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Mevalonate Cascade and Neurodevelopmental and Neurodegenerative Diseases: Future Targets for Therapeutic Application

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Abstract: The mevalonate cascade is a key metabolic pathway that regulates a variety of cellular functions and is thereby implicated in the pathophysiology of most brain diseases, including neurodevelopmental and neurodegenerative disorders. Emerging lines of evidence suggest that statins and Rho GTPase inhibitors are efficacious and have advantageous properties in treatment of different pathologic conditions that are relevant to the central nervous system. Beyond the original role of statins in lowering cholesterol synthesis, they have anti-inflammatory, antioxidant and modulatory effects on signaling pathways. Additionally, Rho GTPase inhibitors and statins share the mevalonate pathway as a common target of their therapeutic actions. In this review, we discuss potential mechanisms through which these drugs, via their role in the mevalonate pathway, exert their neuroprotective effects in neurodegenerative and neurodevelopmental disorders.

Keywords: Neurodegeneration, neurodevelopment, cholesterol, Rho GTPase, statins.

I. INTRODUCTION

The brain and spinal cord are the components of the central nervous system (CNS), and they comprise the highest cholesterol content in the human body, with the brain containing approximately 25% of the body’s total cholesterol [1]. In addition to cholesterol, sphingolipids and glycerophospholipids play a major role in maintaining the structure and function of cellular membranes in the CNS [2]. These amphipathic molecules, found embedded within the cellular membranes, participate in a variety of functions that include the anchoring of marker proteins and signal transduction in the CNS [3]. Cholesterol also plays a key role in the sonic hedgehog (SHH) signaling pathway [4]. Lipids act as reservoirs of cellular second messengers [5] that are important for initiating cascade events to maintain homeostasis within the cellular environment.

Next to adipose tissue, the CNS has the second highest concentration of lipids in the human body [6]. Thus, tight regulation of lipid homeostasis exists in the brain. Cholesterol in the brain is derived primarily by de novo synthesis via the mevalonate cascade within the CNS [7], because the blood-brain-barrier (BBB) prevents cholesterol uptake via lipoproteins from the peripheral circulation.

The mevalonate cascade involves a series of enzymatic reactions that begins with the condensation of three acetyl-CoA to form hydroxymethylglutaryl coenzyme A (HMG-CoA), which is converted through several steps to isopentenylpyrophosphate (IPP) [8]. IPP is important for the prenylation of molecules via farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP) and their respective transferases to produce activated small G proteins and downstream products such as cholesterol (Fig. 1). Prenylation allows for the anchoring of proteins to cell membranes and is essential to cell growth [9]. Cholesterol and its receptors are important signaling molecules for brain development during the embryonic and postnatal stages [10, 11]. A sufficient supply of cholesterol and phospholipids is needed for proper...
CNS cell development. Early human malnutrition has been shown to be detrimental to brain development [12].

Cholesterol is an important constituent of neuronal myelin and plays a role in transmission of nerve impulses. During myelination, cholesterol synthesis is at its peak [13]. In addition, other oxysterols that are involved in pro-apoptotic events, cell differentiation, and inflammation can be derived from the metabolism of cholesterol and act as the intermediates in the synthesis of bile acids and steroid hormones [14].

Regulation of the mevalonate cascade in the brain may differ from that in other organs of the body because the CNS has a unique storage system for cholesterol [15]. In the brain, cholesterol is tightly regulated between neurons and glia [16-20] including astrocytes, microglia and oligodendrocytes. The rate-limiting enzyme in the cascade is HMG-CoA reductase. This enzyme is responsible for the first committed step in cholesterol synthesis, the NADPH-dependent reduction of HMG-CoA to mevalonic acid [21, 22]. Statins are HMG-CoA reductase inhibitors [23] and they are the focus of many studies on cholesterol reduction and neuronal health (summarized in Fig. 1).

Imbalances in lipid metabolism are linked to the development of several CNS disorders [24], including Alzheimer’s disease (AD), Parkinson’s disease (PD), Niemann-Pick type c disease (NPC) [24] and Smith-Lemli-Opitz syndrome (SLOS) [25]. In addition, it is believed to contribute to acute neuronal injuries, such as stroke and brain trauma [24].

There are many mechanisms by which HMG-CoA reductase is regulated [26]. Short-term regulation exists through phosphorylation by a cAMP-activated protein kinase and dephosphorylation by a phosphatase, which allows for rapid conversion from inactive to active states, respectively [27].

Long-term regulation exists through mediating transcription of the HMG-CoA reductase gene by the binding of the sterol regulatory element binding protein (SREBP) to the sterol regulatory element (SRE) on the gene promoter [28]. Translation of mRNA provides a regulatory mechanism as well, whereby inhibition is achieved when there is an excess of one of the mevalonate cascade products, which is thought to be farnesol [29, 30], although the specific product has been disputed [31].

Negative feedback is also achieved during increased levels of sterols, in which HMG-CoA reductase undergoes a conformational change and becomes subject to sterol-induced ubiquitination and degradation by ER-associated degradation (ERAD) and proteolysis [32].

In this review, we will discuss the implications of deregulation of the mevalonate cascade in CNS, the use of statins as HMG-CoA reductase inhibitors and of Rho GTPase inhibitors to improve prognoses of CNS disorders and injuries. We also discuss the significance of the ubiquitin-proteasome system in regulation of the mevalonate pathway.

**Fig. (1). The mevalonate cascade**

Through inhibiting the rate-limiting enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase in cholesterol biosynthesis, statins prevent the conversion of HMG-CoA to mevalonate and subsequent mevalonate-intermediates. Small cytosolic G proteins Ras and RhoA are respectively activated via isoprenylation by farnesyltransferase (FTase) and geranylgeranyltransferase (GGTase), and lead to eosinophilic inflammation and inflammation cell proliferation. As another product of FPP, squalene turns out cholesterol and thus synthesize lipid raft.
Cholesterol Synthesis and the Ubiquitin-Proteasome System

The enzymes of the mevalonate pathway are proteins, the intracellular levels of which are determined by a balance in transcription, synthesis, and degradation. The major organelle regulating degradation of most of the intracellular proteins, as well as transcription of many proteins, is the proteasome. Before degradation, most proteins that are processed by the proteasome have several ubiquitin molecules added to them by an ATP-dependent process. A series of three enzymes is essential for this process: a ubiquitin activating enzyme, E1; a ubiquitin conjugating enzyme, E2; and a ubiquitin ligase E3 that has specificity for one or more substrates. The number of human ubiquitin ligases has been estimated to be between 600 and 1000 [33]. Regulation of cholesterol homeostasis requires the ubiquitin proteasome system. Jiang and Song reviewed the ubiquitin ligases that are significant in cholesterol metabolism [34]. The rate-limiting enzyme in the mevalonate pathway in the liver is HMG-CoA reductase [35]. This enzyme is targeted by statins to reduce total blood cholesterol levels and low density lipoprotein (LDL) cholesterol [36]. Statins which cross the BBB would be expected to reduce cholesterol in the brain as well [37]. Both degradation of HMG-CoA reductase and its transcription are regulated by the ubiquitin proteasome system. HMG-CoA reductase is a substrate for the ubiquitin ligase gp78 [34, 38]. It has been suggested that other ligases, including TRC8, may be involved in HMG-CoA reductase degradation [38]. Transcription of HMG-CoA reductase, and transcription of most other enzymes in the mevalonate pathway [39], is regulated by SREBP; a substrate of the ubiquitin ligase FBW7 [40]. Thus, FBW7 is important in both transcription and degradation of SREBP [40]. Previous investigators have related coupling of transcription to degradation of transcription factors in the ‘black widow’ model, in which a transcription factor is activated by monoubiquitination and subsequently tagged for degradation by polyubiquitination when no longer needed for a particular cycle of transcription (e.g., [41]). Some ubiquitin ligases bind directly to the RNA polymerase complex along with the proteasome [42]; it has been reported that FBW7 binds to SREBP at SRE binding sites on target promoters [40] (see Fig. 2). Thus, FBW7 is considered a major factor in regulating SREBP transcription factors [43]. FBW7 also plays a role in differentiation of neural stem cells, regulating the balance of astrocytes versus neurons [44].

Another substrate of gp78 is the protein ApoB-100, a component of LDL and very low density lipoproteins (VLDLs) [45]. Several substrates of gp78 unrelated to cholesterol metabolism have also been reported [46]. Inhibition of gp78 has been suggested to be a potential method of treating metabolic disease by reducing SREBP [47]. An additional enzyme in the mevalonate pathway that is regulated by the proteasome is squalene monooxygenase (SM), a substrate for the ubiquitin ligase TEB4 [34], also known as the ubiquitin ligase for type 2 deiodinase.

Liver X receptor (LXR) is a transcription factor that protects cells from reaching excessive cholesterol levels by inducing the transcription of enzymes involved in cholesterol transport and bile acid metabolism [51]. Zhao and Dahlman reported that two enzymes are inhibited by LXR in the cholesterol synthesis pathway: squalene synthase and lanosterol 14α-demethylase. LXR binds to the oxidized derivatives of cholesterol, activators of LXR. Activation is reported to contribute to IDOL-induced ubiquitination and degradation of degradation by polyubiquitination when no longer needed for a particular cycle of transcription (e.g., [41]). Some ubiquitin ligases bind directly to the RNA polymerase complex along with the proteasome [42]; it has been reported that FBW7 binds to SREBP at SRE binding sites on target promoters [40] (see Fig. 2). Thus, FBW7 is considered a major factor in regulating SREBP transcription factors [43]. FBW7 also plays a role in differentiation of neural stem cells, regulating the balance of astrocytes versus neurons [44].

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the LDL receptor [52]. LXR activation also induces the expression of IDOL [53].

