Crosstalk between sphingolipids and vitamin D3: potential role in the nervous system.

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Abstract

Sphingolipids are both structural and bioactive compounds. In particular ceramide and sphingosine 1-phosphate regulate cell fate, inflammation, and excitability. 1-alpha,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), is known to play an important physiological role on growth and differentiation in a variety of cell types, including neural cells, through genomic actions, mediated by its specific receptor, and non-genomic actions resulting in the activation of specific signalling pathways. $1,25(OH)_2D_3$ and sphingolipids, in particular sphingosine-1-phosphate, share many common effectors, including calcium regulation, growth factors and inflammatory cytokines, but whether they could act synergistically is still unknown. Alterations in the signalling and content of sphingolipids and $1,25(OH)_2D_3$ have been found in neurodegenerative diseases and fingolimod, a structural analogue of sphingosine, has been approved for the treatment of multiple sclerosis. This review, after a brief description of the role of sphingolipids and $1,25(OH)_2D_3$, will focus on the potential crosstalk of sphingolipids and $1,25(OH)_2D_3$ in neural cells.

Abbreviations:

$1,25(OH)_2D_3$, 1-alpha,25-dihydroxyvitamin D3; 6-OHDA: 6-hydroxydopamine; Aβ, amyloid beta peptide; AD, Alzheimer disease; AMPK, AMP-dependent PK; APP, amyloid precursor protein; BACE1, b-secretase 1; Bcl-XL, B-cell lymphoma protein extralarge; Bcl-Xs, shorter isoform of B-cell lymphoma protein; BDNF, brain derived neurotrophic factor, C1P, ceramide-1-phosphate; CBS, cystathionine-β-synthase; CDase, ceramidase; Cer, ceramide; CerK, ceramide kinase; CerS, ceramide synthase; CSF, cerebrospinal fluid; cGSN, cytoplasmatic gelsolin; cPLA2, cytosolic phospholipase A2; CNTF, ciliary neurotrophic factor; DRG: dorsal root ganglion; GBA1, lysosomal glucosylceramidase; GBA2: cytosolic glucosylceramidase; GC, glucosylceramide; GCS, Glucosylceramide synthase; GCDase, glucosylceramidase; GDNF, glial derived neutrophic factor, HDAC, histone deacetylases; HO, hemoxygenase; IGF-1, insulin-like growth factor 1; iNOS, inducible NOS; KO, Knockout; LRM, lipid rich microdomains; LRP1, low-density lipoprotein receptor-related protein 1; LVSCC, L-type voltage-sensitive calcium channels; MBP , myelin basic protein; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NADPH, Nicotinamide adenine dinucleotide phosphate; nd, not determined; NGF, nerve growth factor; NR3A: NMDA receptor subunit 3A; NT-3, neurotrophin 3; OPC, oligodendrocyte precursor cell; PD, Parkinson disease; pGSN, plasma gelsolin; PHB2, prohibitin 2; PP, protein phosphatase; RAGE: receptor for advanced glycation end products; S1P, sphingosine 1-phosphate; S1P(1-5)R: S1P receptor type 1-5; S1PL, S1P lyase; S1PR, S1P receptor; SGPPS1 PPase, S1P phosphatase, si, small interference RNA; SL, sphingolipid; SM, sphingomyelin; SMase, sphingomyelinase; aSMase, acid SMase; nSMase,

neutral SMase; SMS, sphingomyelin synthase; Sph, sphingosine; SPHK SphK, sphingosine kinase; SPL, sphingosine-1-phosphate lyase; spns2, spinster 2; TRAF2, TNF receptor-associated factor 2; VDCC, voltage-dependent calcium channel; VDR, 1-alpha,25-dihydroxyvitamin D3 receptor; VDRE, vitamin D3 response element.

Roles of bioactive SLs in the nervous system

Sphingolipids (SLs) have long been regarded as inactive and stable structural components of the membrane but some of them including ceramide (Cer), sphingosine (Sph), ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P) are biologically active molecules. The cellular effect of SLs results from the combination of the effects of several interconvertible SLs (Fig. 1), which are localized in distinct subcellular compartments and regulate distinct cellular processes and functions, including neural cell survival, apoptosis, autophagy, differentiation, migration, inflammation, and neurotransmitter release (see Table 1) (Colombaioni and Garcia-Gil, 2004; Mencarelli and Martinez-Martinez, 2012; Shamseddine et al., 2015; Ghasemi et al., 2016).

The intracellular levels of these bioactive SLs are fine-tuned and alterations of the SL profile in nervous system contribute to the development of neurological and neuroinflammatory diseases such as photoreceptor degeneration, retinitis pigmentosa, Alzheimer disease (AD), Parkinson (PD) disease, multiple sclerosis (MS) (see Table 2) and major depression, Huntington disease, and epilepsy (Acharya et al., 2003; Strettoi et al. 2010; Haughey et al., 2010; Grimm et al., 2013; Mielke et al., 2010; Pyszko and Strosznajder, 2014; Halmer et al., 2014; Desplats et al., 2007; Gulbins et al., 2015; Vanni et al., 2014). Moreover, inherited defects of both synthesis and catabolism of SLs cause varying degrees of central nervous system dysfunction such as in inherited sensory and autonomic neuropathy, Niemann Pick disease type A and B and lisosomal storage disorders (Sabourdy et al., 2015).

The modulatory role of Cer in growth and $1,25(OH)_2D_3$-induced differentiation was first reported in leukemic HL60 cells (Okazaki et al., 1989; Bielawska et al., 1992). Twenty years ago it was proposed that the ratio of the intracellular content of S1P and Cer was a major determinant of cell fate (Cuvillier et al., 1996): S1P enhances growth and survival, whereas its precursors (Cer and Sph) promote growth arrest and cell death (Colombaioni and Garcia-Gil, 2004; Mencarelli and Martinez-Martinez, 2012; Shamseddine et al., 2015; Ghasemi et al., 2016). However, there is increasing evidence showing that the Cer containing specific acyl chain lenghts (Cer species) have different functions (Ben-David and Futerman, 2010; Hannun and Obeid, 2011): C18:0-Cer is

synthesized by Cer synthase 1 (CerS1), an isoenzyme abundant in the brain, and it has been suggested to act as a protective factor because the lack of CerS1 caused neural death in mice cerebellum and impaired motor coordination (Zhao et al., 2011; Ginkel et al., 2012); however, CerS1 ablation decreases gangliosides levels, and this might be one of the causes of neural cell death in mice (Ginkel et al., 2012). Moreover, serum deprivation-induced apoptosis in embryonic hippocampal cells determine the increase of C16:0-Cer and the decrease of C24:0-Cer content (Garcia-Gil et al., 2015). It is worth noting that compensatory mechanism can occur following gene knockout (KO) or decrease of protein expression by siRNA. For example, the treatment of neuroblastoma cells with CerS2 siRNA results in higher CerS5 and CerS6 expression with reduction of C24-Cer and -SM and increase of C14- and C16-Cer levels (Spassieva et al., 2009).

Other facts, in addition to the different acyl chain composition, increase the complexity of the study of the role of SLs on cell fate: i) S1P acts non only intracellularly, but also as ligand of specific G-protein coupled receptors (Maceyka et al., 2012) (Fig. 1B); ii) other SL metabolites, such as C1P, can also mediate apoptosis or proliferation depending on the cell type (Miranda et al., 2011, Bini et al., 2012, Presa et al., 2016); iii) the SL synthesis and signaling that can occur at different cellular compartments (Newton et al., 2015).

Ceramide and C1P

The apoptotic role of Cer in the nervous system has been extensively reviewed (Garcia-Gil and Colombaioni, 2004; Mencarelli and Martinez-Martinez, 2012; Shamseddine et al., 2015). Cer is also involved in the control of autophagy (Daido et al., 2004; Spassieva et al., 2009), differentiation (Riboni et al., 1995), inflammation (Gu et al., 2013) and exosome release (Trajkovic et al., 2008; Wang et al., 2012). Generation of Cer by activation of nSMase2 is associated with increase in dopamine uptake (Kim et al., 2010) and modulates excitatory postsynaptic currents by controlling the insertion and clustering of NMDA receptors (Wheeler et al. 2009). Moreover, Caenorhabditis elegans mutants lacking Cer synthase have defects in synaptic transmission and in synaptic vesicle cycling (Chan and Sieburth, 2012). Cer directly regulates the activity of several enzymes including cathepsin D, phospholipase A2, kinase suppressor of Ras, Cer-activated protein serine–threonine phosphatases 1 and 2A, (PP1 and PP2A), PKC isoforms, and ion channels, such as the potassium channel Kv1.3 (Boch et al., 2003). It is also able to form channels in mitochondria, which are involved in the release of pro-apoptotic factors (Colombini et al., 2016). It directly inhibits mitochondrial complex III and increases generation of ROS (Garcia-Ruiz et al., 1997). Cer inhibits Akt pathway and stimulates the stress-activated kinase JNK and upregulates the apoptosis-

promoting variants Bcl-xS and caspase-9, while correspondingly downregulating the antiapoptotic variants Bcl-xL and caspase-9b (Chalfant et al., 2002).

Accumulating evidences support the involvement of Cer in the modulation of neural plasticity. For example, spatial memory and extinction learning are impaired when SMase2 is inhibited or Cer levels are reduced (Tabatadze et al., 2010, Carrasco et al., 2012; Huston et al., 2016). Furthermore, genetic deletion of CerS1 is associated with deficits in motor learning and spatial working memory, as well as reduced anxiety (Ginkel et al., 2012).

Astrocytes are mediators of CNS responsiveness to inflammation and injury (Claycomb et al., 2013). They display increased Cer following ischemia/reperfusion with nSMase2-dependent generation of the pro-inflammatory cytokines TNF-α, IL-1 and IL-6 (Gu et al., 2013). In neural stem and progenitor cells of the developing brain Cer influences cell polarity, motility and apoptosis (Bieberich, 2012) and induces ciliogenesis, a critical step in differentiation (He et al., 2014).

On the other hand, the phosphorylated form of Cer, C1P, induces proliferation and promotes survival and differentiation of photoreceptors in rat retina neuronal cultures (Miranda et al., 2011), while inhibition or downregulation of CerK, which appears to be the only enzyme responsible for its synthesis, decreases proliferation in human neuroblastoma cells (Bini et al., 2012). Moreover, C1P directly binds and activates α-type cytosolic phospholipase A2 (cPLA2) stimulating arachidonic acid release (Pettus et al., 2004). Activation of cPLA2 by C1P induces spinal neuronal death (Liu et al., 2014), while treatment of SH-SY5Y cells with TNFα increases CerK activity. Depleting CerK activity blocks NADPH oxidase activation and eicosanoid biosynthesis and rescues neuronal viability in the presence of TNFα (Barth et al., 2012). The CerK-null mouse has been generated. Although CerK is highly expressed in Purkinje cells, this mouse did not display histological abnormalities or impairment in motor coordination but emotional behavior was slightly affected (Mitsutake et al., 2007).

Outside ~~of~~ the nervous system, C1P stimulates migration of macrophages via a specific plasma membrane receptor coupled to Gi proteins (Presa et al., 2016) and it is released from damaged myocardial cells possibly leading to the recruitment of stem/progenitor cells to damaged organs (Kim et al., 2013). Whether C1P is also released from the injured nervous system or whether it induces migration in neural stem cells is unknown.

S1P

S1P modulates survival (Edsall et al., 1996), proliferation (Harada et al., 2004; Miranda et al., 2009), differentiation (Toman et al., 2004; Miranda et al., 2009), cell migration (Novgorodov et al.,

2007; Alfonso et al., 2017), calcium homeostasis (Sato et al., 2000; Giussani et al., 2007; Hagen et al., 2011) , neurite retraction (Toman et al., 2004), angiogenic vascular maturation (Liu et al., 2001; Mizugishi et al., 2005) and cytoskeleton dynamics (Postma et al., 1996; Toman et al., 2004; Jaillard et al., 2005) (for recent reviews see Bieberich et al., 2012; Maceyka et al., 2012, Proia and Hla 2015, Ghasemi et al., 2016). In addition, it is able to modulate excitability (Li et al., 2015) by increasing glutamate release (Kajimoto et al., 2007, Kanno et al., 2011), and by regulating endocytosis and exocytosis (Chan and Sieburth 2012, Riganti et al., 2016).

Regarding S1P intracellular effects, S1P induces calcium release from the ER, inhibits histone deacetylases (HDAC), acts as a cofactor required for the E3 ligase activity of TNF receptor-associated factor 2 (TRAF2), activates recombinant human PKC□, and binds the mitochondrial protein prohibitin 2 (a highly conserved protein that regulates mitochondrial assembly and function (Maceyka et al., 2012) (Fig.2). In agreement with the role of S1P in proliferation, sphingosine kinase 1(SphK1) is overexpressed, while S1P lyase is often deleted in human cancers, including glioblastoma (Steck et al., 1995, van Brocklyn et al., 2005). SphK1 overexpression is associated with resistance to chemotherapeutic drugs and to a poor prognosis (van Brocklyn et al., 2005).

S1P functions not only inside cells, but also as ligand for five specific-protein coupled receptors (as reviewed in Spiegel and Milstien, 2003). S1P can be exported outside the cells by transporters belonging to the ATP-binding cassette family and the putative transporter Spinster 2 and, therefore, act as an autocrine or paracrine factor (Maceyka et al., 2012), (Fig.1B). S1P receptors are expressed in CNS cells (neurons, oligodendrocytes, astrocytes and microglia). Signalling through S1P receptors involves activation of Gi, Go, Gq or G12/13 (Figs. 1B and 2) and, therefore, signal transduction pathways involving PLC, MAPKs, PI3K/Akt, Rac, and Rho/Rho kinase (Spiegel and Milstien, 2003).

The G-coupled receptors specific for S1P [S1P(1-5)R] trigger different signalling pathways and are expressed and localized differently during tissue development or following stimulation. ÷ ~~(i.e.~~ S1P1 regulates migration of neural stem progenitor cells both during development (Alfonso et al., 2015) and in response to injury (Kimura et al., 2007). S1P1 is also involved in oligodendrocyte development, morphological maturation and early myelination (Jung et al., 2007; Dukala and Soliven, 2016), while the activation of S1P5 on the oligodendrocyte progenitor cells leads to process retraction and inhibits migration (Jaillard et al., 2005, Novgorodov et al., 2007).

