was used to profile white and gray matter lipid levels in postmortem brain samples from schizophrenia and bipolar patients, along with normal controls (n=45 subjects in total) (46). Levels of various phosphatidylcholines and free fatty acids were found to be altered in gray and white matter regions of subjects with schizophrenia and bipolar disorder, consistent with previous findings (42, 47). Reductions in phosphatidylcholine levels been linked to an increase in sphingomyelin turnover, as phosphatidylcholine is the choline donor to sphingomyelin in neurons and oligodendrocytes, although this was not specifically measured (42). Most interestingly, ceramide levels were found to be significantly increased mainly in white matter samples from subjects with schizophrenia and bipolar disorder compared to controls (46). This could result from the lower expression levels of *ASAH1* or *UGT8,* which convert ceramide to sphingosine and galactosylceramide, respectively, as stated above. Regarding the potential for drug exposure to affect ceramide levels, the changes in ceramide levels were similar in non-drug- versus drug-treated schizophrenia and bipolar patients, suggesting that the observed alterations were not influenced by drug treatment (46).

5.4. Studies on depression

Studies have also implicated altered glycolipids in major depressive disorder, by means of decreased levels of the enzyme, acid sphingomyelinase, the lysosomal hydrolase that catalyzes the degradation of sphingomyelin to ceramide. This enzyme is encoded by one of four genes, *SMPD1-4* (Figure 2). Kornhuber and colleagues reported elevated activity of acid sphingomyelinase in peripheral blood mononuclear cells in patients with major depression (48). This elevated activity would putatively lead to an increase in production of ceramide, which would have a diversity of downstream consequences, as mentioned previously. The acid sphingomyelinase/ceramide pathway might explain several independent findings in neurobiology and the treatment of major depressive disorder, such as therapeutic latency, oxidative stress, immune activation and increased risk of cardiovascular disease (49).

In contrast to the lack of deduced effects of antipsychotic medication on sphingolipid enzymes,

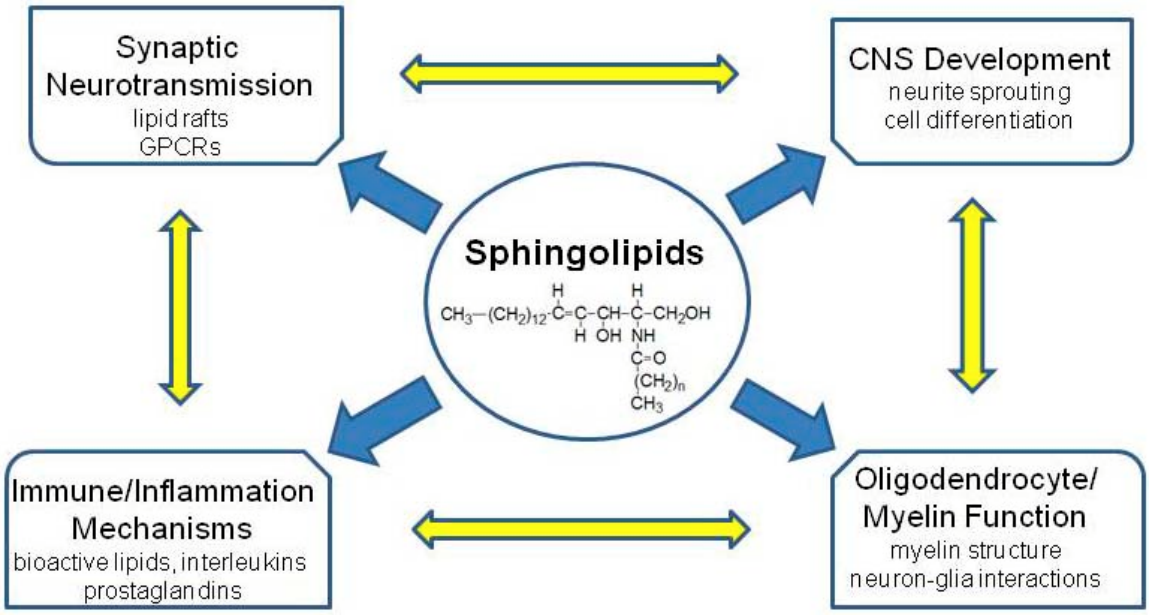

Figure 3. Overview of different functional pathways and systems associated with psychiatric disorders and modulated by, or involving, sphingolipids.

antidepressant drugs were found to modulate this pathway in multiple studies. It was found that the antidepressant medications, imipramine and amitriptyline, both reduced acid sphingomyelinase activity in cultured blood mononuclear cells from normal subjects (48). This was consistent with previous *in vitro* studies demonstrating that phenothiazines and tricyclic antidepressants resulted in decreased sphingomyelinase activity in C6 rat glioma cells and human fibroblasts (50, 51). Together, these findings would suggest acid sphingomyelinase as a potential target of antidepressive drugs, whereby drugs would act to normalize the abnormally high levels found in patients.

6. SPHINGOLIPIDS AS A MISSING LINK BETWEEN MOLECULAR AND CLINICAL ABNORMALITIES IN SCHIZOPHRENIA

Sphingolipids were initially thought to represent structural membrane components only; however, emerging studies now reveal additional biological and functional roles for this class of lipids, including cellular recognition and adhesion, signal transduction, growth regulation, and differentiation, among others. Because sphingolipids have been associated with a diversity of biological processes, a dysfunction in the synthesis and/or dysregulation of sphingolipids would be expected to have a major impact on neuronal function. Hence, this system may represent an important link in schizophrenia pathology. The sphingolipid pathway, on a broad scale, might explain several molecular and clinical aspects of psychiatric disorders. Most of the observed deficits in sphingolipids point to oligodendrocyte and myelin dysfunction; however, other aspects of this complex pathway can affect many systems important to psychiatric disorders. Here we focus on four systems that have been widely implicated in the pathogenesis or pathophysiology of schizophrenia and other psychiatric disorders: 1). CNS development, 2). myelin and oligodendrocyte function. 3). synaptic neurotransmission and 4). immune/inflammatory mechanisms (Figure 3).