Statins, which inhibit HMG-CoA, have been compared functionally to proteasome inhibitors [54]. Some of the biological actions are similar. The β-lactone form of lovastatin, which reportedly does not inhibit HMG-CoA, is a proteasome inhibitor [55]. Mevalonate, on the other hand, stimulates proteasome activity [55].

It should be noted that cholesterol does not cross the BBB. Therefore, the regulation of cholesterol in the brain is different from the regulation of circulating cholesterol. Pfrieger and Ungerer [56] have reviewed evidence that astrocytes produce cholesterol-containing lipoproteins used as a source of cholesterol by neurons of the adult brain. Thus, it is important to investigate the role of the ubiquitin ligases in the interaction of neurons and astrocytes in the regulation of the mevalonate pathway. Identifying specific ligases for critical enzymes in this pathway may provide therapeutic targets for neurodevelopmental and neurodegenerative disease.

II. BRAIN LIPOPROTEIN TRANSPORT SYSTEM

Lipoproteins

The structure of lipoproteins consists of a triglyceride and cholesteryl ester core, which is surrounded by phospholipids, a free cholesterol shell, and transport lipids in a polar environment. Apolipoproteins on the surface of lipoproteins serve as both co-factors for enzymatic reactions, and ligands for lipoprotein receptors. Plasma lipoproteins are classified into four major groups based on their size, density and apolipoprotein composition: chylomicrons, VLDLs, LDL and high density lipoproteins (HDLs) [57, 58].

Lipoproteins in the Central Nervous System

Together with the plasma, lipoproteins are found in the CNS including interstitial space and the cerebrospinal fluid (CSF). Even though lipoprotein metabolism has been well investigated in plasma, it needs to be elucidated in the brain tissue. The most recent studies of lipoproteins in the brain are concentrated on the particles in CSF [59-61]. Astrocytes are the main source of apolipoproteins. In contrast to plasma, apolipoprotein E (ApoE) is one of the most abundant lipoproteins in the brain, and it is mainly produced by astrocytes, microglia, and to a lesser extent, by neurons. Cholesterol is transported to neurons through ApoE receptors, which are members of the low density lipoprotein receptor (LDLR) gene family [59] (Fig. 3).

ApoE was primarily identified because of its function in lipoprotein metabolism and cardiovascular diseases. It is a 35-kDa glycoprotein that is found in chylomicrons and intermediate density lipoproteins (IDLs), and has an important role in catabolism of triglyceride-rich lipoproteins via several receptors in the human liver [62]. One of the key roles for ApoE is transportation of lipoproteins in the bloodstream, where it plays a role in the delivery and clearance of plasma cholesterol. Human ApoE contains 299 amino acids and three alternative isoforms: E2 (Cys112Cys158), E3 (Cys112Arg158) and E4 (Arg112Arg158). Single changes in the amino acid sequence can alter the functionality among ApoE isoforms, including their relative affinities for both LDL receptors and lipoprotein subtypes. As a consequence of changes in only one or two amino acids at positions 112 and 158 of these allelic forms, ApoE4 is the strongest known genetic risk factor for heart disease, as well as for AD. The role of ApoE-containing lipoproteins in the brain has been the target of much research, based on the wide array of literature available. Recently, three essential roles have been

Fig. (3). Cholesterol transport and homeostasis in the brain.
Cholesterol (Chol) in neurons is predominantly synthesized in astrocytes. Through the LRP1/LDLR receptors, neurons take up cholesterol as apoE-containing cholesterol form (LpE). The excess cholesterol is converted to 24-hydroxycholesterol (24-OHC) and released to the blood. In this way, it will cross the blood-brain barrier (BBB) and delivered to the liver.
introduced for astrocyte-derived ApoE-containing lipoproteins: (i) LRP1-dependent cellular uptake in amyloid plaque deposition; (ii) interaction with the LDLR super family of proteins that are stabilized on the surface of neurons, to improve neuronal survival and axonal growth; and (iii) transfer of phospholipids and cholesterol through ATP-binding cassette (ABC) transporters (ABCG1 and ABCA1 interactions) [63].

Lipoprotein Transport System

Lipid transportation in the brain has not been thoroughly investigated. Compared to other tissues, the amount of cholesterol in the brain is high. Lipid homeostasis, specifically cholesterol homeostasis, is essential for the environment surrounding the neurons. ABCA1 and ABCG1, which are expressed in the CNS, play vital roles in the transfer of phospholipids and cholesterol to ApoE. Lipoproteins, which are derived from astrocytes and contain ApoE, can bind and internalize through receptors from the LDL receptor superfamily, which are located on the surface of neurons. Besides having an endocytosis role, several of these receptors serve as signaling receptors in neurons and trigger signals for axonal growth and survival in neurons [19].

This pathway is better served by ApoE3 than ApoE4. The main function of glial lipoproteins is to transport lipids from glia to neurons, via the LDLR family members, to protect and adapt the network of membranes to the synaptic networks of a dendritic tree. Neurons can synthesize cholesterol via the HMG-CoA reductase pathway, but ApoE-containing glial lipoproteins are important for keeping the balance between supply and clearance. Nascent glial lipoproteins, which are secreted as discs, acquire free cholesterol (FC) from ABCA1 and ABCG1. Intermediate particles that are intended to pass via the CSF first obtain extra phospholipid (PL) and a cholesteryl ester (CE) core. As a result, astrocytes play a crucial part in the nervous system and are vital for synaptic transmission and neuronal excitability [57].

Differences Between Lipoproteins in Brain Compared with Plasma

Cholesterol transport and its homeostasis in the peripheral circulation is different from the CNS. The CNS is responsible for producing only the HDLs, because HDLs are the only proteins that are able to cross the BBB. ApoE and ApoJ, the most common apolipoproteins in the brain, are generally synthesized by astrocytes, and they are found on HDL. Even though the BBB facilitates transport of smaller circulating HDL to the brain, it is believed that a large percentage of the ApoE- and ApoJ-containing lipoproteins that are present in the CSF originated from the surrounding astrocytes [64].

Cholesterol transporters, such as Niemann-Pick type C protein 1 and cholesterol 24(S) hydroxylase, are essential for cholesterol metabolism in the brain, and surprisingly changes in the plasma cholesterol concentration or loss of function of ABCA1, scavenger receptor class B type 1 (SR-B1 also known as Scarb1), LDLR, or ApoE or ApoA-I, have no effect on sterol turnover in the brain [64].

III. NEURAL TUBE FORMATION

Formation of neural tubes, which are primary components of the CNS, is the result of a neurulation process that occurs in the early embryogenesis stages [65]. Initiation and progression involve ectoderm thickening and neural plate formation, in which a flat sheet of neuroepithelial cells roll up and form the neural tube [66, 67]. There are four basic protein morphogenetic signals participating in neural tube wall proliferation and differentiation, including wingless-int protein (WNT), hedgehog (HH), bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) [68]. The patterning of neural tube relies on centralized factor of sonic hedgehog (SHH) and dorsaling factor of BMP, which are produced from the floor plate and the roof plate, respectively [69, 70].

In the process of cerebral and cerebellar corticogenesis, neurons migrate from their place of origin in the ventricular zone (VZ) in the cerebrum and the VZ and rhombic lip (RL) in the cerebellum to their final destination in the cortex [71-73]. Similar to all the developmental processes that are controlled by genes, corticogenesis is an event that is highly dependent on Reelin signaling cascades. Reelin is an extracellular glycoprotein with a high molecular weight (~400 kDa) and is produced by Cajal-Retzius cells in the cerebrum embryonic marginal zone and the cerebellum external germinal zone [71, 74]. It binds to two basic receptors that are generated in migrating neurons: apolipoprotein E receptor 2 (ApoER2) and VLDL receptor (VLDLR). Disabled homolog 1 (Dab1) is an intracellular adaptor protein that is phosphorylated by Reelin at a later stage. Phosphorylated Dab1 then induces other signaling molecules such as the Crk family adaptor proteins [75].

In the cerebral cortex, in the absence of the Reelin gene, neurons are not positioned according to age, because the newly born cortical plate (CP) neurons attack the marginal zone, and neurons born at later stages migrate toward the older ones and settle below them. In the cerebellum, in absence of the Reelin gene, Purkinje cells cannot migrate properly to form the Purkinje cell layer [76].

Role of Cholesterol in Neural Development

Despite the lack of intensive studies on the role of cholesterol in CNS, it is likely that cholesterol is an important limiting factor in the process of synaptogenesis, restricting the formation of synaptic structures [77]. During the process of active myelination, production of cholesterol reaches the highest amount in oligodendrocytes and finally reduces to 90% when the myelination is complete, while the rate of cholesterol biosynthesis in adult brains stays higher in astrocytes compared to the other types of neurons [78]. Cellular expansion, which occurs during neural development of an embryo, is highly dependent on a sufficient amount of cholesterol and phospholipids. A checkpoint is provided during evolution to limit or expand the amount of cholesterol. Biosynthesis of cholesterol in the embryo starts at the stage of preimplantation and reaches its highest rate in the first few postnatal weeks [10, 79]. Cholesterol is imported by synapses from astrocytes via the use of lipoprotein and their receptors, and is possibly distributed at synapses in different locations, including synaptic vesicle membranes, presynaptic
and postsynaptic zones, extra synaptic pools, and at the edge of synapses to facilitate axonal transportation, cell adhesion and exocytic organization [77].

Role of SHH in Embryonic and Postnatal Neural Development Related to the Mevalonate/Cholesterol Pathway

The Hedgehog protein family is essential during the process of neural development and embryonic patterning. This signaling glycoprotein is secreted from axial mesodermal cells of the notochord and the floor plate in the neural tube, and triggers neural subtype differentiation. Drosophila Hedgehog (HH) and murine Sonic Hedgehog (SHH) proteins are two important members of the Hedgehog family [74]. Two kinds of proteins are produced as a result of SHH proteolytic cleavage. The N-terminal protein (N-SHH) is 19 kDa and facilitates the signaling activity and C-terminal protein (C-SHH), which is 25 kDa, and is involved with protease activity [80]. During the autocatalytic processing of SHH, the catalytic domain of C-terminal protein (HH-C) is cleaved and a cholesterol moiety is added to the N-terminal (HH-N) side of the protein. During neural development of an embryo, hydrophobic addition of cholesterol has a limiting role in Hedgehog signaling and is considered to be an essential factor in appropriate spatial patterning [79].

