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Review

Synuclein, dopamine and oxidative stress: co-conspirators in Parkinson's disease?

Kathleen A. Maguire-Zeiss[a,b], Douglas W. Short[b,c], Howard J. Federoff[a,b,*]

[a]Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, United States
[b]The Center for Aging and Developmental Biology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, United States
[c]Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, United States

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Abstract

The etiology of Parkinson's disease (PD) is presently unknown. The unifying hallmark of disease is depletion of dopamine and loss of nigrostriatal dopamine neurons. Familial and sporadic forms of the disease are described. The familial mutations occur within α-synuclein and molecules involved in protein degradation and mitochondrial function. Sporadic PD is thought to involve the interplay of genetic and environmental factors. Despite disparate initiating triggers, a convergent pathobiologic model for this common neurodegenerative disease has been proposed. Likely players have emerged that may form the basis for this common pathway model of disease. In this review, we examine the role of three most implicated PD pathogenic conspirators: synuclein, dopamine and oxidative stress.

Theme: Disorders of the nervous system
Topic: Degenerative disease: Parkinson's

Keywords: α-Synuclein; Parkinson's disease; Dopamine; Mitochondria; ROS

Contents

1. Introduction

Parkinson's disease (PD) is one of the most common chronic neurodegenerative diseases of man. The incidence of PD was estimated in 1995 to be between 1:100 and 1:500 individuals [45]. PD is typified clinically by motor symptoms including bradykinesia, resting tremor, rigidity and gait

* Corresponding author. Center for Aging and Developmental Biology, Box 645, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Rochester, NY 14642, United States. Fax: +1 716 442 6646.
E-mail address: howard_federoff@urmc.rochester.edu (H.J. Federoff).

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abnormalities followed by postural instability and less frequent non-motor complications such as dementia, depression and autonomic dysfunction. Pathologically, the PD brain is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta as well as dopaminergic ventral tegmental area (VTA) neurons and noradrenergic neurons of the locus coeruleus. The PD brain also harbors intracellular proteinaceous inclusions known as Lewy bodies, most commonly in the brainstem and midbrain. Ubiquitinated intracellular and extracellular fibrils are also present in other neurodegenerative disorders but a key distinguishing component of Lewy bodies is inclusion of a protein with yet unknown function, α-synuclein (SYN). While intensively studied, the presumptive pathogenic role of misfolded SYN has failed to be defined. Through an understanding of the molecular mechanisms underlying protein unfolding and aberrant folding, a common pathogenic pathway will emerge, one that may enable new therapeutics [15,32].

2. Parkinson's disease etiology

Parkinson's disease (PD) exists as both an idiopathic and familial disorder. Although the exact mechanisms underlying all forms of PD are unknown, the common pathway for most, perhaps all, forms of PD results in damage to and subsequent loss of dopamine (DA) neurons [32]. Importantly, this decline in DA neuron number below a critical threshold produces early symptomatic PD (reviewed in Ref. [11]). Although rare, mutations in or overexpression of the *SYN* gene cause intracytoplasmic SYN inclusions and early-onset disease [23,25,38–40,50,53]. Two other familial PD genetic mutations, *parkin* and *ubiquitin carboxy-terminal-hydrolase-L1*, are involved in proteasome function and suggest dysregulation of protein disposal in the pathophysiology of PD [1,17,21,29,56,65]. Most recently, mutations in the nuclear-encoded mitochondrial protein, PINK 1, have been linked to a hereditary early-onset PD [62,63]. This is the first direct link between PD and mitochondrial dysfunction. Furthermore, these human mutations suggest a collaboration between SYN, protein mishandling and mitochondrial dysfunction in PD pathogenesis.

Genetic mutations account for less than 10% of the total PD cases suggesting that sporadic PD arises from a combination of genetic vulnerability and environmental exposure. Environmental factors such as pesticides, herbicides and industrial chemicals have been identified as potential risk factors for PD, primarily through their mediation of increased oxidative stress [14,35,46,57–60]. A seminal observation highlighting the role of dopaminergic neurotoxicants involved the unfortunate self-administration of the synthetic by-product of meperidine production, 1,2,3,6-methyl-phenyl-tetrahydropyridine (MPTP). MPTP treatment of mice and monkeys has become a common method to achieve dopaminergic neuronal loss and produce a "model" of PD. The toxic compound, MPTP, is converted in glia to the pyridinium ion (MPP+) by monoamine oxidase type B (MAO-B) and subsequently taken up by dopamine neurons via the dopamine transporter. MPP+ is then actively transported to the mitochondria where it inhibits complex I, interfering with mitochondrial respiration and resulting in increased production of the superoxide anion [49]. Likewise, linkage of toxicant injury to SYN aggregation has been provided by evidence that MPTP stimulates production and oxidative modification of SYN [10,13,43]. Together, these studies suggest that both familial and sporadic PD despite different initiating mechanisms follow a convergent pathway to PD pathogenesis which involves SYN, mitochondrial dysfunction and protein aggregation.

3. Role of SYN and oxidative stress

The exact mechanism by which SYN promotes PD neurodegeneration is unknown but data suggest that in its normal context the molecule participates in regulating synaptic function and plasticity [6,20,55]. The critical interaction between SYN, oxidative stress, and PD is supported by experiments which demonstrate both in vitro and in vivo that oxidative stress promotes the formation of SYN aggregates and inclusions (reviewed in Refs. [18,64]). Vila et al. [64] have demonstrated that treatment of mice with MPTP results in an increase in SYN positive neurons exclusively in the substantia nigra pars compacta. Non-human primate studies corroborate MPTP treatment inducing SYN aggregation and dopaminergic dysfunction, further supporting a role of oxidative stress [24]. Another mitochondria complex I inhibitor, rotenone, also triggers increased SYN aggregation as well as increased SYN production [48]. We have demonstrated that systemic treatment of wildtype C57Bl/6 mice with paraquat, a CNS active pro-oxidant, results in dopaminergic dysfunction and cell loss [4]. Consequently, it was shown that SYN aggregation occurs in paraquat-treated mice [33]. MPTP, paraquat and rotenone treatment with the attendant increase in SYN aggregation results in dopaminergic dysfunction supporting the hypothesis that environmental agents and genetic factors act in concert to produce selective neurodegeneration.

Oxidative stress and mitochondrial dysfunction are also implicated in the etiology of PD in other models [3,9,22,31]. Transgenic mice overexpressing superoxide dismutase (SOD-1) are more resistant to MPTP toxicity than are wildtype littermates [41]. While nitric oxide (NO) has been implicated as an active partner in the oxidative damage caused by an accumulation of superoxide anion. It is believed that both glial-derived inducible nitric oxide synthase (iNOS) and neuronal NOS (nNOS) produce nitric oxide that upon reaction with a superoxide anion forms peroxynitrite which is known to damage DNA and proteins resulting in cell death [65]. In support of this mechanism, transgenic nNOS−/− mice are more resistant to MPTP