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Review Article

Reprint of: Revisiting oxidative stress and mitochondrial dysfunction in the pathogenesis of Parkinson disease—resemblance to the effect of amphetamine drugs of abuse

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ABSTRACT

Parkinson disease (PD) is a chronic and progressive neurological disease associated with a loss of dopaminergic neurons. In most cases the disease is sporadic but genetically inherited cases also exist. One of the major pathological features of PD is the presence of aggregates that localize in neuronal cytoplasm as Lewy bodies, mainly composed of α-synuclein (α-syn) and ubiquitin. The selective degeneration of dopaminergic neurons suggests that dopamine itself may contribute to the neurodegenerative process in PD. Furthermore, mitochondrial dysfunction and oxidative stress constitute key pathogenic events of this disorder. Thus, in this review we give an actual perspective to classical pathways involving these two mechanisms of neurodegeneration, including the role of dopamine in sporadic and familial PD, as well as in the case of abuse of amphetamine-type drugs. Mutations in genes related to familial PD causing autosomal dominant or recessive forms may also have crucial effects on mitochondrial morphology, function, and oxidative stress. Environmental factors, such as MPTP and rotenone, have been reported to induce selective degeneration of the nigrostriatal pathways leading to α-syn-positive inclusions, possibly by inhibiting mitochondrial complex I of the respiratory chain and subsequently increasing oxidative stress. Recently, increased risk for PD was found in amphetamine users. Amphetamine drugs have effects similar to those of other environmental factors for PD, because long-term exposure to these drugs leads to dopamine depletion. Moreover, amphetamine neurotoxicity involves α-syn aggregation, mitochondrial dysfunction, and oxidative stress. Therefore, dopamine and related oxidative stress, as well as mitochondrial dysfunction, seem to be common links between PD and amphetamine neurotoxicity.

Contents

Abbreviations: α-syn, α-synuclein; ASK1, Apoptosis signaling-regulating kinase 1; CMA, Chaperone-mediated autophagy; DAT, Dopamine transporter; ETC, Electron transport chain; iPS, Induced pluripotent stem; LAMP-2A, Lysosome-associated membrane protein 2A; LB, Lewy body; L-DOPA, *levo*-3,4-dihydroxyphenylalanine; LN, Lewy neurite; LRR, Leucine-rich repeat domain; LRRK2, Leucine-rich repeat kinase 2; MAO, Monoamine oxidase; MAP, mitogen-activated protein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrapyridine; MPP^+, 1-methyl-4-phenylpyridinium; mtDNA, Mitochondrial DNA; NAC, Non-amyloid-β component; NMDA, *N*-methyl-d-aspartate; 6-OHDA, 6-hydroxydopamine; PD, Parkinson disease; PINK1, PTEN-induced putative kinase 1; Roc, Ras of complex protein; ROS, Reactive oxygen species; siRNA, Short-interfering RNA; SN, Substantia nigra pars compacta; SNCA, α-synuclein; TH, Tyrosine hydroxylase; Trx1, Thioredoxin 1; Ub, Ubiquitin; UCHL1, Ubiquitin C-terminal hydrolase 1; UPS, Ubiquitin proteasome system; VMAT2, Vesicular monoamine transporter 2; WT, Wild type

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Introduction to Parkinson disease