Two genes responsible for encoding the transmembrane proteins are necessary for SHH signaling pathway: the Patched (PTC) gene, a 12-transmembrane protein producing that acts as a negative regulator, and Smoothened (SMO) gene, a seven-transmembrane protein, which is a positive inducer for SHH signaling. Both proteins together generate a receptor complex. When the HH is not present, PTC stops the transduction by SMO and when cholesterol activates it, HH protein binds to PTC, and the receptor complex undergoes a conformational change so that SMO can freely signal and facilitate gene transcription [81].

SHH that is modified by cholesterol can diffuse through the tissues and is 15-times more effective compared with unmodified protein [82]. In addition, auto-introduced modification of C-SHH by cholesterol affects SHH signaling by controlling its production and mediating the long-term activity through covalent coupling [80]. SHH is capable of inhibiting patched-mediated apoptosis by eliminating the GLI repressor (GLI3R), to suppress cell death [83].

Fibroblast growth factors (FGFs) FGF8/17/18 and WNT1 are signaling molecules that are regulated by the isthmic organizer (IsO). WNT1 and FGF8 are two necessary components for development of the hindbrain and midbrain. WNT1 is expressed in the caudal midbrain region and FGF8 is limited to the rostral rhombomere1. Regulation of FGF8 is influenced by GLI3 that is activated by SHH signaling [83, 84].

Role of BMP in Embryonic and Postnatal Neural Development Related to the Mevalonate/Cholesterol Pathway

BMPs are important members of the transforming growth factor (TGF) family, and they are essential in embryological development of different organs such as the brain, heart, eyes and kidney [85]. During the developmental process, BMPs are present as signaling factors that facilitate mesoderm in-duction, dorsoventral patterning of the limb, odontogenesis and patterning of skeletal structure, and they mediate the differentiation of mesenchymal stem cells to both osteoblasts and chondrocytes [85, 86]. BMP4 and BMP7 expression occurs in the epidermal ectoderm of the neural plate and is responsible for the dorsalizing patterning of the epidermal ectoderm [87]. A diet rich in cholesterol revealed a reduction in factors that induce bone formation, such as BMPs, TGF-β and Wnt. In addition, it is speculated that free cholesterol limits the formation of the bones through the BMP2 pathway [88].

IV. NEURODEGENERATIVE DISEASE

a. Alzheimer’s Disease and the Mevalonate Pathway

Ageing is accompanied by a marked increase in the prevalence of neurological diseases such as dementia [89, 90]. Statins, beyond their original role as HMG-CoA reductase inhibitors, also show effectiveness in treatment of a variety of neurodegenerative disorders including AD [91], PD [92, 93], multiple sclerosis [94], cerebral ischemic stroke and vascular dementia [95].

Statins are widely prescribed medications that are relatively safe to use for people with cardiovascular disorders [96]. Research increasingly indicates that statins not only have therapeutic effects in cardiovascular disorders, but also are beneficial against development of dementia [91, 97]. The mechanism underlying the effects of statins in AD remains elusive. However, there is evidence suggesting that advantageous effects of statins may be associated with their ability to reduce lipids, oxidative stress and β-amyloid, as well as ApoE levels that result in the mitigation of the neurodegenerative and neuro-inflammatory processes. Statins have also been reported to enhance endothelial nitric oxide synthase (eNOS) activity, which increases cerebral blood flow, alleviating cerebrovascular diseases [95, 98, 99].

Simvastatin and lovastatin have been shown to exert protective effects against development of AD through lowering the levels of cholesterol and amyloid beta plaques (Aβ42 and Aβ40), indicating the impact of lipids in the pathophysiology of AD [100, 101]. Moreover, investigations on the amyloid precursor protein (APP) in transgenic mice revealed that these drugs decrease cholesterol, decrease the APP and ameliorate the disease severity [96].

b. Huntington Disease

Huntington disease (HD) is a neurodegenerative disease that is characterized by a triad of signs and symptoms comprising of motor, cognitive and emotional disorders [Reviewed in 102]. HD is characterized by more than 35 CAG repeats in the huntingtin gene (HTT) that codes polyQ in the huntingtin protein [103]. The age of onset inversely correlates with the number of CAG repeats, with full onset shown with 40 or more CAG repeats [102, 103]. Although clinical symptoms of movement disorders such as rigidity, tremor, chorea and dystonia are similar in HD patients who have HD phenocopies, no CAG repeats are found in the genetic test results, but rather C9orf72 repeats are the most common genetic indicator [104].
The earliest pathogenic indicator proposed for HD is misfolding and aggregation of mutant HTT (mHTT), which affects cell metabolism and results in cell death [105, 106]. These aggregates can sequester heterologous proteins, making them inactive [106], or produce toxic depolarizing channels by penetrating cell membranes [106]. In addition, aggregates can have different conformations, some of which are less toxic but some can spread in a prion-like manner [105]. Histopathology of HD features striatum-specific neuron loss, attributed to the increased cytotoxicity of mHTT after binding to Rhes, a striatum-specific protein [107]. Other studies propose additional mechanisms involved in the pathophysiology of HD. Several proteins have been identified that interact with huntingtin interacting proteins (HIPs) and modulate mutant HTT toxicity, including Rho GTPase signaling components, which potentially interfere with HD mechanisms [108].

Another clinical characteristic of HD patients is energy deficiency [109], which may be the result of defective energy metabolism. Dysfunction of brown fatty tissue has been proposed as the main cause of this feature [109], although dysfunction of other energy metabolism components such as coenzyme Q [110] or glycolysis deficiency [111] may also be responsible for this defect.

Lin et al. found that peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a key component of energy metabolism that regulates mitochondrial function and has a strong link with CNS activity [112]. Studies revealed that PGC-1α and its target genes have a decreased expression in the striatum of a mouse model of HD [113, 114]. The correlation of a single nucleotide polymorphism of PGC-1α gene with the age of onset of symptoms in HD patients represents profound effects of this gene in HD pathogenesis [115-117].

There is currently no cure for HD, only treatment to manage the symptoms of the disease [Reviewed in 102]. Atorvastatin has been shown to be effective in upregulation of PGC-1α [118] and may represent a new approach to treatment of HD. The ubiquitin ligase for PGC-1α has been identified as the protein RNF2 [119]. This protein has not been targeted in attempts to upregulate PGC-1α.

c. Parkinson’s Disease

Definition of Parkinson’s Disease

Parkinson’s disease (PD) is a debilitating progressive neurodegenerative disorder that is the second most common age-related disease after AD. PD has a high prevalence in industrialized countries [120, 121] and a strong correlation with age. Worldwide, it has a 1% prevalence rate in people over the age of 50, and that number increases to 4% in those over the age of 65 [120, 122-125]. Factors affecting the occurrence of disease include sex, genetic and ethnical factors, geographical location, and an unfavorable combination of genetic background and lifestyle increases the risk of disease occurrence by two- to seven-fold [126]. PD is classified as a terminal disease that greatly influences a patient’s life expectancy. The mortality rate among PD patients is three-times higher than that of the general population [127]. PD is characterized by a tetrad of progressively debilitating clinical traits, including bradykinesia, resting tremor, muscle rigidity, postural instability and impaired motor function [126, 128, 129]. In addition to motor symptoms, PD patients also develop non-motor symptoms (NMS), including depression, autonomic dysfunction, sensory abnormalities and cognitive decline [130]. Although the pathologic causes of motor dysfunction in PD (i.e. dopaminergic system impairment following dephosphination of substantia nigra (SN) and cytoplasmic Lewy bodies (LBs), which stain positive for α-synuclein (α-syn)) are well understood, the causes of NMS in PD are unclear and this remains an area of active research [131-133].

Pathogenesis of Parkinson’s Disease

The neurodegeneration associated with PD is correlated with the selective death of different types of neurons. In the initial stages, loss of dopaminergic neurons located in the substantia nigra pars compacta (SNc), in basal nuclei, and in the mesencephalic tectum is observed [120, 126, 134-136]. The decrease in dopamine levels in the putamen and corpus striatum followed by neuronal cell death in the SN leads to the emergence of motor symptoms described above. Clinical studies have demonstrated that motor symptoms emerge when there is death of 60–80% of dopaminergic neurons of the SNc and an 80% decrease in the level of dopamine in the putamen [126, 135, 136]. In PD, the aggregation of LBs and Lewy neurites consisting of proteins, fats and polysaccharides, with radiating filaments (including α-syn, neurofilaments, ubiquitin, parkin, and synphilin) is observed in the substantia innominata [120, 137]. Lewy bodies play a neuroprotective role in PD and other neurodegenerative diseases such as multiple systemic atrophy and AD, as well as in healthy elderly persons [138, 139]. By contrast, Lewy body aggregation in presence of SN neuronal death is considered to be a neuropathological feature of PD. Another feature of neurodegeneration in this disease is the development of gliosis, leading to activation of microglia in the corpus striatum and in the SN [126, 140]. Other mechanisms described as potential underlying predisposing factors include oxidative stress, associated with the damage of dopaminergic neurons in PD and MPP, which can exert neurotoxicity on dopaminergic neurons through opening the mitochondrial permeability transition pore (MPTP) and altering mitochondrial function [141]. Furthermore, disrupted catabolism of unwanted, misfolded, or mutated proteins in LBs and Lewy neurites, most notably α-syn, leads to cellular aggregation and neuronal death [120, 142-145]. In addition, alterations in the inflammatory cytokines interleukin-1α (IL-1α), IL-1β and tumor necrosis factor-α (TNF-α) in the brain, and inducible nitric oxide synthase (iNOS), were discovered in activated microglia; excitotoxicity also appeared to be another pathogenic mechanism for neuronal cell death in PD [120, 146]. Consequently, although microglia activation and inflammatory changes were thought to be the two major causes of neuronal destruction, there is evidence of more general systemic inflammatory reactions that are involved in the pathogenesis of PD. Because the neuropathological profile of PD is widespread, it is assumed that the degenerative processes can also occur in many nondopaminergic nuclei, including the locus coeruleus, pedunculopontine nucleus, reticular formation of the brainstem, raphe nucleus, dorsal motor nucleus of the vagal nerve, in olfactory bulbs, basal
Meynert nucleus, amygdala, parasympathetic and sympathetic postganglionic neurons, hippocampus, and the cerebral cortices. Degeneration of these structures by LBs leads to occurrence of non-motor clinical symptoms [147]. Motor and non-motor symptoms of PD slowly manifest following pathological changes in the dorsal motor neurons of the vagal nerve, medulla oblangata, mesencephalic tectum and the olfactory apparatus, leading to olfactory disorders, constipation and sleep disturbances [148]. Typical signs of PD develop when the dopamine level is low in the putamen and the corpus striatum, following the death of SN neurons and the limbic system. Ultimately, disturbance of the neocortex causes memory loss and cognitive disorders [149, 150].

