Role of Sphingolipid Metabolism Played in Neurodegenerative Disease: A Descriptive Review

Mohit Agrawal[1]*, Manmohan Singhal[2], Hema Chaudhary[3], Neha Minocha[4], Shalini kumari[5], Yash Jasoria[6]

Abstract

Sphingolipid comprise an important group of biomolecules, some of which have been shown to play important roles in the neurodegenerative disease and regulation of many cell functions. Sphingolipid are a ubiquitous membrane lipid present in every cell & found most abundantly in neural tissue. Sphingolipid metabolism alterations in the neurodegenerative disease. It appears that alteration in the gene expression pattern in these disease conditions are biased to manipulate the system in order to result in a particular disease. The pathogenesis of AD is highly linked to Amyloid beta deposition & oxidative stress. We report that alterations in Sphingolipid metabolism during normal brain aging and in the brain of AD patients. In the Parkinson's disease the enzyme which degrades the glycolipid glucosylceramide (GlcCer) is encoded by a gene known as glucocerebrosidase-1 (GBA1) which is one of the hallmarks in the pathology of PD. In the Huntington Disease, the imbalance in S1P-metabolizing enzymes results in decreased bioavailability of S1P and increased levels of Ceramide species as reported in HD models. Deregulated metabolism of lipids is an important factor of modified activity of brain. Similarly, the altered metabolism of sphingolipids also points towards its crucial role in the pathogenesis of epilepsy. In this review, we provide an overview of Sphingolipid metabolism and synthesis. We focus on the deregulation of Sphingolipid metabolism pathway in neurodegenerative disease like Alzheimer's disease, Parkinson's disease, Huntington disease and Epilepsy. In the present review, we have highlighted the altered metabolism to neurodegenerative diseases.

Keywords: Neurodegenerative disease, Sphingolipid metabolism, S1PR, Ceramide, S1P, FTY720

DOI Number: 10.14704/Nq.2022.20.17.Nq88007 **Neuroquantology 2022; 20(17):41-50**

1. Introduction

Sphingolipids (SLs) are ubiquitous lipids found in all mammalian cell membranes, including myelin, as well as in the plasma lipoproteins. They form a very diverse family of lipid molecules, the backbone of which is ceramide, i.e., a long chain sphingoid base that can be N-acylated by a variety of fatty acids (Astudillo et.al 2014). Sphingolipid were discovered over 120 years ago and for many decades were considered to serve only as structural components of biological membranes. Now a days, many of them are known to be highly bioactive compounds that play a significant role in signal transduction and regulation of a host of cellular process such as proliferation, maturation and apoptosis, and are also involved in cellular stress response.

One of the most important sphingolipids is ceramide (CER), which serves as a precursor for

***Corresponding Author:** Mohit Agrawal
Address:[1]*Assistant Professor, School of Medical & Allied Sciences, K.R. Mangalam University, Gurugram, Haryana, India 122103, Email: mohitagrawalmohu@gmail.com
[2]Associate Professor, Faculty of Pharmacy, DIT University, Mussoorie-Diversion Road, Makkawala, Dehradun, Uttrakhand, India 248009
[3]Professor & Dean, School of Medical & Allied Sciences, K.R. Mangalam University, Gurugram, Haryana, India 122103
[4]Assistant Professor, School of Pharmacy, Chitkara University, Himachal Pradesh 17410
[5]Assistant Professor, Faculty of Pharmacy, MET College, Moradabad
[6]Research Scholar, School of Medical & Allied Sciences, K.R. Mangalam University, Gurugram, Haryana, India 122103
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

