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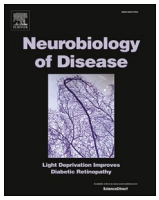

Oxidative stress and synaptic dysfunction in rodent models of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a multifactorial disorder involving a complex interplay between a variety of genetic and environmental factors. In this scenario, mitochondrial impairment and oxidative stress are widely accepted as crucial neuropathogenic mechanisms, as also evidenced by the identification of PD-associated genes that are directly involved in mitochondrial function. The concept of mitochondrial dysfunction is closely linked to that of synaptic dysfunction. Indeed, compelling evidence supports the role of mitochondria in synaptic transmission and plasticity, although many aspects have not yet been fully elucidated. Here, we will provide a brief overview of the most relevant evidence obtained in different neurotoxin-based and genetic rodent models of PD, focusing on mitochondrial impairment and synaptopathy, an early central event preceding overt nigrostriatal neurodegeneration. The identification of early deficits occurring in PD pathogenesis is crucial in view of the development of potential disease-modifying therapeutic strategies.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting 1% of the population above 60 years and up to 4% above 80 years (Ascherio and Schwarzschild, 2016; Tysnes and Storstein, 2017).

It is characterized primarily by cardinal motor symptoms (akinesia/bradykinesia, rigidity, resting tremor and postural instability), but with a significant preclinical phase (estimated as >20 years).

Except for rare inherited cases, PD is an idiopathic condition with multifactorial origin. Most of PD cases are triggered by a complex interplay between environmental and genetic factors (Ascherio and Schwarzschild, 2016; Kalia and Lang, 2016; Trinh and Farrer, 2013). They both concur in molecular events leading to the progressive loss of dopaminergic neurons (DAns) in the substantia nigra pars compacta (SNpc) and the accumulation of α-synuclein (α-syn) cytoplasmic inclusions, termed Lewy bodies, that represent the neuropathological hallmarks of the disease (Fares et al., 2021; Marinus et al., 2018).

There is growing recognition of non-motor symptoms and additional cell loss in multiple brain regions, including the cortex and thalamus, with involvement of other neurotransmitter systems even at early stages of the disease (Halliday et al., 2005; Kalia and Lang, 2016; Pifl et al., 2012; Poewe et al., 2017).

In the last two decades, the identification of several PD-risk associated genes (Karimi-Moghadam et al., 2018; Keller et al., 2012; Klein and Westenberger, 2012; Spatola and Wider, 2014; Yao et al., 2021) has provided incredible advance to our understanding of the molecular pathways involved in disease pathogenesis. Many of these genes are implicated in mitochondrial homeostasis, and indeed most PD associated mutations result in mitochondrial dysfunction and oxidative stress (Cherubini and Wade-Martins, 2018; Gusdon et al., 2012; Pereira et al., 2014; Li et al., 2021a, 2021b). Mitochondrial impairment is widely accepted as a main neuropathogenic mechanism in PD, affecting different biological pathways (i.e. proinflammatory, antioxidant and autophagic) and contributing to the Lewy pathology and neuronal loss (Li et al., 2021a, 2021b; Poewe et al., 2017).

In this brief review, we aim to provide an overview of findings from preclinical studies focused on mitochondrial dysfunction and oxidative stress and their impact on synaptic dysfunction, in order to elucidate their role in the pathophysiology of PD. We are aware that PD is a complex disorder with multifactorial ethiology that involves many others pathogenic processes, ranging from misfolding of α-syn to neuroinflammation. Indeed, the classical "neurocentric" view has changed and PD is increasingly seen as a "multi-system" disorder with notable

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neuroinflammation and immune dysfunction, and emerging evidence supports the contribution of monogenic PD genes also in the regulation of the immune system. This aspect will be also briefly discussed later. However, an exhaustive description of all pathogenic mechanisms of the disease is beyond our scope, thus the reader is referred to other recent excellent reviews (Chen et al., 2021; Cherubini and Wade-Martins, 2018; Scorziello et al., 2020; Surmeier et al., 2017; Tansey et al., 2022).

In this regard, animal models are the best tools to study the pathogenesis of PD. Three animal groups are commonly used for modeling PD, each one with its own advantages and limitations: rodents, non-human primates and non-mammalian species. Non-human primates provide important insights into PD pathology, given their genetic and anatomo-physiological similarities to humans, however their use involves complex ethical considerations. Non-mammalian species have been used in a small fraction of experimental studies to date, and translating them to humans can be challenging. Rodents are involved in the majority of animal studies of PD (Fig. 1) and represent the mammalian model more closely related to humans after non-human primates. This group includes traditional neurotoxin-based models, in which a pharmacological agent (i.e. MPTP, 6-OHDA) is administered either systemically or locally to induce selective degeneration of nigrostriatal neurons, and genetic models, crucial to dissect molecular pathways and disease mechanisms (Bezard et al., 2013; Imbriani et al., 2018a, 2018b). The focus of this review is mostly restricted to rodent models.

2. Mitochondrial dysfunction and oxidative stress in PD

It has long been recognized that mitochondrial dysfunction and oxidative stress are implicated in the aging process, as well as in the pathogenesis of age-related neurodegenerative diseases, such as amyotrophic lateral sclerosis, Alzheimer's disease and PD.

Mitochondria are complex self-replicating organelles, essential for the maintenance of cellular homeostasis. They are surrounded by two membranes (inner and outer mitochondrial membrane) separated by an intermembrane space, they possess their own genome (mtDNA), formed by a circular DNA molecule, and have an autonomous protein synthesis machinery. Mitochondria represent the cellular "powerhouses", as they generate most of the cell's energy through oxidative phosphorylation, a process in which electrons are transferred from donors to acceptors via redox reactions catalysed by four multiprotein complexes (I–IV) (electron transport chain) to synthesize ATP. Accordingly, they are contained in all eukaryotic cells, but their number varies depending on the metabolic requirements of each cell type, being particularly abundant in neurons; furthermore, as dynamic structures, they can move within the cell to specific critical compartments with high energy demand, like axon terminals (Elfawy and Das, 2019; Niescier et al., 2016; Vos et al., 2010). Besides their crucial role in the generation of energy, mitochondria are also involved in many other cell processes relevant for neuronal function, such as calcium homeostasis and apoptosis (Clapham, 2007; Murali Mahadevan et al., 2021).

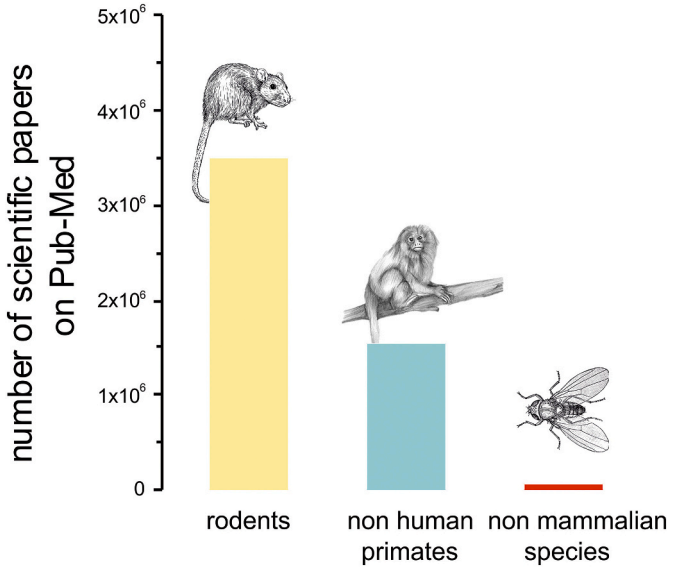

Fig. 1. Proportion of animal models used in 528,171 research articles on Parkinson's disease published until May 20, 2020. Numbers of original article publications were obtained from following searches on PubMed: "non-human primates", "non-mammalian species", and "rodents".

Oxidative phosphorylation generates reactive oxygen species (ROS), like superoxide radicals (O_2^-) and hydrogen peroxide (H_2O_2). Moderate levels of ROS are physiological, inducing pathways that ensure proper functioning (i.e. intracellular signaling cascades aimed at maintaining cell homeostasis). However, if there is an imbalance between ROS production/accumulation and the intrinsic anti-oxidant defences to detoxify these reactive products, then oxidative stress occurs, leading to irreversible cell and tissue damage, and eventually to disease (Apostolova and Victor, 2015). Indeed, increased ROS levels can damage mitochondrial lipids, proteins and mtDNA by inducing mutations, which impairs oxidative phosphorylation and leads to mitochondrial fragmentation and mitochondrial functioning disruption. Mitochondrial damage will ultimately bring about the depletion of ATP, influx in calcium, and the opening of the mitochondrial permeability pore, eventually leading to apoptosis. Mitochondrial dysfunction, in turn, can amplify oxidative stress by generation of uncontrollable ROS in a vicious cycle, which ultimately causes cellular injury/organ failure and diseases (Calabrese et al., 2010; Elfawy and Das, 2019).

It has been amply demonstrated that ROS and oxidative stress are major driving forces in the pathogenesis of PD (Hauser and Hastings, 2013; Schapira et al., 1990; Singh et al., 2019). Indeed, SNpc DAns, due to their characteristic physiological and morphological properties, are particularly susceptible to injury induced by oxidative stress, which negatively impacts neuronal physiology and survival. They have an autonomous pace-making activity and are more prone to frequent transients of calcium, necessary to allow DA release. They show high metabolic activity that is required to support their axonal arborization (Pacelli et al., 2015). Moreover, DAns have enhanced sensitivity to oxidative damage due to the generation of ROS secondary to dopamine metabolism (Burbulla et al., 2017; Dunnett and Björklund, 1999). They critically depend on mitochondrial function for the highly energy-demanding processes of neurotransmission and plasticity. Mitochondria are directly involved also in the maintenance of pacemaker activity, by maintaining cytosolic calcium within physiological ranges (Zaichick et al., 2017). It has been demonstrated that the disruption in mitochondrial fission, which reduces mitochondrial mass in axon terminals in mice, causes a preferential degeneration of nigral DAns. This degeneration begins at axon terminals, as evidenced by the loss of the striatal tyrosine hydroxylase (TH) signal, while about 65% of TH-positive SNpc neurons is spared (Berthet et al., 2014).