During nerve growth factor- (NGF)-induced neuronal differentiation there is a relocalization of S1PRs: while S1P1R, which induces neurite growth is maintained in the plasma membrane, S1P2R is internalized (Toman et al., 2004) to prevent loss of neurites. Growth factors, such as

NGF, increase SphK activity and S1P formation and viceversa, S1P can induce growth factor release (Yamagata et al., 2003; Sobue et al., 2005; Murakami et al., 2007). Deletion of genes encoding S1P1R or both SphK1 and SphK2 in mice severely disrupts neurogenesis and angiogenesis leading to intrauterine death (Liu et al., 2000; Mizugishi et al., 2005) highlighting the role of S1P in the development of the nervous system.

1,25(OH)$_2$D$_3$ in nervous system physiology

The active form of vitamin D$_3$ has hydroxyl groups in the positions 1 and 25. The enzymes 1-α hydroxylase (CYP27B1), required to synthesize 1,25(OH)$_2$D$_3$, and the 24-hydroxylase (CYP24A1), needed to degrade 25-(OH)D3 and 1,25(OH)$_2$D$_3$, are present in the brain (Zehnder et al., 2001; Naveilhan et al., 1993). The 1,25(OH)$_2$D$_3$ receptor (VDR) is expressed in both neurons and glial cells (microglia, astrocytes, oligodendrocytes, Schwann cells) in different regions of the nervous system (DeLuca et al., 2013). Neural stem cells constitutively express VDR, which can be upregulated by 1,25(OH)$_2$D$_3$ (Shirazi et al., 2015). Genomic 1,25(OH)$_2$D$_3$ effects require heterodimerization between VDR and retinoid X receptor. This complex binds to response elements (VDRE), thus regulating the transcription of genes (Christakos et al., 2016). It increases the transcription of the genes encoding growth factors, such as NGF, glial derived neutrophic factor (GDNF), neurotrophin 3 (NT3), brain-derived neutrophic factor (BDNF) and ciliary neurotrophic factor (CNTF), and for enzymes involved in the synthesis of neurotransmitters (tyrosine hydroxylase, tryptophan hydroxylase 2, glutamate decarboxylase), whereas it represses that of voltage-dependent calcium channel (VDCC) (DeLuca et al., 2013; Patrick and Ames, 2015; Shirazi et al., 2015). VDR is also localized in the caveolae and induces non-genomic rapid effects (Fig 3). Activation of PKA, Ca^{2+}/calmodulin-dependent PK, PI3K, and MAPK p38 results in phosphorylation of neurofilaments, and in modulation of chloride, potassium and voltage-dependent calcium channels in rat cortical neurons (Zanatta et al., 2012). In addition, other kinases including ERK1/ERK2, ERK5 and JNK1/JNK2 and PKC and other enzymes, such as PLA2, Src and p21ras (Bi et al., 2016; Hii and Ferrante, 2016) are also targets of 1,25(OH)$_2$D$_3$.

The combination of *in vitro*, and *in vivo* experiments provides compelling evidence that 1,25(OH)$_2$D$_3$ has a crucial role in synaptic transmission and neuroplasticity (Smith et al., 2006; Groves et al., 2013; Eyles et al., 2013; Patrick and Ames, 2015; Latimer et al., 2014; Grecksch et al., 2012; ~~Taghizadeh et al., 2014~~) as well as in proliferation, differentiation, and neuroprotection as summerized in Table 2. Increasing evidence derived from studies of 1,25(OH)$_2$D$_3$ deficiency and from VDR polymorphisms suggest that 1,25(OH)$_2$D$_3$ influences the susceptibility to a number of psychiatric and neurological diseases which include Alzheimer disease (AD), Parkinson disease (PD), schizophrenia, autism, depression, amyotrophic lateral sclerosis, epilepsy, and is especially

strong for multiple sclerosis (MS) (Eyles et al., 2013; Shen and Ji, 2015; Peterson et al., 2014; Spedding, 2014; Burton and Costello 2015). The effect of $1,25(OH)_2D_3$ deficiency has been studied in female rats or mice fed with a $1,25(OH)_2D_3$-deprived diet during pregnancy and the pups showed increased overall brain size and larger lateral ventricles that were not modified by the addition of $1,25(OH)_2D_3$ to the diet after birth. In adult life, the rats demonstrated subtle alterations in learning and memory (Eyles et al., 2013; Fernandes de Abreu et al., 2010; Hawes et al., 2015). Interestingly, prenatal $1,25(OH)_2D_3$-depleted rats exhibited the impairment of latent inhibition, mimicking some features found in schizophrenia (Grecksch et al., 2009). Offspring language impairment has been demonstrated in humans after maternal $1,25(OH)_2D_3$ insufficiency during pregnancy (Whitehouse et al., 2012). The sumministration of $1,25(OH)_2D_3$ exerts a neuroprotective effect in cognitive decline of aging rats (Latimer et al., 2014). The hormone prevents the beginning and reversibly blocks progression of pathological manifestations of the experimental allergic encephalomyelitis, which is the animal model of MS. This protective effect is absent in VDR knockout mice (DeLuca et al., 2013; Eyles et al., 2013). The effect of $1,25(OH)_2D_3$ depends on its neuroimmunomodulatory properties (Eyles et al., 2013) and also on its action on neural cells. In fact, $1,25(OH)_2D_3$ increases both neural stem cell proliferation and differentiation into neurons and oligodendrocytes, the myelinating cells of central nervous system (Shirazi et al., 2015; de la Fuente et al., 2015).

Neurodegenerative diseases, including PD and AD show impairment in adult neurogenesis in hippocampal dentate gyrus and in the subventricular zone (Winner and Winkler, 2015). Therefore, the factors that promote neurogenesis are considered potential treatments for these disorders. The anti-proliferative and pro-differentiating effects of $1,25(OH)_2D_3$ in neural cells were described more than 10 years ago (Brown et al., 2003; Ko et al., 2004) through the regulation of cyclin expression and NGF production in cultured hippocampal cells (Brown et al., 2003; Ko et al., 2004). Recently, CerK signalling pathway has been involved in the cell growth arrest promoted by $1,25(OH)_2D_3$ in human neuroblastoma cells (Bini et al., 2012). In fact, the pharmacological inhibition and the silencing of CerK drastically reduced cell proliferation. $1,25(OH)_2D_3$ and the VDR agonist ZK191784 induced a significant decrease in CerK expression and C1P content. The involvement of VDR/COUP-TFI/histone deacetylase complex in CerK regulation has also been reported in (Bini et al., 2012). Accumulating data suggest that $1,25(OH)_2D_3$ has complex effects on neurogenesis of neural stem cells. Cui et al., (2007) have studied the effect of fetal $1,25(OH)_2D_3$ deprivation and they have observed the formation of an increased number of neurospheres in cultures from the neonatal subventricular zone. Exogenous $1,25(OH)_2D_3$ added to the culture medium reduced neurosphere number in control, (in agreement with the presumed anti-proliferative

effect of $1,25(OH)_2D_3$), but not in cultures from the hormone-deprived pups (Cui et al., 2007). In contrast, *in vivo* experiments have shown that fetal $1,25(OH)_2D_3$) deficiency leads to reduced neurogenesis in the dentate gyrus of the hippocampus (Keilhoff et al., 2010). In another model of $1,25(OH)_2D_3$ deficiency, the 1α-hydroxylase knockout mice, $1,25(OH)_2D_3$ increases proliferation, but decreases survival of newborn neurons in the dentate gyrus (Zhu et al., 2012). The different effects probably depend on the time window of exposition and/or the different sensibility to the hormone of distinct neurogenic niches.

Crosstalk between SLs and $1,25(OH)_2D_3$ actions

One or more components of the signal transduction pathway promoted by $1,25(OH)_2D_3$ affects SLs metabolism and viceversa (Fig. 4). For example, $1,25(OH)_2D_3$ regulates the expression of S1P-phosphatase 2 (Reardon et al., 2013) and of CerK (Bini et al., 2012). Cholecalciferol, the non hydroxylated precursor of $1,25(OH)_2D_3$ induces activation of SMase, increase of Cer and cell death in human glioblastoma cells (Magrassi et al., 1998). On the other hand,$1,25(OH)_2D_3$ increases the transcription of neurotrofic factors, such as NGF and BDNF, which require SphK activity to execute the neuroprotective or prodifferentiating activity (Saini et al., 2005; Edsall et al., 1997; Culmsee et al., 2002; Murakami et al., 2007) or the modulation of excitability (Zhang et al., 2008). Similarly, many protective or differentiating actions of $1,25(OH)_2D_3$ in non neural cells are due to stimulation of SMase, and of SphK and S1P generation (Okazaki et al., 1989; Kleuser et al., 1998; Manggau et al., 2001; Sauer et al., 2003).

$1,25(OH)_2D_3$ is able to modulate S1PR expression: the hormone reduces the chemorepulsive S1P2R levels on circulating osteoblast precursors (Kikuta et al., 2013) and decreases S1P3R expression in human breast cancer cells (Dolezalova et al., 2003). Interestingly, VDR expression is correlated with calcitriol-mediated reduction of migration in glioblastoma multiforme (Salomón et al., 2014) but it is unknown whether this effect involves differential expression of S1P receptors.

SLs and $1,25(OH)_2D_3$ have some common targets, including cathepsins. Cer and C1P directly interact and activate cathepsin D (Heinrich et al., 2000; Zebrakovska et al., 2011) which is involved in cell death in many cell types. For example, gemcitabine activates aSMase, leading to lysosomal accumulation of Cer, cathepsin D activation and glioma cell death (Dumitru et al., 2009). Cathepsin D is able to migrate to the nucleus. Indeed, nuclear translocation of mitochondrial cytochrome c, lysosomal cathepsins B and D, and other death-promoting proteins has been observed within the first 60 minutes of generalized seizures (Zhao et al., 2010). Both cathepsin D and its inhibitor cystatin A have VRE in their promoters (Wang et al., 2005). This may explain, at least in part, the prosurvival and pro-death effects of $1,25(OH)_2D_3$ in different cells.

Histone acetylation and methylation are often present at sites of VDR action and $1,25(OH)_2D_3$-induced binding of the VDR to these sites is associated with an increase in the level of histone modification as well as in changes in chromatin packaging (Carlberg and Campbell, 2013). . Similarly, S1P formed inside the nuclei by SphK2 activation can inhibit HDACs and regulate gene transcription (Fig.2). Therefore, it could be possible that both $1,25(OH)_2D_3$ and S1P epigenetically modulate the same genes (Huang et al., 2015; Hait et al., 2009).

Furthermore, SLs are important components of lipid rich microdomains (LRM), also named lipid rafts, fluctuating nanoscale assemblies that can be stabilized to coalesce, forming platforms that function in membrane signaling and trafficking (Lingwood and Simons, 2010; Gulbins and Grassmé 2002). LRM have been described in the plasma membrane, mitochondria and nuclei. In the inner nuclear membrane LRM play a role in active chromatin anchoring, transcription factor binding and DNA duplication (Cascianelli et al., 2008; Albi et al., 2009, 2012, 2013; Cataldi et al., 2014). VDR seems to be partly localized in nuclear LRM (Marini et al., 2010, Bartoccini et al., 2011). Changes in SM levels and/or a shift in SM composition (from C24:0-SM to C16:0-SM) have been associated with a reduction of VDR content in nuclear LRM of tumour cells (Lazzarini et al., 2015) and embryonic hippocampal cell differentiation (Bartoccini et al., 2011). Whether these alterations in nuclear LRM are involved in neurodegeneration is unknown. In the nervous system, LRM play a role in many processes, including neurotrophic factor signaling, cell adhesion and migration, axon guidance and myelin formation and stabilization (Aureli et al., 2015). Notably, recent evidence also suggests that LRM alterations are implicated in neurodegenerative disorders including PD, AD, amyotrophic lateral sclerosis, Huntington's disease, and prion diseases (Schengrund, 2010; Marin et al., 2016; Aureli et al., 2015).

Recent data have uncovered that the crosstalk between S1P and $1,25(OH)_2D_3$ also occurs in the extracellular fluids. It has been reported that patients with acute or chronic inflammation exhibit a low content of plasma gelsolin (pGSN) (Osborn et al., 2008; Lee et al., 2009). Gelsolin has two isoforms with similar structure and function: the cytoplasmic actin-binding protein form, important for the regulation of cell shape and motility (cGSN), and pGSN, a multifunctional protein that acts as an extracellular actin scavenger system crucial for the removal of actin released from injured cells (Chauhan et al., 2008; Carro, 2010). Although the functions of pGSN and the mechanisms of its protective action are poorly known, it is clear that low levels of pGNS are indicator of poor prognosis or critical care complications. Notably, pGNS is able to bind to S1P in humans. This pGSN-S1P interaction in extracellular fluids may have several important consequences by impairing either the ability of gelsolin to bind actin or that of S1P to bind to S1PR. In fact, pGSN-S1P complex affects the S1P-S1P1R module that regulates lymphocyte distribution and the

immunomodulatory balance at inflammatory sites (Bucki et al., 2010). It has been observed that patients suffering from lymphatic meningitis show low concentration of pGSN and a high concentration of S1P in the cerebrospinal fluid (CSF) samples (Bucki et al., 2010). Notably, another recent study has demonstrated that $1,25(OH)_2D_3$ treatment can affect either S1P and pGNS. In fact, the hormone alleviates inflammation in experimental allergic encephalomyelitis, a model of MS, and this therapeutic effect might be derived from the ability of the hormone to reduce S1P (which is elevated in CSF and spinal cord of rats with experimental allergic encephalomyelitis). However, this effect might be limited by its simultaneous action in reducing pGSN and cGSN (Zhu et al., 2014).

All together, the accumulating evidences suggest that $1,25(OH)_2D_3$ and SLs can converge and share some targets: 1) the activation of similar pathways (through activation of protein kinases); 2) the modulation of enzyme expression/activity (i.e, cathepsin); 3) the control of genes encoding for key enzymes of SLs metabolism and, likely, of S1PRs by $1,25(OH)_2D_3$; 4) the modulation by S1P-dependent histone acetylation of VDR-dependent transcription. In addition, changes in SLs composition in LRM can also affect the localization and therefore the function of VDR.