other biologically active sphingolipids, including sphingosine (SPH) and sphingosine-1-phosphate (S1P). Many factors such as glucocorticosteroids, growth factors, interleukins, interferons, ionizing radiation and several chemotherapeutics induce cellular production of ceramide. (Borodzicz et al. 2015). Any imbalance in the level of bioactive sphingolipids, such as ceramide (Cer), sphingosine (Sph), and their respective phosphorylated products-namely, ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P) - can alter the signaling for cell survival, cell growth, inflammation, senescence, and apoptosis. (chen et al, 2014). Sphingolipids are particularly abundant in the brain and are essential for the development and maintenance of the functional integrity of the nervous system (Olsen & Faergeman, 2017). Deregulation of sphingolipid metabolism may contribute to the pathophysiology of a number of ocular diseases (e.g., diabetic retinopathy and retinal degenerative disorders), neuro degenerative disorders (e.g., Alzheimer disease and Parkinson disease), cardiovascular diseases, chronic inflammation and cancer (Becker et al, 2010, Gangoiti et al, 2010). The recent development of the synthetic sphingosine analog fingolimod (FTY720) and its application in neuroinflammatory diseases, strengthens the putative role of sphingolipids in inflammatory neural and ocular diseases because FTY720 modulates both biosynthesis of Cer and S1P signaling. (Chun et al, 2010, Balatoni et al, 2007). Sphingolipid play an essential role for the proper brain function & development. A well known class of lipid named as SP (Sphingolipid) plays an important role, synaptogenesis & synaptic plasticity involve various phenomenon such as recurrent presynaptic stimulation & long term potentiation (Sonnino & Prinetti, 2016). Interestingly, sphingosine-1- Phosphate (S1P) regulates the localization of synapsin-I in pre-synaptic compartments and hence it has the greatest impact on the modulation of presynaptic functions. The following figure illustrates the modulation of synaptic function by SP **(Figure 1)**.

We review the findings on sphingolipid metabolism- associated in a pathogenesis conditions of a better understanding of the sphingolipids roles in the neurodegenerative disorder such as, Alzheimer's disease, Parkinson's disease, Huntington Disease and Epilepsy.

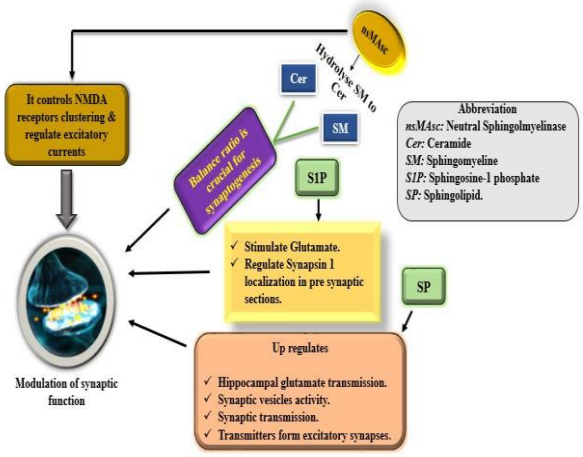

Fig.1 Role of Sphingolipid on synaptic functions & formation.

2. Sphingolipid Metabolism & Synthesis: An Overview

Sphingolipid Metabolic pathway is an important cellular pathway that represents a highly coordinated system linking together various pathways, where ceramide occupies a central position in both Biosynthesis & catabolism, there by crafting a metabolic Hub (Rao et al, 2013).

Sphingolipids synthesis can occur via de novo biosynthetic pathway or the hydrolysis of sphingomyelin, or can also derive by the "salvage pathway" which determines the recovery of sphingosine, by the recycling of complex sphingolipids (gangliosides) through a coordinated action of several enzymes & the reaction sequences involved in the formation of ceramide and other sphingolipids are represented in **Figure 2** (Pardo and Maglione, 2018).

2.1 De Novo Synthesis.

De novo ceramide synthesis occurs in the ER. The first step in de novo synthesis is catalyzed by serine palmitoyl transferase (SPT) and involves the condensation of serine and palmitoyl- CoA to form 3-ketosphinganine, which is then reduced to form sphinganine. Ceramide synthases catalyze the Nacylation of sphinganine to form dihydroceramide (DH) (Patwardhan et al, 2015). Among various organisms, several metabolic divergences appear after the formation of sphinganine (dihydrosphingosine). Ceramide thus generated

needs to be transported to the Golgi complex, where it serves as a substrate for production of complex sphingolipids like sphingomyelin and glycosphingolipids (Rao et al, 2013). Both vesicular and nonvesicular transport mechanisms can mediate this process. The non-vesicular transport is mediated by the ceramide transfer protein (CERT) in mammals, in an ATP-dependent manner (hanada et al, 2009). Once transported to the Golgi complex, several different head groups can be added to ceramide to form different classes of complex sphingolipids. These complex sphingolipids will traverse different cellular locations mainly through vesicular transport. (Rao et al, 2008).