6.1. CNS development

The neurodevelopmental model of schizophrenia posits that abnormalities during critical developmental periods increase the risk for the subsequent emergence of clinical symptoms (52, 53). This model is supported by findings from epidemiology, neuropathological, imaging and genetic studies, and, more recently, experimental outcomes in animal models (54). The exact developmental insult(s) remain unclear, although genetic and environmental triggers are known to both contribute to disease susceptibility. Several candidate genes for schizophrenia have been shown to have specific roles in development. In particular, genes involved with cell migration, cell proliferation, axonal outgrowth, myelination, synaptogenesis, and apoptosis are affected in subjects with schizophrenia. Interestingly, glycolipids play critical roles in many of these functions.

Mounting evidence supports the notion that glycosphingolipids play important roles in the developing nervous system (55-58). In particular, glycosphingolipids have been suggested to have specific functional roles essential for cell-survival, proliferation, and differentiation during brain development. Early findings for the involvement of gangliosides were based on developmental expression patterns of gangliosides at different stages of development. Dramatic changes in the expression of complex ganglioside were found during human development, with the most rapid increase of GM1 and GD1a occurring during dendrite arborization, outgrowth of axons and synaptogenesis (56). However, it wasn't until

the generation of genetically altered mice with targeted knock-outs of specific genes that explicit roles for gangliosides and other glycosphingolipids were revealed.

Knock-out mice with a disruption in the gene for a key enzyme in complex ganglioside biosynthesis (GM2/GD2 synthase; *B4galnt1*) resulted in mice that expressed only simple gangliosides (GM3/GD3) (59). Despite this dramatic biochemical change, the knockout mice were reported to undergo normal brain development, differentiation, morphogenesis and synaptogenesis, indicating that *complex* gangliosides are not essential for brain development (59). However, *Ugcg* gene knockout mice revealed a dramatically different phenotype. *Ugcg* encodes the enzyme catalyzing the first step in the synthesis of glucosylceramide, the precursor to all gangliosides (see Figure 2). These mice die at 7.5 days gestation (57). Further studies on embryos from these mice have provided important information into their specific developmental dysfunctions. Mouse embryos from *Ugcg* knock-out mice exhibit normal endoderm, mesoderm, and ectoderm layers. However, further differentiation is arrested and they appear unable to form more differentiated tissues (57). In conditional knock-out mice, in which disruption of the *Ugcg* gene occurred specifically in neural cells, late embryonic development was not impaired, however, structural and functional dysfunction in the cerebellum and peripheral nerves was observed (60). In particular, reduced axon branching of Purkinje cells and disorganized myelin sheaths of peripheral nerves was observed in association with a down-regulation of the expression of genes involved in brain development and homeostasis. These mice die in the third postnatal week (60). Cultured primary neurons from these mice further showed diminished dendritic complexity and early pruning (60). These results strongly point to a crucial role for glucosylceramides in brain maturation.

The enzyme encoded by *B4GALT6* drives the first step in ganglioside biosynthesis from glucosylceramide (See Figure 2). A decrease in the levels of this gene, as we detected in the brains from subjects with schizophrenia (43), might cause defects in gangliosides synthesis and have a subtle effect on developmental processes, consistent with what has been proposed for disease development in schizophrenia (53).

6.2. Oligodendrocyte/myelin function

Multiple lines of evidence now converge to implicate oligodendrocyte /myelin dysfunction in schizophrenia. Neuroimaging, histological and molecular studies have shown reductions in white matter volume, decreased anisotropy of white matter tracts, reduced oligodendrocyte cell numbers and density and decreases in the expression of myelin-related genes in the brains of subjects with psychiatric disorders (reviewed by (44, 45)). The myelin sheath, which is an extension of the oligodendrocyte plasma membrane, is essential for proper neuronal signal propagation and connectivity in the brain (61). The production of myelin depends upon synthesis of several myelin-specific proteins and glycolipid components, which play essential roles in myelin structure and function, and neuron-glial interactions, as described below.

6.2.1. Oligodendrocyte development

Oligodendrocyte maturation proceeds through several steps of differentiation and proliferation. Evidence indicates that terminal differentiation of oligodendrocytes into mature, myelin-producing cells is dependent upon the expression of galactocerebrosides and sulfatides. *In vitro* studies have demonstrated perturbation of this final step with specific anti-galactolipid antibodies directed against galactocerebrosides and sulfatides (62-64). Further evidence comes from studies on mice lacking the enzyme UDP-galactose ceramide galactosyltransferase *(Ugt8*, a.k.a. *Cgt*) (65); this enzyme is responsible for the biosynthesis of galactosylceramide, the precursor of cerobrosides and sulfatide (Figure 2). *Ugt8*-deficient mice showed abnormalities in oligodendrocytes and their terminal differentiation (65).

6.2.2. Myelin structure and function

Studies on *Ugt8* -deficient mice support an important role for galactolipids in stabilizing the ultrastructure of the myelin sheath and in myelin function (66-68). The conduction velocity of myelinated axons in *Ugt8* knock-out mice was reduced to levels found in unmyelinated axons, indicating a block of saltatory conduction (66-68). The impaired insulator function of myelin was due to the lack of the main glycolipids, galactocerebrosides and sulfatides, and was not compensated by other lipids. This led to obvious phenotypes of body tremor, loss of locomotor activity, and eventual death. The elimination of galactosylceramide 3′-sulfotransferase (encoded by *Gal3st1*, formerly known as *Cst*) resulted in the complete absence of sulfated galactolipids (69-71). *Gal3st1* KO mice were born healthy, but displayed hindlimb weakness by 6 weeks of age and subsequently showed a pronounced tremor and progressive ataxia.

Although *B4galnt1* knock-out mice, expressing only simple gangliosides (GM3/GD3) as described above, did not exhibit defects in the gross development of the nervous system (59), myelination defects were observed later in life. Knock-out mice at 3-4 months of age showed axonal degeneration in the CNS and PNS, decreased myelination in the CNS, and demyelination in peripheral nerves These results provide strong evidence for the role played by complex gangliosides in central myelination and the maintenance of the integrity of axons and myelin (59).

