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REVIEW

Dopaminergic Axons: Key Recitalists in Parkinson's Disease

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Abstract
Parkinson's disease (PD) is associated with dopamine depletion in the striatum owing to the selective and progressive loss of the nigrostriatal dopaminergic neurons, which results in motor dysfunction and secondary clinical manifestations. The dopamine level in the striatum is preserved because of the innervation of the substantia nigra (SN) dopaminergic neurons into it. Therefore, protection of the SN neurons is crucial for maintaining the dopamine level in the striatum and for ensuring the desired motor coordination. Several strategies have been devised to protect the degenerating dopaminergic neurons or to restore the dopamine levels for treating PD. Most of the methods focus exclusively on preventing cell body death in the neurons. Although advances have been made in understanding the disease, the search for disease-modifying drugs is an ongoing process. The present review describes the evidence from studies involving patients with PD as well as PD models that axon terminals are highly vulnerable to exogenous and endogenous insults and degenerate at the early stage of the disease. Impairment of mitochondrial dynamics, Ca^{2+} homeostasis, axonal transport, and loss of plasticity of axon terminals appear before the neuronal degeneration in PD. Furthermore, distortion of synaptic morphology and reduction of postsynaptic dendritic spines are the neuropathological hallmarks of early-stage disease. Thus, the review proposes a shift in focus from discerning the mechanism of neuronal cell body loss and targeting it to an entirely different approach of preventing axonal degeneration. The review also suggests appropriate strategies to prevent the loss of synaptic terminals, which could induce regrowth of the axon and its auxiliary fibers and might offer relief from the symptomatic features of PD.

Keywords Parkinson's disease · Axon degeneration · Mitochondrial dynamics · Synaptic homeostasis · Ca^{2+}

Introduction

Parkinson's disease (PD) is a basal ganglia disorder caused by progressive and selective degeneration of the neurons. This degeneration consequently depletes the dopamine levels in the striatum, which results in motor dysfunction and loss of cognitive functions in late-stage PD. Dopamine is a neurotransmitter that regulates the fine motor activities, higher cognitive functions, and feelings of pleasure and rewards. Moreover, dopamine is the metabolic precursor of norepinephrine, another crucial neurotransmitter in the brain. Dopamine is also involved in controlling synaptic transmission, axonal excitability, and dendritic integration [1]. This catecholamine is metabolized and stored in the specialized tyrosine hydroxylase (TH)-positive nerve cells, the dopaminergic neurons. A set of identically derived dopaminergic projections forms a dopaminergic pathway, and each pathway innervates into a specific region of the brain. The mammalian brain consists of various major and minor dopaminergic pathways [1, 2]. Among the 10 different pathways, only four are prominent. The nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways are the key pathways, and in PD pathology, the degeneration selectively occurs in the nigrostriatal system. The soma or cell bodies of the nigrostriatal dopaminergic neurons are embedded in the substantia nigra (SN), and the axons are innervated into the striatum. Thus, the idiopathic loss of SN neurons depletes the striatal dopamine level.

Numerous studies on genetics, post-mortem human brain, and animal and cellular models have revealed the role of redundant proteins, damaged mitochondria, apoptosis,

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Silymarin Protects Against Impaired Autophagy Associated with 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Induced Parkinsonism

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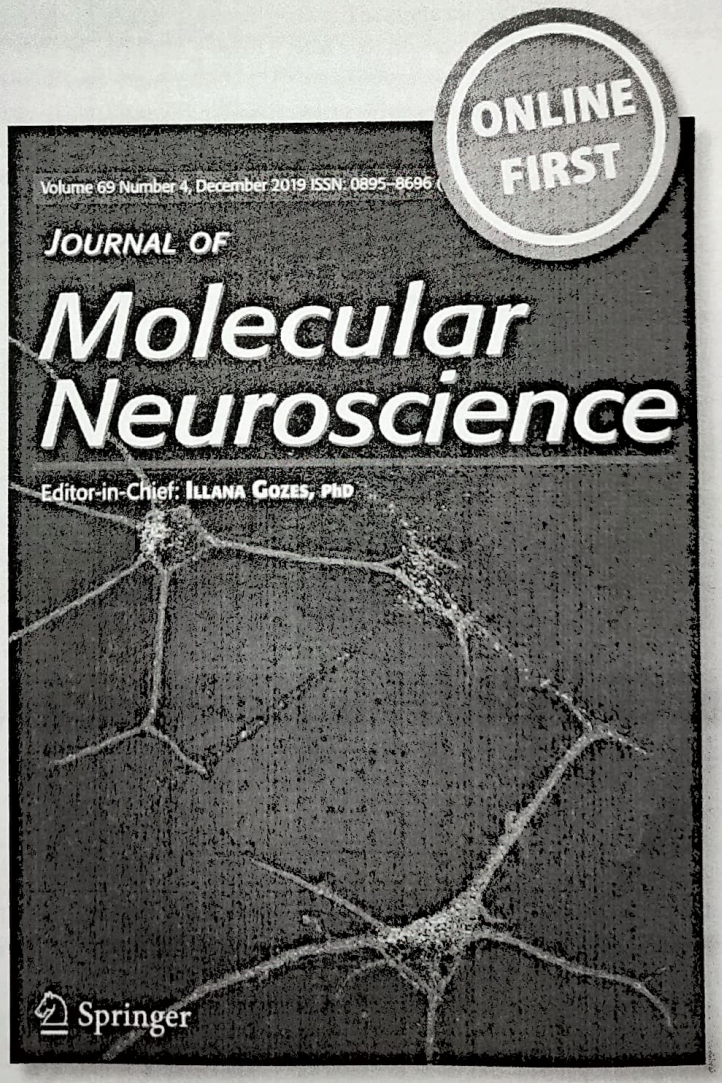

