Journal of
Alzheimer's Disease & Parkinsonism

Meenalochani et al., J Alzheimers Dis Parkinsonism 2015, 5:3
DOI: 10.4172/2161-0460.1000199

Review Article Open Access

Molecular Mechanism Underlying PD Pathogenesis-A Possible Role for Sphingosine Kinases and Sphingosine-1-Phosphate

Meenalochani S, Dheen ST and Tay SSW*

Department of Anatomy, National University Health system, National University of Singapore, Singapore

Abstract

Parkinson's disease is a neurodegenerative disorder that results in the degeneration of dopaminergic neurons in the substantia nigra (SNc) of the midbrain. Understanding the molecular mechanisms underlying the cause of Parkinson's disease (PD) has attracted the attention of many researchers in the last few decades. In spite of the recent technical advances in the field of neuroscience, the complete pathophysiology of PD is not fully understood. Dysregulated sphingolipid metabolism has been shown to underlie the pathophysiology of many neurodegenerative disorders. However, the role of these sphingolipids in the pathophysiology of PD is still not known. This paper focuses on the, metabolic pathways that are involved in PD pathogenesis with emphasis on sphingolipids and the possible role played by them in the pathogenesis of PD.

Keywords: Parkinson's disease; Sphingosine kinase 1; Sphingosine kinase 2 (Sphk2); Sphingosine-1-phosphate (S1P); Sphingosine 1 phosphate receptors

Introduction

Parkinson's disease (PD) is a debilitating condition of the brain characterized by gradual deterioration of motor functions due to the loss of dopaminergic (DA) neurons in the substantia nigra (SNc) of the mid brain. The exact cause of this cell death is still not clear. The first comprehensible medical description about PD was written in 1817 by an English physician James Parkinson in his work entitled "An Essay on the Shaking Palsy" [1]. However it was Jean-Martin Charcot and Alfred Vulpian who coined the name "Parkinson's disease" by adding more symptoms to James Parkinson's clinical description [2].

PD is the second most widespread neurodegenerative disorder after Alzheimer's disease (AD). Nonetheless, appraisals of occurrence and predominance differ widely around studies; this is due to the differences in the methodologies used. The occurrence of PD reported by studies representing all age gatherings ranged from 1.5 and 22 for every 100,000 man years. This rate may be higher when recognizing just populations over the age of 60 [3]. Approximately 1–2 % of the population over 65 years suffers from PD. This estimate increases to 3 % to 5 % in people 85 years and older [4]. In some rare cases, PD-like symptoms has been observed in youngsters. Epidemiological studies have also shown that the occurrence and prevalence of PD are 1.5 to 2 times more in men than in women [5]. Future epidemiologic investigations of PD ought to be broad, incorporate definite quantifications, and gather data on natural exposures and hereditary polymorphisms. One of the most important questions put forth by the neurobiology of aging apprehends the pathogenic mechanisms causing PD. Age and gender has always been the cardinal risk factors in PD. However, various studies have shown that exposure to pesticides could be the main cause of PD [6]. An alternative explanation is the genetic component, which has been suggested to be an important risk factor. Epidemiological studies have identified a positive family history of Parkinson as one of the most important risk factors for the disease.

The substantia nigra of the midbrain contains the dopaminergic neurons which produce dopamine. Dopamine is a neurotransmitter responsible for coordinating movements. In Parkinson's disease, there is a severe depletion in the levels of dopamine due to the degeneration of dopaminergic neurons. This results in the lack of control over body movements [7]. The symptoms of PD have a gradual onset and usually develop simultaneously with the progression of the disease. The symptoms tend to worsen over time; if left untreated, it may lead to disability with associated immobility and falling. The early classic symptoms of PD include motor symptoms like postural instability, resting tremor, bradykinesia, and rigidity [8]. The above symptoms are related to progressive loss of nigrostriatal dopamine and are usually corrected by treatment with Levodopa or dopamine agonists [9]. Nevertheless, as the disease progresses, symptoms that fail to respond to Levodopa develop [10]. Although the motor symptoms lead the clinical picture of PD, some patients are also associated with a range of non-motor symptoms like sleep, sensation, autonomic, mood disturbances as well as cognitive disturbances like dementia [11]. These symptoms have a severe impact on the patient's quality of life [12]. However, there is a considerable amount of heterogeneity among the individuals during the course of the disease.

