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Sphingolipids in neurodegeneration (with focus on ceramide and S1P)

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Abstract

For many decades, research on sphingolipids associated with neurodegenerative disease focused on alterations in glycosphingolipids, particularly glycosylceramides (cerebrosides), sulfatides, and gangliosides. This seemed quite natural since many of these glycolipids are constituents of myelin and accumulated in lipid storage diseases (sphingolipidoses) resulting from enzyme deficiencies in glycolipid metabolism. With the advent of recognizing ceramide and its derivative, sphingosine-1-phosphate (S1P), as key players in lipid cell signaling and regulation of cell death and survival, research focus shifted toward these two sphingolipids. Ceramide and S1P are invoked in a plethora of cell biological processes participating in neurodegeneration such as ER stress, autophagy, dysregulate protein and lipid transport, exosome secretion and neurotoxic protein spreading, neuroinflammation, and mitochondrial dysfunction. Hence, it is timely to discuss various functions of ceramide and S1P in neurodegenerative disease and to define sphingolipid metabolism and cell signaling pathways as potential targets for therapy.

1. Introduction to sphingolipids in neurodegeneration

Most neurodegenerative diseases, regardless of being acute or chronic, are accompanied by alterations of sphingolipid composition in a variety of cell types in the central or peripheral nervous system (CNS or PNS). This is not surprising since sphingolipids are important cell signaling molecules in cellular membranes and susceptible to enzymatic hydrolysis. However, for many of these sphingolipid alterations, profound questions remain unanswered. Firstly, because most sphingolipids are precursors as well as derivatives of other sphingolipids, it is often unclear which specific sphingolipid is associated with a disease and whether it is causative or a byproduct in the disease process. Secondly, molecular and cellular targets and mechanisms affected in the disease process are often unclear, ranging from individual proteins to alterations of the membrane structure in specific organelles, from apoptosis to sphingolipid-induced protein aggregation and oxidative stress. Thirdly, unless neurodegeneration emerges from enzyme deficiencies in sphingolipid

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metabolism, the immediate cause for alterations of the sphingolipid composition is often unknown. Enzymes generating ceramides such as ceramide synthases (CerSs) or sphingomyelinases (SMases) may be up-regulated, while those turning over ceramide (mainly ceramidases) may be down-regulated. Other mechanisms such as aberrant transport of sphingolipids by proteins (e.g., ceramide transport protein or CERT) or vesicles (e.g., endosomes) may also lead to dysregulated sphingolipid metabolism in neurodegenerative disease. On the other hand, since any alteration of the sphingolipid composition results from an enzymatic reaction, either of the enzyme generating or turning over a particular sphingolipid, drug targets are easier to define and offer promising therapeutic approaches.

This review will first discuss sphingolipid species that are up- or downregulated during neurodegenerative diseases. Emphasis will be on the rheostat of ceramide and sphingosine-1-phosphate (S1P) in regulation of neuronal cell survival and apoptosis. Then, we will discuss pathophysiological mechanisms and sphingolipid targets with focus on cellular transport processes and mitochondrial dysfunction. Finally, we will discuss neurodegeneration as a systemic disease involving inflammatory and immune processes regulated (and dysregulated) by sphingolipids. In all of these aspects, we approach sphingolipid metabolism and neuronal health as an integrative process and emphasize shared mechanisms. In the case of ceramide, several potential mechanisms shared between individual neurodegenerative diseases will be discussed. Therefore, we will not dedicate separate sections to individual diseases. However, in the case of S1P, common pathogenic mechanisms are less clear and we will discuss the role of S1P separately and for individual diseases. If we do not go into further detail for other sphingolipids and neurodegenerative diseases, we will provide references for excellent reviews on the topics discussed.

2. Sphingolipid levels in nervous system injuries and neurodegenerative diseases

Neurodegeneration is associated with alteration of sphingolipid metabolism and composition. In acute injuries such as stroke, concussion, spinal cord injury (SCI), or traumatic brain injury (TBI), activation of SMases and glycosidases and upregulation of ceramide and glycolipid levels are among the first responses of the injured tissue (Abe et al., 2018; Barbacci et al., 2017; Brunkhorst et al., 2015; Gu et al., 2013; Horres and Hannun, 2012; Jones and Ren, 2016; Kubota et al., 1989; Novgorodov and Gudz, 2011; Ong et al., 2015; Roux et al., 2016; Sajja et al., 2018). C18:0 and C18:1 ceramide, typical neuronal ceramides synthesized by CerS1, are dysregulated within 24 h after the insult and can be used as biomarkers for TBI (Sajja et al., 2018). Despite efforts to use S1P receptor agonists to protect neurons from injury, there is no information on actual S1P levels during TBI, SCI, or stroke available as of today. Following injury, in a delayed and prolonged response, the immune system is activated and antibodies against myelin glycolipids are generated. For example, anti-galactosylceramide antibodies are detectable for more than 40 years after the injury (Taranova et al., 1992). Despite this breadth of impressive data, it is still not known how alterations in sphingolipid composition affect the pathophysiology of injury and stroke.

Loss of function experiments using mice with deficient SMases, glycosphingolipid glycosidases, or CerS exposed to TBI, SCI, or stroke are rare. Only knockout mice for acid SMase, and SK1 and 2 were tested as critical players or drug targets in acute brain injury. For example, SK2 was shown to be critical for ischemic preconditioning to protect against stroke (Song et al., 2017; Song et al., 2018). Apart from genetic enzyme deficiencies, inhibitors specific for enzymes in sphingolipid metabolism were used to test the effect of sphingolipids on the course of acute brain or spinal cord injuries. Among those, imipramine, a tricyclic antidepressant and functional inhibitor of acid SMase showed success in TBI therapy (Han et al., 2011). However, this type of inhibitor is not specific for acid SMase and beneficial outcomes of inhibiting ceramide generation in acute brain injury are still debated. Probably, most promising are results to ameliorate SCI using inhibitors of ceramide generation, although the mechanism by which sphingolipids may prevent or cure injuries of the spinal cord is not clear. It is also unclear, which injury-related triggers activate enzymes that generate ceramide.