2.2 Salvage Pathway.

The salvage pathway of long-chain sphingoid bases, leading to the regeneration of sphingolipids, has been estimated to contribute from 50% to 90% of sphingolipid biosynthesis (Tettamanti et al., 2003). These metabolic considerations suggest a crucial role for sphingolipid breakdown in sphingolipid biosynthesis/turnover as well as in cellular signal transduction. (Kitatani et al, 2008). The salvage pathway re-utilizes long-chain sphingoid bases to form ceramide through the action of ceramide synthase (Merrill et al., 1995). The ceramide salvage pathway differs from the ceramide de novo pathway in metabolic features (catabolism vs. anabolism), but these pathways share a singular step where long-chain sphingoid bases are acylated to ceramide in a (dihydro) ceramide synthase-dependent manner (Delgado et al, 2007).

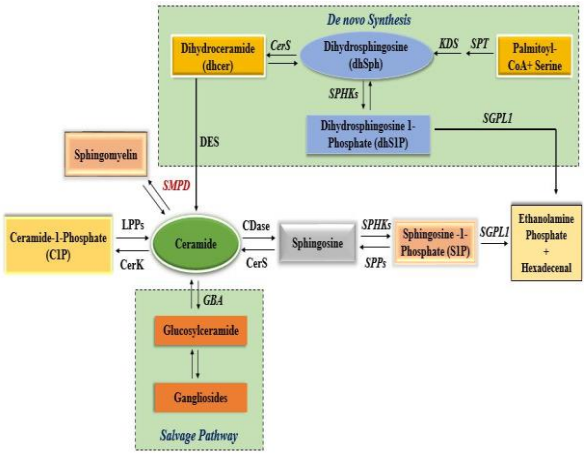

Figure 2 | Simplified schematic representation of sphingolipid biosynthesis. Serine palmitoyltransferase (SPT) catalyzes the initial reaction of the de novo biosynthesis of sphingolipids.

Dihydrosphingosine (dhSPH) is generated after an intermediate step by the action of 3-keto-dihydrosphingosine reductase (KDS). Successively, dhSph can be either phosphorylated, with the generation of dhSphingosine-1-phosphate by sphingosine kinases (SPHKs), or acetylated by ceramide synthase (CERS) and desaturated by ceramide desaturase (DES) to form ceramide. Ceramide may also derive from the Salvage pathway through either the hydrolysis of sphingomyelin or by the recycling of gangliosides by Sphingomyelin Phosphodiesterase (SMPD) and Glucosylceramidase (GBA) respectively. Ceramide can be phosphorylated by Ceramide kinase (CerK) with the generation of ceramide-1-phosphate (C1P) which in turn can be re-converted in ceramide by Lipid Phosphate Phosphatases (LPPs). Ceramide can be subsequently metabolized by Ceramidase (CDase) to generate sphingosine which, in turn, produces sphingosine-1-phosphate (S1P) through phosphorylation by SPHKs. S1P can be either dephosphorylated and re-converted to sphingosine by S1P Phosphatases (SPPs), or irreversible catabolized into hexadecenal + phospho-ethanolamine by S1P Lyase (SGPL1).

Several studies showed that these sphingolipid mediators and their enzymes are likely to have an integral role in different cell processes including proliferation, inflammation, apoptosis, and migration (Pardo and Maglione, 2018). S1P metabolism involves a number of different highly specialized enzymes. S1P is normally synthesized by sphingosine kinase-1 and−2 (SPHK1 and 2) and degraded by sphingosine-1-phosphate phosphatase (SGPP) or lyase (SGPL1) (Lestunff et al, 2002). SPHK1 activity is mainly associated with cell survival, while SPHK2 is widely described as being a dual-function protein whose activity may either guarantee the proper occurrence of physiological events like mitochondrial function and homeostasis as well as regulation of gene expression through inhibition of Class I HDACs or result detrimental mainly suppressing cell growth and promoting apoptosis (Morozov et al., 2013).

