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Review

Are dopamine derivatives implicated in the pathogenesis of Parkinson's disease?

Marco Bisaglia*, Roberta Filograna, Mariano Beltramini, Luigi Bubacco

Molecular Physiology and Biophysics Unit, Department of Biology, University of Padova, Via Ugo Bassi 58/B, 35121 Padova, Italy

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ABSTRACT

Parkinson's disease (PD) is the most common motor system disorder affecting 1–2% of people over the age of sixty-five. Although PD is generally a sporadic neurological disorder, the discovery of monogenic, hereditable forms of the disease, representing 5–10% of all cases, has been very important in helping to partially delineate the molecular pathways that lead to this pathology. These mechanisms include impairment of the intracellular protein-degradation pathways, protein aggregation, mitochondria dysfunction, oxidative stress and neuroinflammation. Some of these features are also supported by *post-mortem* analyses. One of the main pathological hallmarks of PD is the preferential degeneration of dopaminergic neurons, which supports a direct role of dopamine itself in promoting the disorder. This review presents a comprehensive overview of the existing literature that links the aforementioned pathways to the oxidative chemistry of dopamine, ultimately leading to the formation of free radicals and reactive quinone species. We emphasize, in particular, how the reaction of dopamine-derived quinones with several cellular targets could foster the processes involved in the pathogenesis of PD and contribute to the progression of the disorder.

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Parkinson's disease (PD) was first discovered in 1817 by James Parkinson, who described this disorder as the "shaking palsy". It is a chronic and progressive neurodegenerative disorder that affects more than 6 million people worldwide (www.epda.eu.com). The main clinical feature of PD is the presence of several motor symptoms, which include resting tremor, rigidity, slowness of movements and postural instability. Pathologically, PD is characterized by a preferential degeneration of neurons in the *Substantia Nigra pars compacta* (SNpc), resulting in a decrease of dopamine levels in its striatal projections. Dopamine is pivotal for normal movement because it allows information on movement to be transmitted from the SNpc to the *striatum*, which then initiates and controls the ease and balance of movement (Iversen and Iversen, 2007). In addition to the loss of dopaminergic neurons, a second pathological feature of PD is the presence of cytoplasmic inclusions known as Lewy bodies (LB). Numerous molecules have

* Corresponding author. Tel.: +39 0498276329; fax: +39 0498276300.
E-mail address: marco.bisaglia@unipd.it (M. Bisaglia).

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been identified within LBs (Shults, 2006), but the most prominent of these are ubiquitin and fibrillar aggregates of α-synuclein (Spillantini et al., 1997), although the role of LB in causing the disease has been the subject of considerable debate and uncertainty (Ross and Poirier, 2005).

Most forms of PD are sporadic, but in approximately 5% of cases, familiar inheritance is observed. Although the etiopathogenesis of PD remains elusive, genetic-associated forms have provided some interesting evidence on pathways involved in such a multifactorial disorder, including ubiquitin–proteasome system deregulation, leading to protein misfolding and aggregation, mitochondrial dysfunction and increased oxidative stress (Cookson, 2012; Lee and Liu, 2008; Shen and Cookson, 2004). Evidence from *post-mortem* analyses on PD patients also supports the impairment of mitochondrial function, especially at the level of complex I, and oxidative damage as contributing factors (Beal, 2003). In addition, previous studies also emphasized the presence of neuroinflammation, highlighting its role in the progression of the disease (Beal, 2003; Hirsch et al., 2005).

1. Molecular pathways in PD

1.1. Clearance system impairment and protein aggregation

The first evidence of genetic inheritance in PD was the discovery in 1997 of a point mutation in the *SNCA* gene, which encodes α-synuclein (Polymeropoulos et al., 1997). α-Synuclein was also found to be the major component of LB (Spillantini et al., 1997). This observation, together with the discovery that α-synuclein gene duplication (Chartier-Harlin et al., 2004) and triplication (Singleton et al., 2003) cause autosomal dominant PD, demonstrated the role of protein aggregation in the pathogenesis of PD. Remarkably, the presence of LB in the brains of patients with sporadic PD also suggests a key role for α-synuclein in the pathogenesis of the disease. As α-synuclein aggregation is dependent on concentration (Wood et al., 1999), a way to induce protein aggregation is through impairment of the cellular clearance pathways. In eukaryotic cells, the ubiquitin–proteasome and autophagy-lysosome pathways are the two main routes of proteins clearance (Rubinsztein, 2006). The role of the ubiquitin–proteasome system in PD became evident after mutations in the parkin protein were found in familiar forms of PD (Kitada et al., 1998; Leroy et al., 1998). Parkin is an E3 ubiquitin-protein ligase responsible for ubiquitin labeling of substrate proteins in preparation for their degradation by the 26S proteasome. Parkin also plays a fundamental role in promoting mitophagy of dysfunctional mitochondria following the loss of mitochondrial membrane potential (Narendra et al., 2009). At the same time, malfunctioning of chaperone-mediated autophagy (CMA) has also been described in PD (Cuervo et al., 2004). In particular, the pathogenic A53T and A30P α-synuclein mutants described in familial forms of PD have a high binding affinity for the CMA receptor, but, despite their tight interaction with the lysosomal membrane, they cannot translocate into the lysosomal lumen. More importantly, they block the uptake and degradation of other CMA substrates, leading to a general CMA blockage (Rumchev et al., 2004).