In contrast to acute injuries, the functional significance for dysregulated sphingolipids in chronic neurodegeneration is more thoroughly investigated. Lysosomal storage disorders or sphingolipidoses such as Gaucher (β-glucosylceramidase deficiency), Krabbe (β-galactosylceramidase deficiency), Niemann Pick type 1 (acid SMase (aSMase) deficiency), Fabry (α-galactosidase deficiency), Tay Sachs (α-hexosaminidase deficiency), and metachromatic leukodystrophy (arylsulfatase deficiency deficiency) are caused by genetically inherited enzyme deficiencies in the hydrolytic degradation of glycosphingolipids and often involve chronic neurodegeneration as a fatal outcome of a multi-symptomatic disease process (Arenz, 2017; Eckhardt, 2010; Farfel-Becker et al., 2014; Fuller and Futerman, 2018; Grassi et al., 2018; Haughey, 2010; Sandhoff, 2016; Spassieva and Bieberich, 2016). Neurotoxicity involves accumulation of glycosylated and non-glycosylated sphingolipids or lipid byproducts, which provided the first clear evidence that dysregulation of sphingolipid metabolism leads to neurodegeneration (Ariga et al., 1998; Ariga et al., 2008; Di Pardo and Maglione, 2018b; Fuller and Futerman, 2018; Grassi et al., 2018; Mencarelli and Martinez-Martinez, 2013; Mielke and Lyketsos, 2010; Schnaar, 2016; Yu et al., 2012). However, for many of these diseases the mechanism underlying neurotoxicity is not clear and hypotheses range from lysosomal dysfunction, dysregulation of mitochondria and autophagy, to accumulation of highly neurotoxic metabolic byproducts such as lysophingolipids (Audano et al., 2018; Folts et al., 2016; Piccinini et al., 2010; Seranova et al., 2017; Spassieva and Bieberich, 2016; Sural-Fehr and Bongarzone, 2016). Because impaired or loss of enzyme activity in sphingolipid degradation is the root cause of the disease, treatment approaches encompass enzyme replacement therapy or pharmacological inhibitors of enzymes in the generation of the otherwise accumulated lipids. Apart from neurodegeneration resulting from sphingolipidoses, there are diseases that are not primarily caused by mutations of enzymes in sphingolipid metabolism, but may affect sphingolipid composition and levels. Diseases with documented elevation of ceramide are Multiple Sclerosis (MS), AD, and Parkinson’s disease (PD). Alterations of S1P levels vary in these diseases and will be discussed in separate sections on S1P and neurodegenerative disease.

MS

In MS, the appearance of aberrant sphingolipid composition is not surprising since demyelination releases a variety of myelin sphingolipids and their degradation products into the brain and blood stream. However, the specific function of individual sphingolipids such as ceramide was only recently investigated and suggested new therapeutic strategies. Since MS is an autoimmune disease, a central nervous and peripheral component has to be considered. The peripheral component relies on the ability of the immune system to mobilize leukocytes that attack the CNS. It was found that in the experimental autoimmune encephalomyelitis (EAE) model, egress of leukocytes from lymph nodes and the autoimmune reaction(Eberle et al., 2014) is suppressed in CerS2 knockout mice, while it is enhanced in CerS6-deficient mice (Barthelmes et al., 2015; Schiffmann et al., 2012). CerS2 specifically catalyzes biosynthesis of very long chain (C24:0, C24:1) ceramides, while CerS6 mainly generates C16 ceramide (Levy and Futerman, 2010; Park et al., 2014; Stiban et al., 2010), suggesting a pro-inflammatory role for C24- and anti-inflammatory role for C16 ceramide. Prior to these exciting observations, it was shown that downregulation of S1P receptor 1 (S1P1) by the S1P precursor analog fingolimod (FTY720) also suppresses leukocyte egress and ameliorates MS, which led to a clinically approved MS therapy (see section on S1P). Hence, there appears to be an interplay of specific ceramides and S1P in the autoimmune response of MS, probably on the level of S1P receptor activation or turnover. In addition to these peripheral effects, knockout or inhibition of aSMase was shown to ameliorate MS by preventing apoptosis of oligodendrocytes, the cells generating myelin in the brain (Chami et al., 2017; Jana and Pahan, 2010). Hence targeting sphingolipid metabolism is a valid strategy for MS therapy.

AD and PD

Similar to MS, progression of other neurodegenerative diseases includes a CNS and a peripheral (immunological) component. In AD and PD, elevation of ceramide is often associated with neuronal cell death and often accompanied by generation of antibodies against specific sphingolipids indicative of activation of the immune system. Our group has made several discoveries showing involvement of ceramide in neuronal cell death, as well as astrocyte malfunction and immune response toward ceramide during progression of AD (Bieberich et al., 2000; Bieberich et al., 2003; Bieberich et al., 2001; Dinkins et al., 2014; Dinkins et al., 2016a; Kong et al., 2018; Wang et al., 2012; Wang et al., 2008b). More than 95% of AD cases do not rely of mutations in amyloid precursor protein (APP) or proteases processing APP to neurotoxic amyloid beta (Aβ) peptide (Sanabria-Castro et al., 2017; Tomita, 2017). These non-familial and late-onset cases of AD are of unknown etiology. In a proportion of these cases, genetic risk factors such as ApoE4 or TREM2 were identified, but exact mechanisms how these factors contribute to AD are not clear. One factor that clearly contributes to AD in any of these cases is aging. About 50 years ago, it was shown that in the gray matter of the aging brain, the level of cerebrosides continuously increases, which is further elevated in AD (Suzuki et al., 1965). Sulfatides, the derivatives of cerebrosides, are reduced in AD, suggesting that progression of the disease is associated with dysregulated sphingolipid metabolism (Han et al., 2002). While glycolipids of the aging and diseased brain were thoroughly analyzed from early on, it took several decades before ceramide became focus of aging and AD research, probably due to studies showing that it is a pro-

apoptotic lipid in neurons (Brugg et al., 1996). Application of newly developed mass spectrometric methods, particularly liquid chromatography-tandem mass spectrometry (LC-MS/MS) showed that during aging and more so in AD, ceramide levels are increased in brain, cerebrospinal fluid (CSF), and serum (Kim et al., 2017; Mielke et al., 2008; Mielke et al., 2012; Mielke et al., 2010; Satoi et al., 2005). Of particular interest is the rheostat of ceramide and its derivative S1P in the regulation of neuronal cell survival and cell death in neurodegeneration.