Existing treatments for PD

Although less effective in the advanced stage of the disease, medications are available to control the symptoms of PD. Amongst them, Levodopa continues to be the most effective treatment for PD [13]. But this treatment is coupled with complications in motor activities such as dyskinesias, wearing off, and 'on-off' phenomenon [14,15]. One recent study has reported that reported that levodopa intake in dyskinetic patients seem to alter the functioning of some parts of the neural network implicated in motor inhibition [16]. Another viable option at this stage is deep brain stimulation, although some patients meet the necessity for surgery. New medications that offer better control over the symptoms stay on developmental demand. However, both genes-as well

***Corresponding author:** Tay SSW, Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Tel: (65) 6516 3210; Fax: +65-6778-7643; Email: anttaysw@nus.edu.sg

Received October 28, 2015; **Accepted** November 26, 2015; **Published** December 03, 2015

Citation: Meenalochani S, Dheen ST, Tay SSW (2015) Molecular Mechanism Underlying PD Pathogenesis-A Possible Role for Sphingosine Kinases and Sphingosine-1-Phosphate. J Alzheimers Dis Parkinsonism 5: 199. doi: 10.4172/2161-0460.1000199

as cell–based therapies have shown guarantee in early clinical studies [17]. A key need yet to be fulfilled is a treatment that stops or at least slows down the progression of the disease.

Pathological Hallmarks of PD

The archetypal pathological characteristic of PD involves the loss of the dopaminergic neurons. The DA neurons of the substantia nigra contains conspicuous amount of neuromelanin [18]. The loss of these neurons produces the depigmentation found in the substantia nigra of PD patients. The depletion of DA neurons is most prominent in the dorsolateral putamen [19]. At the beginning of the symptoms, 80 % of putamenal DA is degenerated, and 60% of SNc dopaminergic neurons has been lost. The pattern of SNc cell loss appears to be similar to the expression of the DA transporter (DAT) mRNA [20]. However, the DA neurons, which reside in the neighboring ventral tegmental area (VTA), are least affected in PD [21]. The other pathological characteristic that is classic of PD is the occurrence of intraneuronal proteinacious cytoplasmic inclusions, termed "Lewy Bodies" (LBs) [22]. The α-synuclein in the LBs is misfolded, post-translationally modified and ubiquitinylated. LBs comprise of a heterogeneous combination of more than 90 molecules, comprising PD-linked gene products (α-synuclein, DJ-1, LRRK2, Parkin, and PINK-1), mitochondria-related proteins, and molecules implicated in the ubiquitin-proteasome system (UPS), autophagy, and aggresome formation [22]. These interfere with the mechanisms of microtubule-based subcellular transport, thereby causing synaptic dysfunction and other disruptions to neuronal homeostasis [23]. Several studies have shown that LBs are being constantly formed as the disease advances and they disappear when the neuron dies [24]. Reports have indicated that fibrillar aggregates of α-synuclein (LBs and pale bodies) may represent a cyto-protective mechanism in PD [25]. Lewy bodies thus offer a diagnostic marker and are extremely important for the pathological diagnosis.

Possible Pathways involved in the pathogenesis of PD

Before the discovery of genes causing monogenic types of PD, several intriguing speculations have shown that different molecular pathways are involved in the propagation of PD pathogenesis. Accumulating evidences have confirmed that mitochondrial dysfunction, impairment of the ubiquitin proteasome system and oxidative stress may perhaps represent the prime molecular pathways that generally lie beneath the pathogenesis of both sporadic and familial forms of PD [26-28]. In addition to this, inflammation and loss of neurotropic factors have also been shown to play a major role in the progress of PD.

Inflammation

The steady findings acquired by different animal models of PD suggest that neuro-inflammation is an essential patron to the pathogenesis of PD and may further impel the progressive loss of nigral dopaminergic neurons. Although not the primary cause of PD, exaggerated inflammatory responses caused by glial reactions [29], T cell infiltration [30] and increased expression of inflammatory cytokines are presently recognized as major characteristics of PD. Increased levels of pro-inflammatory cytokines such as tumour necrosis factor-a (TNFα), interleukin-1β (IL1β), IL6, inducible nitric oxide synthase (i NOS) and cyclooxygenase 2 have been found in the substantia nigra of PD patients [31, 32]. This might be due to the activation of microglia in that region. Research has shown that inflammatory mediators like (IL1β) promote the aggregation of α-synuclein [33]. In addition to this, activated macrophages have been shown to increase the nitrosylation of α-synuclein in the neuronal cells [34].

Excitotoxicity

In spite of the specific ultra-structural findings connected with dynamic excitotoxic degeneration; there are no specific pathological characteristics of excitotoxicity. However, there is a decline in the glutamate receptor in the PD brain [35], thus proposing that neurons expressing these receptors are susceptible to neurodegeneration. Moreover, neurotoxins such as MPTP, 6-hydroxydopamine and methamphetamine used to model PD exert their toxic effects through the stimulation of excitotoxic glutamate receptors [36]. Increased calcium influx also plays a crucial role in excitotoxicity in PD [37].