Despite the previously-mentioned neuropathological causes of PD, the putative role of genetic factors in the pathogenesis of PD has long been discussed, and epigenetic modifications, influenced by lifestyle, environmental factors and genetic mutations, are vital players in the development and regeneration of the disease [151]. Investigation of genetic factors that affect the pathogenesis of PD revealed that mutations in at least 17 autosomal dominant and autosomal recessive genes are underlying causes of disease variations [152]. These mutations include α-syn triplication and mutation, parkin, ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), parkin, phosphatase and tensin homolog-inducible kinase 1 (PINK1), DJ-1, glucocerebrosidase (GBA) and leucine-rich repeat kinase 2 (LRRK2) [120]. While further studying the role of LBs in the pathogenesis of PD, researchers discovered an important role for the protein α-syn, a major component of the radiating filaments. They found that accumulation of α-syn in LBs and Lewy neurites is a pathologic hallmark of PD. This neurodegeneration, as a result of dominant mutations in the α-syn gene (SNCA), suggests a distinct role for α-syn in the pathogenesis of PD [153-156].

New Approaches to Pathogenesis of Parkinson’s Disease

In the past two decades, significant advances have been made in determining the mechanism behind PD pathogenesis, with respect to the death of nigral dopaminergic neurons. Although available therapeutics include those aimed at slowing the worsening of motor symptoms [157-161], new treatment strategies under investigation aim to stop or slow the development of the disease process. Currently, mevalonic acid, the substrate for cholesterol and isoprenoid ubiquinone, is being studied to determine its effect on pathogenic factors associated with PD. This phenomenon was first introduced in 1995, when Muller et al. suggested a link between the effects of lovastatin, an HMG-Co A inhibitor, and PD in two patients [162]. They demonstrated that an inborn error of mevalonate kinase resulted in decreased synthesis of cholesterol and coenzyme Q10, and led to the presence of a neurological disorder [162, 163], suggesting that cholesterol synthesis is impaired in PD [164]. This means that statins may show neuroprotective effects in neurodegenerative disorders such as stroke, AD and PD. Some studies show that statins attenuate α-syn aggregation in vitro in transfected neurons [93, 165, 166], while other studies indicate that statins exert their neuroprotective effects via a variety of mechanisms including lowering cholesterol, anti-inflammatory responses, anti-thrombotic effects, suppression of intercellular adhesion molecule-1 (ICAM-1), modification of cognition related receptors, reduction of β-amyloid production and serum Apo E levels, and augmentation of endothelial nitric oxide synthase (eNOS) along with an increase in cerebral perfusion [165-168]. The most important mechanism in statin neuroprotectivity may be attenuation of the enzyme complex (decreased complex-I and III activity), which represents a key step in the progression of neurodegenerative disorders. Oxidative stress-induced damage (nitrite concentration, lipid peroxidation, and depleted glutathione peroxidase activity) and neuroinflammation (enhanced TNF-α and IL-6 levels) are also augmented via statin treatment. Neuroinflammation is strongly associated with infiltration of inflammatory cells into the CNS [165, 169-171]. Therefore, mevalonate can reverse the inhibition of T-cells that is caused by statins [172], while statins, in contrast to mevalonate, can reduce leukocyte infiltration, the surface expression of chemokine receptors on leukocytes and the level of circulating chemokines [173, 174]. Statins down-regulate mRNA expression of NADPH oxidase (Nox1) and inhibit Rac1 membrane translocation in a mevalonate-dependent manner, suppressing O2- generation and thereby exerting their neuroprotective effect against oxidative stress [175, 176]. Selley and Xu et al. emphasized the ability of simvastatin to completely reverse the impaired striatal dopamine activity and the synthesis of nitrosylated free radicals, resulting in neuroprotection [166, 175, 177]. They established the preventative activity of simvastatin on striatal dopamine depletion by reducing the release of pro-inflammatory mediators from microglia, through blocking of the mevalonate pathway. In addition, the typical symptoms of neurodegeneration that occur, followed by an excessive amount of mevalonate in mevalonate kinase deficiency (MKD, the second enzyme of the mevalonate pathway), are linked to both the intrinsic apoptosis pathway (caspase-3 and -9; triggered by mitochondrial damage) and to pyroptosis (caspase-1) in combination with neuroinflammation. This leads to impairment of neuronal-supporting and anti-inflammatory molecule production (e.g. TGF-β and IL-10), and to activation of IL-1β, an important pro-inflammatory cytokine [178-180]. In addition, mitochondrial dysfunction, which causes release of reactive oxygen species (ROS) and other oxidative molecules, is at the center of neurodegenerative disorders, marked by accumulation of mevalonate. The role of the mevalonate pathway in the pathogenesis of neurodegenerative disease is crucial and controversial. In a study by Lim et al., it was reported that lanosterol, the downstream metabolite of mevalonate, may have neuroprotective activity by causing mitochondrial uncoupling via reduction in superoxide species. This is one possible explanation for improved neuronal survival [181-183].

In addition to statins, peroxisome proliferator-activated receptor-alpha (PPAR-α) agonists present an interesting pharmacological target to prevent or slow the development of PD. There is some evidence that suggests that inflammation and oxidative stress processes are probably modulated by PPAR-α [184-192], which is involved in the suppression of apoptosis [193]. Mevalonate, as a component of an indirect pathway, enhances PPAR-α’s sensitivity to natural
ligands that leads to its activation, and in turn results in neuroprotective effects in PD [192, 194].

Despite the significant progress made in diagnosing PD, there are currently no distinct biomarkers for PD. Therefore, biomarkers are needed to reliably detect slowing of pathological progression. The majority of available neuroprotective agents (i.e. dopamine agonists) are used to attenuate the symptomatic effects of PD via blocking mitochondrial damage, subsequently causing neuronal death. In addition, statins are observed to be neuroprotective drugs, which can prevent progression of neurodegenerative disease through various mechanisms. There are currently no studies that have fully clarified the neuroprotective mechanism of statins via blockage of the mevalonate pathway in neurodegenerative disorders such as PD. However, recent studies have emphasized the potential of statins in contributing to the treatment of PD. Further research is necessary to explain the complete mechanism of statins, because it is thought that general neuroprotective effects cannot be solely attributed to their inhibitory effect on the mevalonate pathway and subsequent reduction in cholesterol synthesis.

d. Niemann-Pick C

Niemann-Pick disease refers to a group of inherited disorders related to lipid metabolism [195]. The incidence of NPC disease is currently about 1/120,000 live births [195]. This disorder is divided into four main types, based on the genetic cause, and the signs and symptoms: Niemann-Pick disease type A (characterized by hepatosplenomegaly, failure to thrive and progressive deterioration of the nervous system), Niemann-Pick disease type B (non-neurological type), Niemann-Pick disease type C and type D (deficiency of NPC-1 protein) [196].

Acid sphingomyelinase deficiencies result from SMPD1 mutations including types A, B and intermediate forms and also from NPC, which has an abnormality in trafficking of endocytosed cholesterol because of mutations in the NPC1 on chromosome 18 or NPC2 on chromosome 14 mutations [197]. In addition, another type, NPC-D, is no longer justified as a distinct entity. From a practical standpoint, patients diagnosed with NP disease should be classified based on the subgroups acid sphingomyelinas incapacity or type C [198].

NPC disease is one of the most complex and complicated diseases that is caused by defect in lysosomal storage [199]. This disorder is caused by a mutation in the NPC1 (95% of familiar form) or NPC2 gene, although the exact functions of these two genes are still unknown. The first neurological signs differ with age of onset: delay in developmental motor milestones (early infantile period), gait problems, clumsiness, cataplexy, school problems (late infantile and juvenile period) and ataxia that may occur frequently following initial psychiatric disturbances (adult form) [198]. The NPC disease progression is related to the onset of neurological symptoms and patient age [198].

The relationship between NPC and cholesterol was first observed in 1985 by Pentchev et al. [200]. Cholesterol balance is important in maintaining homeostasis in the CNS. The discovery that lipids other than cholesterol also accumulated in late endosomes/lysosomes has led to the debate over whether aberrant trafficking of cholesterol or of other lipids is the primary cause of the NPC phenotype [201]. The exact pathogenic mechanism that links the aggregation of intracellular cholesterol with cell death in NPC disease in both the CNS and the liver is currently unknown [202].