1.2. Oxidative stress and mitochondrial dysfunction

Oxidative stress occurs when the ability of the endogenous antioxidant systems is overwhelmed by the generation of reactive oxygen species (ROS). Nucleic acids, both RNA and DNA, undergo oxidative damage, with DNA damage occurring most readily at guanine bases. Free radicals can peroxidate unsaturated fatty acids, resulting in lipid degradation and cell membrane damage. ROS-induced modification of proteins often leads to either a loss function or protein aggregation. Accordingly, an increase in 8-hydroxy-2-deoxy guanosine, 4-hydroxy-2,3-nonenal and protein carbonylation, which are, respectively, markers of DNA damage, lipid peroxidation and protein oxidation, have all been detected in the SNpc of PD patients (Alam et al., 1997; Floor and Wetzel, 1998; Yoritaka et al., 1996; Zhang et al., 1999).

The direct relationship between mitochondrial dysfunction and PD was proposed after the description of complex I deficiency in the SNpc of patients who had died from PD (Schapira et al., 1989, 1990). Consistent with the notion that complex I is the main mitochondrial site of superoxide radical production (Murphy, 2009), these mitochondrial dysfunctions were observed in association with increased oxidative stress, emphasizing the interrelationship between these events (Owen et al., 1996; Schapira, 1995). Additional support for the involvement of mitochondria in PD pathogenesis emerged from the identification of genetic causes of familial PD. Specifically, mutations in three genes, encoding parkin, DJ-1 and PINK1, are the cause of recessive forms of parkinsonism (Bonifati et al., 2003; Kitada et al., 1998; Valente et al., 2004). Interestingly, the major common functional effects of all three genes relate to mitochondrial function and oxidative damage, suggesting a potential overlap among the pathways that lead to recessive parkinsonism. Both parkin and PINK1 proteins are also critically involved in the regulation of mitochondrial dynamics and in the selective removal of damaged mitochondria through mitophagy. Consequentially, dysfunction of these proteins leads to impaired mitochondrial morphology and integrity (Bueler, 2010; Exner et al., 2007; Pogson et al., 2011). Although the precise biological function of DJ-1 is not known, it has been proposed that it may play a role in the cellular responses to oxidative stress (Cookson, 2012). The impairment of mitochondrial function in sporadic PD is also supported by evidence that exposure to environmental toxins, known to damage mitochondrial functions, have been identified as a significant risk factor for PD. These same toxins produce parkinsonian phenotypes when used in animal models (see (Bove and Perier, 2012) for a review).

1.3. Neuroinflammation

The inflammatory response associated with cell loss in the dopaminergic nigrostriatal tract and, more generally, the role of immune mechanisms is increasingly recognized in PD progression (see (Hirsch and Hunot, 2009) for a review). Microglia cells are the resident macrophages of the brain and, as such, they play critical roles in the development and maintenance of the neural environment. In the mature brain, microglia typically exist in a resting state characterized by a ramified morphology that continuously surveys the surrounding tissue (Nimmerjahn et al., 2005). Upon activation, following perturbations in the brain's microenvironment or changes in the neuronal structure, microglia develop a series of responses to produce mediators that help to eliminate the source of proinflammatory signals (Streit, 2002). However, under some circumstances, such as the presence of α-synuclein aggregates or of neuromelanin (NM) released from dying neurons, microglia can become over-activated and induce significant detrimental neurotoxic effects by perpetuating the proinflammatory response (Kim et al., 2013; Theodore et al., 2008; Zhang et al., 2005). *Post-mortem* studies have reported the presence of activated microglial cells within the SNpc of patients with Parkinson's disease (McGeer et al., 1988). In addition, proinflammatory cytokines, such as IFN-γ, TNFα and IL-1, coordinate the action of microglia and PD patients have been found with elevated levels of TNFα and IFN-γ in the cerebrospinal fluid and brain tissue (Mogi et al., 1994, 1996). Consistent with the notion that DA neurons have an increased vulnerability to oxidative insults, it has

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