Impairment of the Ubiquitin-proteasome system (UPS)

Cellular homeostasis is maintained by all cells by continually degrading proteins, with proteolysis. This occurs in a manner that is both highly specific and highly regulated. The ubiquitin proteasome system (UPS) is crucial for intracellular protein homeostasis and for degradation of aberrant and damaged proteins [27]. The UPS specifically targets individual proteins, comprising short-lived, damaged or defectively folded proteins, which accounts for about 80–90 % of all intracellular proteins [38]. The accumulation of ubiquitinated proteins is a hallmark of many neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, and Huntington's disease, leading to the hypothesis that proteasomal impairment is contributing to these diseases [39]. Rising proof propose that impairment of the ubiquitin-proteasome system may additionally be involved in the pathogenesis of familial and sporadic types of PD [40]. In accordance with this idea, there has been structural and functional dearth in the 20/26S proteasome in the substantia nigra of sporadic PD patients [41]. The accumulation of cytotoxic proteins such as α-synuclein, in Lewy bodies (Lbs) in DA neurons in sporadic PD unequivocally suggests protein misfolding and consequent proteolytic stress, which perhaps imply impaired UPS function [42]. α-synuclein functions by inhibiting the 20/26S proteasome thereby causing UPS dysfunction [43]. Moreover, mutations in the Parkin gene have also been shown to cause impairment in UPS pathway with ensuing proteolytic stress owing to abnormal protein aggregation, which might result in the inevitable death of DA neurons [44].

Oxidative Stress in PD

Oxidative stress is an alternate possibly vital pathway that could be involved in the development of PD-like pathology in the neurons. Numerous evidence from post-mortem studies revealed the involvement of oxidative stress in PD pathogenesis [28]. Oxidative stress may quicken as the disease progresses, and it is involved in a segment of the pathogenesis underlying the progressions of PD. Mitochondria are the source of Reactive oxygen species (ROS) production [45]. Defects in complex 1 of the respiratory chain has been known to cause the death of dopaminergic neurons through decreased synthesis of adenosine triphosphate (ATP) and increased production of ROS, thereby leading to oxidative DNA damage [46] consequently setting off an endless loop between mitochondrial dysfunction and oxidative stress. In addition to this, levels of both free and bound nitrotyrosine, a steady indicator of the association of Reactive nitrogen species (RNS), have been shown to be increased in the affected zones of the MPTP mouse model of PD [47]. Among the ROS-scavenging enzymes, superoxide dismutase (SOD) is frequently viewed as the first line of resistance against a ROS rise. In the post-mortem PD brains, an increase in the mitochondrial isoform of super oxide dismutase 2 (SOD2) was observed [48]. The latter observation is quite interesting since SOD2 is highly inducible in response to an excess of ROS [49]. In addition, some reports have

singled out dopamine as potentially being the primary culprit in the death of dopaminergic neurons [50]. Dopamine is an extremely reactive molecule inclined to easy oxidation. On being oxidized, it can react with several cellular components producing increased amount of ROS [51].

Mitochondrial dysfunction in PD

Mitochondria play a cardinal role in the apoptotic pathway [52]. Opening of the mitochondrial permeability transition pores occur under conditions of oxidative stress leading to the failure of the mitochondrial membrane potential. Mitochondrial dysfunction may consequently retune the threshold for the activation of apoptotic pathways. An excess in apoptosis has been shown to participate in unwarranted acute or chronic cell loss in neurodegenerative diseases. Mitochondrial dysfunction plays a key role in the pathogenesis of PD [53]. Substantial evidence has shown that sporadic and familial variants of PD have common pathways that unite at the mitochondria [54].

Transport of electrons through complexes I–IV in the inner mitochondrial membrane involves a series of coupled redox reactions, which provide the energy to create a proton gradient across the inner mitochondrial membrane. Complex I is the central gateway for electrons to enter the respiratory chain. The source of complex I deficiency in PD are not well understood. It has been advocated that mutations in complex I genes in the mitochondrial genome can cause dysfunction in complex I activity, assembly and/or stability [55]. Many studies on complex I inhibition and ROS formation have been performed with rotenone, an inhibitor of complex I that binds in proximity to the quinone-binding site [56]. The link between mitochondrial dysfunction and Parkinson's disease became evident with the discovery of MPTP in the early 1980's. MPTP has been shown to inhibit complex 1 activity thereby causing the death of DA neurons [57]. Several epidemiological studies have proposed that MPTP and other complex 1 inhibitors like the pesticides rotenone and paraquat are implicated in sporadic PD [57]. When administered MPTP and paraquat cause aggregation of α-synuclein in the non-human primates and in mice [58, 59]. In accordance with this data, some evidences have shown that mice that lack α-synuclein are resistant to the effects of MPTP, while, transgenic mice overexpressing α-synuclein show increased susceptibility [60,61]. Mitochondrial dysfunction and complex 1 deficiency have been shown to impair striatal dopamine homeostasis due to depletion in the level of ATP, thereby leading to reduced vesicular uptake of dopamine and enhanced cytosolic dopamine metabolism [62]. Many pro-apoptotic mitochondrial proteins, for example, cytochrome c and apoptosis initiating factor (AIF), and their redistribution to the cytosol and nucleus throughout neuronal cell demise in vitro and in vivo have been extensively reported [63]. Many factors are capable of triggering the release of pro-apoptotic proteins from mitochondria, including elevated Ca2+, ROS, ceramides, and other cell death proteins [63]. While much has been documented about the role of ROS, Ca2+ in PD, the role of sphingolipid metabolites like ceramides(Cer) and sphingosine-1-phosphate (S1P) in neurodegenerative diseases (like PD) is still not known.