Through the concurrent action of at least two distinct proteins: NPC1 and NPC2, cholesterol is effluxed from late endosomes/lysosomes. Normally, lipids are transported from lysosomes to the endoplasmic reticulum (ER) and plasma membrane, but in NPC, this transport is disrupted and results in lipid accumulation [198]. The aggregation of these lipids leads to neurodegeneration in a process that is not fully understood.

The current therapeutic approaches to treat patients with NPC involve sphingolipid reduction therapy (miglustat) such targeting the sterol pathway using cyclodextrins and neurosteroids drugs, and also by pathway modification using curcumin, apoptosis inhibitors, antioxidants, histone deacetylase inhibitors, stem cell and gene therapy [203].

e. Smith-Lemli-Opitz Syndrome

SLOS was first defined in 1964 as an inborn error of the mevalonate pathway with a deficiency in 7-dehydrocholesterol reductase (DHCR7) activity that leads to decreased cholesterol synthesis and elevation of its precursors, 7-dehydrocholesterol (7DHC) and 8-dehydrocholesterol (8DHC) [204, 205]. The syndrome is characterized by prenatal symptoms such as growth retardation, microcephaly, a spectrum of intellectual disability and multiple malformations of the face, toes, dactyls, heart and external genitalia [206, 207]. SLOS patients show behavioral anomalies including self-injury, irritability, disturbed sleep cycle, autistic behavior and feeding problems [206-210]. Recently, some other phenotypic anomalies reported for SLOS include ulnar hypoplasia, congenital pulmonary adenomatoid malformation, vertebral segmentation anomalies, holomyelia, fused lungs, gastrochisis, hypothalamic hamartoma and hippocampal hypoplasia, which differentiate SLOS from Pallister-Hall syndrome [211, 212]. Although the physical defects in these patients are adversely associated with DHCR7 activity, their behavioral features show no significant association [Reviewed in 213]. Nowaczyk et al. reported some individuals with established DHCR7 mutations and increased 7DHC serum levels had a normal intelligence quotient (IQ) when tested [213]. In contrast, Freeman et al. showed that subtype classification of challenging behavior in SLOS patients was associated with cholesterol synthesis defects [214].

Clinical diagnosis of SLOS can be made using 7DHC measurement in neonate serum [215], cultured fibroblasts, amniocytes or amniotic fluid and in the case of borderline 7DHC levels, skin fibroblasts or amniocytes can be cultured in cholesterol-free media and sterol measurement is performed [213, 216]. Measurement of unconjugated estriol, beta-human chorionic gonadotropin (hCG) and alphafetoprotein on the maternal serum is an established test for prenatal diagnosis of SLOS [217]. Low concentration of these biochemical parameters in the 15-20 weeks of gestation can suggest prenatal SLOS [217]. For diagnosis of SLOS in the first trimester of gestation, cholesterol levels and the 7DHC assay in chorionic villus can be tested [216].
Tsukahara et al. reported that SLOS is most prevalent in north and central Europe, and is rare in Asia and Africa [218]. The exact molecular mechanism of SLOS pathogenesis is not yet known. It is suspected that total sterol deficiency in combination with toxic effects of accumulated 7DHC and other 7DHC-derived oxysterols may be the cause [219-221]. Cholesterol has several critical biological roles, including being a major component of SHH signaling [222], which affects organ development. The simplest explanation for observed malformations in SLOS patients is the inactivation of SHH pathway that results from cholesterol deficiency [223].

Cholesterol is also a rudimentary component of lipid rafts and caveoleae [224] that plays an important role in signal transduction [225, 226] and cell response to ligands such as serotonin or histamine receptors, the receptors for which are localized in caveoleae [227, 228]. Accumulation of 7DHC in the caveoleae in SLOS patients used as a surrogate for cholesterol can result in disturbed cell signaling [229]. Cholesterol is a basic member of the cellular membrane along with myelin, and its deficiency can significantly affect neural function and neuroplasticity [230-232]. Recent studies show that neurons are ten-fold more susceptible to 7DHC and its oxysterol metabolite accumulation, as well as to the subsequent differentiation and arborization compared with glias, especially in midbrain and cortical neurons [233].

Protein expression in brain tissue of mutated Dhcr7 mice was compared with normal mice, and mutant mice showed an increased phosphorylation level of coflin-1, a known factor that depolymerizes actin and has a critical role in regulation of formation of dendrites and axons [234]. This elevation in coflin-1 phosphorylation is a result of enhanced Rho GTPase activation, which is a consequence of Dhcr7 mutation, and results in disturbance in axon and dendrite function [234].

A high cholesterol content of the CNS reveals the pathological mechanism of behavioral and intellectual phenotypes in SLOS patients and suggests that cholesterol supplementation in combination with cholesterol antioxidants and cholesterol pathway inhibitors will benefit these patients.

f. Brain Stroke

Cerebrovascular diseases cause heavy economic and spiritual burdens, and have a high associated morbidity, lethality and disability rate. Among these diseases, ischemic stroke is the most common type of cerebral injury (80% of all cerebrovascular disease) [235]. Many neuroprotective agents are currently available, but the outcomes are not yet satisfactory. Patients who survive a stroke usually continue to have permanent physiological or psychological disorders, such as hemiplegia, post stroke depression and cognitive impairments. The first aim of therapeutic strategies is to inhibit neuronal injury, specifically focused on reduction of grey matter damage [236]. However, the impact of white matter on brain function after stroke remains an open field of investigation. The purpose of this section is to provide an overview of the research on white matter injury (WMI) and associated challenges in stroke prognosis.

White Matter and Ischemic Stroke

White matter is primarily composed of myelinated axons and supporting oligodendrocytes, astrocytes, microglia and blood vessels. Oligodendrocytes are the cell type that is responsible for myelinating CNS axons. Oligodendrocyte precursor cells (OPCs) are the major source of myelinating oligodendrocytes during development and they comprise about 2-9% of the cell population in the adult CNS [237, 238]. OPCs in the CNS are usually characterized as unipotent, but they still have a multipotent signature. Certain extracellular signals can cause OPCs to revert to their pluripotent state, and generate cells of various lineages [239-241]. OPCs proliferate and migrate to generate oligodendrocytes and myelinate the entire CNS during postnatal life. The OPCs express the proteoglycan NG2 and platelet-derived growth factor receptor a [240-242], and have been called NG2-expressing OPCs [238], synantocytes [243] or polydendrocytes [244].

The primary white matter disease is multiple sclerosis. White matter can also be affected by acute conditions, including hypoxia and ischemia, brain and spinal cord trauma [245-247]. In white matter, arteries are long, thin and without collateral circulation. The unique structure of white matter makes it vulnerable to invasion by hematogenous inflammatory cells [248]. White matter is therefore at more risk of serious vascular events.

OPCs are no less vulnerable than neurons to ischemia. It has been demonstrated that oligodendrocytic metabolism is the risk factor for OPC pathology. OPCs require extraordinary metabolic support to maintain myelin lipid synthesis initiation. Uncoupling oxygen consumption in OPCs leads to accumulation of toxic byproducts such as hydrogen peroxide and ROS [249]. Oligodendrocytes and OPCs have the largest intracellular stores of iron [250], but with a low glutathione content, they control the susceptibility of oligodendroglial precursors to oxidative stress [250, 251].

Excitotoxicity is considered to be another major mechanism that is involved in OPC vulnerability. Oligodendrocytes and their precursors both express the three main types of ionotropic glutamate receptors: a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainite receptors, which are located predominantly on the cell body, and N-methyl-D-aspartic acid (NMDA) receptors, which are clustered on the myelinating processes [252, 253]. These ionotropic glutamate receptors are located in OPC processes and adult myelin, where the limited intracellular space could allow a large, toxic increase in intracellular ion concentrations. The over activation of AMPA/kainate and NMDA receptors mediate calcium ion influx, leading to dysregulation of calcium homeostasis. Moreover, glutamate-induced OPC death is related to increased production of ROS and release of pro-apoptotic factors. Glutamate and ROS can exacerbate each other’s neurotoxic effects because of their relationships with the cysteine/glutamate exchange system [252, 253].

The importance of ischemic WMI in oligodendrocyte loss remains to be further elucidated. At stroke onset, energy metabolism uncoupling and excitotoxicity are key events. Complex ischemic cascades and pathological progression at the sub-acute and chronic stages should also be taken in to
consideration. Ischemic myelin injury and oligodendrocyte loss may trigger endogenous attempts at regeneration. With disease progression, it is possible that remyelination failure eventually occur because of impaired survival, proliferation and maturation of OPCs. Although white matter repair has broad clinical implications for functional recovery, far less is known about precisely harnessing the potential of OPCs to yield effective regenerative strategies in myelin-mediated diseases.

**Clinical Manifestations After Ischemic White Matter Injury**

WMI accounts for up to 25% of all stroke subtypes [254, 255]. The risk of ischemic WMI increases with age but may also affect younger adults [256]. Composed of nerve fibers and myelin, white matter connects one region to another and traffics communication going into and out of grey matter. Ischemic WMI damages the nerve fibers belonging to major ascending or descending cortical-spinal pathways, and therefore has symptoms that parallel cognitive impairment and mental abnormality. Individuals who have ischemic WMI may develop psychiatric and psychological disorders such as mental hyper- or hypo-activity and schizophrenia. Ischemic WMI is a complex disease that sometimes has clinical symptoms and signs that are often atypical and hard to recognize [257]. The brain relies on an adequate supply of oxygen and nutrients through blood flow for optimal functioning [258]. Depending on the location and volume of the brain damage, a single stroke can be enough to cause dementia [259]. Approximately 10% of people develop vascular dementia (VaD) after their first stroke [260]. The risk of dementia increases with the number of strokes or transient ischemic attacks (TIAs) that occur, and after the second stroke, the risk of dementia rises to 30% [261]. Over time, even a minor ischemic stroke or TIA will cause damage and subsequent cognitive impairment.