SLs / $1,25(OH)_2D_3$ crosstalk: potential role in neurogenerative diseases

AD

The actual most common form of dementia is AD, a neurodegenerative disorder of the CNS characterized by extracellular amyloid-containing plaques, intracellular neurofibrillary tangles consisting of hyperphosphorylated Tau protein and by the death of cholinergic neurons of the basal forebrain. Amyloid plaques are mainly formed by aggregated amyloid beta peptide (Aβ) generated by the hydrolysis of amyloid precursor protein (APP), first, by β-secretase 1 and, then, by γ-secretase. The fibrils of the senile plaques are mainly formed by the self-assembled Aβ1–42 peptide that forms a heterogeneous mixture of oligomers and protofibrils. The small soluble Aβ1-42 oligomers are considered to be the major neurotoxic species in AD and it has been hypothesized that cerebral accumulation of Aβ1-42 precedes and drives the deposition of the Tau protein in neuronal perikarya and their processes (Selkoe and Hardy, 2016).

Alterations in the expression or in the activity of enzymes involved in SLs metabolism have been found in the brain of AD patients (Table 2, Fig. 4). They include SMases (Katsel et al., 2007; He et al., 2010), CDase (Huang et al., 2004), S1P lyase and SphK (Ceccom et al., 2014), serine palmitoyl transferase, UDP-glucose Cer glucosyltransferase, CerS1,2,6 (Katsel et al., 2007; Couttas

et al., 2016). Changes in SL content (Cer, S1P, SM, gangliosides and sulfatides) have also been reported in animal models of AD (see ref. in Grimm et al., 2013) and in brain tissue and CSF of AD patients (Han et al., 2002; Cutler et al. 2004; He et al., 2010; Couttas et al., 2014; Couttas et al., 2016; Satoi et al., 2005, Mielke et al., 2010; Fonteh et al., 2016).

In vitro experiments indicate that Aβ1-42 directly binds and activates neutral SMase, decreasing SM content (Grimm et al., 2005). Aβ1-42 also activates aSMase through increased ROS accumulation via NADPH oxidase activation and reduced glutathion depletion (Jazvinšćak Jembrek et al., 2015). Cer generated by the degradation of SM due to the activation of SMase induces neuronal apoptosis (Jana and Pahan, 2004; Satoi et al., 2005; Malaplate-Armand et al., 2006) or impairs autophagy (Yang et al., 2014). Cer increases the stability, while S1P increases the activity of β-secretase 1 (Puglielli et al., 2003; Takasugi et al., 2011). On the other hand, SM decreases Aβ1-42 production by inhibiting the γ-secretase (Grimm et al., 2005). Therefore, some SLs might be protective by lowering Aβ levels (either by decreasing its production or by increasing its clearance), while others might increase Aβ1-42 oligomerization and toxicity. Simultaneously, APP processing also leads to changes in lipid metabolism, resulting in complex regulatory feed-back cycles, which appear to be dysregulated in AD (Grimm et al., 2013).

Recently it has been demonstrated that exosome release in neural cells requires SMase activity (Wang et al., 2012). The role of exosomes in AD is controversial. One study shows that in vitro neuronal exosomes are able to capture Aβ and their infusion into brains of AD mice decreases Aβ and amyloid depositions (Yuyama et al., 2015). More recently, it has been suggested that Cer-enriched exosomes promote the aggregation of Aβ (Dinkins et al., 2016) since an AD mouse model lacking nSMase2, exhibits decrease of exosome release associated with reduction of plaque burden and improved cognition (Dinkins et al., 2016).

Increasing evidence derived from epidemiological studies indicates that $1,25(OH)_2D_3$ deficiency and VDR polymorphisms influence susceptibility to AD (Gezen-Ak et al., 2012; Annweiler et al., 2014), whereas Aβ1-42 may disrupt the hormone-VDR pathway and cause defective utilization of $1,25(OH)_2D_3$ by suppressing the level of the VDR, and by elevating the level of 24-hydroxylase, and, thereby, increasing the catabolism of the hormone (Dursun et al., 2011, 2013a). In addition to neuroprotective effects involving calcium homeostasis, decrease of ROS and inflammation, $1,25(OH)_2D_3$ is able to exert other specific effects important for AD. For example, $1,25(OH)_2D_3$ may regulate the expression of many genes associated with AD, and attenuate the build up of Aβ deposits either by enhancing its clearance (transport to the blood or to the CSF) or by stimulating the phagocytosis of Aβ. Likely, the hormone may alter APP processing and prevent the Ach defect by increasing the activity of choline acetyltransferase (thus Ach synthesis) in the

brain (Annweiler et al., 2014; Briones and Darwish, 2012; Durk et al., 2014, Landel et al., 2016).

Epigenetic modifications are involved in the regulation of many genes and aberrant epigenetic changes are associated with AD. For example, hyperacetylation of histone H4 at lysine 12 in peripheral monocytes appears to be an early event in AD-pathology (Plagg et al., 2015). Recently, HDAC inhibitors have emerged as promising compounds to rescue cognitive deficits in a mouse model of AD (Kilgore et al., 2010). Therefore, upon treatment with $1,25(OH)_2D_3$ or /and FTY7120, a possible effect on acetylation and DNA methylation of AD-related genes (i.e. β-secretase 1) could result in beneficial effects against Aβ-induced toxicity.

Niemann-Pick type C (NPC)

Niemann-Pick type C (NPC) disease is an autosomal recessive storage disorder due to mutations of two proteins NPC1 and NPC2 which mediate intracellular cholesterol trafficking in mammals. NPC is characterized by abnormal sequestration of unesterified cholesterol within the late endolysosomes and accumulation of Sph and gangliosides, formation of meganeurites and neurofibrillary tangles, neuroinflammation and axonal dystrophy. As the disease progresses, neuronal death of Purkinje cells of the cerebellum becomes prominent. AD and NPC share some molecular pathways, including abnormal cholesterol metabolism, and involvement of Aβ and Tau pathology (Malnar et al., 2014; Vanier et al., 2015). Miglustat is an inhibitor of the enzyme GCS that converts Cer into glucosylCer (Fig. 1), the first step in the synthesis of gangliosides. Miglustat has neuroprotective effects in NPC models (Table 2). It has been approved for the use in several gangliosidosis and recently, for NPC (Patterson et al., 2015). Therefore, SLs appear to play a role in the pathogenesis of NPC. Indeed, it has been demonstrated that SM inhibits while Cer increases NPC2-mediated cholesterol transport (Abdul-Hammed et al., 2010). On the other hand, Lloyd-Evans et al., (2008) have proposed that Sph, by altering calcium homeostasis, could play a role in the onset of NPC.

It is possible that $1,25(OH)_2D_3$ and S1P could have some protective effect on NPC. It is already known that stem cells induce survival of cerebellar NPC1-/- cells (Lee et al., 2010) by increasing S1P and, as discussed above, that $1,25(OH)_2D_3$ is able to reduce Aβ load in AD models. In addition, autophagy is dysregulated in NPC and $1,25(OH)_2D_3$ exerts some neuroprotective effects through the modulation of autophagy (Li et al., 2015a).

PD

PD is a neurodegenerative disease characterized by loss of dopamine cells in the basal ganglia, and accumulation and/or aggregation of α-synuclein. Mutations in genes causing lysosomal storage disorders, such as those encoding GCDase A, aSMase, and NPC1 may increase the risk for developing PD (for a recent review see Migdalska-Richards and Schapira, 2016). Moreover, reduced GCDase activity (GBA1) has been found in patients with sporadic PD (Murphy et al.,

2014; Table2). The concentration of glucosylCer and that of α-synuclein are inversely correlated. Total Cer and SM levels are reduced in anterior cingulate cortex of PD patients compared to controls (Abbot et al., 2014). A shift towards Cer containing short acyl chains and an upregulation of Cer1S gene expression (which could be a compensatory effect to the reduction of Cer) have also been reported (Abbot et al., 2014). S1P and $1,25(OH)_2D_3$ have a neuroprotective effect in cellular models of PD (Shinpo et al.,2000; Smith et al., 2006; Pyszko and Strosznajder, 2014; see Table 3). $1,25(OH)_2D_3$ has shown neuroprotection also in different animal models of PD that have been correlated with increase in GDNF, increase in tyroxine hydroxylase expressing cells and decrease in inflammation (Smith et al., 2006; Wang et al., 2001, Kim et al., 2006). $1,25(OH)_2D_3$ supplementation was associated with significantly reduced risk of PD (Shen and Li, 2015a). The mechanism by which GCDase deficiency increases risk for developing PD is still unclear but it is known that GlucosylCer can stabilize α-synuclein oligomers (Mazulli et al., 2011) and that activation of GCDase reduces accumulation of α-synuclein and restores lysosomal function *in vitro* (Mazzulli et ala., 2016). Indeed, small increases in GlucosylCer or GlucosylSph have been reported primary cultured cortical neurons with GCDase knockdown (Mazulli et al., 2011), and in dopaminergic neurons harboring heterozygote GCDase/GBA1 mutations (Schöndorf et al., 2014) and in the hippocampus of PD patients without GBA1 mutation (Rocha et al., 2015) (Table 2). Another possibility is that the changes in SL metabolism derived from GCDase deficiency impair autophagy, which has been suggested to contribute to α-synuclein accumulation in cellular and animal models of GCase deficiency (Mazzulli et al., 2011; Schöndorf et al., 2014).

SLs, in particular S1P, and $1,25(OH)_2D_3$ display their neuroprotective actions through common effectors such calcium regulation, synaptic modulation, growth factor expression, etc., but whether $1,25(OH)_2D_3$ and SLs, could act synergistically on neuroprotection and/or neurogenesis in neurodegenerative diseases, such as AD, PD and NPC is still unknown and deserves further investigation. Preliminary results in our laboratory indicate that the crosstalk between SLs and $1,25(OH)_2D_3$ leads to a specific balance between neurodegeneration/neuroprotection in neuronal cells. In particular, in human SH-SY5Y differentiated cells we found that $1,25(OH)_2D_3$ treatment counteracts the downregulation of S1P1-mediated signalling promoted by Aβ1-42 (Pierucci et al., 2016, submitted).

Potential implications for $1,25(OH)_2D_3$ and FTY720 supplementation in AD

Several observations in clinical trials have demonstrated that $1,25(OH)_2D_3$ supplementation may

have protective effects in AD, however, in other studies no beneficial outcome has been reported (Landel et al., 2016, DeLuca et al., 2013) and evidence for a correlation between hypovitaminosis D and reduced neuroprotection against AD or AD progression is missing. Similarly, the ability of $1,25(OH)_2D_3$ supplementation to prevent other neurodegenerative diseases, such as MS, needs further investigation. On the other hand, some data suggest that the combination of $1,25(OH)_2D_3$ supplementation with the anti-neurodegenerative drug nemantidine could contrast the cognitive decline better than that with the single compound (Annweiler et al., 2014).

On the contrary, the neuroprotective effect of S1P analogues in neurodegenerative diseases is well established. Fingolimod, the commercial name of FTY720, is an analogue of Sph which acts as an immunosuppressant and has been recently approved for the treatment of MS. Phosphorylation of FTY720 by SphK generates FTY720-phosphate, a molecule structurally similar to S1P that can bind to all the S1P receptors, except S1P2. In lymph nodes, it acts as a highly potent functional antagonist of S1P1, leading to S1P1 receptor internalization in T cells that become unable to egress from the nodes. FTY720 also is active on different cells of the nervous system, including neurons, astrocytes, oligodendrocytes, microglia (Brunkhorst et al., 2014) and its protective function affects the process of myelination, the activation of microglia, proliferation and migration of precursor cells, neuronal differentiation and survival (Kawabori et al., 2013). In vivo, it has been shown that experimental allergic encephalomyelitis was attenuated by FTY720 supplementation, and no effect was observed in astrocytes that did not express S1P1. However, neurons lacking S1P1 were positively affected by the compound (Choi et al., 2011). In vitro, FTY720 decreases Aβ production in cultured neuronal cells (Takasugi et al., 2013).

Regarding the therapeutical potentiality in AD, it has been reported that when FTY720 supplementation was given to rats injected with Aβ1-42, there was a reduction in hippocampal and cortex cell death as well as an increase of memory compared with control rats (Asle-Rousta et al., 2013; Hemmati et al., 2014). The in vivo beneficial effect on the nervous system is due to many factors including the increase in BDNF production which leads to increase in striatum size (Deogracias et al., 2012) and contributes to favour neuronal repair in diseases linked to a decrease of BDNF levels, such as Huntington diasease (Di Pardo et al., 2014; Miguez et al., 2015).

Recently, it has been shown that FTY720 has also inhibitory effects on epigenetic modifications by reducing HDAC and regulating gene expression programs associated with memory and learning (Hait et al. 2014). All together these observations lead to speculate that $1,25(OH)_2D_3$ supplementation and FTY720 could act synergically in the prevention of neurodegenerative diseases. Preliminary studies in vivo performed in our laboratory suggest the possibility of a crossaction between the hormone and FTY720. In fact, damage was reduced when

1,25(OH)2D3 supplementation in mice injected with a submaximal dose of Aβ1-42 was combined with FTY720 treatment. Further investigations are in progress (Meacci et al., personal communication).

In conclusion, the potential for expanding the use of $1,25(OH)_2D_3$ to neurodegenerative diseases is worth investigating. Additionally, the therapeutic potential of 1,25(OH)2D3 structural analogues (see ref. in Leyssens et al., 2014) remains unexplored. In the long term, $1,25(OH)_2D_3$ and its analogues might provide valuable tools either for basic research in the dissection of the mechanisms of neuroprotection and for subsequent designer drug development. The combined treatments with $1,25(OH)_2D_3$ and agonists/antagonists of S1P(1-5)R and the improvement of the characterization and quantification of Cer species, may offer significant advances in terms of understanding of, and ability to predict, the protein aggregation-induced toxicity in vivo.

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Author contributions

MG-G and EM conceived the outline of the review and wrote the manuscript. FP and AV contributed to some parts of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

References

Acharya U, Patel S, Koundakjian E, Nagashima K, Han X, Acharya JK (2003). Modulating sphingolipid biosynthetic pathway rescues photoreceptor degeneration. Science 299: 1740-1743.