Role of Sphingolipids in the Pathogenesis of PD

Lipids in the CNS

Lipids are gaining increasing importance with respect to their roles in the CNS. Deregulated lipid metabolism has been reported in several CNS disorders and injuries. Lipid peroxidation leading to oxidative stress has been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease [64]. Lipids encompass a large number of chemically different molecules arising from combinations of fatty acids with different backbone structures. Mammalian cells contain more than 1000-2000 lipid species. In general, lipids are classified into eight different categories. They are glycerolipids, glycerophospholipids, sphingolipids, fatty acyls, prenol lipids, sterol lipids, saccharolipids, and polyketides [65]. In particular, great strides have been made in order to understand the mechanisms by which sphingolipids regulate numerous cellular processes in the CNS.

Sphingolipids (the enigmatic class of Lipids)

Sphingolipids consists of eighteen carbon amino-alcohol backbones which are synthesized in the endoplasmic reticulum (ER) from non-sphingolipid precursors. This vast family of lipids plays important roles in membrane biology and offer many bioactive metabolites that regulate cell functions [66]. These compounds have numerous roles, such as regulating signal transduction pathways, directing protein sorting, and mediating cell-to-cell interactions and recognition functions [67, 68]. Cer and S1P are the two major sphingolipid metabolites which have diverse biological functions.

De novo synthesis of sphingolipids begins at the cytoplasmic side of the ER. It is instigated by the condensation of serine and palmitate to generate 3-keto-sphinganine catalyzed by serine palmitoyltransferase [69].3-keto-sphinganine is further reduced to sphinganine (dihydro-sphingosine, DHS) in two rapid enzymatic reactions by 3-keto-sphinganine reductase. DHS is then N-acylated by dihydroceramide synthase by means of various fatty acyl CoAs to form dihydroceramide (DHCer) which is then converted to Cer by a desaturase. Cer is later translocated from the ER to the Golgi apparatus in a non-vesicular transport approach by ceramide transport protein (CERT) [70], a protein which contains a phosphatidylinositol-4-phosphate-binding domain and a recognized catalytic domain which aids in lipid transfer. Cer and DHCer are later used up by the enzyme sphingomyelin synthase to form sphingomyelin (SM) and dihydrosphingomyelin (DH-SM) respectively [71]. Inside the Golgi lumen, GlcCers are further converted to lactosylceramides and glycosphingolipids [72]. The other major metabolite sphingosine (Sph) is formed from Cer by ceramidase-catalyzed hydrolysis. Sph can also be produced during degradation of plasma membrane glycosphingolipids and SM in the endocytic recycling pathway. Sph and DHS are usually phosphorylated by Sphingosine kinases (SphKs) to form S1P and dihydro-S1P, which are the substrates for S1P phosphatases which reside in the ER [72].

Sphks and S1P in the Brain

The brain has profuse concentration of S1P when compared to the other organs [73]. During pathological conditions, the concentration of S1P further increases [74]. There have been conflicting reports as to which one of the two Sphk isoforms mainly produces S1P in the brain. Although several reports have depicted Sphk1 to be the major isoform in the brain tissue, recent reports indicate that both the isoforms are substantially present in the CNS. This is evident from a report showing that neither of the Sphk knockdown mice displays a notable CNS phenotype. However, the double knock down of SphK1–SphK2 in mice showed a striking brain defect [75, 76]. FTY720 is a potent S1P receptor agonist that is phosphorylated *in vivo* by Sphk2 [76]. In experimental allergic encephalitis models, phosphorylated FTY720 restores nerve function by affecting the BBB and glial repair mechanism [77]. FTY720 has also been shown to be a potential therapeutic drug for multiple sclerosis and is presently in phase 3 clinical trials [78]. S1P also plays an essential role in the motility of glioblastoma cells [79].

Current evidence has shown that sphingosine kinases have the ability to modulate the production of amyloid β precursor protein by the SH-SY5Y neuroblastoma cells.