3. Sphingosine-1-Phosphate Receptors

Sphingosine-1-phosphate (S1P) is a bioactive lipid that signals through a family of G protein-coupled receptors, consisting of 5 members, termed S1P1, S1P2, S1P3, S1P4 and S1P5. S1P can act as a second messenger intracellularly through 5 G-protein coupled receptors, including S1P1, S1P2 S1P3, S1P4, and S1P5, which are differentially distributed and expressed in various cell types (Punsawad, 2013). The human brain demonstrates high levels of expression of several S1P receptors, such as S1P1 and S1P5, and also differentially regulates relative expression of these receptors by downregulating them, leading to regulation of cellular processes. There are five specific cell surface G-protein-coupled receptors for S1P, termed as S1PR1–5. S1PRs have been found to be involved in the physiological and pathophysiological process (Aris et al., 2017). S1P receptor subtypes are differentially expressed in diverse cell types. S1PR1-3 are expressed on macrophages and neurons (Weichand et al., 2013). However, S1PR4 and S1PR5 were found to be expressed at later developmental stage in neuron. S1PR4 is found to be expressed in lymphoid and hematopoietic cells, whereas S1PR5 is expressed on by dendritic cells (DCs) and natural killer cells (Meng et al., 2009). The S1P levels found in lymph appear to be regulated by lymphatic endothelium. S1P receptors are thought to play a number of roles in brain cell function, including astrocyte proliferation and migration, oligodendrocyte differentiation and cell survival, and neurite outgrowth and neurogenesis (Yamagata et al., 2002; Jaillard et al., 2005). The concentration of S1P is increased during pathological situations, such as ischemia, traumatic injury, and disruption of the blood brain barrier (BBB) (Edsall and Spiegel, 1999).

The cellular distributions of S1P receptor subtypes is shown in **Table 1** (Rosen et al., 2009).

Subtypes	Distribution (mRNA)	Cellular functional expression and consequences
S1P1	Brain, Heart, Spleen, Liver, Lung, Thymus, Kidney, Skeletal muscle, Lymphoid	Astrocyte: migration B cell: blockade of egress, chemotaxis Cardiomyocyte: increased β-AR positive inotropy Endothelial cell: early vascular system development, adherens junction assembly, APC-mediated increased barrier integrity. Neural stem cell: increased migration. Pericyte: early vascular system development T cell: blockade of egress, chemotaxis, decreased late-stage maturation VSMC (early vascular system development)
S1P2	Brain, Heart, Spleen, Liver, Lung, Thymus, Kidney, Skeletal muscle	Cardiomyocyte: survival to ischemia-reperfusion Epithelial cell (stria vascularis): integrity/development Epithelial hair cells (cochlea): integrity/development Endothelial cell (retina): pathological angiogenesis, adherens junction disruption Fibroblast (MEF) Mast cell: degranulation
S1P3	Brain, Heart, Spleen, Liver, Lung, Thymus, Kidney, Skeletal muscle, Testis	Cardiomyocyte: survival to ischemia-reperfusion Dendritic cell (hematopoietic): worsening experimental sepsis lethality/inflammation/coagulation
S1P4	Lymphoid, Lung	T cell : migration/cytokine secretion
S1P5	Brain, Skin, Spleen	NK cell: trafficking Oligodendrocyte: survival OPC: glial process retraction; inhibition of migration

4. Deregulation of the Sphingolipid Pathway in Neurodegenerative Disease

A fine balance between synthesis of Sphingolipid and their degradation is normally required for many biological processes (Pardo and Maglione, 2018), thus changes in their metabolism may profoundly affect brain homeostasis and function. Over the past few years, perturbed metabolism of the interconvertible bioactive Sphingolipid, ceramide and S1P is increasingly becoming recognized as potential pathogenic factor in different neurodegenerative disorders **(Table 2).**

Molecule	Alzheimer's Disease	Parkinson Disease	Huntington Disease
Ceramide	Increased Levels	Increased Levels	Increased Levels
CERS2	Downregulated	Not available	Not available
SPHK1	Downregulated	Downregulated	Downregulated
SPHK2	Upregulated	Downregulated	Upregulated
SGPL1	Upregulated	Not Available	Upregulated
S1P	Reduced Levels	Not available	Reduced Levels