Abbott SK, Li H, Muñoz SS, Knoch B, Batterham M, Murphy KE, *et al.* (2014). Altered ceramide acyl chain length and ceramide synthase gene expression in Parkinson's disease. Mov Disord 29(4):

518-526.

Abdul-Hammed M, Breiden B, Adebayo M A, Babalola J O, Schwarzmann G, Sandhoff K (2010). The roles of endosomal membrane lipids and NPC2 in cholesterol transfer and membrane fusion. J Lipid Res 51: 1747–1760.

Albi E, Villani M (2009). Nuclear lipid microdomains regulate cell function. Commun Integr Biol 2(1):23-24.

Albi E, Lazzarini A, Lazzarini R, Floridi A, Damaskopoulou E, Curcio F, *et al.* (2013) Nuclear lipid microdomain as place of interaction between sphingomyelin and DNA during liver regeneration. Int J Mol Sci 14(4): 6529-6541.

Alfonso J, Penkert H, Duman C, Zuccotti A, Monyer H (2015). Downregulation of Sphingosine 1-Phosphate Receptor 1 Promotes the Switch from Tangential to Radial Migration in the OB. J Neurosci 35(40): 13659-13672.

Annweiler C, Karras SN, Anagnostis P, Beauchet O (2014). Vitamin D supplements: a novel therapeutic approach for Alzheimer patients. Front Pharmacol. 5:6.

Asle-Rousta M, Kolahdooz Z, Oryan S, Ahmadiani A, Dargahi L(2013). FTY720 (fingolimod) attenuates beta-amyloid peptide (Aβ42)-induced impairment of spatial learning and memory in rats. J Mol Neurosci 50(3): 524-532.

Aureli M, Grassi S, Prioni S, Sonnino S, Prinetti A (2015). Lipid membrane domains in the brain. Biochim Biophys Acta 1851(8): 1006-1016.

Bartoccini E, Marini F, Damaskopoulou E, Lazzarini R, Cataldi S, Cascianelli G, *et al.* (2011). Nuclear lipid microdomains regulate nuclear vitamin D3 uptake and influence embryonic hippocampal cell differentiation. Mol Biol Cell 22(17): 3022-3031.

Barth BM, Gustafson SJ, Hankins JL, Kaiser JM, Haakenson JK, Kester M, *et al.* (2012). Ceramide kinase regulates TNFα-stimulated NADPH oxidase activity and eicosanoid biosynthesis in neuroblastoma cells. Cell Signal 24(6): 1126-1133.

Ben-David O, Futerman AH (2010). The role of the ceramide acyl chain length in neurodegeneration: involvement of ceramide synthases. Neuromolecular Med 124: 341-350.

Bi X, Shi Q, Zhang H, Bao Y, Hu D, Pohl N, *et al.* (2016). c-Jun NH2-teminal kinase 1 interacts with vitamin D receptor and affects vitamin D-mediated inhibition of cancer cell proliferation. J Steroid Biochem Mol Biol 163:164-172.

Bieberich E (2012). It's a lipid's world: bioactive lipid metabolism and signaling in neural stem cell differentiation. Neurochem Res 37(6): 1208-1229.

Bielawska A, Linardic CM, Hannun YA (1992). Modulation of cell growth and differentiation by ceramide. FEBS Lett 307(2):211-214.

Bini F, Frati A, Garcia-Gil M, Battistini C, Granado M, Martinesi M, *et al.* (2012). New signalling pathway involved in the anti-proliferative action of vitamin D_3 and its analogues in human neuroblastoma cells. A role for ceramide kinase. Neuropharmacology 63(4): 524-537.

Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, Porter NM (2001). Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. J Neurosci 21(1): 98-108.

Briones TL, Darwish H (2012). Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden. J Neuroinflammation 9: 244.

Brown J, Bianco JI, McGrath JJ, Eyles DW (2003). 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett 343(2): 139-143.

Brunkhorst R, Vutukuri R, Pfeilschifter W (2014). Fingolimod for the treatment of neurological diseases-state of play and future perspectives. Front Cell Neurosci 8:283.

Bucki R, Kulakowska A, Byfield FJ, Zendzian-Piotrowska M, Baranowski M, Marzec M, *et al.* (2010). Plasma gelsolin modulates cellular response to sphingosine 1-phosphate. Am J Physiol Cell Physiol 299(6): C1516-1523.

Burton JM, Costello FE (2015). Vitamin D in multiple sclerosis and central nervous system demyelinating disease--a review. J Neuroophthalmol 35(2): 194-200.

Carlberg C, Campbell MJ (2013). Vitamin D receptor signaling mechanisms: integrated actions of a well-defined transcription factor. Steroids 78(2): 127-136.

Carrasco P, Sahún I, McDonald J, Ramírez S, Jacas J, Gratacós E, *et al.* (2012). Ceramide levels regulated by carnitine palmitoyltransferase 1C control dendritic spine maturation and cognition. J Biol Chem 287(25): 21224-21232. doi: 10.1074/jbc.M111.337493.

Carro E (2010). Gelsolin as therapeutic target in Alzheimer's disease. Expert Opin Ther Targets. Jun; 14(6): 585-592.

Cascianelli G, Villani M, Tosti M, Marini F, Bartoccini E, Magni MV *et al.* (2008). Lipid microdomains in cell nucleus. Mol Biol Cell 19(12):5289-5295.

Cataldi S, Codini M, Cascianelli G, Tringali S, Tringali AR, Lazzarini A, *et al.* (2014). Nuclear lipid microdomain as resting place of dexamethasone to impair cell proliferation. Int J Mol Sci 15(11):19832-19846.

Ceccom J, Loukh N, Lauwers-Cances V, Touriol C, Nicaise Y, Gentil C, *et al.* (2014). Reduced sphingosine kinase-1 and enhanced sphingosine 1-phosphate lyase expression demonstrate deregulated sphingosine 1-phosphate signaling in Alzheimer's disease. Acta Neuropathol Commun 2(1):12.

Celli A, Treves C, Nassi P, Stio M (1999). Role of 1,25-dihydroxyvitamin D3 and extracellular calcium in the regulation of proliferation in cultured SH-SY5Y human neuroblastoma cells. Neurochem Res 24(5): 691-698.

Celli A, Treves C, Stio M (1999). Vitamin D receptor in SH-SY5Y human neuroblastoma cells and effect of 1,25-dihydroxyvitamin D3 on cellular proliferation. Neurochem Int 34(2): 117-124.

Chalfant CE, Rathman K, Pinkerman RL, Wood RE, Obeid LM, Ogretmen B, Hannun YA (2002). De novo ceramide regulates the alternative splicing of caspase 9 and Bcl-x in A549 lung adenocarcinoma cells. Dependence on protein phosphatase-1. J Biol Chem 277(15): 12587-12595.

Chan JP, Sieburth D (2012). Localized sphingolipid signaling at presynaptic terminals is regulated by calcium influx and promotes recruitment of priming factors. J Neurosci 32(49): 17909-17920.

Chauhan V, Ji L, Chauhan A (2008). Anti-amyloidogenic, anti-oxidant and anti-apoptotic role of gelsolin in Alzheimer's disease.Biogerontology 9(6): 381-389.

Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K, *et al.* (2011). FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. Proc Natl Acad Sci U S A 108: 751–756.

Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G (2016). Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev 96(1): 365-408.

Claycomb KI, Johnson KM, Winokur PN, Sacino AV, Crocker SJ (2013). Astrocyte regulation of CNS inflammation and remyelination. Brain Sci 3(3): 1109-1127.

Colombaioni L, Garcia-Gil M (2004). Sphingolipid metabolites in neural signalling and function. Brain Res Brain Res Rev 46(3): 328-355.

Colombini M (2016). Ceramide channels and mitochondrial outer membrane permeability. J Bioenerg Biomembr. DOI:10.1007/s10863-016-9646-z

Couttas TA, Kain N, Daniels B, Lim XY, Shepherd C, Kril J, *et al.* (2014). Loss of the neuroprotective factor Sphingosine 1-phosphate early in Alzheimer's disease pathogenesis. Acta Neuropathol Commun 2: 9.

Couttas TA, Kain N, Suchowerska AK, Quek LE, Turner N, Fath T, *et al.* (2016). Loss of ceramide synthase 2 activity, necessary for myelin biosynthesis, precedes tau pathology in the cortical pathogenesis of Alzheimer's disease. Neurobiol Aging 43:89-100.

Culmsee C, Gerling N, Lehmann M, Nikolova-Karakashian M, Prehn JH, Mattson MP, *et al.* (2002). Nerve growth factor survival signaling in cultured hippocampal neurons is mediated through TrkA and requires the common neurotrophin receptor P75. Neuroscience 115(4): 1089-1108.

Cui X, McGrath JJ, Burne TH, Mackay-Sim A, Eyles DW (2007). Maternal vitamin D depletion alters neurogenesis in the developing rat brain. Int J Dev Neurosci 25(4): 227-232.

Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, Hatanpaa K, *et al.,* (2004). Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. Proc Natl Acad Sci U S A 101(7): 2070-2075.

Cuvillier O, Pirianov G, Kleuser B, Vanek PG, Coso OA, Gutkind S *et al.* (1996). Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. Nature 381(6585): 800-803.

D'Arcangelo G, Grossi D, Racaniello M, Cardinale A, Zaratti A, Rufini S, *et al.,* (2016). Miglustat Reverts the Impairment of Synaptic Plasticity in a Mouse Model of NPC Disease. Neural Plast 2016: 3830424.

Daido S, Kanzawa T, Yamamoto A, Takeuchi H, Kondo Y, Kondo S (2004). Pivotal Role of the Cell Death Factor BNIP3 in Ceramide-Induced Autophagic Cell Death in Malignant Glioma Cells. Cancer Res 64: 4286–4293.

DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC (2013). Review: the role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol 39(5): 458-484.

de la Fuente AG, Errea O, van Wijngaarden P, Gonzalez GA, Kerninon C, Jarjour AA, *et al.* Vitamin D receptor-retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. J Cell Biol. 2015 Dec 7;211(5):975-85.

Deogracias R, Yazdani M, Dekkers MP, Guy J, Ionescu MC, Vogt KE, *et al.* (2012). Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. Proc Natl Acad Sci USA 109(35): 14230-14235.

Desplats PA, Denny CA, Kass KE, Gilmartin T, Head SR, Sutcliffe JG, *et al.* (2007). Glycolipid and ganglioside metabolism imbalances in Huntington's disease. Neurobiol Dis 27(3): 265-277.

Di Pardo A, Amico E, Favellato M, Castrataro R, Fucile S, Squitieri F (2014). FTY720 (fingolimod) is a neuroprotective and disease-modifying agent in cellular and mouse models of Huntington disease. Hum Mol Genet 23(9): 2251-2265.

Diesel B, Radermacher J, Bureik M, Bernhardt R, Seifert M, Reichrath J, *et al.* (2005). Vitamin D(3) metabolism in human glioblastoma multiforme: functionality of CYP27B1 splice variants, metabolism of calcidiol, and effect of calcitriol. Clin Cancer Res. 11(15): 5370-5380.

Dinkins MB, Enasko J, Hernandez C, Wang G, Kong J, Helwa I, *et al.* (2016). Neutral Sphingomyelinase-2 Deficiency Ameliorates Alzheimer's Disease Pathology and Improves Cognition in the 5XFAD Mouse. J Neurosci 36(33): 8653-8667.

Dolezalova H, Shankar G, Huang MC, Bikle DD, Goetzl EJ (2003). Biochemical regulation of breast cancer cell expression of S1P2 (Edg-5) and S1P3 (Edg-3) G protein-coupled receptors for sphingosine 1-phosphate. J Cell Biochem 88(4): 732-743.

Dukala DE, Soliven B (2016). S1P1 deletion in oligodendroglial lineage cells: Effect on differentiation and myelination. Glia 64(4): 570-582.

Dumitru CA, Sandalcioglu IE, Wagner M, Weller M, Gulbins E (2009). Lysosomal ceramide mediates gemcitabine-induced death of glioma cells. J Mol Med 87(11): 1123-1132.

Durk MR, Han K, Chow EC, Ahrens R, Henderson JT, Fraser PE, *et al.* (2014). 1α,25-Dihydroxyvitamin D3 reduces cerebral amyloid-β accumulation and improves cognition in mouse models of Alzheimer's disease. J Neurosci 34(21): 7091-7101.

Dursun E, Gezen-Ak D, Yilmazer S (2011). A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-β and preventing the amyloid-β induced alterations by vitamin D in cortical neurons. J Alzheimers Dis 23(2): 207-219.

Dursun E, Gezen-Ak D, Yilmazer S (2013a). Beta amyloid suppresses the expression of the vitamin d receptor gene and induces the expression of the vitamin d catabolic enzyme gene in hippocampal neurons. Dement Geriatr Cogn Disord 36(1-2): 76-86.

Dursun E, Gezen-Ak D, Yilmazer S (2013b). A new mechanism for amyloid-β induction of iNOS: vitamin D-VDR pathway disruption. J Alzheimers Dis 36(3): 459-474.

Edsall LC, Pirianov GG, Spiegel S (1997). Involvement of sphingosine 1-phosphate in nerve growth factor-mediated neuronal survival and differentiation. J Neurosci 17(18): 6952-6960.

Eyles DW, Burne TH, McGrath JJ (2013). Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol 34(1): 47-64.

Fan M, Sidhu R, Fujiwara H, Tortelli B, Zhang J, Davidson C, *et al.,* (2013). Identification of Niemann-Pick C1 disease biomarkers through sphingolipid profiling. J Lipid Res 54(10):2800-2814.

Fernandes de Abreu DA, Nivet E, Baril N, Khrestchatisky M, Roman F, Féron F (2010). Developmental vitamin D deficiency alters learning in C57Bl/6J mice. Behav Brain Res 208(2): 603-608.

Fu J, Xue R, Gu J, Xiao Y, Zhong H, Pan X, Ran R (2013). Neuroprotective effect of calcitriol on

ischemic/reperfusion injury through the NR3A/CREB pathways in the rat hippocampus. Mol Med Rep 8(6): 1708-1714.