S1P receptors in the CNS

In spite of the CNS having the highest concentration of S1P receptors, not much is known about the function of S1P; S1P has been shown to promote the excitability of cultured Dorsal root ganglion (DRG) neurons which is mediated via S1P receptors. Blocking of these receptors abolished these effects [80]. Previous research has shown that nerve growth factor (NGF) prompts the translocation of SphK1 to the plasma membrane which inturn leads to the activation of S1P1 resulting in Rac activation and neurite extension [81]. S1P2 knockout mice have been shown to exhibit occasional seizure activity [82]. In addition, research has shown that S1P2 knockout mice are deaf and display a progressive loss of vestibular function [83, 84]. S1P has been shown to potentiate depolarisation-induced glutamate release in hippocampal neurons which was dependent on Sphk1 and S1P1 receptors, suggesting for its possible role in synaptic plasticity [85]. Moreover, S1P induces migration of transplanted neural stem/progenitor cells to the injury site through its receptor S1P1 in spinal cord injury [86]. S1P plays a main role in the growth and survival of oligodendrocytes [87]. The S1P receptor S1P5 is selectively expressed only in the oligodendrocytes. This receptor enhances the survival of mature oligodendrocytes by mediating the process retraction of the oligodendrocyte precursors and [88]. In addition to this, the receptor S1P1 has also been shown to be involved in the proliferation of oligodendrocyte precursors. Hence, it seems likely that both S1P1 and S1P5 function differently in the development of oligodendrocytes [89]. Astrocytes (the major type of glial cells in the CNS) have been shown to express $S1P_1$, $S1P_2$ and $S1P_3$ receptors [90]. S1P1 receptor agonists have been shown to potentiate astrocyte migration. The receptors S1P1, S1P2, S1P3, and S1P5 were all been shown to be expressed by microglia. However, S1P3 expression in the microglia was lost after 2 weeks in culture [91].

Role of Sphks and S1Ps in Neurodegenerative Disorders

Sphks and S1P play a major role in maintaining a delicate balance between neuronal survival and death. In recent years, the roles of Sphks/S1P in neurodegenerative disorders are gaining increasing importance. Disturbed sphingolipid metabolism has been reported in AD [92]. One study has shown that SphK2 is up-regulated in the brains of AD patients, via the modulation of BACE-1 activity through its metabolite S1P [93]. Furthermore, Aβ treatment of SH-SY5Y cells resulted in a strong inhibition of SphK1 activity coupled with an elevation of the ceramide/S1P rheostat [94]. Another study has revealed that SPHK1/S1P1 signaling axis plays an essential role in the proliferation of astrocytes thus protecting hippocampal neurons from kainic acid-induced neurodegeneration [95]. Furthermore, Sphk1/S1P receptor signaling has a control over the proliferation of glial cells in mice with Sandhoff disease [96]. Deletion of Sphk2 has been shown to increase the lesion size and affects neurological function in an experimental stroke model [97]. While Sphk2 has always been considered as a "villainous gene" promoting cell death, the above study throws light on the protective effect of Sphk2/S1P signaling in the brain. Changes in sphingolipid metabolism have also been reported in other neurological disorders like HIV dementia, brain ischemia, hypoxia and inflammation [98, 99]. Although the general view for Sphingolipid in neurodegeneration seems more consistent, the role of these inexplicable category of lipids in the pathogenesis of PD still remains an enigma.

S1P and Sphks in PD Pathogenesis

Den Jager in 1969 reported that Sphingomyelin accumulated inside the Lewy bodies in PD pathogenesis. Although, these studies have shown that sphingolipids could possibly play a role in PD. There has been a dearth in the information on the role of these enigmatic compounds in PD pathogenesis since then. It was only recently that emerging data on sphingolipids have shed light on the protective role of these lipids in the pathogenesis of PD. A recent study has reported that inhibition of Sphk1 in the SH-SY5Y cells reduced the cell viability and concurrently increased the reactive oxygen species (ROS) level in an *in vitro* model of PD [100]. In addition to this, our recent study has revealed that Sphk2, the second isoform of Sphks and its metabolite S1P has a potential role to play in the pathogenesis of PD by protecting the neurons from mitochondrial dysfunction induced by MPTP insult [101]. Our study has revealed the significance of Sphk2 alteration in the pathogenesis of MPTP - induced PD mouse model. This appears to be the first report to study the role of Sphk2/S1P signalling in the pathogenesis of PD. Nonetheless, the signalling mechanism through which S1P offers protection to the mitochondria still remains unknown. On this note, it would be reasonable to state that Sphks, S1P and their analogs could aid as prospective therapeutic targets in the treatment of PD. However, further studies are warranted in order to understand the underlying mechanisms by which these molecules function in order to take these studies to the next phase.

Conclusion

The remarkable ability of these simple sphingolipids to regulate numerous processes in the CNS sheds light on the fact that these lipids have a pivotal role in neuronal function. The ability for high potency signaling molecules such as S1P to protect neurons from MPTP insult appears to be firming the case for therapeutics targeting the SPHK-S1P signaling system in PD. Future, studies targeting the co-ordinated regulation of these molecules and related metabolites through transcriptomic, and lipidomic approaches will enhance our overall understanding of these inexplicable compounds.

References

1. Langston JW (2002) Parkinson's disease: current and future challenges. Neurotoxicology 23: 443-450.
2. Goetz CG1 (2011) The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med 1: a008862.
3. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J (2011) Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 26 Suppl 1: S1-58.
4. Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 991: 1-14.
5. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, et al. (2003) Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 157: 1015-1022.
6. Beitz JM (2014) Parkinson's disease: a review. Front Biosci (Schol Ed) 6: 65-74.
7. Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 : 2283-2301.
8. Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79: 368-376.
9. Rinne UK, Sonninen V, Siirtola T (1970) L-Dopa treatment in Parkinson's Disease. Eur Neurol 4: 348-369.
10. Shaw KM, Lees AJ, Stern GM (1980) The impact of treatment with levodopa on Parkinson's disease. Q J Med 49: 283-293.
11. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ (2002) Non-recognition

of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 8: 193-197.