A very recent study explored the mitochondrial life cycle in neurons. The Authors tracked individual mitochondria in neurons lacking the fission-promoting protein dynamin-related protein 1 (Drp1) and observed the kinetics of PINK1-dependent pathways of mitochondrial quality control, defining a distinct neuronal mitochondrial life cycle and contributing to explain the selective vulnerability of neurons to PINK1 and Parkin mutations (Li et al., 2021a, 2021b).

DAns are exposed to high levels of ROS and oxidative stress, and are forced to work under stressful conditions because of their physiological and morphological characteristics. This metabolic stress may synergistically act with the consequences of genetic mutations and/or of environmental factors, thus exacerbating mitochondrial aging-related decline and contributing to neuronal aging and death (Giasson et al., 2000; Imbriani et al., 2018a, 2018b; Surmeier et al., 2017).

The first evidence of the role of mitochondria dysfunction in the

pathophysiology of the disease emerged in the 1980s, when it was reported that young drug users from Northern California developed Parkinsonism after having used a meperidine analogue contaminated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a potent mitochondrial toxin inhibiting multiple complexes of the respiratory chain (Langston et al., 1983).

Some epidemiologic studies revealed an increased risk of developing PD associated with the environmental and/or occupational exposure to toxicants and pollutants, such as pesticides, herbicides, detergents, solvents, and heavy metals, with an established mitochondrial toxicity (Ascherio and Schwarzschild, 2016; Belvisi et al., 2020; Kanthasamy et al., 2019; Shukla et al., 2015). Also a greater consumption of dairy products, which in turn could concentrate pollutants and pesticides, has been associated with an increased risk of PD and a higher rate of neuron loss into the SNpc of postmortem brains collected from individuals unaffected by PD (Abbott et al., 2016; Ascherio and Schwarzschild, 2016).

Through the years, the notion that mitochondrial dysfunction plays a role in PD pathogenesis has come from the increasing identification of mutations in PD-associated genes that specifically induce mitochondrial impairment, especially the autosomal recessively inherited PD genes Parkin, PINK1 and DJ-1 (Bonifati et al., 2003a, 2003b; Larsen et al., 2018; Lücking et al., 2000; Valente et al., 2004a, 2004b). Some of these genes and how their products are related to mitochondrial function will be briefly illustrated later in this review. Even if monogenic forms represent a minority of PD cases, the lessons learned on the role of mitochondrial dysfunction in PD was found to be relevant also for the most common sporadic cases, although to what extent these genes are dysregulated in sporadic PD is still a matter of debate. It is likely that mitochondrial dysfunction is associated with sporadic PD in elderly people, as confirmed by the finding of an increased frequency of somatic mitochondrial DNA (mtDNA) deletions, a cumulative damage due to excess exposure to free radicals, determining respiratory chain deficiency and oxidative stress in midbrain tissue of these patients (Bender et al., 2006; Schapira, 1998). Similar changes have been found in brain tissue from patients with presymptomatic PD, suggesting that mitochondrial dysfunction and oxidative stress may precede clinical manifestations (Dexter et al., 1994; Jankovic and Tan, 2020).

3. Early synaptic dysfunction in PD

The loss of nigrostriatal dopaminergic projections to the dorsal striatum leads to the appearance of the classical motor manifestations of PD. However, there is a long time window, corresponding to a 30%–50% decrease in striatal dopamine levels, that precedes the onset of clinical symptoms and suggestive of the existence of changes in the basal ganglia able to compensate for neurodegeneration (Hilker et al., 2005; Imbriani et al., 2018a, 2018b; Morrish et al., 1996). The neuropathological process occurs early in PD, and multiple lines of evidence indicate that it starts at the synaptic terminal (Calo et al., 2016; Caudle et al., 2007; Stoica et al., 2012). The increasingly popular term synaptopathy has been coined to indicate disruptions in synaptic structure and function which represent the major determinant of PD and other neurodegenerative disorders (including Huntington's disease, Alzheimer's disease and neuropsychiatric disorders), and early pathophysiological events that precede neuronal death and degeneration (Cardinale et al., 2021; Lepeta et al., 2016; Milnerwood and Raymond, 2010; O'Donovan et al., 2017).

What drives synapthopaty? Multiple elements work coordinately in a delicate balance to ensure the correct synapse function, including components of the pre-synaptic and post-synaptic terminal, cell-adhesion molecules, glial cells and matrix, pre- and post-synaptic receptors, and endoplasmic reticulum (ER)-mitochondria crosstalk (Ardiles et al., 2017; Bridi et al., 2021; Lepeta et al., 2016; Parnell et al., 2021; Santos and Outeiro, 2020). It is easy to guess that impairing the function of a single component in this intricate assembly can lead to dysfunctional axon terminals. On the other hand, it remains to be elucidated whether the synaptic changes observed in experimental models of PD reflect a pathophysiological process driving further dysfunction and degeneration or reflect compensatory mechanisms within the circuitry, or both.

Recent advances have yielded insights into the link between different genes associated with familial PD and synaptic dysfunction. The most prominent actor in the synaptopathy is the SNCA gene encoding α-syn, a small soluble protein physiologically localised in the presynaptic terminal, where it exerts several functions including fusion and clustering activity of the synaptic vesicles, regulation of ion channels and neurotransmitter release (Bridi and Hirth, 2018; Burré, 2015; Choi et al., 2013). The aggregation of toxic α-syn oligomers and fibrils in the synaptic terminals promotes synapse deconstruction (α-synucleinopathy), which results in early synaptic impairments that precedes axon degeneration, with subsequent retrograde progression through a dying-back mechanism (Calo et al., 2016; Cardinale et al., 2021; Rockenstein et al., 2014). Moreover, α-syn can interact with mitochondria contributing to their dysfunction (Park et al., 2020; Prots et al., 2018; Reeve et al., 2018). Knock-down of PINK1, Parkin or DJ-1 induce synaptic dysfunction at dopaminergic terminals too, as it will be better illustrated later. In recent years, it has been demonstrated that also LRRK2 is a key regulator of synaptic function and interacts with a number of synaptic proteins to control the mobilization of synaptic vesicles (Inoshita et al., 2017; Kuhlmann and Milnerwood, 2020; Shin et al., 2008) (Fig. 2).

Synaptic transmission is a complex process requiring high levels of energy consumption. It is easy to understand how the concept of synaptic dysfunction is closely linked to that of mitochondrial dysfunction.

In neurons, mitochondria are distributed to maintain energy homeostasis in those cellular regions that are particularly metabolically demanding, such as axons and synapses. Here, mitochondria provide ATP necessary for synaptic functions, including synapse assembly, generation of action potentials and synaptic vesicle mobilization, and mediates Ca2 + buffering (Lee and Peng, 2008; Lee et al., 2018; Sheng, 2017; Sun et al., 2013). They are mainly stored in presynaptic terminals and postsynaptic dendritic spines during sustained synaptic activity. As highly mobile organelles, mitochondria are able to move within and between subcellular compartments involved in neuroplasticity (Cheng et al., 2010; Miller and Sheetz, 2004). Moreover, dysfunctional mitochondria are transported retrogradely to the cell body for lysosomal degradation, to ensure a constant supply of healthy mitochondria in the synapse and axon (Sheng and Cai, 2012).

Numerous evidence supports an interplay of synaptic, mitochondrial, and lysosomal dysfunction in the pathogenesis of PD, including the existence of a dysfunctional synaptic vesicle endocytosis which contributes to the selective vulnerability of midbrain DAns (Nguyen et al., 2019).

An old study of electron microscopy performed on PD patients' brain showed an increase in the synaptic area occupied by mitochondria in dopaminergic terminals (Anglade et al., 1996). More recently, in another study in *PD postmortem brain* tissue, Reeve and coworkers explored mitochondrial function within dopaminergic axons and their connections. They found that surviving presynaptic terminals were enlarged in PD compared with controls, suggesting an increase of mitochondrial numbers. Moreover, the total mitochondrial volume and the expression of mitochondrial complex I and IV subunits were significantly increased in PD. The Authors assumed that they all represent mechanisms to compensate for the loss of neighbouring axon terminals and to maintain synaptic transmission (Reeve et al., 2018).

In conclusion, growing evidence supports the function of mitochondria in synaptic transmission and plasticity, although many aspects still remain to be elucidated. Nevertheless, given the crucial role of mitochondria for neuronal integrity, it is not hard to believe that dysregulation in mitochondrial functions, signaling or transport, especially under stress condition, could bring to detrimental effects at synaptic levels, which may further contribute to impaired neuroplasticity and neuronal degeneration in PD as in other neurological disorders (Sheng and Cai, 2012; Zhou et al., 2016). Our hypothesis is that in PD any