Garcia-Gil M, Lazzarini A, Lazzarini R, Floridi E, Cataldi S, Floridi A, Albi E (2015). Serum deprivation alters lipid profile in HN9.10e embryonic hippocampal cells. Neurosci Lett 589: 83-87.

García-Ruiz C, Colell A, Marí M, Morales A, Fernández-Checa JC (1997). 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(17): 11369-11377.

Gezen-Ak D, Dursun E, Bilgiç B, Hanağasi H, Ertan T, Gürvit H, *et al.* (2012). Vitamin D receptor gene haplotype is associated with late-onset Alzheimer's disease. Tohoku J Exp Med 228(3): 189-196.

Ghasemi R, Dargahi L, Ahmadiani A (2016). Integrated sphingosine-1 phosphate signaling in the central nervous system: From physiological equilibrium to pathological damage. Pharmacol Res 104: 156-164.

Ginkel C, Hartmann D, vom Dorp K, Zlomuzica A, Farwanah H, Eckhardt M, *et al.* (2012). Ablation of neuronal ceramide synthase 1 in mice decreases ganglioside levels and expression of myelin-associated glycoprotein in oligodendrocytes. J Biol Chem 287(50): 41888-41902.

Giussani P, Ferraretto A, Gravaghi C, Bassi R, Tettamanti G, Riboni L, *et al.* (2007). Sphingosine-1-phosphate and calcium signaling in cerebellar astrocytes and differentiated granule cells. Neurochem Res 32(1): 27-37.

Grecksch G, Rüthrich H, Höllt V, Becker A (2009). Transient prenatal vitamin D deficiency is associated with changes of synaptic plasticity in the dentate gyrus in adult rats. Psychoneuroendocrinology 34 Suppl 1:S258-64.

Grimm MO, Grimm HS, Pätzold AJ, Zinser EG, Halonen R, Duering M, *et al.* (2005). Regulation of cholesterol and sphingomyelin metabolism by amyloid-beta and presenilin. Nat Cell Biol 7(11): 1118-1123.

Grimm MO, Zimmer VC, Lehmann J, Grimm HS, Hartmann T (2013). The impact of cholesterol, DHA, and sphingolipids on Alzheimer's disease. Biomed Res Int 2013: 814390.

Groves NJ, Kesby JP, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH (2013). Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. Behav Brain Res 241: 120-131.

Gu L, Huang B, Shen W, Gao L, Ding Z, Wu H, *et al.* (2013). Early activation of nSMase2/ceramide pathway in astrocytes is involved in ischemia-associated neuronal damage via

inflammation in rat hippocampi. J Neuroinflammation 10:109.

Gulbins E, Grassmé H (2002). Ceramide and cell death receptor clustering. Biochim Biophys Acta 15852-3:139-145.

Gulbins E, Walter S, Becker KA, Halmer R, Liu Y, Reichel M, *et al.* J (2015). A central role for the acid sphingomyelinase/ceramide system in neurogenesis and major depression. J Neurochem 134(2): 183-192.

Gumireddy K, Ikegaki N, Phillips PC, Sutton LN, Reddy CD (2003). Effect of 20-epi-1alpha,25-dihydroxyvitamin D3 on the proliferation of human neuroblastoma: role of cell cycle regulators and the Myc-Id2 pathway. Biochem Pharmacol 65(12): 1943-1955.

Gumireddy K, Reddy GS, Ikegaki N, Binderup L, Sutton LN, Phillips PC, *et al.* (2003). Anti-proliferative effects of 20-epi-vitamin-D3 analogue, KH1060 in human neuroblastoma: induction of RAR-beta and p21(Cip1). Cancer Lett 190(1): 51-60.

Guo YX, He LY, Zhang M, Wang F, Liu F, Peng WX (2016). 1,25-Dihydroxyvitamin D3 regulates expression of LRP1 and RAGE in vitro and in vivo, enhancing Aβ1-40 brain-to-blood efflux and peripheral uptake transport. Neuroscience 322: 28-38.

Halmer R, Walter S, Faßbender K (2014). Sphingolipids: important players in multiple sclerosis. Cell Physiol Biochem 34(1): 111-118.

Hagen N, Hans M, Hartmann D, Swandulla D, van Echten-Deckert G (2011). Sphingosine-1-phosphate links glycosphingolipid metabolism to neurodegeneration via a calpain-mediated mechanism. Cell Death Differ 18: 1356–1365.

Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, *et al.* (2009). Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science 325: 1254-1257.

Hait NC, Wise LE, Allegood JC, O'Brien M, Avni D, Reeves TM, *et al.* (2014). Active, phosphorylated fingolimod inhibits histone deacetylases and facilitates fear extinction memory. Nat Neurosci 17(7): 971-980.

Han X, M Holtzman D, McKeel DW Jr, Kelley J, Morris JC (2002). Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. J Neurochem 82(4): 809-818.

Hannun YA, Obeid LM (2011). Many ceramides. J Biol Chem. 28632:27855-27862.

Hao W, Tashiro S, Hasegawa T, Sato Y, Kobayashi T, Tando T, *et al.* (2015). Hyperglycemia Promotes Schwann Cell De-differentiation and De-myelination via Sorbitol Accumulation and Igf1 Protein Down-regulation. J Biol Chem 290(28):17106-17115.

Harada J, Foley M, Moskowitz MA, Waeber C (2004). Sphingosine-1-phosphate induces proliferation and morphological changes of neural progenitor cells. J Neurochem 88:1026–1039.

Haughey NJ, Bandaru VV, Bae M, Mattson MP (2010). Roles for dysfunctional sphingolipid

metabolism in Alzheimer's disease neuropathogenesis. Biochim Biophys Acta 1801(8): 878-886.

Hawes JE, Tesic D, Whitehouse AJ, Zosky GR, Smith JT, Wyrwoll CS (2015). Maternal vitamin D deficiency alters fetal brain development in the BALB/c mouse. Behav Brain Res 286: 192-200.

He X, Huang Y, Li B, Gong CX, Schuchman EH (2010). Deregulation of sphingolipid metabolism in Alzheimer's disease. Neurobiol Aging 31(3): 398-408.

He Q, Wang G, Wakade S, Dasgupta S, Dinkins M, Kong JN, Spassieva SD, Bieberich E (2014). Primary cilia in stem cells and neural progenitors are regulated by neutral sphingomyelinase 2 and ceramide. Mol Biol Cell 25(11): 1715-1729.

Heinrich M, Wickel M, Winoto-Morbach S, Schneider-Brachert W, Weber T, Brunner J, *et al.* (2000). Ceramide as an activator lipid of cathepsin D. Adv Exp Med Biol 477: 305-315.

Hemmati F, Dargahi L, Nasoohi S, Omidbakhsh R, Mohamed Z, Chik Z, *et al.* (2013). Neurorestorative effect of FTY720 in a rat model of Alzheimer's disease: comparison with memantine. Behav Brain Res 252: 415-421.

Hii CS, Ferrante A(2016). The Non-Genomic Actions of Vitamin D. Nutrients 2;8(3): 135.

Huang YN, Ho YJ, Lai CC, Chiu CT, Wang JY (2015). 1,25-Dihydroxyvitamin D3 attenuates endotoxin-induced production of inflammatory mediators by inhibiting MAPK activation in primary cortical neuron-glia cultures. J Neuroinflammation 12:147.

Horinouchi K, Erlich S, Perl DP, Ferlinz K, Bisgaier CL, Sandhoff K, *et al.* (1995). Acid sphingomyelinase deficient mice: a model of types A and B Niemann-Pick disease. Nat Genet 10: 288–293.

Huang J, Yang G, Huang Y, Kong W, Zhang S (2015) 1,25(OH)2D3 inhibits the progression of hepatocellular carcinoma via downregulating HDAC2 and upregulating P21(WAFI/CIP1). Mol Med Rep 13(2): 1373-1380.

Huston JP, Kornhuber J, Mühle C, Japtok L, Komorowski M, Mattern C, Reichel M, *et al.* (2016). A sphingolipid mechanism for behavioral extinction. J Neurochem 137(4): 589-603.

Jaillard C, Harrison S, Stankoff B, Aigrot MS, Calver AR, Duddy G, *et al.* (2005). Edg8/S1P5: an oligodendroglial receptor with dual function on process retraction and cell survival. J Neurosci 25(6): 1459-1469.

Jana A, Pahan K (2004). Fibrillar amyloid-beta peptides kill human primary neurons via NADPH oxidase-mediated activation of neutral sphingomyelinase. Implications for Alzheimer's disease. J Biol Chem 279(49): 51451-51459.

Jang W, Kim HJ, Li H, Jo KD, Lee MK, Song SH, *et al.* (2014). 1,25-Dyhydroxyvitamin D3 attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. Biochem Biophys Res Commun 451(1): 142-147.

Jazvinšćak Jembrek M, Hof PR, Šimić G (2015). Ceramides in Alzheimer's Disease: Key Mediators

of Neuronal Apoptosis Induced by Oxidative Stress and Aβ Accumulation. Oxid Med Cell Longev 2015:346783.

Jiang P, Zhu WY, He X, Tang MM, Dang RL, Li HD, *et al.* (2015). Association between Vitamin D Receptor Gene Polymorphisms with Childhood Temporal Lobe Epilepsy. Int J Environ Res Public Health 12(11): 13913-13922.

Jin J, Hou Q, Mullen TD, Zeidan YH, Bielawski J, Kraveka JM, *et al.* (2008). Ceramide generated by sphingomyelin hydrolysis and the salvage pathway is involved in hypoxia/reoxygenation-induced Bax redistribution to mitochondria in NT-2 cells. J Biol Chem 283(39):26509-26517.

Jung CG, Kim HJ, Miron VE, Cook S, Kennedy TE, Foster CA, *et al.* (2007). Functional consequences of S1P receptor modulation in rat oligodendroglial lineage cells. Glia 55(16): 1656-1667.

Jung JS, Shin KO, Lee YM, Shin JA, Park EM, Jeong J, *et al.* (2013). Anti-inflammatory mechanism of exogenous C2 ceramide in lipopolysaccharide-stimulated microglia. Biochim Biophys Acta 1831(6): 1016-1026.

Kajimoto T, Okada T, Yu H, Goparaju SK, Jahangeer S, Nakamura S (2007). Involvement of sphingosine-1-phosphate in glutamate secretion in hippocampal neurons. Mol Cell Biol 27(9): 3429-3440.

Kajta M, Makarewicz D, Ziemińska E, Jantas D, Domin H, Lasoń W, *et al.* (2009). Neuroprotection by co-treatment and post-treating with calcitriol following the ischemic and excitotoxic insult in vivo and in vitro. Neurochem Int 55(5): 265-274.

Kanno T, Nishizaki T, Proia RL, Kajimoto T, Jahangeer S, Okada T, *et al.* (2010). Regulation of synaptic strength by sphingosine 1-phosphate in the hippocampus. Neuroscience 171(4): 973-980.

Katsel P, Li C, Haroutunian V (2007). 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 Apr- 32(4-5): 845-856.

Kawabori M, Kacimi R, Karliner JS, Yenari MA (2013). Sphingolipids in cardiovascular and cerebrovascular systems: Pathological implications and potential therapeutic targets. World J Cardiol 5(4): 75-86.

Keilhoff G, Grecksch G, Becker A (2010). Haloperidol normalized prenatal vitamin D depletion-induced reduction of hippocampal cell proliferation in adult rats. Neurosci Lett 476(2): 94-98.

Kikuta J, Kawamura S, Okiji F, Shirazaki M, Sakai S, Saito H, Ishii M (2013). Sphingosine-1-phosphate-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D. Proc Natl Acad Sci U S A 110(17): 7009-7013.

Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, Sweatt JD, *et al.* (2010). Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology 35(4): 870-880.

Kim C, Schneider G, Abdel-Latif A, Mierzejewska K, Sunkara M, Borkowska S, *et al.* (2013). Ceramide-1-phosphate regulates migration of multipotent stromal cells and endothelial progenitor cells--implications for tissue regeneration. Stem Cells 313:500-510.

Kim JS, Ryu SY, Yun I, Kim WJ, Lee KS, Park JW, *et al.* (2006). 1alpha,25-Dihydroxyvitamin D(3) Protects Dopaminergic Neurons in Rodent Models of Parkinson's Disease through Inhibition of Microglial Activation. J Clin Neurol 2(4): 252-257.

Kim SK, Ahn KH, Ji JE, Choi JM, Jeon HJ, Jung SY, et al. (2010) Neutral sphingomyelinase 2 induces dopamine uptake through regulation of intracellular calcium. Cell Signal 22: 865–870.

Kim S, Steelman AJ, Zhang Y, Kinney HC, Li J (2012). Aberrant upregulation of astroglial ceramide potentiates oligodendrocyte injury. Brain Pathol 22(1):41-57.

Kimura A, Ohmori T, Ohkawa R, Madoiwa S, Mimuro J, Murakami T, *et al.* (2007). Essential roles of sphingosine 1-phosphate/S1P1 receptor axis in the migration of neural stem cells toward a site of spinal cord injury. Stem Cells 25(1): 115-124.

Kleuser B, Cuvillier O, Spiegel S (1998). 1Alpha,25-dihydroxyvitamin D3 inhibits programmed cell death in HL-60 cells by activation of sphingosine kinase. Cancer Res 58(9): 1817-1824.

Ko P, Burkert R, McGrath J, Eyles D (2004). Maternal vitamin D3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain Res Dev Brain Res 153(1): 61-68.

Lachmann RH, te Vruchte D, Lloyd-Evans E, Reinkensmeier G, Sillence DJ, Fernandez-Guillen L, *et al.* (2004). Treatment with miglustat reverses the lipid-trafficking defect in Niemann-Pick disease type C. Neurobiol Dis 16(3):654-658.

Landel V, Annweiler C, Millet P, Morello M, Féron F (2016). Vitamin D, Cognition, and Alzheimer's Disease: The Therapeutic Benefit is in the D-Tails. J Alzheimers Dis 53(2): 419-444.

Latimer CS, Brewer LD, Searcy JL, Chen KC, Popović J, Kraner SD, *et al.* (2014). Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats. Proc Natl Acad Sci U S A 111(41): E4359-4366.