3. Ceramide and S1P rheostat in neurodegeneration

Discovery of the cell signaling function of ceramide and S1P was intimately linked to knowledge on their metabolism. About 30 years ago, several seminal studies showed that lysosphingolipids and degradation products of sphingomyelin such as ceramide and sphingosine, can inhibit protein kinase C and are metabolically regulated by what was termed the “sphingomyelin cycle” (Hannun and Bell, 1993; Hannun et al., 1986; Okazaki et al., 1989; Okazaki et al., 1990). It was also found that acid and neutral SMase were activated by cytokines such as TNF-α, Fas-ligand, or interleukins, radiation, and intracellular cell signaling factors arresting the cell cycle or inducing apoptosis, a discovery that soon led to a wealth of studies investigating the role of ceramide in the regulation of these processes (Clarke et al., 2008; Cutler and Mattson, 2001; Devillard et al., 2010; Farooqui et al., 2010; Haimovitz-Friedman et al., 1994; Hannun, 1996; Kolesnick, 1987; Ohanian and Ohanian, 2001; Testai et al., 2004). Most of these studies were performed in non-neural cells and it took almost another 10 years until the first studies appeared on the role of the sphingomyelin cycle in the regulation of apoptosis in neurons with controversial outcomes (Brugg et al., 1996; Ito and Horigome, 1995). About 25 years ago, the regulation of cell proliferation and survival by sphingolipids was then complemented by S1P, which soon led to the idea of a “ceramide/S1P rheostat” with ceramide being pro- and S1P anti-apoptotic (Cuvillier et al., 1996; Edsall et al., 1997; Gault et al., 2010; Hait et al., 2006; Hannun and Obeid, 2008; Maceyka et al., 2002; Mao and Obeid, 2008; Mao et al., 1997; Olivera et al., 1992; Olivera et al., 1999; Osawa et al., 2005; Spiegel et al., 1998b; Taha et al., 2006). Regulation of cell signaling pathways by sphingolipids is unique in that three lipid signaling molecules, sphingomyelin, ceramide, and S1P, are tightly regulated by signaling factor and stressor response enzymes such CerS, SMases, SKs, ceramidases, and phosphatases. While the anti-apoptotic effect of S1P is mediated by a variety of S1P-specific GPCRs, which implies secretion of S1P to counteract cell death, the precise mechanism of ceramide-induced apoptosis is still debated (see also section on S1P).

More recent studies show that in addition to cell survival and death, ceramide and S1P are invoked in numerous other processes regulating neuronal and glial biology. We and others reported that ceramide is critical for establishing cell polarity and migration of neuroepithelial cells, while S1P promotes oligodendroglial differentiation (Bieberich, 2010, 2011, 2012; Coelho et al., 2010; Jung et al., 2007; Krishnamurthy et al., 2007; Pitson and Pebay, 2009; Wang et al., 2008a; Wang et al., 2018). Other studies showed that ceramide and S1P induce neurite retraction as well as outgrowth depending on the neuronal cell type investigated (Singh and Hall, 2008; Toman et al., 2004). Some of these apparently contradictory effects may emerge from extracellular signaling factors such as TNF-α

activating SMases promoting generation of ceramide (e.g., as pro-apoptotic signal) as well as inducing SKs leading to metabolic turnover of ceramide into S1P (e.g., as pro-inflammatory signal) (Pettus et al., 2003; Snider, 2013; Snider et al., 2010). Most of these apparently contradictory effects, however, are likely to rely on a specific composition of target proteins specifically expressed in different types of cells, namely distinct S1P receptors or cell signaling proteins interacting with ceramide. The first proteins shown to interact with ceramide were protein phosphatases and kinases (Bieberich et al., 2000; Bourbon et al., 2000; Carlson and Hart, 1996; Dobrowsky and Hannun, 1992; Hannun, 1996; Igarashi et al., 1990; Lee et al., 1996; Lozano et al., 1994; Merrill et al., 1986; Muller et al., 1995; Wang et al., 2005; Wang et al., 1999). Particularly, ceramide activation of protein phosphatases PP2a and PP1 was reported to be involved in apoptosis induction and regulation of cell growth and cortical actin (Canals et al., 2012; Chalfant et al., 1999; Chalfant et al., 2004; Dobrowsky et al., 1993; Galadari et al., 1998; Mukhopadhyay et al., 2008; Perry et al., 2012). Our group showed that ceramide activation of atypical PKCς/λ (aPKC) promotes cell polarity, neuroprogenitor motility, and ciliogenesis, while expression of the aPKC inhibitor protein prostate apoptosis response 4 (PAR-4) renders ceramide pro-apoptotic (Bieberich, 2011, 2012; Bieberich et al., 2000; He et al., 2012; He et al., 2014; Krishnamurthy et al., 2007; Wang and Bieberich, 2010; Wang et al., 2012; Wang et al., 2009; Wang et al., 2005). More recently, we identified glycogen synthase 3β (GSK3) and tubulin as additional proteins ceramide interacts with (He et al., 2014; Kong et al., 2015; Kong et al., 2018). Our studies suggest that ceramide activation of GSK3 is critical for biogenesis and function of primary and motile cilia in the brain, while ceramide-associated tubulin (CAT) regulates voltage-dependent anion channel 1 (VDAC1), the key ADP/ATP transporter in the outer mitochondrial membrane (OMM). Activation of GSK3 is important for neurodegeneration in that it has been discussed as one of the protein kinase phosphorylating tau, the protein forming neurofibrillary tangles in AD (Drulis-Fajdasz et al., 2018; Takashima, 2006). Ceramide-activated protein kinases such as GSK3 or apoptosis-signal regulating kinase 1 (ASK1) may be critical for the etiology of neurodegenerative disease and suggest that inhibition of ceramide generation (or its interaction with the respective kinases) is a promising new strategy for therapy (Guo et al., 2017). We will devote the next sections to a more detailed discussion on the role of ceramide in neurodegeneration and therapeutic strategies. In addition to ceramide binding activating protein kinases or phosphatases and affecting mitochondrial function in neurodegeneration, ceramide is also important for autophagy and inflammation, two processes critical for neuronal cell survival by preventing intra- and extracellular accumulation of toxic proteins such as parkin or huntingtin and other polyglutamine (polyQ) proteins, and promoting clearance mechanisms such as amyloid or tau uptake and disposal by astrocytes and microglia (Audano et al., 2018; Fujikake et al., 2018; Grosch et al., 2012; Harvald et al., 2015; Jiang and Ogretmen, 2014; Karunakaran and van Echten-Deckert, 2017; Tommasino et al., 2015; van Echten-Deckert and Alam, 2018).