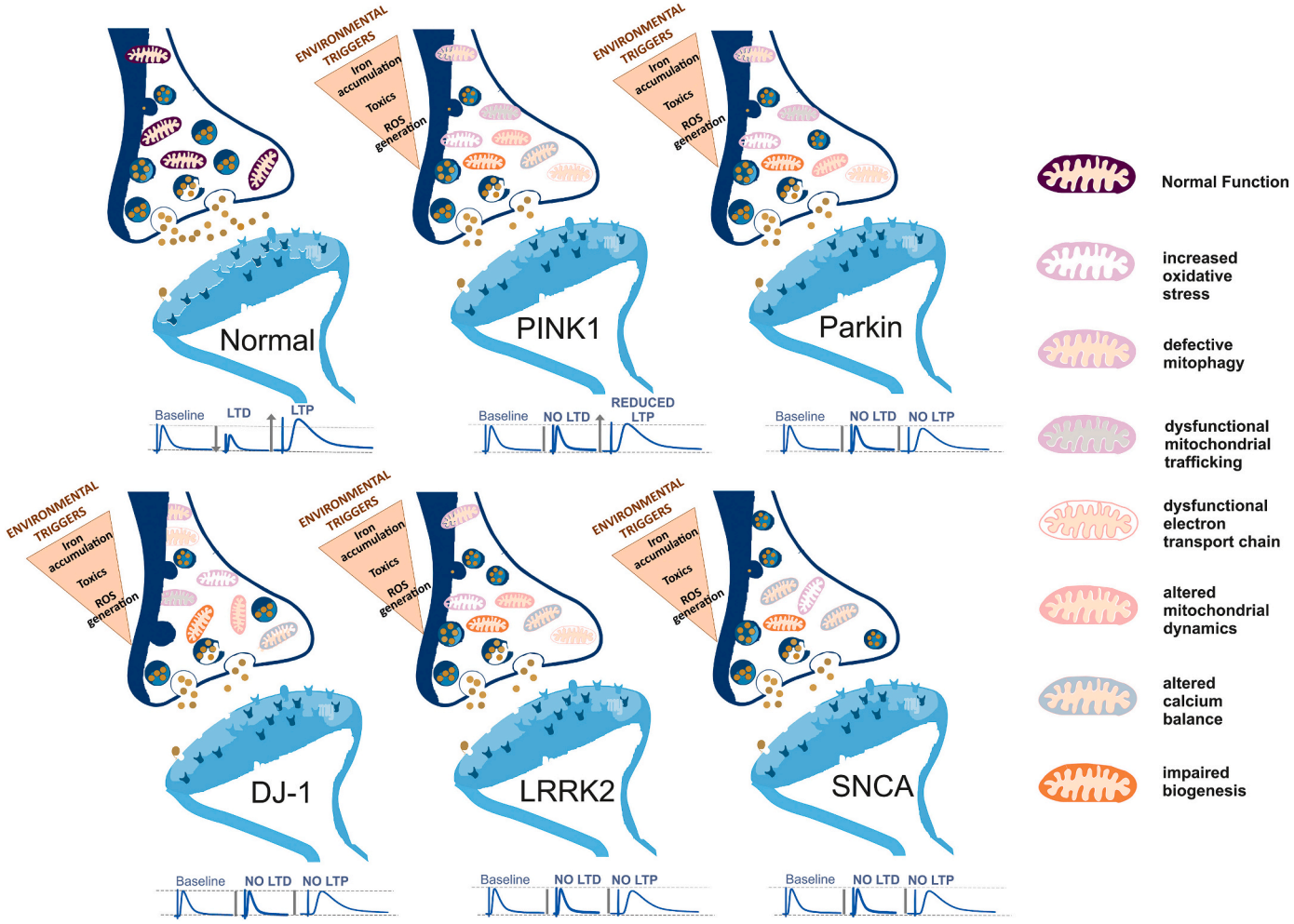

Fig. 2. Early mitochondrial dysfunction in Parkinson's disease concurs to generate synaptic alteration. Genetic factors and environmental exposure are thought to be major contributors to the etiology of PD. Many PD genetic mutations are associated to mitochondrial impairment. Neurotoxins can promote mitochondrial dysfunction too, by increasing oxidative stress. Any dysregulation in mitochondrial function, especially under stress condition, could bring to detrimental effects at synaptic levels, which may further contribute to impaired neuroplasticity in PD.

mitochondrial perturbation (for example derived from an environmental neurotoxin, a genetic predisposition, or aging) may have deleterious consequence for synaptic transmission, even earlier during the preclinical stage of the disease.

In this regard, we aim to illustrate how different rodent models of PD have contributed over time to a better comprehension of these pathogenic mechanisms occurring at prodromal stages of the disease.

4. Neurotoxin-based models

Neurotoxin-based models are the classic and oldest experimental models of PD. The ability of neurotoxins to induce marked and long-lasting lesions of the nigrostriatal pathway is widely accepted, however their specificity for the dopaminergic system while sparing other neuronal types involved in PD, represents a remarkable limitation, together with the tendency to fail to model early stages of PD and the risk of adverse systemic toxicity (Bezard et al., 2013). Nonetheless, toxin-induced models have paved the way to several studies aimed at exploring mitochondrial-related mechanisms of neurodegeneration in PD (Blandini and Armentero, 2012; Bové et al., 2005; Goldman, 2014; Imbriani et al., 2018a, 2018b).

The most used neurotoxins are 6-hydroxy-dopamine (6-OHDA) and MPTP, which are locally or systemically administered to induce degeneration of dopaminergic cells. Further neurotoxic models have been developed after environmental studies reporting an increased risk of PD in people exposed to pesticides for agricultural purposes (Belvisi et al., 2020; Hatcher et al., 2008; Johnson and Bobrovskaya, 2015; Konnova and Swanberg, 2018).

MPTP began to be used to mimic PD in mice and non-human primates after the discovery that it causes Parkinsonism in humans (Langston et al., 1983). Administered acutely or chronically, MPTP can cross the blood–brain barrier, where it is transformed into its active metabolite MPP+ by monoamine oxidase B. Then, the dopamine transporter carries MPP+ into dopaminergic neurons of the SNpc, where it exerts its toxic effects by blocking mitochondrial complex I activity, reducing ATP production and increasing oxidative stress. Moreover, MPP+ can rapidly inhibit overall mitochondrial motility within dopaminergic axons leading to synaptic loss (Kim-Han et al., 2011). It is hypothesized that the mitochondrial dysfunction induced by MPTP is primarily dependent on oxidative stress. Support for this hypothesis is provided by the observation that transgenic mice overexpressing the antioxidant enzyme Cu/Zn-superoxide dismutase have less evident MPTP-induced DAns loss (Przedborski et al., 1992).

Initially, parkinsonism was modelled through repeated injections of MPTP in monkeys. The MPTP model in non-human primates is a typical model of nigrostriatal degeneration occurring in late stage of human PD, although without progression nor presence of Lewy bodies (Langston et al., 1999). Later, several protocols to induce MPTP-dependent

parkinsonism in mice were developed, since different regimens of intoxication (acute/subacute/chronic) and route of administration give different extent of lesions. Mice are preferentially chosen since rats are more resistant to moderate MPTP doses (Giovanni et al., 1994). Large lesions are obtained to model late stages of PD; more commonly, acute doses by intraperitoneal (i.p.) injections are administered to cause a rapid and selective loss of SNpc dopaminergic neurons, which correlates with motor abnormalities. Alternatively, a prolonged MPTP exposure (for example through daily i.p. injections of subacute doses) induces a delayed nigrostriatal neurodegeneration, with neuroinflammation, α-syn pathology and molecular changes preceding cell death, better resembling human PD (even if without apparent motor impairment) (Zhang et al., 2017). It has also been shown that lower doses of MPTP can result in decreased TH expression rather than actual SNpc dopamine neuron loss, which can represent a limit of some MPTP-based models (Alam et al., 2017).

Over the time MPTP models have been refined to achieve distinct degrees of dopaminergic denervation. For instance, severely dopamine-depleted monkeys treated with MPTP show a significant reduction in spine density in both the caudate nucleus and putamen, while monkeys treated with low doses of MPTP, which lead to only a partial striatal dopamine denervation, show a lower reduction of striatal dendritic spines density and do not develop motor signs of parkinsonism, which demonstrates that striatal spine loss is an early pathological feature of PD and is related to the extent of dopamine denervation (Villalba et al., 2009).

A new chronic PD mouse model has been recently developed, utilizing subcutaneous administration of low doses of MPTP for 3 months. The consequent nigrostriatal neurodegeneration and decrease in striatal dopamine levels were progressive and accompanied by motor impairment and by characteristic neuroinflammatory changes (microglial activation and astrogliosis), resembling the slow evolution of the human disease (Muñoz-Manchado et al., 2016).

The structural resemblance between MPTP and many pesticides/herbicides have paved the way for further studies exploring the connection between environmental toxins and PD.

Like MPTP, exposure to the herbicide paraquat and the pesticide rotenone causes selective dopaminergic neurodegeneration in rodents and non-human primates, inducing Parkinsonian features (Betarbet et al., 2000; Sherer et al., 2003; Tanner et al., 2011). Rotenone can easily cross the blood–brain barrier and, once in DAns, it acts as another potent mitochondrial complex I inhibitor, leading to generation of ROS, decreased levels of ATP, opening of the mitochondrial permeability transition pore with mitochondrial depolarization and caspase-3 activation, dysregulation of Ca2+ homeostasis and glutamatergic excitotoxicity; nigral DAns show a peculiar sensitivity to all these processes, with deleterious effects (Betarbet et al., 2000; Sherer et al., 2003; Martinez and Greenamyre, 2012).

In rats, chronic administration of rotenone causes a selective degeneration of nigrostriatal DAns, which begins in nerve terminals within the striatum and retrogradely progresses to the cell bodies and, in contrast to MPTP-based models, induces Lewy body-like cytoplasmic inclusions containing α-syn and ubiquitin, thus reproducing the neuropathological hallmark of human sporadic PD (Betarbet et al., 2000; Inden et al., 2011; Sherer et al., 2003; but see: Höglinger et al., 2003).

Although its structural similarity to MPTP, paraquat is a weak inhibitor of mitochondrial complex I activity; it seems to exert its toxicity through impairment of cellular redox cycling of glutathione and thioredoxin, via the formation of superoxide anion (Bonneh-Barkay et al., 2005; Sherer et al., 2003). In fact, the overexpression of superoxide dismutase (SOD) or glutathione peroxidase protects from the adverse effects of paraquat.

A study showed that chronic administration of paraquat in rats results in minor decreases in DAns and slight increases in dopamine neurotransmission at 4 weeks, while at 24 weeks it causes significant DAns loss and dopamine depletion, again useful to model preclinical stage of PD (Ossowska et al., 2005).

Pesticides models can contribute to our understanding of the potential role of environmental factors in PD pathogenesis. It is likely that environmental toxins inhibiting mitochondrial complex I act in concert with other environmental factors and genetic predisposition in the pathogenesis of PD. In this regard, many rodent models have been generated to explore the synergistic combinations of low doses of rotenone or paraquat with other PD risk factors, including aging (Cannon et al., 2009), genetic mutations (Martella et al., 2016; Tozzi et al., 2018; Zharikov et al., 2015), gut dysbiosis (Dodiya et al., 2020) and neuroinflammation (Ling et al., 2004).