Experiments on invertebrate animals have demonstrated a potential role for myelin glycolipids on myelin compactation and the arrangement of myelin layers. Shrimp lacking glucocerebroside, the major glycosphingolipid of shrimp nerve, show a loosely structure, uncompacted myelin (72), and earthworms that lack galactocerebrosides, sulfatides and sphingomyelin show a similar result (73).

6.2.3. Neuron-glia interaction

Proper function of myelin requires several processes involving neurons, including oligodendrocyte recognition and adhesion to the axon, stabilization of the axonal contacts, and initiation of the spiral wrapping and

compacting of the myelin around the axon. While much remains unknown about this process, emerging studies have implicated glycosphingolipids in these functions. Recent studies have indicated that galactoceramide and sulfatide are essential for glycosynapses between myelin membranes and that this is important for myelin-axon communication (74). Mice deficient in the gene *Ugt8*, as described above, also display a delay in axo–glial interactions, which are essential for the structure and function of the nodes of Ranvier (68). Further, studies interbreeding the *Ugt8* mutant mice with mice that lack myelin-associated glycoprotein showed that that these specialized myelin lipids and proteins act in concert to promote axo–glial adhesion during myelinogenesis (75). Other studies found that *Gal3st1*-deficient mice displayed abnormalities in paranodal junctions, suggesting that sulfatides play a role in mediating axoglial interactions (69).

6.3. Synaptic neurotransmission

6.3.1. G protein-coupled receptors and lipid rafts

G protein-coupled receptors (GPCRs) play key roles in a wide range of cellular signaling and functions. It is known that dysfunction of these receptors is associated with psychiatric and neurological disorders. For example, the dopamine hypothesis of schizophrenia, formulated over 40 years ago (76), has been one of the most enduring ideas in psychiatry. Neuroimaging, clinical and molecular and genetic studies have now revealed changes in several other neurotransmitter receptors, including, serotoninergic, glutamatergic, GABAergic and cholinergic systems in the brains of patients with schizophrenia (77).

Many GPCRs have been shown to form homo- and/or heterodimers on the cell membrane and at nearly 20 GPCRs have been specifically localized to lipid rafts (78). Recent research has shown lipid raft environment plays a prominent role in GPCR localization trafficking, signaling and internalization (78). For example, disruption of lipid rafts with methyl-beta-cyclodextrin caused a loss of the agonist response of the gonadotropin-releasing hormone receptor (79). Alternatively, manipulation of lipid raft domains using methyl-beta-cyclodextrin and filipin caused an increase in signaling of the beta-adrenergic receptor (80). These are consistent with computational modeling studies that have predicted that lipid rafts have a role in either amplification or attenuation of G-protein signaling (81). Given this putative control of GPCR function by lipid raft domains, it would seem clear that alterations in raft environment due to changes in the levels of one or many sphingolipids, could have dramatic consequences for GPCR activation and signaling.

6.3.2. Synaptic machinery

Data from molecular studies have implicated signal transduction at the synapse in the pathology of schizophrenia. Microarray results revealed significant decreases in the expression of multiple genes related to presynaptic function, especially SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) proteins, in the prefrontal cortex of subjects with schizophrenia (82, 83). These include syntaxin, synaptosomal-associated protein 25 (SNAP25) and N-ethylmaleimide sensitive factor, findings later replicated by several groups (84-86). The SNARE complex is essential for membrane fusion and synaptic vesicle exocytosis. Evidence now suggests that synaptic vesicle fusion may be subject to regulation by plasma membrane lipids, or lipid rafts (87). It is thought that lipid rafts can modulate neurotransmitter release, as they support essential components of the vesicular exocytic machinery such as syntaxin, SNAP25 and synaptobrevin (88). Specifically, studies have demonstrated that sphingosine, the backbone of all sphingolipids, specifically could activate synaptobrevin in synaptic vesicles to form the SNARE complex (89). Consistent with this result, sphingosine was found to increase exocytosis in isolated nerve terminals, neuromuscular junctions, neuroendocrine cells and hippocampal neurons (89). Decreased expression of both *ASAH1* and *SGPP1*, as was shown in brains from subjects with schizophrenia (see section 5.1 and Figure 2), would lead to lower levels of sphingosine. This could result in detrimental effects on synaptic activity that is presumed in schizophrenia.

6.4. Immune /inflammatory pathways

Evidence from epidemiological, clinical, molecular and experimental mouse-model studies, has emerged during the past decade linking inflammation to the development of schizophrenia, bipolar disorder and major depression (90-96). The inflammatory response is part of the innate immune response and employs a variety of cellular and plasma-derived agents/pathways, including interferons, cytokines, histamine, prostaglandins and other arachidonic acid derivatives; many of these mediators have been linked to the pathophysiology of psychiatric diseases. The arachidonic acid/prostaglandin pathway has drawn particular attention in this field recently, in light of the potential for cylcooxygenase 2 (COX-2) inhibitors to represent new therapeutic options for schizophrenia and depression (91, 97-99). Importantly, sphingolipid metabolites, including ceramide, sphingosine, and their phosphorylated forms, have been linked to inflammatory pathways and immune function (100), in particular, modulation of the arachidonic acid/prostaglandin pathways.

In vitro studies found that ceramide triggers arachidonic acid release from two different cell types, mouse macrophages and renal mesangial cells, by directly activating cytosolic phospholipase A_2 (PLA_2) (101, 102). The phosphorylated derivative of ceramide, ceramide 1-phosphate (C-1-P), formed by the action of ceramide kinase, can also can directly activate PLA_2 (103, 104) and mediate arachidonic acid release in lung adenocarcinoma cells (105). This effect was independent of the activity of ceramide kinase, which drives its formation (105). Other studies have demonstrated that ceramide enhances interleukin-1beta- mediated PGE_2 production in human dermal fibroblasts, and further, that ceramide enhanced COX-2 mRNA expression independent of PLA_2 mRNA expression (106, 107). The elevated levels of ceramide that have been reported in schizophrenia and bipolar disorder (see Section 5), may trigger inflammatory pathways in these disorders via these mechanisms.