With regard to the regulation by sphingolipids, effects on autophagy and inflammation are critical because they operate at the intersection of several compartments including ER, mitochondria, and lysosomes. There is evidence that the different effects of ceramide on apoptosis, cell growth, polarity, autophagy, and inflammation rely on the chain length (and

degree of saturation) of the fatty acid attached to sphingosine (Grosch et al., 2012; Mencarelli and Martinez-Martinez, 2013; Mullen et al., 2011; Park and Park, 2015; Pinto et al., 2011). This appears to be reasonable if associated with protein interaction or membrane structural effects depending on ceramide chain length. While it is not known if ceramide interacts directly with any protein of the inflammasome, it was recently found that ceramide-1phosphate (C1P) transport protein (CPTP) downregulates early autophagy and stimulates inflammasome assembly (Mishra et al., 2018). The exact mechanism by which ceramide regulates autophagy is still unclear, but appears to involve chain length specificity and direct interaction of specific ceramide (C18:0 ceramide) with LC3B, a key regulatory protein of autophagy (Sentelle et al., 2012). It should be noted that C18 (C18:0 and C18:1) ceramide is one of the ceramides elevated in AD and PD, and generated by CerS4, CerS5, and CerS1, a predominantly neuronal CerS (Ben-David and Futerman, 2010; Mielke et al., 2013; Savica et al., 2016; Wang et al., 2012; Xing et al., 2016). In addition to C18 ceramide, the levels of very long chain ceramides such as C24 (C24:0 and C24:1) ceramide, all of which synthesized by CerS2, are increased in AD and are also enriched in extracellular vesicles such as exosomes (Wang et al., 2012). Since CerS-deficient mice were not yet tested after cross-breeding with AD or other neurodegenerative disease models, the specific role of individual CerS or ceramide species in neurodegeneration remains elusive. Even without crossbreeding with disease models, the phenotypes of several CerS knockout mice, particularly for CerS1 and CerS2 invoke neurodegenerative processes. A recent study suggests that Purkinje cell death in CerS1 mice is rather due to elevation of long chain bases such as dihydrosphingosine or sphingosine than loss of specific ceramides (Spassieva et al., 2016). The phenotypes are at least in part consistent with the neurotoxic effect of the fungus toxin fumonsin B1, a specific inhibitor of CerS leading to defects in neural development (Gelineau-van Waes et al., 2005; Gelineau-van Waes et al., 2009; Wang et al., 1991). Of the two knockout mice deficient of CerS generating C16:0 ceramide, CerS5 and 6, only CerS6 knockout mice showed behavioral abnormalities indicating a brain phenotype, although the exact mechanism was not elucidated yet (Ebel et al., 2013; Novgorodov et al., 2011). Probably, some of the brain phenotype is associated with mitochondrial dysfunction in oligodendrocytes caused by CerS6 deficiency (Novgorodov et al., 2011). The difficulty to understand phenotypes of CerS knockout mice results from multiple effects on sphingolipid composition as the consequence of enzyme deficiencies in *de novo* biosynthesis of ceramide. A potential solution to test the effect of ceramide depletion are knockout mice for enzymes generating ceramide by hydrolysis of a derivative such as sphingomyelin.

Unfortunately, knockout mice for acid SMase and galactosyl- or glucosylceramidase, although clearly showing a neural developmental or neurodegenerative phenotype, are burdened by elevation of multiple sphingolipids, including that of the original substrate and neurotoxic lysosphingolipids (Eckhardt, 2010; Grassi et al., 2018; Haughey, 2010; Horres and Hannun, 2012; Ledesma et al., 2011). On the other hand, deficiency of neutral sphingomyelinase 2 (nSMase2) is a promising model to study loss of function (and dysfunction) of ceramide. We will discuss its phenotypes in the next paragraph on sphingolipids in intracellular transport and mitochondrial dysfunction. In addition to ceramide depletion, knockout mice showing ceramide elevation have been generated. These include deficiencies of enzymes hydrolyzing ceramide (ceramidases) as well as enzymes

using ceramide or the product of its hydrolysis, sphingosine, as the substrate (SKs). Among these, knockout of acid ceramidase (ASAH1) causes early embryonic lethality, and cells could not survive beyond the 4 to 8 cell stage due to apoptotic cell death. This is the earliest lethal phenotype observed for a lysosomal hydrolase. Notably, treatment of 2-cell embryos from heterozygous intercrosses with S1P, rescued the ASAH1−/− embryos (Eliyahu et al., 2007). Double knockout of SKs leads to embryonic death at around E12 partly due to increased apoptosis and decrease in mitosis in the developing nervous system (Mizugishi et al., 2005).