Many more studies are carried out on rodents treated with 6-OHDA, an analogue of dopamine with high affinity for dopamine transporter DAT. 6-OHDA does not cross the blood–brain barrier and needs to be administered using stereotaxic injection directly into different parts of the nigrostriatal pathway, for example the SNpc (to achieve a specific and moderate dopamine depletion) or subregions of the caudate - putamen complex, where it induces damage of striatal terminals, followed by progressive nigral degeneration through a retrograde “dying back” process (Deumens et al., 2002). Given the higher mortality with bilateral injections, hemiParkinsonian models with unilateral injection are more frequently used.

Like MPTP, 6-OHDA inhibits mitochondrial complex I and produces ROS, thus oxidative stress is widely considered to be the primary mechanism of DAns loss in the 6-OHDA models (Schober, 2004). Moreover, the nigrostriatal dopaminergic degeneration triggers proinflammatory glial reactions (Kuter et al., 2020). 6-OHDA models proved to be useful to examine the effects of neuroprotective and neurorestorative compounds, including antioxidants and iron chelators, showing positive results (Haleagrahara et al., 2013; Jing et al., 2016). Despite these possibilities, 6-OHDA-based models lack the progressive time course and the presence of intracellular α-syn aggregates, characteristic of PD.

Studies on complete 6-OHDA models have contributed to explore the mechanisms by which endogenous striatal dopamine influences corticostriatal plasticity, in the form of long-term potentiation (LTP) and long-term depression (LTD). Corticostriatal transmission is crucial in the regulation of voluntary movement. A great striatal dopaminergic denervation produces a substantial imbalance in striatal neurotransmission in favour of glutamatergic inputs, with the consequent loss of dopamine-dependent bidirectional corticostriatal synaptic plasticity, mimicking advanced stages of PD. Conversely, minor degrees of dopaminergic deafferentation can selectively impair plasticity at corticostriatal synapses (Calabresi et al., 2007; Schirinzi et al., 2016). Paillé et al. generated a model of “early” PD in which rats were unilaterally injected with mild doses of 6-OHDA in order to obtain a partial dopaminergic denervation. Behavior analysis showed mild motor symptoms. Electrophysiological recordings of spiny projection neurons (SPNs) revealed an uncorrected composition of NMDA receptors in the postsynaptic density and, accordingly, a selective impairment of NMDA-dependent LTP, with sparing of LTD (Paillé et al., 2010). The hypothesis is that the loss of LTP, requiring higher levels of striatal dopamine, may represent an early marker of synaptic dysfunction in PD.

5. Genetic models

The identification of monogenic forms of PD, albeit rare, accounting for about 30% of the familial and 3%–5% of the sporadic cases (Bloem et al., 2021; González-Pérez et al., 2009; Klein and Westenberger, 2012), has provided significant advance in the comprehension of the pathophysiology of this disorder, through the study of the effects of mutated proteins and the generation of reliable PD animal models.

Among PD associated genes, Parkin, PINK1 and DJ-1 are associated to autosomal recessive forms of the disease and are known to be implicated in mitochondrial quality control system, and mitophagy in particular (Billingsley et al., 2019; Kumaran and Cookson, 2015; Mullin

and Schapira, 2015). Moreover, mutations in different genes turned out to be causative for synaptic dysfunction (Table 1) (Imbriani et al., 2018a, 2018b; Kitada et al., 2007; Madeo et al., 2012; Mancini et al., 2020; Tozzi et al., 2012).

Overall, in contrast to classical neurotoxic models, models of monogenic PD do not display dopaminergic neuronal loss nor a clear phenotype; nevertheless they show peculiar subtle functional alterations. It is plausible that early rearrangement of the basal ganglia circuitry occurs in these models, in an attempt to compensate for the alterations induced by gene mutation. This makes them suitable models for testing neuroprotective and disease-modifying therapeutic approaches.

6. Parkin

Mutations in PRKN (*PARK2*), encoding the protein Parkin, account for the majority of autosomal recessive forms of PD (Kitada et al., 1998). They cause early-onset cases with typical levodopa responsiveness, slow progression and dystonia as peculiar initial symptom (Kasten et al., 2018). However, there is evidence of Parkin inactivation also in sporadic PD, although whether here it drives neurodegeneration or is just a mere spectator is still unknown.

Parkin is an E3 ubiquitin ligase with an important role in the ubiquitin-proteasome system and in mitochondrial integrity (Imai et al., 2000; Yoboue and Valente, 2020). This enzyme protein is closely related to PINK1 in the regulation of mitochondrial homeostasis. It exerts neuroprotective activity through three independent mechanisms: 1) ubiquitination of toxic substrates and proteasomal degradation, 2) non-degradative ubiquitin signaling for the regulation of cell death pathways, 3) mitochondrial quality control regulation through autophagy/selected degradation of damaged mitochondria (termed mitophagy) (Borsche et al., 2021; Narendra et al., 2008; Quinn et al., 2020).

Genetic mouse models of PD based on Parkin inactivation have been generated and characterized, contributing to unravel the role of Parkin in the regulation of mitochondrial function and in the pathogenesis of the disease.

Parkin knockout (KO) mice show an increase in extracellular dopamine concentration in the striatum leading to reduced synaptic excitability in striatal SPNs and dysfunction of the nigrostriatal pathway, even with normal number of DAns in the substantia nigra, thus supporting the role of Parkin in dopamine regulation and nigrostriatal function (Goldberg et al., 2003).

Through a proteomic approach on the same Parkin model, the Authors demonstrated that loss of Parkin function induces decreased levels of proteins involved in mitochondrial function and protection from oxidative stress, together with decreased serum antioxidant capacity and increased protein and lipid peroxidation (Palacino et al., 2004).

Another mouse model with Parkin gene inactivation (obtained through deletion of exon 3, one of the most common Parkin mutations found in patients) displays behavioral, biochemical and electrophysiological alterations suggestive of initial damage to the presynaptic terminals of DAns (i.e. reduced striatal levels of dopamine transporter protein, impairment in amphetamine-induced dopamine release) in the absence of signs of neurodegeneration. The limbic regions show increased levels of endogenous dopamine. The Authors also observed a shift towards increased intraneuronal metabolism of dopamine by MAO. The enhanced oxidative reduction of dopamine by MAO could lead to increased production of H_2O_2 and excessive generation of free radicals, harmful for neurons. However, these mice may develop compensatory mechanisms to protect DAns from death, like more powerful free radical protecting systems, as suggested by the detection of increased levels of GSH in dopamine rich areas including the striatum (Itier et al., 2003).

On this line, we previously supported the notion that Parkin insufficiency may impair dopaminergic circuit by performing a functional analysis of the nigrostriatal circuit in the Parkin KO mouse (Kitada et al., 2009a, 2009b). Through amperometric recordings, we described a decrease in evoked dopamine release in acute striatal slices and, in line with this result, a reduction in total catecholamine release and quantal size in dissociated chromaffin cells from both homozygous and heterozygous Parkin KO mice. The intracellular recordings of striatal SPNs showed an impaired bidirectional corticostriatal synaptic plasticity, that is a dopamine-dependent phenomenon, represented by a failed induction of LTD and LTP in Parkin KO mice, while synaptic plasticity was not altered in the hippocampus of these animals (Kitada et al., 2009a, 2009b). These same mice showed a selective enhanced sensitivity to striatal group II metabotropic glutamate receptor activation, as an adaptive change to abnormal dopamine signaling (Martella et al., 2009).

The role of Parkin at glutamatergic synapses was more recently explored by Cortese et al., who demonstrated reduced AMPA receptor-mediated currents and cell-surface expression in Parkin-deficient neurons, resulting from decreased expression of the postsynaptic protein Homer1, which is required for coupling AMPA receptor endocytic zones with the postsynaptic density. Accordingly, Parkin inactivation causes reduced density of postsynaptic endocytic zones and impaired AMPA receptors internalization. The Authors also observed significantly decreased miniature excitatory postsynaptic currents (mEPSC) frequency in hippocampal neurons from Parkin KO rats, suggesting a role for Parkin also in presynaptic neurotransmitter release (Cortese et al., 2016).

However, other studies on Parkin-deficient rodents failed to identify significant impairments of dopaminergic markers. A recent study on 2 month-old Park2 knockout rats found unaltered dopamine release (Gemechu et al., 2018). Sanchez and colleagues examined 6–8 week old mice carrying a deletion of the Parkin gene, which did not show significant impairments in activity-dependent dopamine release compared to controls (Sanchez et al., 2014). The Authors argued that the age of the mice is an important variable to consider, and that it is likely that deficits only appear at older ages. On the contrary, Oyama and colleagues reported reduced in vivo dopamine overflow in 3 and 6 months old male Parkin KO mice, but not in 9 or 12 months old mice, suggesting the existence of age-dependent compensations (Oyama et al., 2010).

Even triple deficiency in parkin/DJ-1/PINK1 did not cause drastic phenotypical changes in aged mice (Kitada et al., 2009a, 2009b). The absence of other cellular stressors, like age, environmental toxins or genetic background, and the development of adaptive changes to compensate for Parkin inactivation in some Parkin KO rodent models may account for the absence of any detectable neurochemical or pathological changes nor robust signs of Parkinsonism (Perez and Palmiter, 2005). Consistent with this, Shin et al. showed that only controlled conditional knockdown of Parkin in adult mice could cause dopaminergic neuronal loss (Shin et al., 2011). In this study, the Authors found that Parkin also interacts with the substrate PARIS (ZNF746), a zinc finger protein that accumulates in animal models of Parkin inactivation and in human PD brains. The dopaminergic neuronal loss in Parkin KO animals was found to be in a PARIS-dependent manner, and PARIS overexpression causes selective loss of DAns in the substantia nigra (Shin et al., 2011).

Recent advances in the knowledge of Parkin putative substrates have contributed to elucidate further potential PD associated neurodegenerative mechanisms. Through an adult knockdown strategy in a mouse model for Parkin-linked PD, thus distinct from the traditional KO approaches, Wang et al. recently demonstrated that synaptotagmin-11 (Syt11), encoded by the novel PD-risk gene SYT11, mediates Parkin-linked neurotoxicity. Parkin deficiency leads to abnormal Syt11 accumulation in dopaminergic neurons, which impairs endocytosis and consequently dopamine release and causes late onset loss of DAns (Wang et al., 2018). This can be reversed by Syt11 knockdown in the SNpc in a Parkin knockdown background, thus suggesting that Syt11 accumulation mediates the pathogenic role of Parkin in PD (Wang et al., 2018).