Parkinson's disease (PD) is a chronic and progressive neurological disease associated with a loss of dopaminergic neurons in the substantia nigra pars compacta (SN), as well as with more widespread neuronal changes that cause complex and variable motor and nonmotor symptoms. PD is the second most prevalent neurodegenerative brain disorder, affecting 1 to 2% of the population above 65 years of age, and its prevalence increases to approximately 4% in individuals above 85 years of age [1,2]. The etiopathogenesis of PD is still not fully understood. In most cases the disease is sporadic: a multifactorial, idiopathic disorder that seems to arise from a combination of environmental exposures and genetic susceptibility. The remaining cases are the result of genetic inheritance. Moreover, 15 to 20% of the patients with PD report a family history of the disease, although monogenic forms of PD are relatively rare [2–„4]. Nevertheless, old age continues to be the main risk factor in the development of the disease [5,6], making it clear that during aging, our cells display a greater degree of dysfunction, leading to cell stress (including decreased capacity to cope with oxidative stress) and greater energy demand. Investigations into postmortem PD brains, particularly in the SN, have consistently demonstrated abnormalities in mitochondrial function and increased levels of oxidative stress [7–„14]. Furthermore, there is evidence of inflammation through microglial activation in the SN, even at the time of death. The finding that α-synuclein (α-syn) is the major component of Lewy bodies (LBs) directed studies on protein metabolism and defects in protein degradation through the ubiquitin (Ub) proteasome system (UPS) and autophagy pathways as contributory factors to PD pathogenesis. These cellular pathways are interconnected, because mitochondrial dysfunction, namely complex I inhibition, leads to increased free radical generation, which further evokes deficits in the respiratory chain. Importantly, the UPS is dependent on oxidative phosphorylation for energy production and oxidatively damaged proteins increase the bulk of substrates to be degraded by the UPS. Moreover, this leads to increased cell dysfunction and a lowered threshold to apoptosis [15], a type of programmed cell death characterized by membrane blebbing, shrinking of organelles, and chromatin condensation and fragmentation [16].

Clinical and pathological aspects

Clinically, PD has often been characterized by the presence of cardinal motor signs, namely resting tremor, rigidity, bradykinesia, and postural instability. One of the main features affecting these patients includes a slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude of sequential motor tasks [17,18]. For a long time, PD was thought to involve a relatively simple neuropathological process primarily centered on the loss of dopaminergic neurons in the SN. This results in the loss of dopaminergic transmission in the striatum, leading to the majority of the classical motor symptoms of PD. The disease becomes evident when approximately 80% of striatal dopamine and 50% of nigral neurons are lost [2,19,20]. However, recent evidence indicates that nonmotor characteristics such as autonomic insufficiency, cognitive impairment, olfactory deficits, sleep disturbance, depression, and psychosis are very common during the course of the disease. The clinical diagnosis of PD is typically based on the presence of cardinal motor features, absence of atypical findings suggestive of an alternate diagnosis, and response to *levo*-3,4-dihydroxyphenylalanine (L-DOPA) [2,21].

In addition to the loss of dopaminergic neurons in the SN, PD is neuropathologically characterized by the presence of LBs and Lewy neurites (LNs) in vulnerable populations of neurons. These are intracytoplasmic insoluble protein inclusions located in either the neuronal cell body or the neuronal processes, respectively. The principal component of LBs and LNs is α-syn, a small protein of 140 amino acids that is predominantly expressed in the neocortex, hippocampus, SN, thalamus, and cerebellum [22]. The pathological definition of PD depends upon the presence of LBs in the SN neurons, although it is clear that pathology is also present outside this area [23,24].

Sporadic and familial forms of PD

Sporadic and inherited forms of PD share pathological, biochemical, and clinical features, with dysfunction of mitochondria, increased oxidative stress levels, and associated molecular pathways representing a link between the two forms of PD, as well as the natural aging process [6]. Environmental factors were long thought to be the principal cause of PD, particularly after the influenza pandemic of 1918, when a significant number of individuals developed postencephalitic parkinsonism. Infectious agents in the environment were then suspected to be the causal factors [25,26]. This environmental theory was subsequently supported by the identification of *N*-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) in the early 1980s, whose metabolite 1-methyl-4-phenylpyridinium (MPP^+) is responsible for the selective degeneration of the nigrostriatal pathways, by inhibiting mitochondrial complex I of the respiratory chain and subsequently increasing oxidative stress levels in dopaminergic neurons. Moreover, MPP^+ was shown to bind vesicular monoamine transporters (VMATs) and redistribute vesicular dopamine to the cytosol [27]. Within the cytosol, MPP^+ may also interact with various cytosolic enzymes, namely xanthine oxidase, aldehyde dehydrogenase and lipoamide dehydrogenase [28]. MPTP leads to a parkinsonian syndrome in