4. Ceramide and mitochondrial dysfunction in neurodegeneration

In addition to interfacing extracellular cues and intracellular cell signaling pathways at the plasma membrane, sphingolipids are now recognized as key regulators of cellular transport and organelle function. The effects of sphingolipids on cellular transport encompasses regulation of membrane curvature, fission, and fusion in endocytosis and vesicular transport, as well as vesicular binding to transported proteins and the cytoskeleton (Adada et al., 2014; Boulgaropoulos et al., 2012; Burgert et al., 2017; Chiantia et al., 2008; Draeger and Babiychuk, 2013; Goni et al., 2005; Schneider-Schaulies and Schneider-Schaulies, 2013; Silva et al., 2012; Stoffel et al., 2016; Trajkovic et al., 2008). Mitochondrial function is another process that is regulated and dysregulated by sphingolipids (Chakrabarti et al., 2016; Hernandez-Corbacho et al., 2017; Kong et al., 2018; Law et al., 2017; Perera et al., 2016; Schwartz et al., 2018). Aberrant intra- and extracellular transport as well as mitochondrial dysfunction are gaining importance when looking for the etiology of neurodegeneration beyond protein aggregation and accumulation. There are three stages of cellular transport the dysregulation of which is critical for neurodegeneration and affected by sphingolipids: 1) processing and degradation of proteins along exo- and endocytotic transport pathways, including secretion and uptake of neuro- and gliotoxic proteins; 2) transport of organelles, including mitochondria, signalosomes, and other vesicles; and 3) extra- and intercellular transport, including that of extracellular vesicles recently gaining attention as contributing factor in neurodegeneration. Currently, it is assumed that in most of these transport processes, the lipid determines the fate of a protein, which when dysregulated becomes neurotoxic. However, we will also discuss the possibility that the protein induces dysregulation of sphingolipid metabolism as the neurotoxic trigger.

In AD, PD, and Huntington's disease, proteins such as APP, Aβ and tau (AD), synuclein and parkin (PD), and huntingtin (HD) are proteolytically processed and secreted or accumulated inside of neurons and glia. Often, proteolytic processing and secretion requires a re-uptake process involving endo- and exocytosis. Twenty years ago, the first evidence was published that ceramide generated by nerve growth factor (NGF)/p75NTR-activated nSMase2 is required for APP processing and secretion, which was then found to involve ceramide-induced upregulation and cerebroside-mediated activation of β-secretase (BACE), the protease generating Aβ from APP in neurons (Costantini et al., 2005; Kalvodova et al., 2005; Ko and Puglielli, 2009; Puglielli et al., 2003; Rossner et al., 1998). However, all of these studies were focused on neuronal APP processing and secretion, while the contribution of sphingolipids in glia remained uninvestigated. In addition, early studies on the function of sphingolipids in neurodegeneration targeted the immediate effects of APP processing such

as Aβ secretion and apoptosis induction, while other transport processes and organelles affected by Aβ and sphingolipids were not investigated until recently. Finally, genetic risk factors altering lipid metabolism and transport such as ApoE4 have not been integrated into a consistent model for the effect of sphingolipids on AD yet.

ApoE4, a lipoprotein transporting cholesterol, is a genetic risk factor for late onset AD. While homozygous carriers of ApoE4 (prevalence 2:100) have a >10-fold increased risk of developing AD at the age of 75, it is still unclear how ApoE4 contributes to AD (Liu et al., 2013; Qian et al., 2017; Ward et al., 2012). Interestingly, deficiency of NPC1, a cholesterol transport protein mutated in Niemann Pick type C disease, also increases the risk of developing AD pathology such as amyloid and tau aggregation (Borbon et al., 2012; Borbon and Erickson, 2011; Burns et al., 2003; Saito et al., 2002; Vance et al., 2005). However, NPC1 deficiencies in humans are extremely rare (prevalence 1:150,000) and lead to 50% lethality before the age of 12. Therefore, most of what we know about NPC1 stems from cell culture and animal studies. In NPC1 knockout cells, cholesterol is no longer sequestered to endosomes, but it is accumulated in lysosomes and mitochondria, where is exacerbates Aβ neurotoxicity (Colell et al., 2009; Fernandez et al., 2009). Not only transport and level of cholesterol is dysregulated, but also that of several sphingolipid classes such as sphingosine, ceramide, sphingomyelin, and glycosphingolipids (Fan et al., 2013; Sun et al., 2001). Similar to NPC1 deficiency, ApoE4 homozygosity is associated with increase of ceramide levels in AD brain, although it is not upregulated in ApoE4 normal brain (Bandaru et al., 2009; den Hoedt et al., 2017). While it is not understood how NPC1 and ApoE4 regulate sphingolipid metabolism, one is tempted to speculate that in both cases, aberrant lipid transport and accumulation, particularly of cholesterol and ceramide, leads to neurotoxicity involving Aβ and tau protein.