Sphingosine-1-phosphate (S-1P) has received the most attention as a bioactive signaling molecule, as it is a ligand for a family of five G-protein-coupled receptors. Originally known as the endothelial differentiation gene (EDG1) family of proteins, these receptors were renamed S-1P1-5 receptors (108, 109). These receptors are expressed in a wide variety of tissues and cell types, and their cellular effects contribute to important biological processes, including angiogenesis, vascular development, lymphocyte trafficking, inflammation and cancer (110). The cellular levels of S-1P are controlled by its formation from sphingosine through the activity of the enzyme sphingosine kinase (encoded by *SPHK1*) and dephosphorylation by S-1P phosphatase (*SGPP1-2). SGPP1* was found to be decreased in the brains of subjects with schizophrenia, implying that S-1P levels may be elevated in schizophrenia (Figure 2) (43). Like ceramide, sphingosine and S-1P have also been shown to induce COX-2 mRNA expression and elevated PGE_2 levels (111). Knock-down of sphingosine kinase expression with RNAi methodology was found to abolish the effects of exogenous sphingosine and ceramide on PGE_2, indicating that the action of these glycolipids were due to intracellular metabolism into S-1P (111). This effect could be mediated via the S1P3 receptor, which directly activates PLA_2 (112), or via the S-1P1 receptor, which has been shown to stimulate intracellular signaling pathways involving COX-2-dependent prostaglandin synthesis (113).

7. PERSPECTIVES

The brain is second, only to adipose tissue, in highest concentration of lipid. Both central and peripheral abnormalities in lipid metabolism and membrane dynamics have been linked with a number of neurodegenerative and neuropsychiatric disorders (47, 114-118), implying that lipid metabolism is of particular importance to brain function and its dysfunction. The hypothesis that schizophrenia, and related illnesses, are particularly related to disrupted lipid metabolism can now incorporate sphingolipids. This hypothesis provides an explanation for the diversity of symptoms associated with psychiatric disorders, as well as the multi-genic nature of these disorders, given the large numbers of genes whose products contribute to glycolipid metabolism or are associated with glycolipid-mediated signaling pathways. While research in the lipidomics field is lagging behind the genomics and proteomics counterparts, the development of improved methodologies for lipid analyses should lead to acceleration of knowledge on lipid mechanisms in psychiatric disorders and will undoubtedly reveal therapeutic relevance.

Targeting sphingolipids and their enzymes for novel therapeutic approaches has found medical application for several disorders, in spite of the fact that the clinical manifestations of sphingolipid dysfunction are only now being understood. Aside from enzyme replacement therapy, which is used for several lysosomal storage disorders (1), the manipulation of sphingolipid metabolism is currently being studied as a novel strategy for cancer and neurodegeneration therapies, whereby small-molecule inhibitors and monoclonal antibodies that target sphingolipid metabolism have shown great promise (19). Furthermore, recent studies have suggested that S-1P receptors are encouraging therapeutic targets for the treatment of pathological inflammation, particularly in asthma and irritable bowel disorder (119). It is hoped that similar targeting strategies can be applied to psychiatric disorders in the near future.

8. REFERENCES

1. T. Kolter and K. Sandhoff: Sphingolipid metabolism diseases. *Biochim Biophys Acta* 1758, 2057-79 (2006)

2. R. Navon: Molecular and clinical heterogeneity of adult GM2 gangliosidosis. *Dev Neurosci* 13, 295-8 (1991)

3. P. I. Rosebush, G. M. MacQueen, J. T. Clarke, J. W. Callahan, P. M. Strasberg, and M. F. Mazurek: Late-onset Tay-Sachs disease presenting as catatonic schizophrenia: diagnostic and treatment issues. *J Clin Psychiatry* 56, 347-53 (1995)

4. N. Zelnik, V. Khazanov, A. Sheinkman, A. M. Karpati, and L. Peleg: Clinical manifestations of psychiatric patients who are carriers of tay-sachs disease. Possible role of psychotropic drugs. *Neuropsychobiology* 41, 127-31 (2000)

5. B. Colsch, C. Afonso, J. C. Turpin, J. Portoukalian, J. C. Tabet, and N. Baumann: Sulfogalactosylceramides in motor and psycho-cognitive adult metachromatic leukodystrophy: relations between clinical, biochemical analysis and molecular aspects. *Biochim Biophys Acta* 1780, 434-40 (2008)

6. S. L. Henderson, W. Packman, and S. Packman: Psychosocial aspects of patients with Niemann-Pick disease, type B. *Am J Med Genet A* 149A, 2430-6 (2009)

7. D. A. Laney, D. J. Gruskin, P. M. Fernhoff, J. F. Cubells, O. Y. Ousley, H. Hipp, and A. J. Mehta: Social-adaptive and psychological functioning of patients affected by Fabry disease. *J Inherit Metab Dis* (2010)

8. W. Packman, T. Wilson Crosbie, A. Riesner, C. Fairley, and S. Packman: Psychological complications of patients with Gaucher disease. *J Inherit Metab Dis* 29, 99-105 (2006)

9. L. M. Shulman, N. J. David, and W. J. Weiner: Psychosis as the initial manifestation of adult-onset Niemann-Pick disease type C. *Neurology* 45, 1739-43 (1995)

10. M. Walterfang, M. Fietz, L. Abel, E. Bowman, R. Mocellin, and D. Velakoulis: Gender dimorphism in siblings with schizophrenia-like psychosis due to Niemann-Pick disease type C. *J Inherit Metab Dis* (2009)

11. M. Walterfang, M. Fietz, M. Fahey, D. Sullivan, P. Leane, D. I. Lubman, and D. Velakoulis: The neuropsychiatry of Niemann-Pick type C disease in adulthood. *J Neuropsychiatry Clin Neurosci* 18, 158-70 (2006)

12. P. A. Desplats, C. A. Denny, K. E. Kass, T. Gilmartin, S. R. Head, J. G. Sutcliffe, and T. T. Seyfried: Glycolipid

and Ganglioside Metabolism Imbalances In Huntington's Disease *Neurobiol Dis* (2007)