Lazzarini A, Macchiarulo A, Floridi A, Coletti A, Cataldi S, Codini M, *et al.* (2015).Very-long-chain fatty acid sphingomyelin in nuclear lipid microdomains of hepatocytes and hepatoma cells: can the exchange from C24:0 to C16:0 affect signal proteins and Vit D receptor? Mol Biol Cell 26(13) : 2418-2425.

Lee H, Lee JK, Min WK, Bae JH, He X, Schuchman EH, *et al.,* (2010). Bone marrow-derived mesenchymal stem cells prevent the loss of Niemann-Pick type C mouse Purkinje neurons by correcting sphingolipid metabolism and increasing sphingosine-1-phosphate. Stem Cells 28(4):821-831.

Lee PS, Sampath K, Karumanchi SA, Tamez H, Bhan I, Isakova T, *et al.* (2009). Plasma gelsolin and circulating actin correlate with hemodialysis mortality. J Am Soc Nephrol 20(5):1140-1148.

Lee V, Rekhi E, Hoh Kam J, Jeffery G201 (2012). Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. Neurobiol Aging 33(10):2 382-2389.

Lemire JM, Archer DC (1991). 1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. J Clin Invest 87(3): 1103-1107.

Leyssens C, Verlinden L, Verstuyf A (2014). The future of vitamin D analogs. Front Physiol 5:122.

Li L, Prabhakaran K, Zhang X, Zhang L, Liu H, Borowitz JL *et al.* (2008). 1Alpha,25-dihydroxyvitamin D3 attenuates cyanide-induced neurotoxicity by inhibiting uncoupling protein-2 up-regulation. J Neurosci Res 86(6): 1397-1408.

Li H, Jang W, Kim HJ, Jo KD, Lee MK, Song SH, *et al.* (2015a). Biochemical protective effect of 1,25-dihydroxyvitamin D3 through autophagy induction in the MPTP mouse model of Parkinson's disease. Neuroreport 26(12): 669-674.

Li C, Li JN, Kays J, Guerrero M, Nicol GD (2015). Sphingosine 1-phosphate enhances the excitability of rat sensory neurons through activation of sphingosine 1-phosphate receptors 1 and/or 3. J Neuroinflammation 12:70.

Lin AM, Fan SF, Yang DM, Hsu LL, Yang CH (2003). Zinc-induced apoptosis in substantia nigra of rat brain: neuroprotection by vitamin D3. Free Radic Biol Med 34(11):1416-1425.

Lingwood D, Simons K (2010). Lipid rafts as a membrane-organizing principle. Science 327: 46-50.

Liu Y, Wada R, Yamashita T, Mi Y, Deng CX, Hobson JP, *et al*. (2000). Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. J Clin Invest 106(8): 951-961.

Liu NK, Deng LX, Zhang YP, Lu QB, Wang XF, Hu JG, *et al.* (2014). Cytosolic phospholipase A2 protein as a novel therapeutic target for spinal cord injury. Ann Neurol 75(5): 644-658.

Lloyd-Evans E, Morgan AJ, He X, Smith DA, Elliot-Smith E, Sillence DJ , *et al.* (2008). Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium. Nat Med 14(11):1247-1255.

Longoni A, Kolling J, dos Santos TM, dos Santos JP, da Silva JS, Pettenuzzo L, *et al.* (2016). 1,25-Dihydroxyvitamin D3 exerts neuroprotective effects in an ex vivo model of mild hyperhomocysteinemia. Int J Dev Neurosci 48: 71-79.

Maceyka M, Harikumar KB, Milstien S, Spiegel S (2012). Sphingosine-1-phosphate signaling and its role in disease. Trends Cell Biol 22(1): 50-60.

Magrassi L, Adorni L, Montorfano G, Rapelli S, Butti G, Berra B, *et al.* (1998). Vitamin D metabolites activate the sphingomyelin pathway and induce death of glioblastoma cells. Acta Neurochir (Wien) 140(7):707-714.

Malaplate-Armand C, Florent-Béchard S, Youssef I, Koziel V, Sponne I, Kriem B, *et al.* (2006). Soluble oligomers of amyloid-beta peptide induce neuronal apoptosis by activating a cPLA2-dependent sphingomyelinase-ceramide pathway. Neurobiol Dis 23(1): 178-189.

Malnar M, Hecimovic S, Mattsson N, Zetterberg H (2014). Bidirectional links between Alzheimer's disease and Niemann-Pick type C disease. Neurobiol Dis 72 Pt A:37-47

Manggau M, Kim DS, Ruwisch L, Vogler R, Korting HC, Schäfer-Korting M, *et al.* (2001). 1Alpha,25-dihydroxyvitamin D3 protects human keratinocytes from apoptosis by the formation of sphingosine-1-phosphate. J Invest Dermatol 117(5): 1241-1249.

Marin R, Fabelo N, Fernández-Echevarría C, Canerina-Amaro A, Rodríguez-Barreto D, Quinto-Alemany D, *et al.* (2016). Lipid Raft Alterations in Aged-Associated Neuropathologies. Curr Alzheimer Res 13(9):973-984.

Marini F, Bartoccini E, Cascianelli G, Voccoli V, Baviglia MG, Magni MV, *et al.* (2010). Effect of 1alpha,25-dihydroxyvitamin D3 in embryonic hippocampal cells. Hippocampus 20(6): 696-705.

Marques AR, Aten J, Ottenhoff R, van Roomen CP, Herrera Moro D, Claessen N, *et al.,* (2015). Reducing GBA2 Activity Ameliorates Neuropathology in Niemann-Pick Type C Mice. PLoS One 10(8):e0135889.

Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, *et al.* (2011). Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 146(1):37-52.

Mazzulli JR, Zunke F, Tsunemi T, Toker NJ, Jeon S, Burbulla LF, *et al.* (2016). Activation of β-Glucocerebrosidase Reduces Pathological α-Synuclein and Restores Lysosomal Function in Parkinson's Patient Midbrain Neurons. J Neurosci. 2016 Jul 20;36(29):7693-706.

Mencarelli C, Martinez-Martinez P (2013). Ceramide function in the brain: when a slight tilt is enough. Cell Mol Life Sci 70(2):181-203.

Mielke MM, Lyketsos CG (2010). Alterations of the sphingolipid pathway in Alzheimer's disease:

new biomarkers and treatment targets? Neuromolecular Med 12(4): 331-340.

Migdalska-Richards A, Schapira AH (2016). The relationship between glucocerebrosidase mutations and Parkinson disease. J Neurochem 139 Suppl 1:77-90

Miranda GE, Abrahan CE, Politi LE, Rotstein NP (2009). Sphingosine-1-phosphate is a key regulator of proliferation and differentiation in retina photoreceptors. Invest Ophthalmol Vis Sci 50:4416–4428.

Miranda GE, Abrahan CE, Agnolazza DL, Politi LE, Rotstein NP (2011). Ceramide-1-phosphate, a new mediator of development and survival in retina photoreceptors. Invest Ophthalmol Vis Sci 52(9): 6580-6588.

Miguez A, García-Díaz Barriga G, Brito V, Straccia M, Giralt A, Ginés S, *et al.* (2015). Fingolimod (FTY720) enhances hippocampal synaptic plasticity and memory in Huntington's disease by preventing p75NTR up-regulation and astrocyte-mediated inflammation. Hum Mol Genet 24(17): 4958-4970.

Mitsutake S, Yokose U, Kato M, Matsuoka I, Yoo JM, Kim TJ, *et al.* (2007). The generation and behavioral analysis of ceramide kinase-null mice, indicating a function in cerebellar Purkinje cells. Biochem Biophys Res Commun 363(3): 519-524.

Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, *et al.* (2013). 1α,25-dihydroxyvitamin D3 and resolvin D1 retune the balance between amyloid-β phagocytosis and inflammation in Alzheimer's disease patients. J Alzheimers Dis 34(1): 155-170.

Mizwicki MT, Menegaz D, Zhang J, Barrientos-Durán A, Tse S, Cashman JR, *et al.* (2012). Genomic and nongenomic signaling induced by 1α,25(OH)2-vitamin D3 promotes the recovery of amyloid-β phagocytosis by Alzheimer's disease macrophages. J Alzheimers Dis 29(1): 51-62.

Mizugishi K, Yamashita T, Olivera A, Miller GF, Spiegel S, Proia RL (2005). Essential role for sphingosine kinases in neural and vascular development. Mol Cell Biol 25(24): 11113-11121.

Murakami M, Ichihara M, Sobue S, Kikuchi R, Ito H, Kimura A, *et al.* (2007). RET signaling-induced SPHK1 gene expression plays a role in both GDNF-induced differentiation and MEN2-type oncogenesis. J Neurochem 102(5): 1585-1594.

Murphy KE, Gysbers AM, Abbott SK, Tayebi N, Kim WS, Sidransky E, *et al.* (2014). Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease. Brain 137(Pt 3): 834-848.

Naveilhan P, Neveu I, Baudet C, Ohyama KY, Brachet P, Wion D (1993). Expression of 25(OH) vitamin D3 24- hydroxylase gene in glial cells. Neuroreport 5: 255–257.

Newton J, Lima S, Maceyka M, Spiegel S (2015). Revisiting the sphingolipid rheostat: Evolving concepts in cancer therapy. Exp Cell Res 333(2): 195-200.

Novgorodov AS, El-Alwani M, Bielawski J, Obeid LM, Gudz TI (2007). Activation of sphingosine-

1-phosphate receptor S1P5 inhibits oligodendrocyte progenitor migration. FASEB J 21(7): 1503-1514.

Oermann E, Bidmon HJ, Witte OW, Zilles K (2004). Effects of 1alpha,25 dihydroxyvitamin D3 on the expression of HO-1 and GFAP in glial cells of the photothrombotically lesioned cerebral cortex. J Chem Neuroanat 28(4): 225-238.

Okazaki T, Bell RM, Hannun YA (1989). Sphingomyelin turnover induced by vitamin D3 in HL-60 cells. Role in cell differentiation. J Biol Chem 264(32):19076-19080.

Orme RP, Bhangal MS, Fricker RA (2013). Calcitriol imparts neuroprotection in vitro to midbrain dopaminergic neurons by upregulating GDNF expression. PLoS One 8(4): e62040.

Osborn TM, Verdrengh M, Stossel TP, Tarkowski A, Bokarewa M (2008). Decreased levels of the gelsolin plasma isoform in patients with rheumatoid arthritis. Arthritis Res Ther 10:R117.

Ohtani R, Tomimoto H, Kondo T, Wakita H, Akiguchi I, Shibasaki H, *et al.* (2004). Upregulation of ceramide and its regulating mechanism in a rat model of chronic cerebral ischemia. Brain Res 1023(1):31–40

Patrick RP, Ames BN (2014). Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. FASEB J 28(6): 2398-2413. doi:10.1096/fj.13-246546.

Patterson MC, Mengel E, Vanier MT, Schwierin B, Muller A, Cornelisse P, *et al.* (2015) Stable or improved neurological manifestations during miglustat therapy in patients from the international disease registry for Niemann-Pick disease type C: an observational cohort study. Orphanet J Rare Dis. 10:65.

Pettus BJ, Bielawska A, Subramanian P, Wijesinghe DS, Maceyka M, Leslie CC, Evans JH, Freiberg J, Roddy P, Hannun YA, Chalfant CE (2004). Ceramide 1-phosphate is a direct activator of cytosolic phospholipase A2. J Biol Chem 279(12): 11320-11326.

Plagg B, Ehrlich D, Kniewallner KM, Marksteiner J, Humpel C (2015). Increased Acetylation of Histone H4 at Lysine 12 (H4K12) in Monocytes of Transgenic Alzheimer's Mice and in Human Patients. Curr Alzheimer Res 12(8): 752-760.

Postma FR, Jalink K, Hengeveld T, Moolenaar WH (1996). Sphingosine-1-phosphate rapidly induces Rho-dependent neurite retraction: action through a specific cell surface receptor. EMBO J 15(10):2388-2392.

Presa N, Gomez-Larrauri A, Rivera IG, Ordoñez M, Trueba M, Gomez-Muñoz A (2016). Regulation of cell migration and inflammation by ceramide 1-phosphate. Biochim Biophys Acta 1861(5):402-409.

Proia RL, Hla T (2015). Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy. J Clin Invest 125(4): 1379-1387.

Puglielli L, Ellis BC, Saunders AJ, Kovacs DM (2003). Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. J Biol Chem 278(22): 19777-19783.

Pyszko JA, Strosznajder JB (2014). The key role of sphingosine kinases in the molecular mechanism of neuronal cell survival and death in an experimental model of Parkinson's disease. Folia Neuropathol 52(3):260-269.

Qin J, Berdyshev E, Goya J, Natarajan V, Dawson G (2010). Neurons and oligodendrocytes recycle sphingosine 1-phosphate to ceramide: significance for apoptosis and multiple sclerosis. J Biol Chem 285(19): 14134-14143.

Rocha EM, Smith GA, Park E, Cao H, Brown E, Hallett P, *et al.* (2015). Progressive decline of glucocerebrosidase in aging and Parkinson's disease. Ann Clin Transl Neurol 2(4): 433-438.

Reardon BJ, Hansen JG, Crystal RG, Houston DK, Kritchevsky SB, Harris T, *et al.* (2013). Vitamin D-responsive SGPP2 variants associated with lung cell expression and lung function. BMC Med Genet 14:122.

Riboni L, Prinetti A, Bassi R, Caminiti A, Tettamanti G (1995). A mediator role of ceramide in the regulation of neuroblastoma Neuro2a cell differentiation. J Biol Chem 270(45):26868-26875.

Riganti L, Antonucci F, Gabrielli M, Prada I, Giussani P, Viani P, *et al.* (2016). Sphingosine-1-Phosphate (S1P) Impacts Presynaptic Functions by Regulating Synapsin I Localization in the Presynaptic Compartment. J Neurosci 36(16): 4624-4634.

Sabourdy F, Astudillo L, Colacios C, Dubot P, Mrad M, Ségui B, *et al.* (2015). Monogenic neurological disorders of sphingolipid metabolism. Biochim Biophys Acta 1851(8): 1040-1051.

Saini HS, Coelho RP, Goparaju SK, Jolly PS, Maceyka M, Spiegel S, *et al*. (2005). Novel role of sphingosine kinase 1 as a mediator of neurotrophin-3 action in oligodendrocyte progenitors. J Neurochem 95(5): 1298-1310.