In many types of neurodegeneration, dysregulated protein and lipid transport in neurons and glia is likely to underlie a shared pathogenic mechanism. Particularly, aberrant traffic of accumulated or aggregated protein and lipid from endosomes to lysosomes and mitochondria has been described for AD, PD, and HD. Once at the target organelle, misdirected proteins and lipids bind to proteins critical for organelle function such as VDAC1 in mitochondria. VDAC1 binds to neurotoxic proteins such as Aβ, tau, parkin, and synuclein, which 1) impairs its transport function for ADP and ATP; 2) prevents its metabolically critical interaction with other proteins such as hexokinase; 3) promotes its interaction with pro-apoptotic proteins such as Bax; and 4) promotes assembly of multimeric VDAC1 pores that allow for the efflux of cytochrome c inducing apoptosis (Caterino et al., 2017; Chu et al., 2014; Geisler et al., 2010; Manczak and Reddy, 2012; Shoshan-Barmatz et al., 2018; Smilansky et al., 2015). As a consequence, neurodegeneration arises from mitotoxicity induced by misdirected protein and probably, lipid transport. The (dys)function of lipids may involve direct effects by binding to VDAC1 or affecting the mitochondrial membrane structure by generating ceramide pores. Lipids may also promote mitotoxic protein interaction with VDAC1 similar to that discovered by our laboratory for ceramide-induced interaction of VDAC1 with tubulin (Kong et al., 2018). The increase of ceramide levels at mitochondria and other organelles may arise from upregulation of endogenous ceramide generation or uptake of ceramide in form of exosomes. Our group has shown that generation of ceramide by nSMase2 activated by Aβ or inflammatory cytokines leads to

secretion of ceramide-enriched exosomes from astrocytes (Wang et al., 2012). These "astrosomes" may transport ceramide (and neurotoxic proteins such as Aβ and tau) into other astrocytes and neurons. Our research showed that astrosomes can induce apoptosis in astrocytes, the effect on neurons is currently investigated in our laboratory. It should be noted that exosomes are not generally glio- or neurotoxic, but may also assist Aβ or tau clearance, probably depending on the cell of origin or exosome (lipid) composition (Dinkins et al., 2016b; Yuyama and Igarashi, 2017; Yuyama et al., 2012; Yuyama et al., 2015). Apart from these unknowns, it becomes increasingly clear that the classical view of pathogenic Aβ or tau accumulation in AD will be replaced by a more physiological or system biological view involving metabolism, protein and lipid transport, and interaction of different organelles and cell types. Sphingolipids such as ceramide and S1P may serve as cell signaling hubs or network nodes to regulate physiological as well as pathophysiological mechanisms in AD and other neurodegenerative diseases.

5. Metabolism and signaling pathways of S1P

S1P is another major bioactive sphingolipid that plays essential cell signaling roles in neurodegeneration (Assi et al., 2013; Blaho and Hla, 2014; Hagen et al., 2011; Proia and Hla, 2015; Pyne et al., 2018). It is a soluble lipid generated intracellularly by SK1 and SK2 (Alvarez et al., 2010; Maceyka et al., 2012; Maceyka and Spiegel, 2014; Proia and Hla, 2015). The level of intracellular S1P is orchestrated by several metabolic enzymes and transporter proteins, such as SKs, S1P lyase, S1P phosphatase, ABC transporters, Spns2, and Mfsd2b (Bradley et al., 2014; Kawahara et al., 2009; Klyachkin et al., 2014; Kobayashi et al., 2018; Kunkel et al., 2013; Long et al., 2005; Nagareddy et al., 2014; Proia and Hla, 2015; Sciorra and Morris, 2002; Spiegel and Milstien, 2011; Vu et al., 2017). Although SK1 can be secreted and generate S1P outside of cells (Sciorra and Morris, 2002), the level of extracellular S1P is regulated by exportation by ABC transporters, Spns2, and mfsd2b from red blood cells, activated platelets, and endothelial cells, which is usually found at much higher concentration than that of tissues (Fukuhara et al., 2012; Hisano et al., 2012; Kobayashi et al., 2018; Sciorra and Morris, 2002; Vu et al., 2017). In the brain, S1P regulates survival, proliferation, migration, and inflammation of all the neural cell types, including neurons, astrocytes, microglia, and oligodendrocytes (Huang et al., 2011; Kleger et al., 2007; Laurenzana et al., 2015; Marfia et al., 2014; Smith et al., 2013). However, the function of S1P is cell type- and context- dependent.

Extracellular S1P functions through five cell surface G-protein-coupled-receptors (GPCRs) S1P1–S1P5 (Huang et al., 2011). S1P stimulates various signal transduction pathways in a cell type- and context-specific manner, usually depending on the type and expression level of S1P receptor(s). Different S1P receptors are coupled to different G-proteins and regulate diverse signaling pathways. For example, S1P1 is coupled exclusively via Gi protein to activate Ras, mitogen activated protein kinase (MAPK), PI3K/Akt, and phospholipase C pathways (Huang et al., 2011). There are excellent reviews on S1P receptor signaling pathways, and the readers are encouraged to refer to those (Blaho and Hla, 2014; Kunkel et al., 2013; Proia and Hla, 2015; Spiegel et al., 1998a; Spiegel and Milstien, 2011). On the other hand, intracellular receptor-independent actions of S1P began to emerge in several cell types, including neurons. Inside of cells, S1P regulates the function of several S1P

interacting proteins, including HDACs, TRAF2, Hsp90 and HRP94, in different cellular compartment of cells, such as the ER and nuclei (Alvarez et al., 2010; Blaho and Hla, 2014; Hait et al., 2009; Park et al., 2016; Proia and Hla, 2015).

6. Physiological functions of S1P in the CNS

S1P plays an essential role in neural development (Mizugishi et al., 2005). During mouse development, SK1 is highly expressed in the brain, while SK2 levels are increased in the limb buds, eyes, and branchial arches. S1P depletion in SK1/K2-double knockout mice exhibits severe defects in neurogenesis and neural cell survival, accompanied by impaired neural tube closure, increased neural cell apoptosis, and embryonic lethality (Mizugishi et al., 2005). Blockade of S1P signaling in S1P1-null mice shows a very similar neural phenotype, indicating a central function of S1P signaling in neurogenesis and brain development (Blaho and Hla, 2014; Mizugishi et al., 2005; Proia and Hla, 2015).