White matter lesions have been implicated in patients’ susceptibility to cognitive disorders. The incidence of white matter lesions is 100% in VaD patients [262]. The diagnostic accuracy of using white matter lesions for VaD is 88% and specificity is approximately 95% [263]. Cognitive disorders are closely related to the region and the degree of white matter lesions [264, 265]. The lesions may evolve over time by expansion of existing lesions, which correlate with the evolution of the cognitive impairment [266]. The resulting brain tissue damage can be detected as lacunes and white matter hyper-intensities on T2-weighted magnetic resonance imaging [267].

Cognitive deficits, on the other hand, may manifest in many different ways. The main features of cognitive deficits are a decline in mental activity speed and executive functions [268] and dysnesia, which is characterized by a significant reduction in short-term memory and declining orientation and calculation [269, 270]. Cognitive impairment may also be mild, and can develop into various types of mental abnormalities [268]. The mental abnormalities in patients after stroke often include post-stroke depression, post-stroke anxiety, major depressive disorder, fear, delusion, hallucination, delirium, autism, manic depression, personality disturbance, abnormal behavior, somniphathy, nyctohemeral rhythm inver-

**Mechanisms of Ischemic White Matter Injury**

Although increasing evidence suggests that the structural and functional changes in white matter contribute to cognitive impairment and dementia, the mechanism of myelinating oligodendrocytes in patients with cognitive deficits after stroke has been only partially explored. Strokes acutely induce mature oligodendrocyte damage, leading to loss of myelin, which is associated with neurological alterations. WMI can be far more complex because white matter progenitor biology plays a central role. At the disease onset, myelin injury and oligodendrocyte loss may trigger endogenous attempts at regeneration. After stroke onset, there is a significant increase in generation of OPCs and some become mature oligodendrocytes. However, with disease progression, remyelination failure may eventually occur because of impaired OPC survival, proliferation and maturation. OPCs recognize ischemic injury that is similar to neurons, such as excitotoxicity, acidosis, electrolyte imbalance, oxidative or nitrite stress, inflammation and apoptosis. OPC injuries disturb white matter homeostasis, and therefore grey matter injury compared to white matter injury has distinguishing features.

**a. Energy Metabolism and Oxidative Stress**

Compared to grey matter, white matter has a higher rate of aerobic glycolysis. Lactate is produced constitutively mainly by astrocytes to support white matter metabolism and function. Lactate is transported across cell membranes by monocarboxylate transporters (MCT) that are present in white matter axons and glia. Astrocytes express mainly MCT4, which are effective in exporting lactate. Lactate enters axons via MCT2 and sustains their function by producing ATP via oxidative phosphorylation. Lactate is taken up by oligodendrocytes and their myelin sheath via MCT1, and utilized for lipid metabolism and myelin synthesis. MCT1 is also a transporter from oligodendroglia to axons. It has been reported that MCT1-regulated lactate exported from oligodendrocytes is a critical component of the local energy supply to axons, and disruption of this transport leads to axon dysfunction and ultimately neuron degeneration [273, 274]. Oligodendrocytes show the highest metabolic rate among all brain cells, to produce and maintain a high volume of membranes and many psychological activities. Cell respiration in oligodendrocytes has been reported to be twice as high as in neurons [275]. These cells are vulnerable to ischemia, and their sensitivity varies with each developmental stage. Coinciding with the metabolic demand, oligodendrocytes at their precursor stage are the most sensitive to oxidative stress and inflammatory injury. OPCs require an extraordinarily high energy supply to differentiate into myelinating oligodendrocytes and synthesize myelin lipids. Therefore, the tolerance for energy failure during OPCs maturation is low. A mild episode of ischemic attack could be fatal. In a worst-case scenario, repeated episodes of minor ischemic attacks can eventually exhaust the OPC pool and disrupt intrinsic reparative capacities.
b. Excitotoxicity

Oligodendrocyte excitotoxicity injury is a major component of brain injury. Under ischemic conditions, oligodendrocyte death induced by activation of AMPA and kainate receptors depends on the intensity and duration of the excitotoxic insult. Prolonged activation of glutamate receptors result in a cytosolic Ca\(^{2+}\) surge, which can be worsened by the activation of voltage-gated calcium channels (VGCC) and the reversal of the Na\(^+/Ca\(^{2+}\) exchanger [276]. Destabilization of Zn\(^{2+}\) homeostasis also participates in glutamate excitotoxicity injury to oligodendrocytes [277]. The accumulation and sequestration of calcium within mitochondria, eventually leads to cell death by apoptosis or necrosis.

ATP is another potent endogenous toxin [278]. Metabolic stress causes ATP release from glial cells, which leads to a surge in the extracellular ATP concentration [279]. It can activate ionotropic P2X and metabotropic P2Y purinoreceptors, which are expressed by oligodendrocytes. P2X receptors consist of P2X1-7 subunits that are most permeable to Ca\(^{2+}\) ions [280, 281]. The sustained ATP-mediated toxicity to oligodendrocytes mainly via P2X7 receptors induces oligodendrocyte death, myelin damage and WMI.

c. Glial Interaction

Within the neurovascular unit, different cell types interact closely for coordinated brain function. OPCs are known to comprise an endogenous pool for replacement of oligodendrocytes throughout the brain. Alteration of glial interactions may be a key factor influencing OPC survival after stroke. It is proposed that a decline in trophic support from damaged astrocytes throughout the brain. Alteration of glial interactions comprise an endogenous pool for replacement of oligodendrocyte death induced by activation of AMPA and kainate receptors mainly via P2X7 receptors induces oligodendrocyte death, myelin damage and WMI.

Protective Strategies of Ischemic White Matter Injury

The absence of extracellular Ca\(^{2+}\) or blocking Ca\(^{2+}\) entry improves white matter function in young, but not older, animals [284]. The inhibition of NMDA receptors worsens the outcome of ischemia in aging animals [285]. These results indicate the importance of WMI treatment. The VGCC antagonist has no protective effect on early premyelinated axons, but it protects oligodendrocyte processes by blocking the NMDA-type glutamate receptor [286]. Pretreatment of focal ischemia in a rat model using the AMPA antagonist NBQX for 40 minutes was previously shown to reduce neuronal damage, but not the number of tau-positive oligodendrocytes in subcortical white matter [287]. Treating the rat middle cerebral artery with SPD 502, another AMPA antagonist, for three hours significantly reduced ischemia in oligodendrocytes [288]. Protective agents are related to factors such as age, biological characteristics of injury region and medicinal property. Because neurotransmitter-mediated damage and oxidative stress are the main pathogenesis of ischemic WMI, therapeutic candidates for oligodendrocytes can be divided into several types, including AMPA antagonists, NMDA antagonists, P2X7 antagonist, ATP degrader, adenosine receptor antagonists and antioxidants [289]. Some medicines may potentially be used to treat WMI. Beta lactam antibiotics are potent activators of glutamate transporter expression [290]. Tetracyclines protect oligodendrocytes and white matter [291], and topiramate and memantine may be protective against ischemic WMI.

Statins, as the most representative inhibitor in the mevalonate pathway or the HMG-CoA reductase pathway, acts on the rate-limiting step in the pathway by which HMG-CoA is converted to mevalonate. Statins reduce the production of cholesterol, thereby modifying dyslipidemia, decreasing other by-products of the mevalonate pathway that involve the synthesis of isoprenoids such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate, and increasing low density lipoprotein cholesterol (LDL-C) receptors and uptake. They improve endothelial function including up-regulation of eNOS and inhibition of iNOS, plaque stabilization, anti-thrombosis, attenuation of inflammatory cytokine responses and antioxidant effects [292]. Based on the multi-factorial beneficial mechanisms, the protective effect of statins following stroke was first shown by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study [293], and increasing amounts of evidence demonstrated that statins reduce the risk in primary and secondary ischemic stroke prevention and therapy beyond what would be anticipated [294-296].

However, conclusions on the association between statin use and WMI are less consistent and sometimes contradictory. The Cardiovascular Health Study observed the association of statin use with changes of WMIs on serial MRI scans and found no significant differences in the evolution of WMIs between statin-treated and non-statin-treated groups [297]. In the subgroup analysis of the VITAmins TO Prevent Stroke (VITATOPS) MRI sub-study, statin use was related to less progression of WMI and less cognitive decline in subjects with severe WMI at baseline [298, 299]. Altogether, future larger randomized studies will be needed to explore the role of statins in WMI.

Summary and Outlook

Stroke is often induced by WMI. After ischemic WMI, cognitive and mental disorders are major clinical manifestations with oligodendrocyte-related changes, which are not specific to any psychiatric impairment. Despite white and gray matter sharing common mechanisms in ischemic stroke, protection from WMI has its own characteristics, including maturity, age and damage regions dependence. Because white and gray matters are both important to maintain integrity of neurological function after stroke, the idea of “whole brain protection” should be established.

IV. STATINS AND NEURODEGENERATIVE DISORDERS

Statins are cholesterol-lowering drugs that competitively inhibit the rate-limiting step in cholesterol biosynthesis, which is catalyzed by HMG-CoA reductase. In the first steps of the mevalonate pathway, conversion of HMG-CoA to mevalonic acid is blocked by statins [300-302]. Following
cholesterol synthesis in the liver, the production of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) and LDL is activated by statins, leading to a decrease in blood LDL cholesterol levels at a range from 20% to 55% [303-306], and subsequently, a decrease in the occurrence of vascular diseases including cardiovascular morbidity and mortality [307-315]. Statins possess protective properties, which encourage physicians to widely prescribe the drugs to combat vascular disorders.