A link between Parkin inactivation, PARIS and α-syn was recently described, too. In three α-*syn*-overexpression mouse models, Parkin is inactivated through c-Abl kinase phosphorylation, with subsequent

Table 1
Synaptic dysfunction in genetic rodent models of Parkinson's disease.

Locus	Gene	Protein	Inheritance	Clinical phenotype	Putative protein function	Rodent model	Synaptic dysfunction	References
PARK1 PARK4	*SNCA*	α-synuclein	Dominant	EOPD with dementia/ cognitive decline	Modulation of neurotransmission and presynaptic vesicle trafficking	BAC transgenic mice	Deficit in DA release Increased clustering of vesicles in DA terminals	(Janezic et al., 2013)
				Variable phenotypes		BAC transgenic mice	Age-dependent degeneration in the dorsal striatum	(Hendrickx et al., 2021)
						A53Tα-*syn*-overexpressing mice	Impaired striatal DA release	(Platt et al., 2012)
						Aged A53T α-syn-overexpressing mice	Increased DA striatal levels Reduced postsynaptic dopaminergic response	(Kurz et al., 2010)
						Rats with intrastriatal injections of α-syn preformed fibrils	Absent striatal LTD Altered firing rate of SNpc DAns Increased striatal glutamatergic transmission Impaired striatal LTD and LTP	(Tozzi et al., 2021)
						PARK1/hA30P and PARK4/h α-syn mutant mice	Presynaptic structural changes	(Vargas et al., 2017)
PARK2	*PRKN*	Parkin	Recessive	EOPD with slow progression and dystonia at onset	Involved in ubiquitin-proteasome system and mitochondrial homeostasis	Parkin KO mice	Decrease in evoked striatal DA release Impaired bidirectional corticostriatal synaptic plasticity, normal hippocampal synaptic plasticity	(Kitada et al., 2009)
						Parkin KO mice	Enhanced sensitivity of striatal neurons to group II mGlu receptor activation	(Martella et al., 2009)
						Parkin KO rats	Impairment of AMPA receptors internalization in hippocampal neurons	(Cortese et al., 2016)
PARK5	*UCHL1*	UCHL1	Dominant	Classical PD	Hydrolase and ligase activity Regulation of ubiquitin stability in the nervous system	Mice with spontaneous deletion in UCHL1 gene	Reduced exploratory behavior and hippocampal LTP	(Sakurai et al., 2008)
PARK6	*PINK1*	PINK1	Recessive	EOPD	Oxidative stress response, maintenance of mitochondrial function	PINK1 KO mice	Decrease in striatal DA release Impaired striatal LTD and LTP	(Kitada et al., 2007)
						PINK1 KO mice	Enhanced sensitivity of striatal neurons to group II mGlu receptor activation	(Martella et al., 2009)
						PINK1 KO mice	Heterozygous mice show a selective impairment of corticostriatal LTP, with sparing of LTD	(Madeo et al., 2014)
						PINK1 KO mice	Age-dependent decrease of striatal DA release	(Zhi et al., 2019)
PARK7	*DJ-1*	DJ-1	Recessive	EOPD	Regulator of transcription and signal transduction pathways,	DJ-1 KO mice	Reduced striatal evoked DA overflow.	(Goldberg et al., 2005)

(*continued on next page*)

Table 1 (*continued*)

Locus	Gene	Protein	Inheritance	Clinical phenotype	Putative protein function	Rodent model	Synaptic dysfunction	References
					sensor of oxidative stress, ROS scavenger		Selective impairment of LTD	
						DJ-1 KO mice	Impairment of hippocampal LTD and slight impairment of hippocampal LTP	(Wang et al., 2008)
PARK8	*LRRK2*	LRRK2 or Dardarin	Dominant	Classical PD	GTPase and kinase activity. Involvement in multiple cellular processes, including vesicle trafficking, autophagy, mitochondrial function, synaptic transmission, immune system modulation	G2019S LRRK2 transgenic mice	Impaired evoked DA release in the dorsolateral striatum Loss of bidirectional corticostriatal synaptic plasticity	(Chou et al., 2014)
						Human wild-type LRRK2 overexpressing mice	Altered glutamatergic short-term plasticity Increased presynaptic dopamine D2 receptors signaling Decreased dopamine tone	Beccano-Kelly et al., 2015
						BAC (G2019S or R1441C) LRRK2 transgenic rats	Reduction in SNpc DAns burst firing Altered striatal DA release	(Sloan et al., 2016)
						LRRK2 KO mice		
						G2019S LRRK2 KI mice	Changes in dendritic morphology of SPNs during aging	(Chen et al., 2020)
							Loss of striatal LTP	(Matikainen-Ankney et al., 2018)
PARK17	*VPS35*	VPS35	Dominant	Classical PD	Recycling of transmembrane cargo proteins from endosomes back to the trans-Golgi network	VPS35 heterozygous mice ($VPS35^{+/m}$)	Impaired AMPA receptor trafficking Decreased dendritic spine maturation	(Tian et al., 2015)
PARK19	*DNAJC6*	Auxilin	Recessive	EOPD with slow progression	Involved in the pathway of clathrin-mediated endocytosis	Auxilin KO mice	Impaired endocytosis of synaptic vesicles in KO hippocampal neurons	(Yim et al., 2010)
PARK20	*SYNJ1*	Synaptojanin 1	Recessive	Parkinsonism with dystonia and cognitive decline	Homeostasis of early endosomal compartments	SYNJ1 KI homozygous mice	Defective clathrin uncoating of synaptic vesicles and dystrophic changes in the nigrostriatal terminals	(Cao et al., 2017)

The table reports some examples of genetic rodent models of PD showing early synaptic dysfunction.
EOPD, early-onset PD; BAC, bacterial artificial chromosome; DA, dopamine; α-syn, α-synuclein; LTD, long-term depression; LTP, long-term potentiation; DAns, dopaminergic neurons; SNpc, substantia nigra pars compacta; SPNs, spiny projection neurons; KO, knockout; KI, knockin; mGluR, metabotropic glutamate receptor.

accumulation of PARIS; more importantly, knockout of PARIS attenuates the neurodegenerative process (Brahmachari et al., 2019).

7. PINK1

Mutations in PINK1 (PTEN-induced kinase 1)(*PARK6*) represent the second most common cause of early-onset PD (Valente et al., 2004a, 2004b). Most mutations are fully penetrant biallelic with autosomal recessive inheritance, but some heterozygous variants have been identified too (Marongiu et al., 2008). They cause a phenotype that is quite indistinguishable from sporadic forms, with slow disease progression and levodopa sustained response, but with onset within the fourth decade of life (Valente et al., 2004a, 2004b).

The PINK1 gene encodes a 581 residue serine-threonine kinase with a N-terminal mitochondrial targeting motif. The protein exerts neuroprotective effects, acting at the crossroad of several signaling pathways, including protection against protein-misfolding, mitochondrial and calcium homeostasis, endoplasmic reticulum and mitochondrial networks (Brunelli et al., 2020; Voigt et al., 2016).

PINK1 closely interacts with Parkin, as key regulators of processes to maintain neuronal homeostasis and survival. They are involved in the first steps of a signaling pathway that activates mitochondrial quality control to remove impaired mitochondria. In healthy mitochondria, PINK1 is located in the intermembrane mitochondrial space, a process that requires the coordinated action of several proteases and translocases, like the translocase of the inner membrane complex (TIM) and the translocase of the outer membrane complex (TOM) (Huang et al., 2017). When mitochondria are depolarized, PINK1 accumulates on the outer membrane, where it forms a complex with TOM proteins (Koyano et al., 2019). Here, it recruits Parkin from the cytosol, which in turn ubiquitinates several outer mitochondrial membrane proteins, inducing autophagic degradation and triggering selective mitophagy (Brunelli et al., 2020; Matsuda et al., 2010; Yoboue and Valente, 2020). Actually, some studies suggest that PINK1 can drive the autophagic degradation of damaged mitochondria also independently from Parkin (Lazarou et al., 2015). Further experiments provided evidence for an interaction

between PINK1 and Miro-Milton, which results in the regulation of neuronal mitochondrial transport to and from dendrites and axons (Weihofen et al., 2009; Brunelli et al., 2020; Sheng and Cai, 2012). Indeed, neurons lacking PINK1 have impaired mitochondrial trafficking and dendrite overgrowth (Das Banerjee et al., 2018).

Different rodent models have been developed to study the consequences of PINK1 deficiency, although with conflicting results obtained by different research groups.

In one model, knocking out PINK1 has been accomplished by germline deletion of exon 4 to 7, which removes the majority of the kinase domain (Kitada et al., 2007). The homozygous PINK1 KO mouse (PINK1$^{-/-}$) is an established model of subclinical PD in which, despite the lack of overt neuronal degeneration and of major phenotypic alteration, even with aging, a significant impairment of both LTP and LTD at corticostriatal synapses has been described. Also gross striatal dopamine levels and dopamine receptor expression are unaltered in these mice, and the loss of bidirectional corticostriatal synaptic plasticity is the consequence of a decrease in striatal dopamine release (Kitada et al., 2007). The changes in corticostriatal synaptic plasticity may represent an early pathophysiological process preceding neuronal death, thus reflecting the early phases of the disease (Imbriani et al., 2018a, 2018b).

A plausible hypothesis for the deficits observed in this model is that PINK1 haploinsufficiency precipitates mitochondrial functioning and ATP production under increased demand, also impairing the synaptic vesicle release at dopaminergic terminals (Calabresi and Ghiglieri, 2014; Heeman et al., 2011; Imbriani et al., 2018a, 2018b; Schirinzi et al., 2016; Zou et al., 2021).