Besides its role in brain development, S1P is implicated in regulation of neuronal function and survival in adult brains. Convincing evidence indicates that S1P plays a role in presynaptic structure, synaptic strength, and synaptic vesicle availability in hippocampal neurons (Brailoiu et al., 2002; Camoletto et al., 2009; Darios et al., 2009; Kanno et al., 2010; Riganti et al., 2016). In addition, experimental data suggest that S1P promotes pro-survival neuronal autophagy (Moruno Manchon et al., 2015). Expression of SK1 enhances autophagic activity, while S1P lyase reduces the activity (Moruno Manchon et al., 2015; Moruno Manchon et al., 2016). Autophagy is crucial for the health and survival of neurons to get rid of damaged and aggregated proteins and organelles during basal, nutrient depletion, aging, and disease conditions, in particular, to counteract cell death induced by ceramide or other pathogens (Moruno-Manchon et al., 2018; Moruno Manchon et al., 2015; Moruno Manchon et al., 2016).

Recently, the functions of S1P in the immune system and neuroinflammation is gaining attention with respect to neurodegeneration, triggered by the approval of the Relapsing Remitting MS (RR-MS) drug Fingolimod (FTY720), a sphingosine analog and S1P1 functional antagonist. In activated microglia, SK1 expression is upregulated (Nayak et al., 2010). Lipopolysaccharide (LPS) activates the SK1/S1P axis leading to translocation of SK1 to the plasma membrane where it converts its substrate sphingosine to S1P (Fernandez-Pisonero et al., 2012; Hammad et al., 2008). Moreover, suppression of SK1 activity in activated mouse microglia inhibits the expression levels of TNF-??, IL-1??, and iNOS and release of TNF-?? and NO [59]. Exogenous addition of S1P to activated microglia enhances inflammatory responses, suggesting that S1P acts as an upstream factor to induce the production of pro-inflammatory cytokines and neurotoxins such as NO (Assi et al., 2013). A recent study shows that supplementation of S1P to primary cultured microglial cells deprived of oxygen and glucose leads to increased IL-17A expression (Lv et al., 2016). These data suggest that the SK1/S1P pathway is involved in the inflammatory response of activated microglia in an autocrine/paracrine fashion in which the secreted or intracellular S1P can regulate the release of pro-inflammatory factors by microglia.

In astrocytes, SK1 and S1P3 are functionally upregulated under pro-inflammatory conditions. Incubation with IL-1 induces the expression of SK1 and exogenous S1P induces astrogliosis (Paugh et al., 2009; Sorensen et al., 2003). In experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, a subset of astrocytes is activated in clusters that progressively expand along white matter tracts. The extent of astrocyte activation is limited by the loss of astrocytic S1P1 (Choi et al., 2011; Dusaban et al., 2017). Moreover, S1P1 modulation by FTY720 in murine and human astrocytes suppressed neurodegeneration-promoting mechanisms mediated by astrocytes, microglia, and CNS-infiltrating proinflammatory monocytes (Karunakaran and van Echten-Deckert, 2017; Rothhammer et al., 2017).

7. S1P in neurodegeneration

Since it plays a versatile roles in neural development and function, deregulation of S1P metabolism and signaling has increasingly been recognized as an essential player in various neurodegenerative diseases, including AD, PD, and HD. Although widely regarded as an autoimmune disease, MS is also a neurodegenerative disease since chronic inflammation drives severe inflammation and massive neurodegeneration (Carassiti et al., 2018; Chaudhuri, 2013; Compston and Coles, 2008; Friese et al., 2014; Stadelmann, 2011). Since the first clinical use of S1P modulators was approved in MS, we will start from MS to discuss the function of S1P and medical application of drugs targeting S1P metabolism and SIP-associated cell signaling pathways in neurodegenerative diseases.

MS

Fingolimod or FTY720, a small molecule S1P receptor modulator, is the first oral drug approved by the Food and Drug Administration to treat RR-MS in 2010 (Brinkmann et al., 2010; Kappos et al., 2006). FTY720 is phosphorylated to form FTY720-phosphate, which resembles naturally occurring S1P. FTY720-phosphate initially activates S1P1, yet subsequently causes internalization and degradation of S1P1 (Huwiler and Zangemeister-Wittke, 2018). Thus, FTY720 is a functional antagonist of S1P1, the major S1P receptor in many organs, including brain and lymphatic cells (Blaho and Hla, 2014). In RR-MS, FTY720 treatment inhibits S1P1 signaling and prevents lymphocyte egress from the lymphoid organs (Chun and Hartung, 2010; Lee et al., 2010). Although initially attributed to sequestration of lymphocytes as a mechanism of action, more recent research suggested that FTY720 directly acts on the central nervous system (Asle-Rousta et al., 2014; Hunter et al., 2016). For example, FTY720 protects against demyelination-independent of lymphocyte infiltration (Jeffery et al., 2016).

Although effective in reducing and delaying RR-MS, FTY720 has minimal effect on Primary or Secondary progressive MS (PP-MS and SP-MS) (Farez and Correale, 2016). Therefore, many emerging studies and clinical trials with various selective S1P receptor modulators are in progress to test their clinical use in PP-MS and SP-MS (Mao-Draayer et al., 2017).

AD

The function of S1P-signaling in AD conditions is elusive and largely controversial. On the one hand, there are reports showing that the ratio of S1P/sphingosine is reduced in post mortem AD patient brains and hippocampus, suggesting a protective role of S1P-signaling (Ceccom et al., 2014; Couttas et al., 2014; He et al., 2010). Accordingly, the levels of SK1 is reduced and S1P lyase increased in these brains (Ceccom et al., 2014; Couttas et al., 2014; He et al., 2010). On the other hand, there are also reports that support a disease-causative role of S1P (Hagen et al., 2011; Lei et al., 2017; Takasugi et al., 2011). S1P interacts with βsecretase BACE1 in neurons. Inhibition of SKs and overexpression of S1P lyase both decreased BACE1 activity and reduced Aβ generation. These data demonstrate that S1P production and Aβ level are directly correlated. Notably, the relative activity of SK2 is upregulated in the AD patient brains (Takasugi et al., 2011).