13. M. O. Grimm, *et al.*: Regulation of cholesterol and sphingomyelin metabolism by amyloid-beta and presenilin. *Nat Cell Biol* 7, 1118-23 (2005)

14. P. Katsel, C. Li, and V. Haroutunian: Gene expression alterations in the sphingolipid metabolism pathways during progression of dementia and Alzheimer's disease: a shift toward ceramide accumulation at the earliest recognizable stages of Alzheimer's disease? *Neurochem Res* 32, 845-56 (2007)

15. I. Y. Tamboli, K. Prager, E. Barth, M. Heneka, K. Sandhoff, and J. Walter: Inhibition of glycosphingolipid biosynthesis reduces secretion of the beta-amyloid precursor protein and amyloid beta-peptide. *J Biol Chem* 280, 28110-7 (2005)

16. M. M. Rapport: Implications of altered brain ganglioside profiles in amyotrophic lateral sclerosis (ALS). *Acta Neurobiol Exp (Wars)* 50, 505-13 (1990)

17. G. van Echten-Deckert and T. Herget: Sphingolipid metabolism in neural cells. *Biochim Biophys Acta* 1758, 1978-94 (2006)

18. T. Wennekes, R. J. van den Berg, R. G. Boot, G. A. van der Marel, H. S. Overkleeft, and J. M. Aerts: Glycosphingolipids--nature, function, and pharmacological modulation. *Angew Chem Int Ed Engl* 48, 8848-69 (2009)

19. Y. H. Zeidan and Y. A. Hannun: Translational aspects of sphingolipid metabolism. *Trends Mol Med* 13, 327-36 (2007)

20. Y. A. Hannun: The sphingomyelin cycle and the second messenger function of ceramide. *J Biol Chem* 269, 3125-8 (1994)

21. P. P. Ruvolo: Intracellular signal transduction pathways activated by ceramide and its metabolites. *Pharmacol Res* 47, 383-92 (2003)

22. C. Luberto, J. M. Kraveka, and Y. A. Hannun: Ceramide regulation of apoptosis versus differentiation: a walk on a fine line. Lessons from neurobiology. *Neurochem Res* 27, 609-17 (2002)

23. S. Spiegel and A. H. Merrill, Jr.: Sphingolipid metabolism and cell growth regulation. *FASEB J* 10, 1388-97 (1996)

24. Y. A. Hannun: Functions of ceramide in coordinating cellular responses to stress. *Science* 274, 1855-9 (1996)

25. T. Ariga, W. D. Jarvis, and R. K. Yu: Role of sphingolipid-mediated cell death in neurodegenerative diseases. *J Lipid Res* 39, 1-16 (1998)

26. A. Jana, E. L. Hogan, and K. Pahan: Ceramide and neurodegeneration: susceptibility of neurons and oligodendrocytes to cell damage and death. *J Neurol Sci* 278, 5-15 (2009)

27. C. Garcia-Ruiz, A. Colell, M. Mari, A. Morales, and J. C. Fernandez-Checa: Direct effect of ceramide on the mitochondrial electron transport chain leads to generation of reactive oxygen species. Role of mitochondrial glutathione. *J Biol Chem* 272, 11369-77 (1997)

28. E. H. Schuchman: The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. *Int J Clin Pharmacol Ther* 47 Suppl 1, S48-57 (2009)

29. K. Ogawa-Goto and T. Abe; Gangliosides and glycosphingolipids of peripheral nervous system myelins--a minireview. *Neurochem Res* 23, 305-10 (1998)

30. W. T. Norton: *Isolation and characterization of myelin*. Myelin, ed. P. Morell. 1977, New York: Plenum Press. 161-199.

31. M. Eckhardt: The role and metabolism of sulfatide in the nervous system. *Mol Neurobiol* 37, 93-103 (2008)

32. K. Simons and E. Ikonen: Functional rafts in cell membranes. *Nature* 387, 569-72 (1997)

33. M. F. Hanzal-Bayer and J. F. Hancock: Lipid rafts and membrane traffic. *FEBS Lett* 581, 2098-104 (2007)

34. K. Jacobson, O. G. Mouritsen, and R. G. Anderson: Lipid rafts: at a crossroad between cell biology and physics. *Nat Cell Biol* 9, 7-14 (2007)

35. G. van Meer, D. R. Voelker, and G. W. Feigenson: Membrane lipids: where they are and how they behave. *Nat Rev Mol Cell Biol* 9, 112-24 (2008)

36. D. Wheeler, V. V. Bandaru, P. A. Calabresi, A. Nath, and N. J. Haughey: A defect of sphingolipid metabolism modifies the properties of normal appearing white matter in multiple sclerosis. *Brain* 131, 3092-102 (2008)

37. G. M. MacQueen, P. I. Rosebush, and M. F. Mazurek: Neuropsychiatric aspects of the adult variant of Tay-Sachs disease. *J Neuropsychiatry Clin Neurosci* 10, 10-9 (1998)

38. N. Baumann, J. C. Turpin, M. Lefevre, and B. Colsch: Motor and psycho-cognitive clinical types in adult metachromatic leukodystrophy: genotype/phenotype relationships? *J Physiol Paris* 96, 301-6 (2002)

39. G. D. Cherayil: Estimation of glycolipids in four selected lobes of human brain in neurological diseases. *J Neurochem* 16, 913-20 (1969)

40. E. G. Brunngraber, L. G. Davis, C. Rieser, and M. V. Reddy: Urinary glycoconjugates in schizophrenic patients. *Biol Psychiatry* 16, 741-51 (1981)

41. U. Haselhorst, H. Schenk, I. Beyer, R. Uebelhack, E. Franke, and V. Kielstein: Abnormality of gangliosides in erythrocyte membranes of schizophrenic patients. *Clin Physiol Biochem* 6, 281-4 (1988)

42. A. Schmitt, K. Wilczek, K. Blennow, A. Maras, A. Jatzko, G. Petroianu, D. F. Braus, and W. F. Gattaz: Altered thalamic membrane phospholipids in schizophrenia: a postmortem study. *Biol Psychiatry* 56, 41-5 (2004)