12. Wolters ECh (2009) Non-motor extranigral signs and symptoms in Parkinson's disease. Parkinsonism Relat Disord 15 Suppl 3: S6-12.

13. Katzenschlager R, Lees AJ (2002) Treatment of Parkinson's disease: levodopa as the first choice. J Neurol 249 Suppl 2: II19-24.

14. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, et al. (2004) Levodopa and the progression of Parkinson's disease. N Engl J Med 351: 2498-2508.

15. Lang AE, Lozano AM (1998) Parkinson's disease. First of two parts. N Engl J Med 339: 1044-1053.

16. Cerasa A (2015) the motor inhibition system in Parkinson's disease with levodopa-induced dyskinesias. Movement Disorders.

17. Correia AS, Anisimov SV, Li JY, Brundin P (2005) Stem cell-based therapy for Parkinson's disease. Ann Med 37: 487-498.

18. Zecca L, Zucca FA, Albertini A, Rizzio E, Fariello RG (2006) A proposed dual role of neuromelanin in the pathogenesis of Parkinson's disease. Neurology 67: S8-11.

19. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973) Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 20: 415-455.

20. Uhl GR, Johnson PS, (1994) Neurotransmitter transporters: three important gene families for neuronal function. Journal of Experimental Biology 196: 229-236.

21. Uhl GR, Hedreen JC, Price DL (1985) Parkinson's disease: loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology 35: 1215-1218.

22. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A 95: 6469-6473.

23. Ebrahimi-Fakhari D, Wahlster L, McLean PJ (2012) Protein degradation pathways in Parkinson's disease: curse or blessing. Acta Neuropathol 124: 153-172.

24. McNaught KS, Jenner P (2001) Proteasomal function is impaired in substantia nigra in Parkinson's disease. Neurosci Lett 297: 191-194.

25. Wakabayashi K, Tanji K, Odagiri S, Miki Y, Mori F, et al. (2013) The Lewy body in Parkinson's disease and related neurodegenerative disorders. Mol Neurobiol 47: 495-508.

26. Winklhofer KF, Haass C (2010) Mitochondrial dysfunction in Parkinson's disease. Biochim Biophys Acta 1802: 29-44.

27. McNaught KS, Olanow CW, Halliwell B, Isacson O, Jenner P (2001) Failure of the ubiquitin-proteasome system in Parkinson's disease. Nat Rev Neurosci 2: 589-594.

28. Jenner P (2003) Oxidative stress in Parkinson's disease. Annals of neurology 53: S26-S38.

29. Tansey MG, Goldberg MS (2010) Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. Neurobiol Dis 37: 510-518.

30. Miklossy J, Doudet DD, Schwab C, Yu S, McGeer EG, et al. (2006) Role of ICAM-1 in persisting inflammation in Parkinson disease and MPTP monkeys. Exp Neurol 197: 275-283.

31. Nagatsu T (2000) Cytokines in Parkinson's disease, in Advances in Research on Neurodegeneration 143-151.

32. Tanse, MG, McCoy MK, Frank-Cannon TC (2007) Neuroinflammatory mechanisms in Parkinson's disease: potential environmental triggers, pathways, and targets for early therapeutic intervention. Experimental neurology 208:1-25.

33. Griffin R, Nally R, Nolan Y, McCartney Y, Linden J, et al. (2006) The age-related attenuation in long-term potentiation is associated with microglial activation. J Neurochem 99: 1263-1272.

34. Shavali S, Combs CK, Ebadi M (2006) Reactive macrophages increase oxidative stress and alpha-synuclein nitration during death of dopaminergic neuronal cells in co-culture: relevance to Parkinson's disease. Neurochemical research 31: 85-94.

35. Difazio MC, Hollingsworth Z, Young AB, Penney JB Jr (1992) Glutamate receptors in the substantia nigra of Parkinson's disease brains. Neurology 42: 402-406.

36. Olney JW, Zorumski CF, Stewart GR, Price MT, Wang GJ, et al. (1990) Excitotoxicity of L-dopa and 6-OH-dopa: implications for Parkinson's and Huntington's diseases. Exp Neurol 108: 269-272.

37. Surmeier DJ, Guzman JN, Sanchez-Padilla J, Schumacker PT (2011) The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease. Neuroscience 198: 221-231.

38. Lilienbaum A (2013) Relationship between the proteasomal system and autophagy. Int J Biochem Mol Biol 4: 1-26.

39. Ciechanover A, Brundin P (2003) The ubiquitin proteasome system in neurodegenerative diseases: sometimes the chicken, sometimes the egg. Neuron 40: 427-446.

40. Giasson BI, Lee VM (2003) Are ubiquitination pathways central to Parkinson's disease? Cell 114: 1-8.

41. McNaught KS, Olanow CW (2006) Protein aggregation in the pathogenesis of familial and sporadic Parkinson's disease. Neurobiol Aging 27: 530-545.