Another study showed that neuronal death is closely correlated with increased S1P in primary cultured neurons derived from S1P lyase-deficient mice (Hagen et al., 2011). This same group also reported that S1P lyase deficiency is associated with tau hyperphosphorylation (Hagen et al., 2011). In addition, the level of S1P is increased in the CSF of patients with mild cognitive impairment (MCI) and MCI-AD (AD developed from MCI) when compared to agematched controls; a longitudinal human study further supporting that S1P plays a major role in the initiation and/or progression of AD. These studies provide elegant molecular and mechanistic insights suggesting that S1P plays a role in Aβ generation, tau phosphorylation, and AD pathology. The function of the S1P receptor modulator FTY720 has been tested in AD models. In rat injected with Aβ peptide in the hippocampus, FTY720 attenuated Aβ-induced cognitive impairment and neuronal damage (Asle-Rousta et al., 2013). In a mouse model of AD, 5×FAD, FTY720 treatment decreased Aβ plaque density as well as soluble and insoluble Aβ (Aytan et al., 2016). However, how FTY720 functions through S1P signaling in this AD model is not clear. Furthermore, the function of S1P signaling in different neural cell types and the crosstalk between them in an AD setting needs to be systematically investigated.

HD

It was recently recognized that sphingolipid metabolism is significantly perturbed in HD. The S1P level is reduced in HD patient and animal model brain samples (Di Pardo et al., 2017; Di Pardo and Maglione, 2018a, b). Consistently, the levels of SK1 is reduced, while that of S1P lyase increased in brain tissues from HD patients and/or HD mouse models, indicating that a defect in sphingolipid metabolism potentially contributes to HD. Therefore, potential pharmacological interventions targeting S1P signaling have been pursued to treat HD. Administration of FTY720 in the R6/2 mouse model of HD improves motor function, prolongs survival, and reduces brain atrophy (Di Pardo et al., 2014). Inhibition of S1P lyase by 2-acetyl-4-tetrahydroxybutyl imidazole (THI**)** improves survival of neurons transfected with mutant huntingtin (Moruno Manchon et al., 2015). Furthermore, activation of SK1 by 2-hexyl-N-[2hydroxy-1-(hydroxymethyl)ethyl]-3-oxo-decanamide (K6PC-5) significantly reduces apoptosis in mouse striatal-derived HD cell lines and leads to the activation of pro-survival signaling pathways (Di Pardo et al., 2017, 2018).

PD

Recently, modulation of S1P signaling was explored in experimental models of PD. SK1 inhibition reduces survival and increases oxygen reactive species in human dopaminergic neuronal cells treated with1-methyl-4-phenylpyridinium, a PD mouse model (Pyszko and Strosznajder, 2014). Conversely, S1P supplementation significantly reduces apoptosis, suggesting that S1P expression protects these neurons (Pyszko and Strosznajder, 2014). On the other hand, SK2 inhibition results in downregulation of mitochondrial-related genes such as proliferator-activated receptor γ coactivator-1a (PGC-1a) and its downstream targets nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (TFAM) in multiple PD experimental models (Sivasubramanian et al., 2015). Furthermore, treatment with S1P enhances the expression of PGC-1a and NRF-1 in a mouse model of the disease and exerts a neuroprotective effect on dopaminergic neurons via S1P1 (Sivasubramanian et al., 2015). The potential role of S1P receptor stimulation in PD has also been explored. Treatment with FTY720 attenuates motor deficit and prevents dopaminergic neuronal loss in two mouse models of PD (Zhao et al., 2017). This beneficial effect of FTY720 was abolished by W146, a S1P1-selective antagonist, indicating that FTY720 acts through S1P1 (Zhao et al., 2017).

Conclusions

Many neurodegenerative diseases are characterized by the accumulation of sphingolipids (sphingolipidoses) or proteins (AD, PD, HD). Recent research suggests that the “classical” view of the accumulated agent being neurotoxic should give way to a systems biological or physiological approach implying the molecular interaction of organelles, cell types, and tissues, namely lysosomes and mitochondria, neurons, astrocytes and microglia, and brain and immune system. At first sight, this “new” view on neurodegeneration appears to be daunting since it implies a plethora of diverse and “moving targets”. However, with the emerging role of ceramide and S1P as cell signaling hubs in the pathophysiology of several neurodegenerative diseases, unified therapeutic approaches are in reach. One of these approaches is the use of FTY720, an S1P modulator initially approved for treatment of MS, may also help in AD, PD, and HD. Enzyme inhibitors preventing generation of ceramide or its derivatives are already in use for treatment of sphingolipidoses, but may also be useful in therapy of AD and other neurodegenerative diseases. Therefore, research on sphingolipids is critical to find novel potential targets for therapy of neurodegenerative disease.

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Abbreviations

AD	Alzheimer’s disease
PKC	atypical PKC
ApoE4	apolipoprotein E4

APP	amyloid precursor protein
aSMase	acid sphingomyelinase
CerS	ceramide synthase
CERT	ceramide transport protein
CNS	central nervous system
EAD	experimental autoimmune encephalomyelitis
ER	endoplasmic reticulum
GSK	glycogen synthase kinase
HD	Huntington’s disease
MS	Multiple Sclerosis
NPC1	Niemann-Pick disease type C1 protein
nSMase2	neutral sphingomyelinase 2
OMM	outer mitochondrial membrane
PD	Parkinson’s disease
PNS	peripheral nervous system
PP1	protein phosphatase 1
PP2a	protein phosphatase 2a
SCI	spinal cord injury
S1P	sphingosine-1-phosphate
SK	sphingosine kinase
SMase	sphingomyelinase
TBI	traumatic brain injury
VDAC1	voltage-dependent anion channel 1

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