43. S. Narayan, S. R. Head, T. J. Gilmartin, B. Dean, and E. A. Thomas: Evidence for disruption of sphingolipid metabolism in schizophrenia. *J Neurosci Res* 87, 278-88 (2009)

44. K. L. Davis, D. G. Stewart, J. I. Friedman, M. Buchsbaum, P. D. Harvey, P. R. Hof, J. Buxbaum, and V. Haroutunian: White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Arch Gen Psychiatry* 60, 443-56 (2003)

45. M. Kubicki, R. W. McCarley, and M. E. Shenton: Evidence for white matter abnormalities in schizophrenia. *Curr Opin Psychiatry* 18, 121-34 (2005)

46. E. Schwarz, S. Prabakaran, P. Whitfield, H. Major, F. M. Leweke, D. Koethe, P. McKenna, and S. Bahn: High throughput lipidomic profiling of schizophrenia and bipolar disorder brain tissue reveals alterations of free fatty acids, phosphatidylcholines, and ceramides. *J Proteome Res* 7, 4266-77 (2008)

47. J. K. Yao, S. Leonard, and R. D. Reddy: Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res* 42, 7-17 (2000)

48. J. Kornhuber, A. Medlin, S. Bleich, V. Jendrossek, A. W. Henkel, J. Wiltfang, and E. Gulbins: High activity of acid sphingomyelinase in major depression. *J Neural Transm* 112, 1583-90 (2005)

49. J. Kornhuber, M. Reichel, P. Tripal, T. W. Groemer, A. W. Henkel, C. Muhle, and E. Gulbins: The role of ceramide in major depressive disorder. *Eur Arch Psychiatry Clin Neurosci* 259 Suppl 2, S199-204 (2009)

50. S. Albouz, F. Le Saux, D. Wenger, J. J. Hauw, and N. Baumann: Modifications of sphingomyelin and phosphatidylcholine metabolism by tricyclic antidepressants and phenothiazines. *Life Sci* 38, 357-63 (1986)

51. M. Kolzer, N. Werth, and K. Sandhoff: Interactions of acid sphingomyelinase and lipid bilayers in the presence of the tricyclic antidepressant desipramine. *FEBS Lett* 559, 96-8 (2004)

52. S. Marenco and D. R. Weinberger: The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. *Dev Psychopathol* 12, 501-27 (2000)

53. J. L. Rapoport, A. M. Addington, S. Frangou, and M. R. Psych: The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry* 10, 434-49 (2005)

54. S. H. Fatemi and T. D. Folsom: The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr Bull* 35, 528-48 (2009)

55. M. Kotani, T. Terashima, and T. Tai: Developmental changes of ganglioside expressions in postnatal rat cerebellar cortex. *Brain Res* 700, 40-58 (1995)

56. L. Svennerholm, K. Bostrom, P. Fredman, J. E. Mansson, B. Rosengren, and B. M. Rynmark: Human brain gangliosides: developmental changes from early fetal stage to advanced age. *Biochim Biophys Acta* 1005, 109-17 (1989)

57. T. Yamashita, R. Wada, T. Sasaki, C. Deng, U. Bierfreund, K. Sandhoff, and R. L. Proia: A vital role for glycosphingolipid synthesis during development and differentiation. *Proc Natl Acad Sci U S A* 96, 9142-7 (1999)

58. R. K. Yu, Y. Nakatani, and M. Yanagisawa: The role of glycosphingolipid metabolism in the developing brain. *J Lipid Res* 50 Suppl, S440-5 (2009)

59. K. A. Sheikh, J. Sun, Y. Liu, H. Kawai, T. O. Crawford, R. L. Proia, J. W. Griffin, and R. L. Schnaar: Mice lacking complex gangliosides develop Wallerian degeneration and myelination defects. *Proc Natl Acad Sci U S A* 96, 7532-7 (1999)

60. R. Jennemann, *et al.*: Cell-specific deletion of glucosylceramide synthase in brain leads to severe neural defects after birth. *Proc Natl Acad Sci U S A* 102, 12459-64 (2005)

61. G. Saher, B. Brugger, C. Lappe-Siefke, W. Mobius, R. Tozawa, M. C. Wehr, F. Wieland, S. Ishibashi, and K. A. Nave: High cholesterol level is essential for myelin membrane growth. *Nat Neurosci* 8, 468-75 (2005)

62. R. Bansal and S. E. Pfeiffer: Reversible inhibition of oligodendrocyte progenitor differentiation by a monoclonal antibody against surface galactolipids. *Proc Natl Acad Sci U S A* 86, 6181-5 (1989)

63. R. Bansal, A. L. Gard, and S. E. Pfeiffer: Stimulation of oligodendrocyte differentiation in culture by growth in the presence of a monoclonal antibody to sulfated glycolipid. *J Neurosci Res* 21, 260-7 (1988)

64. R. Bansal and S. E. Pfeiffer: Regulation of gene expression in mature oligodendrocytes by the specialized myelin-like membrane environment: antibody perturbation in culture with the monoclonal antibody R-mAb. *Glia* 12, 173-9 (1994)

65. R. Bansal, S. Winkler, and S. Bheddah: Negative regulation of oligodendrocyte differentiation by galactosphingolipids. *J Neurosci* 19, 7913-24 (1999)

66. A. Bosio, E. Binczek, and W. Stoffel: Functional breakdown of the lipid bilayer of the myelin membrane in central and peripheral nervous system by disrupted galactocerebroside synthesis. *Proc Natl Acad Sci U S A* 93, 13280-5 (1996)

67. T. Coetzee, N. Fujita, J. Dupree, R. Shi, A. Blight, K. Suzuki, and B. Popko: Myelination in the absence of galactocerebroside and sulfatide: normal structure with abnormal function and regional instability. *Cell* 86, 209-19 (1996)

68. J. L. Dupree, T. Coetzee, A. Blight, K. Suzuki, and B. Popko: Myelin galactolipids are essential for proper node of Ranvier formation in the CNS. *J Neurosci* 18, 1642-9 (1998)