42. Chung KK, Zhang Y, Lim KL, Tanaka Y, Huang H, et al. (2001) Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. Nat Med 7: 1144-1150.

43. Snyder H, Mensah K, Theisler C, Lee J, Matouschek A, et al. (2003) Aggregated and monomeric alpha-synuclein bind to the S6' proteasomal protein and inhibit proteasomal function. J Biol Chem 278: 11753-11759.

44. von Coelln R, Dawson VL, Dawson TM (2004) Parkin-associated Parkinson's disease. Cell Tissue Res 318: 175-184.

45. Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417: 1-13.

46. Henchcliffe C, Beal MF (2008) Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 4: 600-609.

47. Blanchard-Fillion B, Prou D, Polydoro M, Spielberg D, Tsika E, et al. (2006) Metabolism of 3-nitrotyrosine induces apoptotic death in dopaminergic cells. J Neurosci 26: 6124-6130.

48. Bostantjopoulou S, Kyriazis G, Katsarou Z, Kiosseoglou G, Kazis A, et al. (1997) Superoxide dismutase activity in early and advanced Parkinson's disease. Funct Neurol 12: 63-68.

49. Saggu H, Cooksey J, Dexter D, Wells FR, Lees A, et al. (1989) A selective increase in particulate superoxide dismutase activity in parkinsonian substantia nigra. J Neurochem 53: 692-697.

50. Hattori N (2009) Toxic effects of dopamine metabolism in Parkinson's disease. Parkinsonism & Related Disorders 1: S35-S38.

51. Meiser J, Weindl D, Hiller K (2013) Complexity of dopamine metabolism. Cell Commun Signal 11: 34.

52. Desagher S, Martinou JC (2000) Mitochondria as the central control point of apoptosis. Trends Cell Biol 10: 369-377.

53. Exner N, Lutz AK, Haass C, Winklhofer KF (2012) Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J 31: 3038-3062.

54. Burbulla LF, Schelling C, Kato H, Rapaport D, Woitalla D, et al. (2010) Dissecting the role of the mitochondrial chaperone mortalin in Parkinson's disease: functional impact of disease-related variants on mitochondrial homeostasis. Hum Mol Genet 19: 4437-4452.

55. Parker WD Jr, Boyson SJ, Parks JK (1989) Abnormalities of the electron transport chain in idiopathic Parkinson's disease. Ann Neurol 26: 719-723.

56. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, et al. (2011) Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect 119: 866-872.

57. Dauer W, Przedborski S (2003) Parkinson's disease: mechanisms and models. Neuron 39: 889-909.

58. Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL, et al. (2002) The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. J Biol Chem 277: 1641-1644.

59. McCormack AL (2002) Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiology of disease 10: 119-127.

60. Dauer W, Kholodilov N, Vila M, Trillat AC, Goodchild R, et al. (2002) Resistance of alpha -synuclein null mice to the parkinsonian neurotoxin MPTP. Proc Natl Acad Sci U S A 99: 14524-14529.

61. Song DD (2004) Enhanced substantia nigra mitochondrial pathology in human a-synuclein transgenic mice after treatment with MPTP. Experimental neurology 186: 158-172.

62. Exner N, Lutz AK, Haass C, Winklhofer KF (2012) Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J 31: 3038-3062.

63. Fiskum G (2000) Apoptosis-related activities measured with isolated mitochondria and digitonin-permeabilized cells. Methods Enzymol 322: 222-234.

64. Reed TT (2011) Lipid peroxidation and neurodegenerative disease. Free Radic Biol Med 51: 1302-1319.

65. Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH Jr, et al. (2005) A comprehensive classification system for lipids. J Lipid Res 46: 839-861.

66. Gault CR, Obeid LM, Hannun YA (2010) An overview of sphingolipid metabolism: from synthesis to breakdown. Adv Exp Med Biol 688: 1-23.

67. Futerman AH, Hannun YA (2004) The complex life of simple sphingolipids. EMBO Rep 5: 777-782.

68. Tani M, Ito M, Igarashi Y (2007) Ceramide/sphingosine/sphingosine 1-phosphate metabolism on the cell surface and in the extracellular space. Cell Signal 19: 229-237.

69. Merrill AH Jr (2002) De novo sphingolipid biosynthesis: a necessary, but dangerous, pathway. J Biol Chem 277: 25843-25846.

70. Hanada K, Kumagai K, Yasuda S, Miura Y, Kawano M, et al. (2003) Molecular machinery for non-vesicular trafficking of ceramide. Nature 426: 803-809.

71. van Meer G, Holthuis JC (2000) Sphingolipid transport in eukaryotic cells. Biochim Biophys Acta 1486: 145-170.

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

73. Edsall LC, Spiegel S (1999) Enzymatic measurement of sphingosine 1-phosphate. Anal Biochem 272: 80-86.

74. Tosaka M, Okajima F, Hashiba Y, Saito N, Nagano T, et al. (2001) Sphingosine 1-phosphate contracts canine basilar arteries in vitro and in vivo: possible role in pathogenesis of cerebral vasospasm. Stroke 32: 2913-2919.