Intriguingly, in this same model we previously observed that the treatment with the antioxidant agent Vitamin E (both when administered acutely on brain slices and chronically through i.p. injections) was able to rescue both LTD and LTP. Specifically, alpha-tochoperol fully rescued both the forms of synaptic plasticity only when administered chronically in vivo, while the water-soluble vitamin E analogue Trolox restored LTD and LTP also in acute conditions (Schirinzi et al., 2019). Vitamin E may exert its protective action by activating various cellular pathways (i.e. antioxidant, detoxifying and anti-inflammatory ones) and enhancing the mitochondrial metabolism, as demonstrated in other experimental studies (Martin et al., 2014; Shim et al., 2011). Indeed, neurotransmitter release is a process that strongly depends on mitochondrial bioenergetics.

Not only the homozygous PINK1 KO mouse, but also the heterozygous PINK1 mutation-carrying model have been previously characterized, showing early rearrangement within corticostriatal circuitry, represented by a selective impairment of LTP with a physiologically expressed LTD, in the absence of motor phenotype and dopaminergic neuronal loss (Madeo et al., 2014). These observations are in line with what have been observed in clinical neuroimaging and physiological studies, where PINK1 heterozygous mutation carriers manifested initial alterations in the nigrostriatal circuit (Eggers et al., 2010; Klein et al., 2007). The heterozygous condition related to PINK1-associated Parkinsonism is characterized by early alterations which occur before the onset of clinical phenotype, including dysfunction of dopaminergic axon terminals, thus representing a good preclinical model of early stage PD, suitable to test potential disease-modifying therapy.

In this regard, the heterozygous PINK1 mouse model has been useful to study the effect of a gene-environment interaction that better mirrors the clinical condition. Indeed, PD is thought to arise from the combination of genetic susceptibility, environmental exposures and aging. The PINK1 heterozygous KO mouse has been exposed to rotenone, chronically administered at low doses. The minimal exposure to the mitochondrial toxin in a genetic background of susceptibility has been sufficient to induce severe alterations of corticostriatal synaptic plasticity, comparable to those observed in the PINK1 homozygous KO model (Martella et al., 2016).

A recent study in the same PINK1 KO mouse model proposed a further link between mitochondria, synaptic plasticity and PD, mediated by caspases. Caspases are a family of proteases playing key roles in multiple cellular processes, like programmed cell death and inflammation, but also in non-apoptotic pathways, such as dendrite development, axon pruning and synaptic plasticity mechanisms. The Authors explored the role of caspase-3, activated via the mitochondrial pathway, in the modulation of corticostriatal synaptic plasticity. After LTD induction, PINK1 KO mice showed a significant decrease of caspase-3 activity compared with wild-type mice. Moreover, pretreatment of striatal slices with a caspase-3 activator rescued a physiological LTD, while the inhibition of caspase-3 prevented the amphetamine-induced rescue of LTD (Imbriani et al., 2019). These results support that the fine modulation of caspase-3 at the synaptic terminal may be crucial for the physiological expression of LTD (Li et al., 2010). One plausible hypothesis centers around the complex interaction among PINK1, the long-term synaptic plasticity machinery and the mitochondrial apoptotic pathway. This is engaged by BAD activation, a Bcl-2 family member, which activates BAX, in turn promoting the cytosolic release of cytochrome *c*, leading to activation of caspase-9 and caspase-3. The BAD-induced caspase activation is necessary to promote AMPA receptor endocytosis and the expression of long-term synaptic plasticity (Arena et al., 2013; Jiao and Li, 2011). BCL-XL, another Bcl-2 family member, which exerts anti-apoptotic function by inhibiting BAX, is involved in the modulation of LTD too (Li et al., 2010). It has been demonstrated that PINK1 and BCL-XL interact on the outer mitochondrial membrane where PINK1 phosphorylates BCL-XL, preventing its pro-apoptotic cleavage and protecting cell against apoptosis (Arena et al., 2013). Thus, in this complex scenario, PINK1 deficiency may lead to synaptic dysfunction by impairing mitochondrial functional integrity and perturbing one of these pathways, although the exact mechanism remains to be elucidated.

Gispert et al. characterized another PINK1 KO mouse model, in which the pathogenic patient mutation G309D was inserted into exon 5, causing a 97% knock-down of Pink1 transcript and a loss-of-function mutation in the remaining mRNA. Here they could observe a phenotype of motor impairment, that is a reduction of locomotor activity for spontaneous movement, and weight loss at old age. These correlated with evidence of dopaminergic axon terminal dysfunction (i.e. reduction of striatal dopamine content) and mitochondrial impairment (i.e. a prominent deficit of preprotein import and of mitochondrial functions like ATP-generation and respiration), again in the absence of nigrostriatal neurodegeneration. The study of PINK1$^{-/-}$ primary neuron culture revealed a reduced fission and increased mitochondrial aggregation only under stress conditions, supporting the increased susceptibility of DAns in PINK1-associated Parkinsonism (Gispert et al., 2009).

In another PINK1 KO mouse model, where exon 2 to exon 5 were replaced with a LacZ/Neo cassette, the dopamine release was measured at different ages through fast-scan cyclic voltammetry. Single pulse-evoked dopamine release in the dorsal striatum showed an age-dependent decrease, that was ascribed to a reduced presynaptic release rather than alterations of dopamine transporter reuptake function. The impaired dopamine release may be due to low ATP generation, as the Authors found lower basal oxygen consumption rate (OCR), a measurement of ATP production, in striatal slices of PINK1 KO mice compared with wild-type (Zhi et al., 2019).

PINK1 deficiency not only impairs striatal but also hippocampal synaptic plasticity. Recently, a study on mouse cultured hippocampal neurons explored whether PINK1 silencing influences dendritic spine dynamics. It was demonstrated that loss of PINK1 function induces changes in spine morphology (i.e. increase of thin spines density and decrease of head size of stubby spines), which are mediated by changes in actin regulatory proteins RhoGAP29 and ROCK2. Moreover, a decrease in postsynaptic density proteins (PSD95 and Shank) and glutamate receptor subunit NR2B and mGluR5 was found. These data support a role of PINK1 in the regulation of postsynaptic plasticity in hippocampal neurons, inducing changes in dendritic spines that could represent early alterations preceding neurodegeneration in PD

(Hernández et al., 2019).

Besides PINK1 mouse models, novel rat models with targeted disruption of PINK1 gene have been generated to explore the eventual appearance of a progressive PD-like phenotype. PINK1 KO rats show progressive nigral neurodegeneration with 50% dopaminergic cell loss and an increase of striatal dopamine and serotonin levels at 8 months of age. Moreover, significant motor deficits could be observed starting at 4 months of age. These results support the notion that PINK1 gene, in contrast to PINK1 KO mice, may be critical for survival of nigral neurons in the rat (Dave et al., 2014).

Actually, later de Hass et al. were unable to replicate striatal neurochemical alterations or dopaminergic cell loss in the SNpc of PINK1 KO rats at 8 months of age, although they could replicate the behavioral deficits previously described (de Haas et al., 2019). The Authors could not clearly detect a clear reason for conflicting findings in this model, but they did not exclude that environmental and internal factors (like animal housing conditions, stress, food, microbiome) could have contributed to the progression of neurodegeneration. Hence the need for reflection on the validation of the disease model and the appropriate model choice based on the specific research question that has to be answered.

Loss-of-function mutations of Parkin and PINK1 can also contribute to PD pathogenesis through mitochondrial-mediated neuroinflammation. It has been recently demonstrated that PINK1 and Parkin repress a pathway for the presentation of mitochondrial antigens. This pathway is not mediated by mitophagy, but relies on the generation of mitochondrial-derived vesicles (MDVs). In the absence of Parkin or PINK1, high levels of mitochondrial antigens are presented by immune cells in inflammatory conditions. Thus the two proteins have a key role in adaptive immunity, being involved in the suppression of an immune-response-eliciting pathway provoked by inflammation (Matheoud et al., 2016). These results provide a link between mitochondrial dynamics and the potential involvement of autoimmune mechanisms in PD. The same Authors later demonstrated that Gram-negative bacteria intestinal infections in PINK1$^{-/-}$ mice trigger the generation of cytotoxic CD8+ T-cells directed against mitochondrial antigens in the periphery and in the brain, causing loss of dopaminergic axonal varicosities in the striatum and functional motor defects, that are reversed after treatment with L-DOPA. This highlights the relevance of autoimmune mechanisms and of the gut-brain axis in the etiology of PD (Matheoud et al., 2019).

8. DJ-1

DJ-1 is another PD-related protein exerting regulatory effects on mitochondrial activity. Biallelic mutations in DJ-1 (*PARK7*) are responsible for some forms of autosomal recessive PD, but they are less common than mutations in Parkin or PINK1 (Bonifati et al., 2003a, 2003b). DJ-1 orchestrates oxidant defences, acting as a cellular sensor of oxidative stress, and regulates pathogenic pathways that converge with the PINK1/Parkin-mediated mitophagy. Under oxidative conditions, DJ-1 is oxidized at cysteine residue 106 and accumulates on the outer mitochondrial membrane to maintain a healthy mitochondrial environment, similarly to PINK1/Parkin (Canet-Avilés et al., 2004; Larsen et al., 2018; Li et al., 2021a, 2021b). Mitochondria-localised DJ-1 is part of the thioredoxin/apoptosis signal-regulating kinase 1 (Trx/Ask1) complex, which activates the radical scavenging system to regulate the clearance of endogenous ROS (Andres-Mateos et al., 2007). Moreover, DJ-1 may reduce protein misfolding and aggregation, another consequence of oxidative stress, and so counter α-syn aggregation (Batelli et al., 2008; Xu et al., 2017).

Excessive oxidized DJ-1 has been observed in brains of patients with sporadic PD, which indicates an increased ROS scavenging activity (Choi et al., 2006).

Loss of DJ-1 function is associated to elevated mitochondrial oxidant stress and damage (i.e. decreased mitochondrial membrane potential and motility, increased mitochondrial fragmentation, accumulation of autophagy markers) and to an increased vulnerability to complex I inhibition (Guzman et al., 2010; McCoy and Cookson, 2011; Sironi et al., 2020). The mitochondrial fragmentation caused by the loss of DJ-1 can be rescued by overexpression of either Parkin or PINK1 (Irrcher et al., 2010; Thomas et al., 2011).