69. K. Honke, Y. Hirahara, J. Dupree, K. Suzuki, B. Popko, K. Fukushima, J. Fukushima, T. Nagasawa, N. Yoshida, Y. Wada, and N. Taniguchi: Paranodal junction formation and spermatogenesis require sulfoglycolipids. *Proc Natl Acad Sci U S A* 99, 4227-32 (2002)

70. T. Ishibashi, J. L. Dupree, K. Ikenaka, Y. Hirahara, K. Honke, E. Peles, B. Popko, K. Suzuki, H. Nishino, and H. Baba: A myelin galactolipid, sulfatide, is essential for maintenance of ion channels on myelinated axon but not essential for initial cluster formation. *J Neurosci* 22, 6507-14 (2002)

71. J. Marcus, S. Honigbaum, S. Shroff, K. Honke, J. Rosenbluth, and J. L. Dupree: Sulfatide is essential for the maintenance of CNS myelin and axon structure. *Glia* 53, 372-81 (2006)

72. N. Okamura, M. Stoskopf, F. Hendricks, and Y. Kishimoto: Phylogenetic dichotomy of nerve glycosphingolipids. *Proc Natl Acad Sci U S A* 82, 6779-82 (1985)

73. N. Okamura, M. Stoskopf, H. Yamaguchi, and Y. Kishimoto: Lipid composition of the nervous system of earthworms (Lumbricus terrestris). *J Neurochem* 45, 1875-9 (1985)

74. J. M. Boggs, W. Gao, and Y. Hirahara: Myelin glycosphingolipids, galactosylceramide and sulfatide, participate in carbohydrate-carbohydrate interactions between apposed membranes and may form glycosynapses between oligodendrocyte and/or myelin membranes. *Biochim Biophys Acta* 1780, 445-55 (2008)

75. J. Marcus and B. Popko: Galactolipids are molecular determinants of myelin development and axo-glial organization. *Biochim Biophys Acta* 1573, 406-13 (2002)

76. A. Carlsson and M. Lindqvist: Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol* 20, 140-144 (1963)

77. B. Dean: Understanding the pathology of schizophrenia: recent advances from the study of the molecular architecture of postmortem CNS tissue. *Postgrad Med J* 78, 142-8 (2002)

78. A. Becher and R. A. McIlhinney: Consequences of lipid raft association on G-protein-coupled receptor function. *Biochem Soc Symp*, 151-64 (2005)

79. A. M. Navratil, S. P. Bliss, K. A. Berghorn, J. M. Haughian, T. A. Farmerie, J. K. Graham, C. M. Clay, and M. S. Roberson: Constitutive localization of the gonadotropin-releasing hormone (GnRH) receptor to low density membrane microdomains is necessary for GnRH signaling to ERK. *J Biol Chem* 278, 31593-602 (2003)

80. Y. Xiang, V. O. Rybin, S. F. Steinberg, and B. Kobilka: Caveolar localization dictates physiologic signaling of beta 2-adrenoceptors in neonatal cardiac myocytes. *J Biol Chem* 277, 34280-6 (2002)

81. M. Fallahi-Sichani and J. J. Linderman: Lipid raft-mediated regulation of G-protein coupled receptor signaling by ligands which influence receptor dimerization: a computational study. *PLoS One* 4, e6604 (2009)

82. K. Mirnics, F. A. Middleton, A. Marquez, D. A. Lewis, and P. Levitt: Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. *Neuron* 28, 53-67 (2000)

83. K. Mirnics, F. A. Middleton, D. A. Lewis, and P. Levitt: Analysis of complex brain disorders with gene expression microarrays: schizophrenia as a disease of the synapse. *Trends Neurosci* 24, 479-86 (2001)

84. S. Bahn, S. J. Augood, M. Ryan, D. G. Standaert, M. Starkey, and P. C. Emson: Gene expression profiling in the post-mortem human brain--no cause for dismay. *J Chem Neuroanat* 22, 79-94 (2001)

85. M. B. Knable, E. F. Torrey, M. J. Webster, and J. J. Bartko: Multivariate analysis of prefrontal cortical data from the Stanley Foundation Neuropathology Consortium. *Brain Res Bull* 55, 651-9 (2001)

86. M. P. Vawter, J. M. Crook, T. M. Hyde, J. E. Kleinman, D. R. Weinberger, K. G. Becker, and W. J. Freed: Microarray analysis of gene expression in the prefrontal cortex in schizophrenia: a preliminary study. *Schizophr Res* 58, 11-20 (2002)

87. J. Rohrbough and K. Broadie: Lipid regulation of the synaptic vesicle cycle. *Nat Rev Neurosci* 6, 139-50 (2005)

88. L. H. Chamberlain, R. D. Burgoyne, and G. W. Gould: SNARE proteins are highly enriched in lipid rafts in PC12 cells: implications for the spatial control of exocytosis. *Proc Natl Acad Sci U S A* 98, 5619-24 (2001)

89. F. Darios, *et al.*: Sphingosine facilitates SNARE complex assembly and activates synaptic vesicle exocytosis. *Neuron* 62, 683-94 (2009)

90. X. Fan, D. C. Goff, and D. C. Henderson: Inflammation and schizophrenia. *Expert Rev Neurother* 7, 789-96 (2007)

91. N. Muller, A. M. Myint, and M. J. Schwarz: The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders--relation to drug treatment. *Dialogues Clin Neurosci* 11, 319-32 (2009)

92. S. Potvin, E. Stip, A. A. Sepehry, A. Gendron, R. Bah, and E. Kouassi: Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry* 63, 801-8 (2008)

93. B. I. Goldstein, D. E. Kemp, J. K. Soczynska, and R. S. McIntyre: Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry* 70, 1078-90 (2009)

94. D. Arion, T. Unger, D. A. Lewis, P. Levitt, and K. Mirnics: Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. *Biol Psychiatry* 62, 711-21 (2007)