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

76. Meno-Tetang GM, Li H, Mis S, Pyszczynski N, Heining P, et al. (2006) Physiologically based pharmacokinetic modeling of FTY720 (2-amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) in rats after oral and intravenous doses. Drug Metab Dispos 34: 1480-1487.

77. Foster CA (2007) Brain Penetration of the Oral Immunomodulatory Drug FTY720 and Its Phosphorylation in the Central Nervous System during Experimental Autoimmune Encephalomyelitis: Consequences for Mode of Action in Multiple Sclerosis. Journal of Pharmacology and Experimental Therapeutics 323: 469-475.

78. Baumruker T, Billich A, Brinkmann V (2007) an immunomodulatory sphingolipid mimetic: translation of a novel mechanism into clinical benefit in multiple sclerosis. Expert Opinion on Investigational Drugs 16: 283-289.

79. Van Brocklyn JR, Young N, Roof R (2003) Sphingosine-1-phosphate stimulates motility and invasiveness of human glioblastoma multiforme cells. Cancer Lett 199: 53-60.

80. Zhang YH, Vasko MR, Nicol GD (2006) Intracellular sphingosine 1-phosphate mediates the increased excitability produced by nerve growth factor in rat sensory neurons. The Journal of Physiology 575: 101-113.

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

82. MacLennan AJ, Carney PR, Zhu WJ, Chaves AH, Garcia J, et al. (2001) An essential role for the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor in neuronal excitability. Eur J Neurosci 14: 203-209.

83. MacLennan AJ, Benner SJ, Andringa A, Chaves AH, Rosing JL, et al. (2006) The S1P2 sphingosine 1-phosphate receptor is essential for auditory and vestibular function. Hear Res 220: 38-48.

84. Kono M, Belyantseva IA, Skoura A, Frolenkov GI, Starost MF, et al. (2007) Deafness and stria vascularis defects in S1P2 receptor-null mice. J Biol Chem 282: 10690-10696.

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

86. Kimura A, Ohmori T, Ohkawa R, Madoiwa S, Mimuro J, 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: 115-124.

87. Yu N, Lariosa-Willingham KD, Lin FF, Webb M, Rao TS (2004) Characterization of lysophosphatidic acid and sphingosine-1-phosphate-mediated signal transduction in rat cortical oligodendrocytes. Glia 45: 17-27.

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

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

90. Rao TS (2003) Pharmacological characterization of lysophospholipid receptor signal transduction pathways in rat cerebrocortical astrocytes. Brain Research 990: 182-194.

91. Tham CS (2003) Microglial activation state and lysophospholipid acid receptor expression. International Journal of Developmental Neuroscience 21:431-443.

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

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

94. Gomez-Brouchet A, Pchejetski D, Brizuela L, Garcia V, Altié MF, et al. (2007) Critical role for sphingosine kinase-1 in regulating survival of neuroblastoma cells exposed to amyloid-beta peptide. Mol Pharmacol 72: 341-349.

95. Lee DH, Jeon BT, Jeong EA, Kim JS, Cho YW, et al. (2010) Altered expression of sphingosine kinase 1 and sphingosine-1-phosphate receptor 1 in mouse hippocampus after kainic acid treatment. Biochem Biophys Res Commun 393: 476-480.

96. Wu YP, Mizugishi K, Bektas M, Sandhoff R, Proia RL (2008) Sphingosine kinase 1/S1P receptor signaling axis controls glial proliferation in mice with Sandhoff disease. Hum Mol Genet 17: 2257-2264.

97. Pfeilschifter W (2011) Activation of sphingosine kinase 2 is an endogenous protective mechanism in cerebral ischemia. Biochemical and Biophysical Research Communications 413: 212-217.

98. Haughey NJ, Steiner J, Nath A, McArthur JC, Sacktor N, et al. (2008) Converging roles for sphingolipids and cell stress in the progression of neuro-AIDS. Front Biosci 13: 5120-5130.

99. Grin'kina NM, Karnabi EE, Damania D, Wadgaonkar S, Muslimov IA, et al. (2012) Sphingosine kinase 1 deficiency exacerbates LPS-induced neuroinflammation. PLoS One 7: e36475.

100. Pyszko J, Strosznajder JB (2014) Sphingosine kinase 1 and sphingosine-1-phosphate in oxidative stress evoked by 1-methyl-4-phenylpyridinium (MPP+) in human dopaminergic neuronal cells. Mol Neurobiol 50: 38-48.

101. Sivasubramanian M, Kanagaraj N, Dheen ST, Tay SS (2015) Sphingosine kinase 2 and sphingosine-1-phosphate promotes mitochondrial function in dopaminergic neurons of mouse model of Parkinson's disease and in MPP+ -treated MN9D cells in vitro. Neuroscience 290: 636-648.