On the other hand, strong evidence indicates that statins have various mechanisms, indicating that they have cholesterol metabolism-independent effects as well as simple lipid-lowering effects [302]. Most of the pleiotropic effects of statins are secondary to their inhibitory activity on isoprenoid intermediate synthesis in the mevalonate pathway [307, 315-317]. The neuroprotective effects of statins occur via these various mechanisms. Statins have been used to slow the development, and in the management, of neurodegenerative disorders such as PD, AD and stroke. Statins may also be beneficial in treatment of multiple sclerosis [174, 318-320]. Studies showed that the neuroprotection is exerted via a variety of mechanisms including lowering cholesterol, anti-inflammatory responses, anti-thrombotic effects, suppression of intracellular adhesion molecule-1 (ICAM-1), reduction of β-amyloid production and serum ApoE levels, modification of cognition related receptors, and augmentation of eNOS expression along with an increase in cerebral perfusion [166-168]. Statins are also thought to be anti-inflammatory compounds because they increase production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and tumor growth factor (TGF-β), and decrease synthesis of the pro-inflammatory cytokines IL-1β and TNF-α [178-180]. In summary, research has shown that statins activate a general neuroprotective mechanism against neuronal cell death.

**Pharmacology of Statins**

There are two categories of statins based on their origin: fungus-derived (e.g. lovastatin, simvastatin, mevastatin and pravastatin) and synthetic (e.g. atorvastatin, cerivastatin, fluvastatin, pitavastatin and rosuvastatin) statins. Statins are mostly taken up by the liver and they circulate systemically bound to plasma proteins. The liver, where cholesterol synthesis occurs, is the main target of the compounds. Statins have two formulations: active drug and prodrug (simvastatin and lovastatin), which is metabolized to active drug [302, 321, 322].

The most common side effects of statins are gastrointestinal symptoms, myopathy, hepatotoxicity, peripheral neuropathy and skin rash [323]. Animal experiments and human trials demonstrated that the lipophilic statins, simvastatin and lovastatin, can cross the BBB [302, 324-326]. However, there has been no consistent significant difference in the neuroprotective properties of lipophilic and lipobohophic statins.

**How do Statins Activate Neuroprotective Signaling Pathways?**

Some of the neuroprotective effects of statins, such as enhancement of resistance to excitotoxicity, are associated with cholesterol via blockage of HMGCR, which can be reversed by addition of mevalonate or cholesterol [302, 327]. Cholesterol-independent activity of statins also plays various roles in neuroprotection. Statins stimulate neurogenesis and synaptogenesis after brain injury, and promote the release and expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). In addition, statins indirectly activate the protein kinase B (PKB/Akt) and NF-kB signaling cascade via an increase in TNF-receptor 2 expression [328, 329]. Statins activate PKB/Akt, glycogen synthetase kinase 3β (GSK-3β), Rho-associated kinase (ROCK) and PTEN, and inhibit PKB/Akt, a negative regulator [330-332]. An additional mechanism that has been suggested for neuroprotective action of statins is activation of the Ras-ERK (extracellular-signal-regulated kinase) signaling cascade [333].

**Statins and Alzheimer’s Disease**

Intra- and extracellular deposition of amyloid-β peptide and hyperphosphorylated tau-protein occurs in AD pathogenesis, and the mechanism of statins neuroprotection occurs via blocking cholesterol synthesis and reduction in amyloid-β formation [334, 335]. Post-mortem investigations showed no difference in the number of amyloid plaques between patients who had or had not used statins [336, 337]. However, Li et al. (2007) reported that tau-deposits were reduced after statin consumption. These findings did not restrict the protective effects of statins in AD to their influence on the pathological markers because clinical trials have shown that statins may improve the function in AD without a decrease in amyloid-β levels. Consequently, statins can slow the rate of AD progression, although they are unable to prevent AD [302, 334, 335].

**Statins and Parkinson’s Disease**

Recent studies showed that statins might decrease the probable occurrence of PD. Despite controversial reports suggesting that statins increase the risk of developing PD, other clinical studies have emphasized the reduction in the incidence of PD after statin administration. In PD, statins protect dopaminergic neurons against neurodegeneration and decrease dopamine levels in the substantia nigra. Several studies suggested that statins attenuate α-syn, which is included in LBs, and in vitro aggregation in transfected neurons [93, 126, 166]. However, other studies have indicated that statins exert their neuroprotective effects via a variety of mechanisms including suppression of oxidative stress damage by reduction in the associated markers and depletion of radical scavenging enzymes. The neuroinflammation process is also a target for statins via enhancement of anti-inflammatory cytokines such as TNF-α and IL-6, an increase in lipid peroxidation and nitrite concentration, and a depletion in glutathione peroxidase activity [169-171]. In contrast, statins lower cholesterol and ubiquinone levels by blocking the mevalonate pathway, leading to the development of PD [338, 339]. Therefore, more research is necessary to clearly determine the neuroprotective effects of statins in PD.

**Statins and Multiple Sclerosis**

Multiple sclerosis is an autoimmune disease that may be a new target for statin therapy. The drugs exert their immunomodulatory effects via blocking the mevalonate pathway and reducing the downstream metabolite production, and by
inhibition of geranyleranlylation of Rho GTPase, which subsequently deactivates Rho kinase [174, 340]. They also potentiate neuroprotection by improving myelination in neurons. Researchers demonstrated that statins in combination with drugs used for treatment of MS, such as glatiramer acetate, interferon-β and rolipram, have a more suppressive effect on development of multiple sclerosis [341-343]. Therefore, statins may be added to future therapeutic protocols to treat patients with multiple sclerosis.

Statins and Stroke

There is a distinct relationship between statins and a low incidence of vascular attacks including stroke. The risk of ischemic and non-hemorrhagic stroke was reduced after statin administration [300, 301]. Based on the anti-thrombotic and anti-atherosclerotic effects of statins on the cardiac and cerebral vasculature, neuroprotective activity of these drugs on neuronal ischemic damage and cell death is examined. It has also been reported that lesion size and the degenerative neuronal function shortly after brain ischemia could be decreased with statin treatment [344-346]. However, neuroprotective properties of statins in ischemic attack and stroke are not fully understood.

Beneficial properties of statins against neurodegenerative disorders in humans are correlated with the results found in experimental trials. Statins have been shown to have neuroprotective effects, and are useful drugs that could be beneficial in diseases such as AD, PD, multiple sclerosis and stroke. These effects are caused by characteristics of statins, such as improvement in blood flow, immunomodulatory effects and reduction of oxidative damage. The neuroprotection is mediated by inhibitory activity of statins on the mevalonate pathway and production of isoprenoids, and under some conditions it is cholesterol-independent. Further research is required to determine the mechanisms underlying neuroprotection by statins, which can be cholesterol-dependent and -independent. In addition, the role of statins in combination therapy of neurodegenerative diseases is still unclear. Future experiments will present more useful information on the protective roles of these valuable drugs in a variety of neurodegeneration-based disorders.

V. SMALL RHO GTPASE INHIBITORS AND NEURODEGENERATIVE DISEASES

The Rho GTPases are small proteins (21-25 kDa) that belong to the Ras super family [347]. Rho GTPases are found in eukaryotic organisms ranging from yeast to mammals [347]. This group consists of different proteins including Rho, Rac1, Cdc42 and RhoA, which have been well studied and characterized. Each Rho protein affects numerous downstream proteins that are usually called effectors. Over 60 targets of the three common Rho GTPases have been found [348]. The wide range of Rho GTPase functions are determined by the effector proteins, with which they interact. Rho-associated kinases (Rock1 and Rock2 or Rocks), which are effectors of Rho GTPases, are important intracellular signaling proteins and control a wide variety of cellular functions such as cell movement, cell proliferation, organelle development, cytoskeleton dynamics, transcriptional and other common cellular functions [349-351]. Rock usually switches between the GTP-bound and GDP-bound forms to perform its functions in the cells. These proteins are activated via guanine nucleotide exchange factors (GEFs) that instantly replace GDP with GTP [350, 352]. The effectors bind to, and are activated by, the GTP-bound form of the Rocks and they then affect downstream targets and regulate other cellular functions [353] (Fig. 4).

Rocks are well characterized and play important roles in different cellular functions, especially in neuronal architecture and cytokinesis. Various studies have also shown that Rocks are directly involved in many neurodegenerative disorders including spinal cord injury (SCI), AD and HD. Thus, inhibition of Rocks could be beneficial for treatment of some incurable human diseases [354].

SCI is a type of neurological illness that results in major, temporary or permanent changes in the function of the spinal cord. The Rock pathway influences SCI pathophysiology [355, 356]. Several investigations have shown that inhibition of Rock can effectively stimulate the axon regeneration and recovery of hindlimb function leading to an improvement of symptoms [357, 358].

AD is a chronic neurodegenerative disease of the brain that leads to irreversible loss of neurons and behavioral disabilities. The symptoms gradually worsen, from short-term memory loss to intellectual problems [359]. The prevalence of AD has been significantly increasing worldwide. There is no adequate treatment to stop AD progression. However, interference in the Rho/Rock pathway by some Rock inhibitors such as Y27632 and using non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the prevalence of AD. Involvement of the Rho/Rock pathway in producing amyloid β (Aβ42), the main component of amyloid plaques in the brain of Alzheimer’s patients, shows the important role of the Rock inhibitors in the treatment of AD [360]. Herskowitz et al. reported that Rock inhibitors can reduce the level of Aβ42 through independent mechanisms [361]. In addition to Y27632, other Rock inhibitors such as hydroxyfasudil have been shown to improve learning and working memory [362]. Recently, it has been documented that dual inhibition of Rho kinase (Rock) and NADPH oxidase (Nox) could be more effective in the treatment of progressive neurological diseases such as AD [363]. Thus, Rock inhibitors present many advantages to AD patients.

The involvement of Rho/Rock pathway has been investigated in other important neurodegenerative disorders such as PD, HD and amyotrophic lateral sclerosis (ALS), and it is now believed that Rock inhibitors can control the prevalence of these diseases.