An elegant study was recently performed on dopaminergic neurons obtained from differentiation of induced pluripotent stem cells (iPSCs) reprogrammed from fibroblasts of PD patients carrying a homozygous loss of function DJ-1 mutation. DJ-1 mutant DAns were characterized by elevated mitochondrial oxidant stress and oxidized dopamine accumulation, which further trigger downstream toxic effects, including diminished activity of the enzyme glucocerebrosidase (GCase), lysosomal dysfunction and α-syn accumulation. Mitochondrial antioxidants (mito-TEMPO or NAC) and calcium modulators (like isradipine) could attenuate the toxic cascade. This evidence thus links three major pathological features of PD (mitochondrial dysfunction, lysosomal dysfunction, and α-syn) in a pathogenic positive feedback. Interestingly, similar alterations in oxidized dopamine and GCase were also observed in neurons obtained from patients with idiopathic PD (Burbulla et al., 2017).

To explore the role of DJ-1 in the dopaminergic system, a DJ-1 deficient mouse model was generated. DJ-1$^{-/-}$ mice showed decreased body weight gain, decreased grip strength and progressive gait abnormalities compared to wild-type littermates, although selective dopaminergic cell death was absent (Chandran et al., 2008). They showed reduction in evoked dopamine overflow in striatal slices, primarily due to increased dopamine reuptake. Behavioral analysis revealed a decrease in spontaneous activity in the open field test. The physiological inhibition of nigral neurons to dopamine or to D2 receptor agonists (i.e. quinpirole) were decreased in DJ-1$^{-/-}$ mice, suggesting an impairment of D2 receptor-dependent responses. Indeed, induction of corticostriatal LTD, which requires both D1 and D2 receptors activation, was altered and could be restored by D2 receptors agonists, while induction of LTP, requiring only D1 receptors activation, was not impaired in these mice. The Authors concluded that DJ-1 may play an important role in regulating D2 receptor-dependent neuronal signaling mechanisms (Goldberg et al., 2005).

By contrast, a later study focused on a comparative evaluation of striatal dopamine transmission from 6 to 8 weeks old transgenic mouse models of PD failed to detect significant alterations in dopamine overflow responses evoked by single pulses in all mice, including DJ-1 KO. This is compatible with the absence of dopaminergic neuron loss in these models, although the Authors stated that subtle impairments of dopamine transmission cannot be excluded, and that the differences observed with respect to the previous studies could be ascribed to different animal age (Sanchez et al., 2014).

The hippocampus contains high levels of DJ-1, therefore Wang and coworkers explored the effects of DJ-1 inactivation on CA1 hippocampal synaptic plasticity in DJ-1$^{-/-}$ mice. Here, they found that LTD was abolished, but also LTP was slightly reduced, and that quinpirole could rescue LTD, suggesting again a role for altered dopaminergic signaling in these mice (Wang et al., 2008).

DJ-1 KO rodent models show increased susceptibility to MPTP and 6-OHDA, while DJ-1 overexpression protects nigral dopaminergic neurons from MPTP-induced degeneration (Inden et al., 2006; Kim et al., 2012; Paterna et al., 2007), again highlighting the complex interplay between genetic and neurotoxic factors in PD pathology.

When DJ-1 nullizygous mice are backcrossed to a C57BL/6 J background, they exhibit significant early-onset unilateral SNpc dopaminergic neurons degeneration, which progresses into bilateral degeneration of the nigrostriatal axis and of the locus ceruleus with aging, in addition to motor behavior deficits. This progression to a bilateral pathology is of particular interest, reminding of the typical unilateral-to-bilateral involvement of the human disease (Rousseaux et al., 2012).

A recent study on primary cultured neurons confirmed the presence

of DJ-1 in presynaptic terminals, with a distribution that correlates with the size of synaptic boutons. No structural alterations in synapses could be detected in DJ-1 KO neurons; however DJ-1 deficiency significantly impairs synaptic vesicle endocytosis and reavailability, which may be correlated to alterations in cholesterol level and synaptic membrane fluidity (Kyung et al., 2018).

DJ-1 is also expressed in CD4+ T-cells, where it acts as a powerful regulator of ROS production and of the Na^+ /H^+ exchanger 1 (NHE1) expression. $CD4^+$ T-cells from DJ-1 deficient mice show increased ROS formation, NHE1 transcript levels, NHE1 protein, and NHE activity compared with $CD4^+$ T-cells from wild type mice, due to the loss of DJ-1 antioxidant effect (Zhou et al., 2017). Additionally, DJ-1 exerts anti-inflammatory activity independently from the ROS regulatory pathway. It positively regulates anti-inflammatory functions through induction of the synthesis of prostaglandin D2 (Choi et al., 2019), and through the differential regulation of natural and induced regulatory T-cells (Singh et al., 2015).

9. SNCA

In addition to the well characterized pathogenic mutations leading to autosomal recessive forms of PD, other PD-related genes and genetic risk factors have emerged as possibly linked to mitochondrial and synaptic dysfunction.

Mutations in the SNCA gene (*PARK1/4*), encoding the α-syn protein, were the first identified in PD subjects (Polymeropoulos et al., 1996). Both SNCA missense mutations (A53T, A53E, A30P, E46K, H50Q, and G51D) and multiplications (duplications and triplications) have been recognized (Chartier-Harlin et al., 2004; Ross et al., 2008), and both gain-of-function and loss-of-function mechanisms are likely to contribute to disease presentation (Koprich et al., 2017).

Familial Parkinsonism associated with SNCA is rare and characterized by variable clinical phenotypes: duplications cause a phenotype that is indistinguishable from idiopathic PD, while triplications are associated to an earlier onset, a more rapid progression and a higher prevalence of cognitive deficits, autonomic dysfunction and psychiatric symptoms (Farrer et al., 2004).

α-syn is a small and soluble protein, mainly localised in the presynaptic nerve terminals, in the mitochondria-associated endoplasmic reticulum membranes (MAMs), and in the nucleus (Guardia-Laguarta et al., 2014; Kramer and Schulz-Schaeffer, 2007; Pinho et al., 2019). In PD as well as in other synucleinopathies (like dementia with Lewy bodies and multiple system atrophy), α-syn aggregates to form insoluble fibrils. Indeed, α-syn represents the primary component of Lewy bodies and Lewy neurites. According to the "α-synuclein cascade hypothesis", at first a conformational change of the monomeric form occurs, followed by a gradual formation of larger multimeric protein species, among which the soluble oligomeric/protofibrillar aggregates represent the most toxic forms. These, in turn, can potentiate the pathological cascade (Ingelsson, 2016).

The physiological role of α-syn remains poorly understood, although its pre-synaptic location suggests a role in regulating synaptic vesicle-mediated release of neurotransmitters, and thus synaptic activity and plasticity, through an interaction with SNARE complexes, which makes it a suitable biomarker for synaptic dysfunction (Bendor et al., 2013; Cardinale et al., 2021; Lautenschläger et al., 2017; Sulzer and Edwards, 2019). Indeed, mice lacking all three synuclein homologues (α, β, and γ) have reduced size and function of excitatory synapses (Greten-Harrison et al., 2010).

There is a relatively large body of data form preclinical studies on the physiological and pathological role of SNCA for dopaminergic signaling.

It has been demonstrated that mice lacking SNCA (Abeliovich et al., 2000), transgenic mice overexpressing α-syn and viral vector models (Lundblad et al., 2012; Platt et al., 2012; Taylor et al., 2014) have impaired dopamine release.

A study performed on two independent transgenic mouse lines overexpressing human A53T-SNCA evaluated long term in vivo effects of SNCA mutations in the nigrostriatal dopaminergic projection. Aged mice did not develop visible α-syn aggregation nor detectable neuron loss, but they displayed a progressive deficit in spontaneous locomotion, compatible with deficient striatal dopamine signaling. Unexpectedly, an increased dopamine content in the striatum of old A53T-SNCA overexpressing mice was found. Conversely, old SNCA KO mice exhibited decreased striatal dopamine content, suggesting a physiological modulation of dopamine content by the expression level of SNCA. The accumulation of striatal dopamine in overexpressing mice was interpreted as a compensatory effort to enhance dopaminergic signaling, together with an upregulation of postsynaptic dopamine receptors and a down-regulation of extraneural catechol-ortho-methytransferase (COMT). However, the postsynaptic dopaminergic response seemed to be reduced and, as a consequence, LTD was absent in corticostriatal slices from old transgenic mice (Kurz et al., 2010). On the contrary, young adult A53T-SNCA mice of 4 months of age did not show behavioral phenotype and showed normal corticostriatal LTD (Tozzi et al., 2012).

Transgenic mice for truncated human α-syn 1–120 and rats injected with the adeno-associated viral vector carrying wild-type human α-syn exhibited a selective block of the induction of LTP in striatal ChIs, associated to early memory and motor alterations, which was dependent on α-syn modulation of the GluN2D-expressing NMDA receptors, whereas LTP was physiologically expressed by SPNs (Tozzi et al., 2016).

The same research group later demonstrated that the incubation of high concentration of oligomeric α-syn reduces NMDA receptor-mediated synaptic currents and alters corticostriatal LTP of SPNs of both direct and indirect pathways. Moreover, the treatment of striatal slices with antibodies against α-syn rescued LTP and the synaptic localization of GluN2A NMDA receptor subunit (Durante et al., 2019).

Daher et al. developed conditional α-syn transgenic mice, that express A53T or C-terminally truncated (1–119) human α-syn pathological variants selectively in catecholaminergic neurons, including dopaminergic neurons. A dopaminergic neuronal loss was not present in these animals, however α-syn119 expression in nigral dopaminergic neurons caused a relevant reduction in striatal dopamine levels together with other subtle neurochemical alterations (Daher et al., 2009).

Conversely, α-syn BAC mouse model with overexpression of human SNCA displays age-dependent motor impairments and loss of DAns (Janezic et al., 2013). A new α-syn transgenic BAC model shows an age-dependent degeneration in the dorsal striatum (evidenced by a gradual loss of TH-positive axonal projections and DAT-positive axon terminals), without loss of DAns of the SNpc, a phenotype that is reminiscent of early PD (Hendrickx et al., 2021).