95. S. Narayan, B. Tang, S. R. Head, T. J. Gilmartin, J. G. Sutcliffe, B. Dean, and E. A. Thomas: Molecular profiles of schizophrenia in the CNS at different stages of illness. *Brain Res* 1239, 235-248 (2008)

96. U. Meyer and J. Feldon: Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia. *Psychopharmacology (Berl)* 206, 587-602 (2009)

97. N. Muller: COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Investig Drugs* 11, 31-42

98. N. Muller and M. J. Schwarz: COX-2 inhibition in schizophrenia and major depression. *Curr Pharm Des* 14, 1452-65 (2008)

99. M. Riedel, M. Strassnig: M. J. Schwarz, and N. Muller, COX-2 inhibitors as adjunctive therapy in schizophrenia: rationale for use and evidence to date. *CNS Drugs* 19, 805-19 (2005)

100. A. Huwiler and J. Pfeilschifter: Lipids as targets for novel anti-inflammatory therapies. *Pharmacol Ther* 124, 96-112 (2009)

101. A. Huwiler, B. Johansen, A. Skarstad, and J. Pfeilschifter: Ceramide binds to the CaLB domain of cytosolic phospholipase A2 and facilitates its membrane docking and arachidonic acid release. *FASEB J* 15, 7-9 (2001)

102. E. Klapisz, J. Masliah, G. Bereziat, C. Wolf, and K. S. Koumanov: Sphingolipids and cholesterol modulate membrane susceptibility to cytosolic phospholipase A(2). *J Lipid Res* 41, 1680-8 (2000)

103. B. J. Pettus, A. Bielawska, P. Subramanian, D. S. Wijesinghe, M. Maceyka, C. C. Leslie, J. H. Evans, J. Freiberg, P. Roddy, Y. A. Hannun, and C. E. Chalfant: Ceramide 1-phosphate is a direct activator of cytosolic phospholipase A2. *J Biol Chem* 279, 11320-6 (2004)

104. R. V. Stahelin, P. Subramanian, M. Vora, W. Cho, and C. E. Chalfant: Ceramide-1-phosphate binds group IVA cytosolic phospholipase a2 via a novel site in the C2 domain. *J Biol Chem* 282, 20467-74 (2007)

105. B. J. Pettus, A. Bielawska, S. Spiegel, P. Roddy, Y. A. Hannun, and C. E. Chalfant: Ceramide kinase mediates cytokine- and calcium ionophore-induced arachidonic acid release. *J Biol Chem* 278, 38206-13 (2003)

106. L. R. Ballou, S. C. Barker, A. E. Postlethwaite, and A. H. Kang: Sphingosine potentiates IL-1-mediated prostaglandin E2 production in human fibroblasts. *J Immunol* 145, 4245-51 (1990)

107. L. R. Ballou, C. P. Chao, M. A. Holness, S. C. Barker, and R. Raghow: Interleukin-1-mediated PGE2 production and sphingomyelin metabolism. Evidence for the regulation of cyclooxygenase gene expression by sphingosine and ceramide. *J Biol Chem* 267, 20044-50 (1992)

108. M. J. Lee, J. R. Van Brocklyn, S. Thangada, C. H. Liu, A. R. Hand, R. Menzeleev, S. Spiegel, and T. Hla: Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. *Science* 279, 1552-5 (1998)

109. S. Spiegel and S. Milstien: Sphingosine-1-phosphate: an enigmatic signalling lipid. *Nat Rev Mol Cell Biol* 4, 397-407 (2003)

110. N. Young and J. R. Van Brocklyn: Signal transduction of sphingosine-1-phosphate G protein-coupled receptors. *ScientificWorldJournal* 6, 946-66 (2006)

111. B. J. Pettus, J. Bielawski, A. M. Porcelli, D. L. Reames, K. R. Johnson, J. Morrow, C. E. Chalfant, L. M. Obeid, and Y. A. Hannun: The sphingosine kinase 1/sphingosine-1-phosphate pathway mediates COX-2 induction and PGE2 production in response to TNF-alpha. *FASEB J* 17, 1411-21 (2003)

112. L. Y. Chen, G. Woszczek, S. Nagineni, C. Logun, and J. H. Shelhamer: Cytosolic phospholipase A2alpha activation induced by S1P is mediated by the S1P3 receptor in lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 295, L326-35 (2008)

113. A. Damirin, H. Tomura, M. Komachi, M. Tobo, K. Sato, C. Mogi, H. Nochi, K. Tamoto, and F. Okajima: Sphingosine 1-phosphate receptors mediate the lipid-induced cAMP accumulation through cyclooxygenase-

2/prostaglandin I2 pathway in human coronary artery smooth muscle cells. *Mol Pharmacol* 67, 1177-85 (2005)

114. *Phospholipid Spectrum Disorders in Psychiatry and Neurology*. 2nd ed, ed. M. Peet, I. Glen, and D.F. Horrobin. 2003, Lancashire: Marius Press.

115. D. F. Horrobin: The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr Res* 30, 193-208 (1998)

116. D. F. Horrobin and C. N. Bennet: New gene targets related to schizophrenia and other psychiatric disorders: enzymes, binding proteins and transport proteins involved in phospholipid and fatty acid metabolism. *Prostaglandins, Leukotrienes and Essential Fatty acids* 60, 141-167 (1999)

117. W. S. Fenton, J. Hibbeln, and M. Knable: Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. *Biol Psychiatry* 47, 8-21 (2000)

118. J. K. Yao, D. P. van Kammen, and J. A. Gurklis: Abnormal incorporation of arachidonic acid into latelets of drug-free patients with schizophrenia. *Psychiatry Res* 60, 11-21 (1996)

119. G. F. Nixon: Sphingolipids in inflammation: pathological implications and potential therapeutic targets. *Br J Pharmacol* 158, 982-93 (2009)

120. D. N. Black, K. H. Taber, and R. A. Hurley: Metachromatic leukodystrophy: a model for the study of psychosis. *J Neuropsychiatry Clin Neurosci* 15, 289-93 (2003)

121. R. Navon, Z. Argov, and A. Frisch: Hexosaminidase A deficiency in adults. *Am J Med Genet* 24, 179-96 (1986)

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