Salomón DG, Fermento ME, Gandini NA, Ferronato MJ, Arévalo J, Blasco J, Andrés NC, *et al.* (2014). Vitamin D receptor expression is associated with improved overall survival in human glioblastoma multiforme. J Neurooncol 118(1): 49-60.

Sato K, Ui M, Okajima F (2000). Differential roles of Edg-1 and Edg-5, sphingosine 1-phosphate receptors, in the signaling pathways in C6 glioma cells. Brain Res Mol Brain Res 85(1-2):151-160.

Satoi H, Tomimoto H, Ohtani R, Kitano T, Kondo T, Watanabe M, *et al.* (2005). Astroglial expression of ceramide in Alzheimer's disease brains: a role during neuronal apoptosis.

Neuroscience 130(3): 657-666.

Sauer B, Ruwisch L, Kleuser B (2003). Antiapoptotic action of 1alpha,25-dihydroxyvitamin D3 in primary human melanocytes. Melanoma Res 13(4): 339-347.

Schöndorf DC, Aureli M, McAllister FE, , Hindley CJ, Mayer F, Schmid B *et al.* (2014) iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis. Nat Commun 5:4028–4045.

Schengrund CL (2010). Lipid rafts: keys to neurodegeneration. Brain Res Bull 82(1-2): 7-17.

Selkoe DJ, Hardy J (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8(6): 595-608.

Shamseddine AA, Airola MV, Hannun YA (2015). Roles and regulation of neutral sphingomyelinase-2 in cellular and pathological processes. Adv Biol Regul 57:24-41.

Shen H, Giordano F, Wu Y, Chan J, Zhu C, Milosevic I, *et al.* (2014). Coupling between endocytosis and sphingosine kinase 1 recruitment. Nat Cell Biol 16(7): 652-662.

Shen L, Ji HF (2015a). Associations between vitamin D status, supplementation, outdoor work and risk of Parkinson's Disease: A meta-analysis assessment. Nutrients 7(6):4817-4827.

Shen L, Ji HF (2015b). Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis. Nutr J 14:76.

Shinpo K, Kikuchi S, Sasaki H, Moriwaka F, Tashiro K (2000). Effect of 1,25-dihydroxyvitamin D(3) on cultured mesencephalic dopaminergic neurons to the combined toxicity caused by L-buthionine sulfoximine and 1-methyl-4-phenylpyridine. J Neurosci Res 62(3): 374-382.

Shirazi HA, Rasouli J, Ciric B, Rostami A, Zhang GX (2015). 1,25-Dihydroxyvitamin D3 enhances neural stem cell proliferation and oligodendrocyte differentiation. Exp Mol Pathol 98(2): 240-245.

Smith MP, Fletcher-Turner A, Yurek DM, Cass WA (2006). Calcitriol protection against dopamine loss induced by intracerebroventricular administration of 6-hydroxydopamine. Neurochem Res 31(4): 533-539.

Sobue S, Hagiwara K, Banno Y, Tamiya-Koizumi K, Suzuki M, Takagi A, *et al.* (2005).Transcription factor specificity protein 1 (Sp1) is the main regulator of nerve growth factor-induced sphingosine kinase 1 gene expression of the rat pheochromocytoma cell line, PC12. J Neurochem 95(4): 940-949.

Spassieva SD, Mullen TD, Townsend DM, Obeid LM (2009). Disruption of ceramide synthesis by CerS2 down-regulation leads to autophagy and the unfolded protein response. Biochem J 424(2):273-283.

Spedding S (2014). Vitamin D and depression: a systematic review and meta-analysis comparing

studies with and without biological flaws. Nutrients 6(4): 1501-1518.

Spiegel S, Milstien S (2003). Sphingosine-1-phosphate: an enigmatic signalling lipid. Nat Rev Mol Cell Biol 4(5): 397-407.

Steck PA, Ligon AH, Cheong P, Yung WK, Pershouse MA (1995). Two tumor suppressive loci on chromosome 10 involved in human glioblastomas. Genes Chromosomes Cancer 12(4): 255-261.

Stein VM, Crooks A, Ding W, Prociuk M, O'Donnell P, Bryan C, *et al.,* (2012). Miglustat improves purkinje cell survival and alters microglial phenotype in feline Niemann-Pick disease type C. J Neuropathol Exp Neurol 71(5): 434-448.

Stio M, Celli A, Treves C (2001). Synergistic anti-proliferative effects of vitamin D derivatives and 9-cis retinoic acid in SH-SY5Y human neuroblastoma cells. J Steroid Biochem Mol Biol 77(4-5): 213-222.

Strettoi E, Gargini C, Novelli E, Sala G, Piano I, Gasco P, *et al.* (2010). Inhibition of ceramide biosynthesis preserves photoreceptor structure and function in a mouse model of retinitis pigmentosa. Proc Natl Acad Sci U S A 107(43): 18706-18711.

Tabatadze N, Savonenko A, Song H, Bandaru VV, Chu M, Haughey NJ (2010). Inhibition of neutral sphingomyelinase-2 perturbs brain sphingolipid balance and spatial memory in mice. J Neurosci Res 88(13): 2940-2951.

Takasugi N, Sasaki T, Suzuki K, Osawa S, Isshiki H, Hori Y, *et al.* (2011). BACE1 activity is modulated by cell-associated sphingosine-1-phosphate. J Neurosci 31(18): 6850-6857.

Takasugi N, Sasaki T, Ebinuma I, Osawa S, Isshiki H, Takeo K, *et al.* (2013). FTY720/fingolimod, a sphingosine analogue, reduces amyloid-β production in neurons. PLoS One 8(5): e64050.

Taniura H, Ito M, Sanada N, Kuramoto N, Ohno Y, Nakamichi N, *et al.* (2006). Chronic vitamin D3 treatment protects against neurotoxicity by glutamate in association with upregulation of vitamin D receptor mRNA expression in cultured rat cortical neurons. J Neurosci Res 83(7): 1179-1189.

Toman RE, Payne SG, Watterson KR, Maceyka M, Lee NH, Milstien S, *et al.* (2004). Differential transactivation of sphingosine-1-phosphate receptors modulates NGF-induced neurite extension. J Cell Biol 166(3): 381-392.

Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, *et al.* (2008). Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 319: 1244-1247.

Van Brocklyn JR, Jackson CA, Pearl DK, Kotur MS, Snyder PJ, Prior TW (2005). Sphingosine kinase-1 expression correlates with poor survival of patients with glioblastoma multiforme: roles of sphingosine kinase isoforms in growth of glioblastoma cell lines. J Neuropathol Exp Neurol 64(8): 695-705.

Vanier MT (2015). Complex lipid trafficking in Niemann-Pick disease type C. J Inherit Metab Dis 38(1): 187-199.

Vanni N, Fruscione F, Ferlazzo E, Striano P, Robbiano A, Traverso M, *et al*. (2014). Impairment of ceramide synthesis causes a novel progressive myoclonus epilepsy. Ann Neurol 76(2): 206-212.

Wang G, Dinkins M, He Q, Zhu G, Poirier C, Campbell A, *et al.* (2012). Astrocytes secrete exosomes enriched with proapoptotic ceramide and prostate apoptosis response 4 (PAR-4): potential mechanism of apoptosis induction in Alzheimer disease (AD). J Biol Chem 287(25): 21384-21395.

Wang TT, Tavera-Mendoza LE, Laperriere D, Libby E, MacLeod NB, Nagai Y, Bourdeau V, Konstorum A, Lallemant B, Zhang R, Mader S, White JH (2005). Large-scale in silico and microarray-based identification of direct1,25-dihydroxyvitamin D3 target genes. Mol Endocrinol 19(11): 2685-2695.

Wang JY, Wu JN, Cherng TL, Hoffer BJ, Chen HH, Borlongan CV, *et al.* (2001). Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. Brain Res 904(1): 67-75.

Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH (2012). Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics 129(3): 485-493.

Winner B, Winkler J (2015). Adult neurogenesis in neurodegenerative diseases. Cold Spring Harb Perspect Biol 7(4): a021287.

Yamagata K, Tagami M, Torii Y, Takenaga F, Tsumagari S, Itoh S, Yamori Y, Nara Y (2003). Sphingosine 1-phosphate induces the production of glial cell line-derived neurotrophic factor and cellular proliferation in astrocytes. Glia 41(2): 199-206.

Yang DS, Stavrides P, Saito M, Kumar A, Rodriguez-Navarro JA, Pawlik M, *et al.* (2014). Defective macroautophagic turnover of brain lipids in the TgCRND8 Alzheimer mouse model: prevention by correcting lysosomal proteolytic deficits. Brain 137(Pt 12): 3300-3318.

Young MM, Kester M, Wang HG (2013). Sphingolipids: regulators of crosstalk between apoptosis and autophagy. J Lipid Res 54(1): 5-19.

Yu J, Gattoni-Celli M, Zhu H, Bhat NR, Sambamurti K, Gattoni-Celli S, *et al.* (2011). Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AβPP transgenic mice. J Alzheimers Dis 25(2): 295-307.

Yuyama K, Sun H, Usuki S, Sakai S, Hanamatsu H, Mioka T, *et al.* (2015). A potential function for neuronal exosomes: sequestering intracerebral amyloid-β peptide. FEBS Lett 589(1): 84-88.

Zanatta L, Goulart PB, Gonçalves R, Pierozan P, Winkelmann-Duarte EC, Woehl VM, *et al.* (2012). 1α,25-dihydroxyvitamin D(3) mechanism of action: modulation of L-type calcium channels leading to calcium uptake and intermediate filament phosphorylation in cerebral cortex of young rats. Biochim Biophys Acta 1823(10): 1708-1719.

Zebrakovská I, Máša M, Srp J, Horn M, Vávrová K, Mareš M. Complex modulation of peptidolytic activity of cathepsin D by sphingolipids. Biochim Biophys Acta. 2011 Dec;1811(12):1097-104.

Zehnder D, Bland R,Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. (2001). Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab 86: 888–894.

Zhao S, Aviles ER Jr, Fujikawa DG (2010). Nuclear translocation of mitochondrial cytochrome c, lysosomal cathepsins B and D, and three other death-promoting proteins within the first 60 minutes of generalized seizures. J Neurosci Res 88(8): 1727-1737.

Zhao L, Spassieva SD, Jucius TJ, Shultz LD, Shick HE, Macklin WB, Hannun YA, Obeid LM, Ackerman SL (2011). A deficiency of ceramide biosynthesis causes cerebellar purkinje cell neurodegeneration and lipofuscin accumulation. PLoS Genet 7(5): e1002063.

Zhang YH, Chi XX, Nicol GD (2008). Brain-derived neurotrophic factor enhances the excitability of rat sensory neurons through activation of the p75 neurotrophin receptor and the sphingomyelin pathway. J Physiol 586(13): 3113-3127.

Zhang H, Zhuang XD, Meng FH, Chen L, Dong XB, Liu GH, *et al.* (2016). Calcitriol prevents peripheral RSC96 Schwann neural cells from high glucose & methylglyoxal-induced injury through restoration of CBS/H2S expression. Neurochem Int 92: 49-57.

Zheng S, Wei S, Wang X, Xu Y, Xiao Y, Liu H, *et al.* (2015). Sphingosine kinase 1 mediates neuroinflammation following cerebral ischemia. Exp Neurol 272:160-169.

Zhu Y, Qin Z, Gao J, Yang M, Qin Y, Shen T, *et al.* (2014). Vitamin D therapy in experimental allergic encephalomyelitis could be limited by opposing effects of sphingosine 1-phosphate and gelsolin dysregulation. Mol Neurobiol 50(3): 733-743.

Zhu Y, Zhou R, Yang R, Zhang Z, Bai Y, Chang F, *et al.* (2012). Abnormal neurogenesis in the dentate gyrus of adult mice lacking 1,25-dihydroxy vitamin D3 (1,25-(OH)2 D3). Hippocampus 22(3): 421-433.

Table 1. Role of SLs on proliferation, survival, differentiation, neurodegeneration, ischemia, and inflammation

PROLIFERATION				
Cell/Tissue	**Method**	**Effect**	**Mechanism**	**Reference**
Neural progenitor cultured cells	A, exogenous S1P	↑ proliferation		Harada et al., 2004
Oligodendrocyte precursors	A,siS1P1R	↑ proliferation	S1P1R	Jung et al., 2007
Neuronal progenitors retina	A	↑ proliferation	S1P	Miranda et al., 2009
Human neuroblastoma cell	A, siCerK	↓ proliferation	↓ CerK expression	Bini et al., 2012
Neuronal progenitors retina	A	neuronal progenitors retina	C1P	Miranda et al., 2011
SURVIVAL				
Photoreceptor	A	↑ survival	C1P	Miranda et al. 2011
SH-5YSY, TNFα,	A,si CerK	↑ survival	↓ CerK expression	Barth et al., 2012
Photoreceptor	A	↑ survival	S1P	Miranda et al., 2009
SH-SY5Y, MPP+	A	↑ survival	S1P	Pyszko and Strosznajder, 2014
Mature oligodendrocyte	A,si S1P5R	↑ survival	S1P5R/AKT	Jaillard et al., 2005
Drosophila mutants	B	↑ photoreceptor survival	CDase expression	Acharya et al., 2003
Retinitis pigmentosa mouse (eye)	B	↑ photoreceptor survival	SPT inhibition	Strettoi et al., 2010
DIFFERENTIATION				
Neuronal progenitors retina	A	↑ differentiation	S1P	Miranda et al., 2009
PC12	A	neurite retraction ↓differentiation	S1P/S1P2R	Toman et al., 2004
PC12, dorsal root ganglion neurons	A	↑ differentiation ↑neurite	S1P/S1P1R	Toman et al., 2004

		outgrowth		
Oligodendrocyte precursor, S1P1R KO mouse	B	↓differentiation	↓S1P1R	Dukala and Soliven, 2016
INFLAMMATION				
Microglial cultured cells, brain	A, B	↓inflammation	C2-Cer ROS, MAPKs, PI3K/Akt, Jak/STAT	Jung et al., 2013
Murineischemic brain Cultured neurons	A,B,a	↑inflammation ↓inflammation	SphK1inhibition, KO SphK2 inhibition, KO	Zheng et al., 2015
NEURODEGENERATION				
Purkinje cell CerS1 mutants	A	↓cell number ↓ neurite branching	↓C18Cer , ↑C16Cer ↑Sph, ↑dhSph, ↑dhS1P, ↑S1P	Zhao et al., 2011
Purkinje cell, aSMase KO	A	↑ death	↑SM	Horinuchi et al., 1995
Neuroblastoma cell	A,siCerS2	cell growth arrest increased autophagy	↓CerS2, ↑C16Cer, ↓ C24Cer,	Spassieva et al., 2009
ISCHEMIA/HYPOXIA				
Rat brain,glia, chronic hypoxia	B		↑ Cer, ↑ aSMase, ↓GCS	Ohtani et al., 2004
Hypoxia/reoxygenation NT-2 neuronal precursor cells	A		↑ C14Cer, ↑C16 Cer , ↑ SMase, ↑CerS5	Jin et al., 2008
Ischemia, rat hippocampus astrocyte	B	↑TNFα, IL1, IL6	↑ nSMase	Gu et al., 2013

The table illustrates some examples of the involvement of SLs on proliferation and survival, indicating the experimental method used (A, in vitro; B, in vivo; MPP+, 1-methyl-4-phenylpyridinium; si: siRNA; ↑, increase; ↓, decrease).