4.1 Alzheimer's Disease

Alzheimer's disease (AD) is a devastating progressive neurodegenerative disorder with characteristic clinical and pathological features. Since age is a major risk factor for AD, the incidence of this disease is rising as people continue to live longer, especially in developed countries (Possedechaves et al., 2009). Progressive neurodegeneration in brain regions involved in learning and memory results in cognitive decline, loss of memory and changes of social and emotional behavior (Robinswahalin et al., 2010). AD is characterized by extracellular accumulation of amyloid β -peptide (Aβ) toxic aggregates and intracellular deposits of abnormally phosphorylated tau protein (Gouras et al., 2010). The role of Sphingolipid is also emerging, Ceramide elevation in the brain is evident at an early stage in AD patients (Han et al., 2002). Conversely, expression of genes involved in the de novo synthesis of Sphingolipid is Upregulated early in the disease progression (Katsel et al., 2007). Consistently, accumulation of ceramide has been reported in brain tissues from AD patients even at early stages of disease and may contribute to neurotoxic action of Aβ (Cutler et al., 2004; Dinkins et al., 2015). A number of evidence also indicates that, along with ceramide abnormalities, metabolism of other Sphingolipids is affected in AD (Zheng et al., 2006). Also, alteration in the expression and/or in the activity of S1Pmetabolizing enzymes as well as reduced levels of S1P has been widely reported in AD human brains (Katsel et al., 2007; Couttas et al., 2014). In spite of the great effort dedicated to understand the role of lipids in the regulation of Aβ production during disease, much less attention was paid to the physiological functions of APP and Aβ (Possedechaves et al., 2009). In particular, loss of SPHK1 and reduced bioavailability of S1P have been found early in the pathogenesis of the disease even before clinical diagnosis Conversely, upregulation of SPHK2 has been described to modulate Aβ release (Couttas et al., 2014; Takasugi et al., 2011). Intriguingly, the Sphingosine-1-phosphate (S1P) influences the proliferation, cellular survival, cell proliferation, synaptic plasticity, and neurotransmitters secretion. The reduction of S1P receptor 1 (S1PR-1) is also involved in the pathology of AD. Moreover the S1P concomitant genes including ceramide synthases (CERS-1, CERS-2) and Sphingosine-1-phosphate lyase (SGPL-1) were found to be up-regulated in AD patients, whereas sphingosine kinases (SphK-1, SphK-2), ceramide kinase (CERK), and anti-apoptotic Bcl-2 were found to be reduced (Hussain et al., 2019). Following pictures describes the Role of Altered sphingolipids metabolism in AD Pathogenesis **Figure 3**.

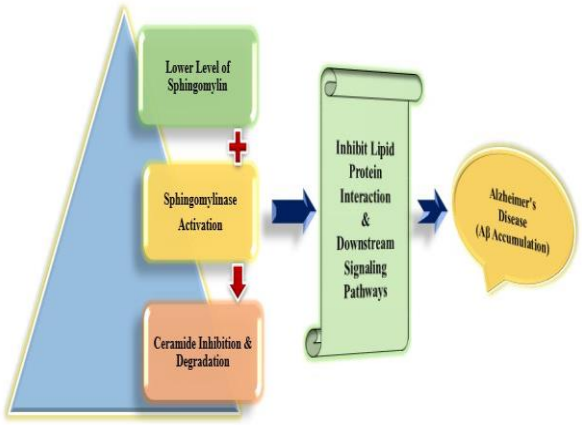

Fig. 3 Sphingolipid & AD Pathogenesis

In conclusions, there is growing and exciting evidence that a reciprocal regulation between lipids (Sphingolipids) & Aβ exists. Sphingolipids have emerged as significant regulators of Aβ production; and Alteration of Sphingolipid metabolism might be associated with the development of Sporadic AD. Hippocampal ceramide and sphingomyelin content correlate with age in men and aging in females leads to reduction in the fraction of phosphorylated sphingosine (S1P/sphingosine ratio), suggesting that age-related changes in bioactive sphingolipids might create pro-apoptotic, neurodegeneration-conductive environment (Coutass et al., 2018).