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Silymarin Protects Against Impaired Autophagy Associated with 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Induced Parkinsonism

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Abstract
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exacerbates mitochondrial impairment and α-synuclein expression leading to Parkinsonism. Impaired mitochondria and over-expressed α-synuclein are degraded and eliminated via macroautophagy and chaperone-mediated autophagy. Owing to multiple properties, silymarin protects from oxidative stress–mediated cellular injury. However, its effect on MPTP-induced changes in autophagy is not yet known. The study aimed to decipher the effect of silymarin on MPTP-induced changes in autophagy. Male mice (20–25 g) were treated with silymarin (intraperitoneally, daily, 40 mg/kg) for 2 weeks. On day 7, a few animals were also administered with MPTP (intraperitoneally, 20 mg/kg, 4 injections at 2-h interval) along with vehicles. Striatal dopamine content was determined. Western blot analysis was done to assess α-synuclein, beclin-1, sequestosome, phosphorylated 5′ adenosine monophosphate–activated protein kinase (p-AMPK), lysosome-associated membrane protein-2 (LAMP-2), heat shock cognate-70 (Hsc-70), LAMP-2A, phosphorylated unc-51-like autophagy activating kinase (p-Ulk1), and phosphorylated mechanistic target of rapamycin (p-mTOR) levels in the nigrostriatal tissue. Silymarin rescued from MPTP-induced increase in beclin-1, sequestosome, p-AMPK, and p-Ulk1 and decrease in LAMP-2, p-mTOR, and LAMP-2A levels. Silymarin defended against MPTP-induced increase in α-synuclein and reduction in dopamine content. The results demonstrate that silymarin protects against MPTP-induced changes in autophagy leading to Parkinsonism.

Keywords MPTP · Silymarin · Macroautophagy · CMA · Neuroprotection

Introduction

Hypokinetic rigid syndrome, universally referred to as Parkinson's disease (PD), is a well-known age-related neurodegenerative disorder primarily characterized with motor disability (Olanow 2007; Singh et al. 2006; Schapira 2009; Yadav et al. 2012). Although the tangible contributors of disease have been mysterious, increased age and hereditary and environmental factors are documented as the key perpetrators that accelerate the degeneration of dopamine-producing neurons in the nigrostriatal pathway (Olanow 2007; Schapira 2009; Dauer and Przedborski 2003; Srivastava et al. 2010; Gupta et al. 2014; Rasheed et al. 2017). The discerning loss of tyrosine hydroxylase (TH)–positive cells in the substantia nigra ends up in the striatal dopamine deficiency (Yadav et al. 2012). 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), initially found to be present in the synthetic heroin, induces the selective degeneration of dopamine-synthesizing cells in the nigrostriatal area of the brain (Yadav et al. 2012; Dauer and Przedborski 2003; Srivastava et al. 2010; Gupta et al. 2014; Rasheed et al. 2017; Langston 2017). Although MPTP is not a very powerful neurodegenerative agent, it does cross the blood-brain barrier owing to its lipophilic nature and subsequently enters the astrocytes where it gets converted to 1-methyl-4-phenylpyridinium cation (MPP^+), a highly potent neurotoxicant, by an enzyme monoamine oxidase (Yadav et al. 2012; Gupta et al. 2014; Langston 2017; Herraiz and Guillén 2011). The adjoining

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