Table 2. Involvement of SLs on neurodegenerative diseases

	Method	Effect	Mechanism	Reference
AD				
Cortical neurons, Aβ 1-42	A	↑exosome release, ↑apoptosis	↑nSMase,	Wang et al., 2012
Human primary neurons, Aβ	A	↑ apoptosis	↑ nSMase	Jana and Pahan, 2004
Cultured hippocampal neurons, Aβ	B	↑apoptosis	↑ C18Cer, C24Cer	Cutler et al., 2004
Presenilin knock-in mouse, primary cultured astrocytes	A	↑cell death	↑ C20Cer, C24Cer, ↑CerS1, ↑CerS4	Wang et al., 2008
Astrocytes, frontal cortex, cerebrospinal fluid, patients	B		↑Cer	Satoi et al., 2005
White matter temporal cortex, white and gray matter, patients	B		↑ C24:1Cer ↓sulfatides	Han et al., 2002
Medial frontal gyrus, patients	B		↑ C24:0 Cer	Cutler et al., 2004
Cultured neurons, Aβ Brain, patients	A B	↑Apoptosis	↑a,nSMase, ↑acid CDase ↑aSMase, ↑acid CDase, ↑Cer, ↓SM	He et al., 2010
Entorhinal cortex,patients Hippocampus temporal gray matter	B	amyloid deposit	↓SphK1 , ↓S1P1R, ↑SPL ↓S1P, ↓SphK1,2 ↑C16:0 Cer	Ceccom et al., 2014
Brodman areas 46,10,20 patients,	B		↑ PPAP2B, ↑ SPL, ↓acid CDase, ↑CerS1,2, ↓CerS6	Katsel et al., 2007
PD				
Anterior cingulate cortex , patients	B		↓total Cer, ↓SM , ↑CerS1 expression	Abbot et al., 2014
Anterior cingulate cortex , patients	B	↑ autophagy ↑α-synuclein	↓GlucosylCDase, ↓Cer,	Murphy et al., 2014
MS				
White matter, patients	B		↓S1P, ↑Sph, ↑C16Cer, ↑C18Cer	Qin et al., 2010

Reactive astrocytes, patients	B		↑ C18:0 Cer	Kim et al., 2012
NPC				
NPC-/- mouse brain	B		↑GlucosylCer, GalactosylCer, GlucosylSph, GM2, GM3	Marques et al., 2015
NPC-/- mouse brain with GBA2 deletion,	B	improved motor coordination	↑Glucosyl Cer, GlucosylSph = cholesterol = gangliosides	Marques et al., 2015
NPC1-/- mouse brain, Miglustat Patients, plasma Patients + Miglustat, plasma patients + Miglustat, CSF	B		GCS inhibition , ↑ monohexylCer ↑ monohexylCer ↑C16:0Cer, ↓Sph, ↑S1P ↓Cer, ↓GM1, ↓GM3 ↑monohexylCer	Fan et al., 2013
NPC1-/- mouse brain, Miglustat,	B	↑synaptic plasticity	GCS inhibition	D'Arcangelo et al., 2016
Purkinje neurons from NPC1-/- cat, Miglustat	A/B	↑survival	GCS inhibition	Stein et al., 2012
NPC1-/- cat, Miglustat	B	↑lifespan ↓ motor deficit	GCS inhibition	Stein et al., 2012
Lymphocytes NPC patients, Miglustat	A	correction of abnormal lipid trafficking	GCS inhibition	Lachmann et al., 2004

The table illustrates some examples of the involvement of SLs on neuroinflammation, ischemia, and in neurogenerative diseases such as PD, MS, AD and NPC, indicating the experimental method used (A: in vitro; B, in vivo; si: siRNA; GBA2, non-lysosomal glucosylCDase). The alterations in SLs content or in expression/activity of enzymes involved in SL metabolism are listed under Mechanism.

Table 3. Effects of 1,25(OH)$_2$D$_3$ on nervous system differentiation, protection and proliferation

DIFFERENTIATION

Cell	Effect	Mechanism	References
Primary embryonic hippocampal cells	↑ neurite outgrowth	↑NGF	Brown et al., 2003
OPC	↑ differentiation	↑MBP	de la Fuente et al., 2015
Neuronal stem cell	↑ differentiation to oligodendrocytes	↑ CNTF	Shrirazi et al., 2015
Schwann cells	↑ differentiation	↑ IGF-1	Hao et al., 2015
HN9.10e	↑ neurite outgrowth	↑ NGF, Bcl-2	Marini et al., 2010

PROTECTION

Animal/Cell	Stimulus	Mechanism	References
Murine experimental allergic encephalomyelitis	MBP	nd	Lemire & Archer, 1991
Dopaminergic cell	MPTP+, sulfoximine	↓ROS, ↑glutathion	Shinpo et al., 2001
Mesencephalic cell	6OH-DA,	↑TH, ↑arborization	Wang et al., 2001
Hippocampal neuron	NMDA, glutamate	↓LVSCC	Brewer et al., 2001
Substantia nigra	Zn	↓lipid peroxidation, ↑ DA	Lin et al., 2003
Cortex	ischemia	↑HO-1, ↓ GFAP	Oermann et al., 2004
Cortical neuron	glutamate	↑MAP2, ↑GAP-43, ↑synapsin 1, ↑VDR	Taniura et al., 2006
Rat, substantia nigra	6OH-DA	↑DA	Smith et al., 2006
rat, mice	MPTP	↓ microglia activation, ↓TNFα mRNA, ↓INFγ mRNA	Kim et al., 2006
cortical cells	cyanide	↓ uncoupling, ↑Ikkb	Li et al., 2008
hippocampus	glutamate, ischemia	↓ caspase-3	Kajta et al., 2009
mesencephalic neuron		↑GDNF	Orme et al., 2013
rat hippocampus	ischemia/reperfusion	NR3A, ERK, pCREB	Fu et al., 2013
SH-SY5Y	Rotenone	↑ autophagy ↑LC3, beclin, AMPK	Jang et al., 2014
Neuron-glia	endotoxin	↓ MAPK, ↓iNOS, ↓IL-6, ↓MIP-2 mRNA	Huang et al., 2015
mouse	MPTP	↑ autophagy	Li et al., 2015
Cortex slices	hyperhomocysteinemia	↓ ROS, ↓ iNOS	Longoni et al. 2016
Schwann	High glucose Methylglyoxal	↑ CBS, ↑H2S, ↓ ROS	Zhang et al. 2016
Tg2576 and TgCRND8 mice		↓plaque formation, ↓ lower soluble Aβ levels, ↑ P-glycoprotein	Durk et al., 2014
AD mouse (AbPP)		↓decrease memory deficit ↓plaque formation, ↑NGF ↓ inflammation	Yu et al., 2011
Aging rats		↓decrease memory deficit	Latimer et al., 2016
		Modulation proinflammatory cytokines ↓decrease amyloid	Briones and Darwish, 2012
		↓decrease amyloid	Yu et al., 2011
Hippocampal neurons and	Aβ	↓cytotoxicity ↓iNOS	Dursun et al., 2011;

cortical neurons	↓ LV CDCC A1C , ↑VDR	2013a,b
Mouse retina	↑ phagocytosis, ↓ Aβ	Lee et al. 2012
AD macrophages	Modulation IL1, IL1R ↑ phagocytosis, ↓ Aβ	Mizwicki et al. 2012,2013
bEnd.3 cells	↑Aβ1-40 brain-to-blood efflux of amyloid-β (Aβ) peptide LRP1 and RAGE regulation	Guo et al., 2016

PROLIFERATION

Cell/animal	Action	Mechanism	References
Neuroblastoma cells	↓	CerK	Bini et al., 2012
		nd	Gummireddy et al., 2003a,b Celli et al., 1999a,b Stio et al., 2001
Stem cells	↑	↑NT-3, BDNF, GDNF and CNTF	Shirazi et al., 2015
Primary embryonic hippocampal cells 1,25(OH)$_2$D$_3$ -deprived	↓		Brown et al., 2003
embryos E19, brain	↑	↑cyclin D ↓ cyclin B, ↓p21	Ko et al., 2004
Glioblastoma cells	↑, no effect		Diesel et al., 2005
1,25(OH)$_2$D$_3$-deprived neuroprogenitors, SVZ	↓		Cui et al., 2007
1α-hydroxylase knockout Mouse, dentate gyrus	↑		Zhu et al., 2012

The table illustrates the effect of 1,25(OH)$_2$D$_3$ in cell types and the mechanism involved. The noxius agent is listed under Stimulus. ↑, increase; ↓, decrease. Abbreviations: 6-OHDA: 6-hydroxydopamine; AMPK: AMP-dependent PK; BDNF: brain derived neurotrophic factor; GDNF: glial derived neurotrophic factor; CNTF: ciliary derived neurotrophic factor; bEnd.3: mouse brain microvascular endothelial cell line; CBS: cystathionine-β-synthase; DRG: dorsal root ganglion; HO: hemoxygenase; i NOS: inducible nitric oxide synthase; LVDCC: L-type voltage-sensitive calcium channels; LRP1: low-density lipoprotein receptor-related protein 1; MBP : myelin basic protein; MPTP : 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ; nd: not determined; NR3A: N-Methyl-D-Aspartate receptor subunit 3A; OPC: oligodendrocyte precursor cell; RAGE: receptor for advanced glycation end products, SVZ, subventricular zone.

Figure legends

Figure 1. Metabolism of sphingolipids. A). *de novo* synthesis of sphingolipids leads to the formation of ceramide (Cer) and sphingosine 1-phosphate (S1P) through four reactions catalized by the serine palmitoyltransferase (SPT), which condenses palmitoyl-CoA and serine into 3-ketosphinganine (3-KS), the 3-ketosphinganine reductase (3-KR), which generates sphinganine (DHSph), the (dihydro) Cer synthase (CerS), which acylates sphinganine to dihydroceramide (DHCer), and the dihydroceramide desaturase (DES), which converts relatively inactive dihydroceramide to ceramide). The latter is converted to sphingosine (Sph) by ceramidase (CDase). Sph can be converted to S1P by sphingosine kinase (SphK) or to Cer by CerS. The degradation of S1P is achieved by the reversible reaction catalized by the S1P phosphatase (S1PPase) and the irreversible reaction catalized by S1P lyase which produces hexadecenal and ethanolamine phosphate. B). The cell membrane constituent sphingomyelinase (SMase/SMPD) generates Cer from sphingomyelin (SM). Phosphorylation of Cer by Cer kinase (CerK) generates ceramide-1-phosphate (C1P). In the Golgi, Cer is converted to SM by SM synthase, or to GlucosylCer by glucosylceramide synthase. GlcCer is then processed to more complex glycosphingolipids (not shown). Glucosylceramidase (also named glucosylcerebrosidase) (GCDase) produces Cer from glucosylCer.

B. S1P can be exported outside the cells by ABC transporters and the putative transporter Spinster 2 (spns2) and elicits autocrine or paracrine signaling by binding to and activating G-protein-coupled receptors (S1PR1-5). G-proteins are composed of three subunits**:** alpha, beta, and gamma and are classified as G(q), G(i/o), G(12/13) and G(s) depending on the function of their alpha subunits.

Figure 2. Biological function of S1P/S1P receptor signaling.

Phosphorylation activates SphK1 and promotes its translocation to the membrane (dashed arrow), where S1P is generated. The bioactive lipid can be released and then bind to S1PRs. Activation of each receptor subtype leads to distinct G-protein mediated signaling pathways. S1P can be also formed by SphK isoform 2 inside the nucleus and in this compartment it can inhibit p21 transcription and histone deacetylase activity (DHAC). ↑: activation; ⊤ :inhibition

Figure 3. Biological function of $1,25(OH)_2D_3$/ VDR signaling.

Non-genomic rapid actions of $1,25(OH)_2D_3$ are mediated by membrane vitamin D_3 receptor (mVDR), localized at plasma membrane. Inactive form of VDR is present in the cytosol (VDR). mVDR activation through MARRS (membrane-associated, rapid response steroid-binding protein) promotes MAPK cascade, Raf kinase with the consequent activation of PKC, PI3K, and PKA. $1,25(OH)_2D_3$ can interact with TGF and EGF receptors to modulate cell cycle processes. Activation of the G-protein coupled receptor S1P1R leads to specific Raf-MAPK-ERK cascade that may cross-talk with the classical VDR pathways.

$1,25(OH)_2D_3$ genomic action leads to gene expression regulation following the nuclear translocation of VDR, the formation of the complex of VDR and 9-cis-retinoic acid receptor (VDR/RXR), and its binding to the vitamin D_3 response elements (VDREs).

Figure 4. Effect of $1,25(OH)_2D_3$ and Aβ on the key reactions involved in the sphingolipid metabolic pathway.

The effect of $1,25(OH)_2D_3$ is shown in blue and dashed lines, whereas the effect of Aβ treatment or alterations associated with AD on the key enzymes involved in the reactions are shown in red and continuous line. ↑: activation or increased expression/activity; ⊤ : inhibition or reduced expression/activity

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