Moreover, higher levels of identified sphingomyelins and hydroxysphingomyelin associate with the risk of future conversion to AD (Varma et al., 2018). The roles of S1P and ceramide in the survival of brain neurons are far

more complex than the antagonism described in the sphingolipid rheostat model. However, it is highly probable that changes in these compounds should significantly alter the rates of neuron degeneration and death **(Figure 4)** (Jesko et al., 2018). S1P is known to modulate the immune response, but the possible outcome of the resulting reaction in the diseased brain is highly unclear.

The roles of S1P in the regulation of secretion mechanisms also deserve more attention in the context of extracellular protein neurotoxicity (Karunakaran and Deckert, 2017).

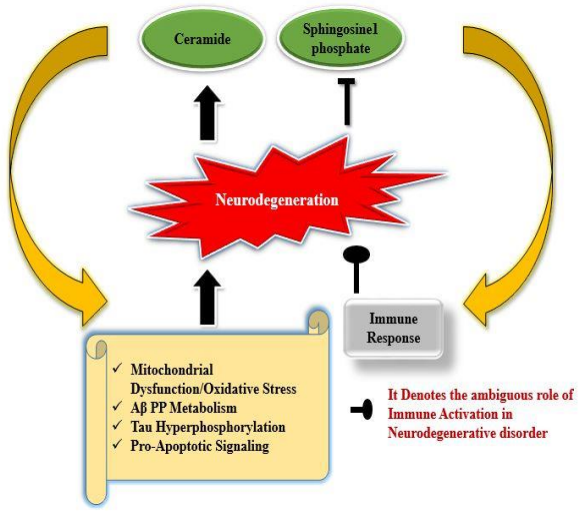

Fig. 4 The significance of bioactive sphingolipids in neurodegeneration. The 'sphingolipid rheostat' model assumes antagonistic roles of ceramide and S1P in the regulation of cellular survival and death. Although exceptions have been identified, the tendency towards accumulation of ceramide and reduced levels of S1P still should generate strong neurodegenerative impulse

4.2 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative movement disorder with a prevalence of approximately 1 to 2% of the population over 65 years which increases up to 5% in people over 85 years old (Fahn 2006).

The pathological hallmarks of PD include the loss of dopaminergic neurons in the ***substantia nigra pars compacta*** and the formation of Lewy bodies mainly composed of aggregated alpha-synuclein (a-syn) protein and other components, including lipids (Gai et al., 2000; Dickson et al., 2009).

Several studies demonstrated that defective ceramide metabolism may contribute to the pathogenesis of PD (Bras et al., 2008). Generally, it is speculated that exact cause of PD is still unknown, but the neurodegeneration followed by the fibrillation and accumulation of α-synuclein in neurons is suggested to be the main contributing factor (Hussain et al., 2018). The enzyme which degrades the glycolipid glucosylceramide (GlcCer) is encoded by a gene known as glucocerebrosidase-1 (GBA1) which is one of the hallmarks in the pathology of PD. Hence, GlcCer facilitates the toxic alteration of α-synuclein. Furthermore, the GBA1 mutation may act as a genetic factor and may also enhance overall risk of PD by 5 to 6 folds (Hussain et al., 2019). The lysosomal enzyme which is encoded by GBA1 is glucocerebrosidase (GCase), predominantly expressed in several types of cells. Within the lysosome, it converts GluCer into glucose and ceramide. Moreover, the mutations in GBA1 are heterozygous in patients with GBA1-associated PD (Gegg and Schapira, 2018). Recently, it has been shown that reduced activity of GCase is linked with the aggregation of α-synuclein. Moreover, the diminished activity of GCase also impacts the activity of protein phosphate 2A (PP2A) via ubiquitous dysfunction of lysosomes, thereby increasing the accumulation of α-synuclein (Rocha et al., 2017). It can be summarized that reduced generation of ceramide is due to mutation in GCase and PP2A contributes to the accumulation of α-synuclein, particularly due to the impairment in secretory autophagy. Levels of SPHK1 and 2 have been described aberrant in both in-vitro and in-vivo models highlighting a potential contribution of S1P metabolism to the pathogenesis of the disease (Sivasubramanian et al., 2015).