PD is a neurological disorder with progressive loss of dopamine-producing nerve cells in the substantia nigra. Symptoms such as muscle rigidity, tremors and change in speech and mobility gradually develop [364]. Recent studies have suggested that Rock inhibitors may promote neuroprotective survival cascades in dopaminergic neurons and provide new therapeutic strategies for PD [365]. Among various Rock inhibitors, Y27623 has been studied in the treatment of PD and its beneficial effects have been demonstrated. However, more selective Rock inhibitors are needed to increase the efficiency of patient treatment [366].
In addition, it has been shown that the Rock inhibitor Y27623 functionally curbs the aggregation of Huntingtin protein leading to improvement of HD symptoms. It blocks the phosphorylation of profilin and maintains profilin in an active form [367]. HD is an inherited neurodegenerative disease with mental and behavioral symptoms, usually beginning between 35 and 44 years of age. The disease is caused by a specific protein called Huntingtin. The accumulation of Huntingtin protein slowly destroys neurons through unknown mechanisms [368]. Inhibition of the Rho/Rock pathway by Rock II siRNA also prevents neuronal death induced by polyQ-Huntingtin [369].

ALS is a fatal disease that involves the death of both upper and lower motor neurons. The cause is unknown in 90% of patients, while it is inherited in the remaining 10% of patients. There is no effective therapy to prevent ALS progression [370]. However, Takata et al. indicated that fasudil might be effective in the treatment of ALS patients. Fasudil suppresses the Rho/Rock pathway and thereby reduces the phosphorylation of phosphatase and tensin homolog (PTEN), resulting in the inhibition of neuronal death and symptom progression [371].

Thus, the Rho/Rock pathway plays a key role in neurodegenerative disorders, and inhibition of the pathway can be a potent healing strategy in the treatment of diverse neurological diseases. Despite these advantages, Rock inhibitors have certain disadvantages such as toxicity, side effects, withdrawal phenomenon and resistance that should be considered in the future studies.

VI. FUTURE PROSPECTIVE AND DIRECTIONS

Statins and agents that interact with the Rho GTPase signaling pathway showed promising therapeutic and protective properties in neurodegenerative and neurodevelopmental disorders, and the important role of the mevalonate cascade as a shared target of these therapeutics support the contribution of this pathway to the pathobiology of these brain diseases. Future studies are required to determine the underlying mechanisms through which these classes of drugs exert their effects. Because immune-inflammatory signaling and oxidative challenge are the main contributors to pathogenesis in the majority of neurological diseases, the modulatory impact of these drugs may be associated with controlling the production of triggering factors for immune-inflammatory signaling. Mevalonate cascade deregulation correlates with overproduction of oxidized cholesterol and other oxidized products that are considered to be damaged associated molecular patterns (DAMPs). Because DAMPs are endogenous ligands for activation of the innate immune system components such as toll-like receptors, investigating whether statins
or Rho GTPase inhibitors may inhibit immune-inflammatory signaling activation by controlling the generation of oxidized cholesterol is unknown. Also, protective effects of these drugs may be associated with controlling ROS formation. Massive ROS production under neurodegenerative conditions is now considered to induce inflammasome formation in the brain. Inhibition of NOD-like receptor activation by controlling ROS formation or improving mitochondrial dysfunction by these agents may account for the therapeutic effects of statins and Rho GTPase inhibitors.

VI. CONCLUSIONS

Multiple etiologies are thought to be involved in pathology of neurodegenerative and neurodevelopmental disorders, and the mevalonate pathway is an important therapeutic target for treating or at least improving the outcomes of such disorders. Additionally, statins and Rho GTPase inhibitors are pharmacological agents that have effects beyond their original role, and are able to use a variety of mechanisms that have preventive effects on progression of these neurological disorders, in part, by modulation of the mevalonate pathway.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain-barrier</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>Hydroxymethylglutaryl coenzyme A</td>
</tr>
<tr>
<td>IPP</td>
<td>Isopentenylpyrophosphate</td>
</tr>
<tr>
<td>FPP</td>
<td>Farnesylpyrophosphate</td>
</tr>
<tr>
<td>GGPP</td>
<td>Geranylgeranylpyrophosphate</td>
</tr>
<tr>
<td>SREBP</td>
<td>Sterol regulatory element binding protein</td>
</tr>
<tr>
<td>SRE</td>
<td>Sterol regulatory element</td>
</tr>
<tr>
<td>ERAD</td>
<td>ER-associated degradation</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>IDOL</td>
<td>Ligase inducible degrader of the LDL receptor</td>
</tr>
<tr>
<td>LXR</td>
<td>Liver X receptor</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low density lipoproteins</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoproteins</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>LDLR</td>
<td>Low density lipoprotein receptor</td>
</tr>
<tr>
<td>IDLs</td>
<td>Intermediate density lipoproteins</td>
</tr>
<tr>
<td>ABC transporters</td>
<td>ATP-binding cassette transporters</td>
</tr>
<tr>
<td>FC</td>
<td>Free cholesterol</td>
</tr>
<tr>
<td>PL</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>CE</td>
<td>Cholesteryl ester</td>
</tr>
<tr>
<td>SR-B1, also known as,</td>
<td></td>
</tr>
<tr>
<td>Scarb1</td>
<td>Scavenger receptor class B type I</td>
</tr>
<tr>
<td>WNT</td>
<td>Wingless-int protein family</td>
</tr>
<tr>
<td>HH</td>
<td>Hedgehog family</td>
</tr>
<tr>
<td>BMP</td>
<td>Bone morphogenetic protein family</td>
</tr>
<tr>
<td>FGF</td>
<td>Fibroblast growth factor family</td>
</tr>
<tr>
<td>SHH</td>
<td>Sonic hedgehog</td>
</tr>
<tr>
<td>VZ</td>
<td>Ventricular zone</td>
</tr>
<tr>
<td>RL</td>
<td>Rhombic lip</td>
</tr>
<tr>
<td>Dab1</td>
<td>Disabled homolog 1</td>
</tr>
<tr>
<td>CP</td>
<td>Cortical plate</td>
</tr>
<tr>
<td>Ptc</td>
<td>Patched</td>
</tr>
<tr>
<td>SMO</td>
<td>Smoothened</td>
</tr>
<tr>
<td>IsO</td>
<td>Isthmic organizer</td>
</tr>
<tr>
<td>TGF</td>
<td>Transforming growth factor</td>
</tr>
<tr>
<td>eNOS</td>
<td>Endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid precursor protein</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington disease</td>
</tr>
<tr>
<td>HTT</td>
<td>Huntingtin</td>
</tr>
<tr>
<td>HIPs</td>
<td>Huntingtin interacting proteins</td>
</tr>
<tr>
<td>PGC-1alpha</td>
<td>Peroxisome proliferator-activated receptor gamma coactivator 1-alpha</td>
</tr>
<tr>
<td>NMS</td>
<td>Develop non-motor symptoms</td>
</tr>
<tr>
<td>SN</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td>LB</td>
<td>Lewy body</td>
</tr>
<tr>
<td>SNc</td>
<td>Substantia nigra pars compacta</td>
</tr>
<tr>
<td>MPTP</td>
<td>Mitochondrial permeability transition pore</td>
</tr>
<tr>
<td>IL-1α</td>
<td>Interleukin-1α</td>
</tr>
<tr>
<td>IL-1b</td>
<td>Interleukin-1b</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor-α</td>
</tr>
<tr>
<td>iNOS</td>
<td>Inducible nitric oxide synthase</td>
</tr>
<tr>
<td>UCH-L1</td>
<td>Ubiquitin carboxyl-terminal hydrolase L1</td>
</tr>
<tr>
<td>PINK1</td>
<td>Phosphatase and tensin homolog-inducible kinase1</td>
</tr>
<tr>
<td>LRRK2</td>
<td>Leucine-rich repeat kinase 2</td>
</tr>
<tr>
<td>GBA</td>
<td>Glucocerebrosidase</td>
</tr>
<tr>
<td>α-syn</td>
<td>α-synuclein protein</td>
</tr>
<tr>
<td>SNCA</td>
<td>α-syn gene</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Intercellular adhesion molecule-1</td>
</tr>
<tr>
<td>Nox1</td>
<td>NADPH oxidase</td>
</tr>
<tr>
<td>MKD</td>
<td>Mevalonate kinase deficiency</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
</tbody>
</table>
PPAR-α = Peroxisome proliferator-activated receptor-alpha
SMPD = Acid sphingomyelinase deficiencies
ER = Endoplasmic reticulum
SLOS = Smith-Lemli-Opitz syndrome
DHCR7 = 7-dehydrocholesterol reductase
7DHC = 7-dehydrocholesterol
8DHC = 8-dehydrocholesterol
IQ = Intelligence quotient
hCG = Beta-human chorionic gonadotropin
WMI = White matter injury
OPCs = Oligodendrocyte precursor cells
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
NMDA = N-methyl-D-aspartic acid
VaD = Vascular dementia
TIA = Transient ischemic attack
MCT = Monocarboxylate transporters
VGCC = Voltage-gated calcium channels
SPARCL = Stroke prevention by aggressive reduction in cholesterol levels
HMGCR = 3-hydroxy-3-methylglutaryl-CoA reductase
BDNF = Brain-derived neurotrophic factor
PKB/Akt = Protein kinase B
GSK-3β = Glycogen synthetase kinase 3β
ROCK = Rho-associated kinase
GEFs = Guanine nucleotide exchange factors
NSAIDs = Non-steroidal anti-inflammatory drugs
Nox = NADPH oxidase
ALS = Amyotrophic lateral sclerosis
PTEN = Phosphatase and tensin homolog
DAMPs = Damaged associated molecular patterns

REFERENCES

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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and impairs serotonergic (5-HT2A) and histaminergic (H1) responses in bovine airway smooth muscle: role of Rho-kinase. Canadian journal of physiology and pharmacology, 2009, 87, 180-95.