4.3 Huntington's Disease

Huntington's disease (HD) is an autosomal dominant condition characterized by movement disorders and cognitive decline. Typically, the motor defects include chorea and loss of coordination (Sanchez et al., 2017). Psychiatric symptoms, such as depression, psychosis, and obsessive–compulsive disorder, are also common in HD and are particularly distressing for patients (Rosenblatt and Leroi, 2000). HD is characterized by a general shrinkage of the brain and degeneration of the striatum (caudate

nucleus and putamen), with specific loss of efferent medium spiny neurons (MSNs) (Reiner et al., 1988). The disease derives fromthe expansion of a polyglutamine stretch (polyQ) (> 36 repeats) in the N-terminal region of the protein huntingtin (Htt) (Sanchez et al., 2017) Although the function of this protein is not completely known, expansion of the polyQ stretch endows mutant Htt (mHtt) with toxic properties, resulting in the development of a number of deleterious effects in both neuronal and non-neuronal cells (Maglione et al., 2005). Among all cellular dysfunctions and biochemical defects, classically associated with the disease, defective metabolism of sphingolipids seems to play a key role in its pathogenesis (Dipardo et al., 2017). Expression of S1P-metabolizing enzymes was reported to be aberrant in multiple HD settings (Pirhaji et al., 2017). Levels of SPHK1 was found reduced in brain tissues form two fully manifest HD mouse models (R6/2 and YAC128 mice), and most importantly, in brain tissues from HD patients (Pardo and Maglione, 2018). First signs of early defective sphingolipid metabolism in HD have been reported also and such further evidence corroborates the hypothesis that similar alterations may conceivably contribute to the pathogenesis of the disease (Dipardo et al., 2017). The imbalance in S1P-metabolizing enzymes results in decreased bioavailability of S1P and increased levels of Ceramide species as reported in HD models. Ultimately, synthesis of de novo sphingolipids is also affected in HD animals, even at early stage of the disease (Pardo and Maglione, 2018). This alteration determines a robust reduction of certain dihydroceramide species along with dihydros phingosine and dihydroS1P (Dipardo et al., 2017).

4.4 Epilepsy

Epilepsy is a braindisorder characterized by a chronic predisposition to generate epileptic seizures with secondary neurobiologic, cognitive, psychological, and social consequences (Valeriejewells et al., 2014). Epilepsy is a disorder with abnormal brain activity, causes unusual behavior and continuous episodes of seizures. Dysregulated metabolism of lipids is an important factor of modified activity of brain. Similarly, the altered metabolism of sphingolipids also points towards its crucial role in the pathogenesis of epilepsy. In this context, the possible mechanistic approach relies on the heterozygous deletion of CERS2 (Ceramide synthase 2) gene and the homozygous mutation in CERS1 and CERS1 gene is primarily involved in the synthesis of C18-ceramide. In neuroblastoma, CERS1 down-regulation initiates pro-apoptotic pathways and induces ER stress. The CERS-2 is known for maintaining membrane integrity and mutation in this gene leads to the detachment and degeneration of myelin sheath and ultimately inadequate neuronal myelination results in their deterioration (Hussain et al., 2018). Unfortunately, there is a dearth of data regarding the role of sphingolipids in epilepsy and more work is needed to decipher its role. Moreover, CERS1 deficiency also lowers the level of Myelin-associated glycoproteins (MAG) in oligodendrocytes, which indicates the impact of lipid composition of neuronal membranes on the expression of proteins (Ginkel et al., 2012; Pirhaji et al., 2017). Moreover, the mutation in CERS-1 with increased production of C-18 ceramide has specifically been observed in progressive myoclonic epilepsy (PME) type-8 (Godeiro et al., 2018).

Conclusion

Sphingolipid affect various aspects of cell physiology like, cell proliferation, Differentiation, cell death & cell signaling and are known to contribute in human disease and Neurodegenerative disease. In this review, we discussed Sphingolipid play a vital role in neurodegenerative disease like, Alzheimer's disease, Parkinson's disease, Huntington disease & Sphingolipid in neurological and psychiatric disorder like, Epilepsy. Although a bias for the Sphingolipid metabolism pathway is apparent under neurodegenerative disease, further analysis is required to verify if such a phenomenon is universally applicable. In this review, we focused on Sphingolipid role in neurodegenerative disease & also Sphingolipid metabolic pathway is a major player in the pathology of neurodegenerative disease.

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