A very recent study described for the first time the effects of intrastriatal injections of α-syn preformed fibrils in rodents, able to induce time-dependent electrophysiological and behavioral alterations, via retrograde transmission (Tozzi et al., 2021). Specifically, the toxic fibrils perturbed the firing rate of dopaminergic neurons of the SNpc, increased striatal glutamatergic transmission and altered the two main forms of corticostriatal synaptic plasticity, before the appearance of overt neurodegeneration. The Authors also obtained a rescue of these α-syn-induced alterations by sub-chronic treatment with L-DOPA, further supporting the role of dopaminergic dysfunction in the early phase of PD (Tozzi et al., 2021).

α-syn misfolding and aggregation lead to numerous other cellular disorders, including mitochondrial dysfunction, oxidative stress and dysregulation of proteasomal and lysosomal pathways (Marvian et al., 2019; Parihar et al., 2009; Petrucelli et al., 2002; Shin et al., 2005).

α-syn accumulation and mitochondrial dysfunction appear to be related in a bidirectional interaction (Di Maio et al., 2016). On one hand, increased levels of α-syn in dopaminergic neurons impairs mitochondrial morphology, membrane potential, respiratory chain complex I function, and enhances oxidative stress and ROS formation (Chinta et al., 2010; Ganjam et al., 2019; Hannestad et al., 2020; Zambon et al., 2019). α-syn accumulates on mitochondria, where it interacts with

components of the ATP synthase complex, affecting the oxidative phosphorylation. Toxic oligomers also induce mitochondrial lipid peroxidation, with the opening of permeability transition pores and activation of the apoptotic pathway, leading to neuronal death (Ludtmann et al., 2018). Calcium can trigger α-*syn*-mediated mitochondrial dysfunction (Luth et al., 2014). Moreover, α-syn interacts with several other mitochondrial components, including the TOM20 presequence receptor of the mitochondrial protein import machinery (Di Maio et al., 2016), voltage-dependent anion channel (VDAC), PINK1, Parkin, DJ-1 (Rostovtseva et al., 2015; Bernal-Conde et al., 2020), and mitochondrial sirtuin 3 (SIRT3) involved in mitochondrial quality control and prevention of oxidative stress (Park et al., 2020). A conformationally distinct, nonfibrillar, phosphorylated species of α-syn (named "pα-syn*") has been recently discovered too, which targets mitochondria inducing their fragmentation, energy deprivation and mitophagy (Grassi et al., 2018).

On the other hand, mitochondrial impairment causes α-syn accumulation and oligomerization, as confirmed by paraquat and rotenone PD models (Dastidar et al., 2020; Nisticò et al., 2011).

In mice overexpressing human wild-type (hWT) α-syn, a mitochondrial dysfunction in dopaminergic nigrostriatal neurons preceding dopamine loss in the striatum has been demonstrated (Subramaniam et al., 2014). Specifically, the Authors observed: defects in mitochondrial respiratory complexes I, II, IV and V in the midbrain, and IV and V in the striatum, of these mice compared to wild type littermates; high level of lipid peroxidation in the ventral midbrain; low level of the neuronal antioxidant enzyme peroxiredoxin 2 in the midbrain and, by contrast, increased level of peroxiredoxin 2 in the striatum and cortex, as a protection mechanism in the presence of elevated levels of α-syn.

Mild α-syn overexpression promotes the formation of ER-mitochondria contact sites, favouring Ca2+ transfer from the ER to mitochondria, while its silencing impairs mitochondrial function by loosening the ER-mitochondria interface (Calì et al., 2012).

An interesting recent study on rat ventral midbrain cultures explored the combined effects of overexpression of wildtype or mutant A53T α-syn, and PINK1 knockdown on mitochondrial integrity. The Authors found a significant increase of mitochondrial fission correlated to a reduction in neurite length, which was much greater than what observed in cultures with α-synuclein overexpression or PINK1 knockdown alone (Furlong et al., 2020).

Gleave and colleagues tested if the viral overexpression of myc-tagged Sirtuin 3 (SIRT3), a mitochondrial deacetylase that stabilizes the electron transport chain and reduces oxidative stress, would counteract the progression of PD pathology in a viral A53T-SNCA-overexpressing rat model. In these animals, SIRT3-myc could improve striatal dopamine turnover, behavioral impairment and prevent the degeneration of SNpc DAns, by increasing the functional capacity of mitochondria (Gleave et al., 2017).

Chronic oral administration of rotenone to transgenic mice overexpressing human A53T α-syn impaired spontaneous locomotor activity and increased cytoplasmic α-syn expression and PINK1 brain levels, thus provide another useful model for presymptomatic PD (George et al., 2010).

Another PD rotenone model showed that α-syn expression modulates the specific vulnerability of dopaminergic neurons to mitochondrial toxicity and that α-synuclein knockdown is neuroprotective (Zharikov et al., 2015).

The role of α-syn as modulator of immune cell maturation and response deserves a mention. As a ubiquitous protein, α-syn is also expressed in different immune cells, and the observed colocalization of neuroinflammatory spots at Lewy neurites/Lewy bodies suggests a potential implication of immune mediated mechanisms regulated by this protein in the pathogenesis of PD (Braak et al., 2007).

α-syn mediates non-cell-autonomous neurotoxic effects. When secreted from degenerated neurons to the extracellular space, it can act as a ligand of toll-like receptors 2 and 4 and launch a proinflammatory response of microglia, with the release of neurotoxic mediators causing further neurodegeneration (Kim et al., 2016).

α-syn presentation by the microglial and astrocytes major histocompatibility complex class-II (MHC-II) proteins leads to the recruitment and activation of other peripheral phagocytes, like monocytes, macrophages and lymphocytes (Ferreira and Romero-Ramos, 2018; Rostami et al., 2020). Moreover, it has been demonstrated that α-syn can intervene in the regulation of adaptive immune responses, being involved in the development and activation of humoral immunity (Xiao et al., 2014) and in the differentiation of T-cells (Shameli et al., 2016).

A recent study showed that silencing α-syn in SNpc nigral neurons of adult rats induces an up-regulation of MHC class I within these neurons, with the induction of neuroinflammation (recruitment of specific reactive microglia and T-cells). As a result, a 50% loss of SNpc DAns and a corresponding loss of nigrostriatal terminals and dopamine concentrations within the striatum were observed. Interestingly, silencing α-syn in glutamatergic neurons of the cerebellum failed to elicit inflammation or cell death, suggesting that α-*syn*-silencing-mediated toxicity is specific to SNpc DAns (Benskey et al., 2018).

Preclinical research on PD has taken considerable advantages of several animal models of α-synucleinopathy, each presenting specific advantages and limitations (Koprich et al., 2017). What emerges is that α-syn represents a point of convergence of multiple pathologies, and an attractive drug candidate.

10. LRRK2

Multiple pathogenic mutations within the same gene, in the *PARK8* locus are responsible for autosomal-dominant Parkinsonism, with a phenotype that is usually quite indistinguishable from idiopathic PD (Martin et al., 2014; Paisán-Ruíz et al., 2005; Zimprich et al., 2004). This gene encodes the large multidomain protein Leucine-rich repeat kinase-2 (LRRK2), a member of a leucine-rich repeat kinase family. LRRK2 mutations account for about 4% of all familial cases, representing the most frequent genetic cause of PD, but have been also identified in about 1% of sporadic cases (Healy et al., 2008; Paisán-Ruíz et al., 2005; Tolosa et al., 2020).

To date, 6 pathogenic mutations and more than 30 potentially pathogenic variants have been found; the most common and studied mutation is the glycine to serine substitution at position 2019 (G2019S), which leads to a higher kinase activity (Cookson et al., 2007; Mancini et al., 2020; Reed et al., 2019).

Although its physiological cellular function is still under exploration, it seems that LRRK2 is implicated in multiple cellular processes, including autophagy regulation, endolysosomal trafficking, cytoskeletal dynamics, regulation of neurite outgrowth and synaptogenesis, and immune system modulation (Mancini et al., 2020; Pellegrini et al., 2017; Rivero-Ríos et al., 2019; Sepulveda et al., 2013; Wallings et al., 2019). At the synaptic site, LRRK2 connects synaptic vesicles to cytoskeletal elements through a complex panel of protein-protein interactions (Belluzzi et al., 2016). Substantial evidence indicates that LRRK2 is implicated in synaptic transmission (Beccano-Kelly et al., 2015; Sweet et al., 2015; Tong et al., 2009), especially in striatal neurophysiology (Volta and Melrose, 2017). Indeed, after birth, LRRK2 mRNA expression significantly increases within the putamen, and evidence from human, rodent and primate studies describes high LRRK2 expression levels in the cortex and striatum, with a lower expression in the SNpc (Galter et al., 2006; Melrose et al., 2006; Simón-Sánchez et al., 2006).

Normal LRRK2 serine-threonine kinase activity is critical for proper synaptic vesicle endocytosis, as demonstrated by the accumulation of clathrin-coated vesicles and the decrease of synaptic vesicle density in dopaminergic terminals of LRRK2 mutant mice (Xiong et al., 2018).

Several rodent models have been developed in the attempt to shed light on LRRK2 cellular functions and pathogenic pathways. Many of these confirm that LRRK2 mutations impair dopamine transmission and signaling and corticostriatal synaptic plasticity, in the absence of

neurodegeneration. Consistently, subtle abnormalities in motor and non-motor abilities have been described, as preclinical manifestations of early dopaminergic dysfunction. On the contrary, LRRK2 KO mice and wild-type mice in which LRRK2 is knocked-down do not present marked behavior changes or abnormalities in the dopaminergic striatal transmission (Andres-Mateos et al., 2009; Beccano-Kelly et al., 2014, 2015; Hinkle et al., 2012; Lin et al., 2009; Tozzi et al., 2018; Volta et al., 2015). This can be because the lack of LRRK2 may trigger some compensatory mechanisms, or because the described alterations of the nigrostriatal pathway are mediated by a LRRK2 gain of function, as observed in overexpressing LRRK2 models. It should be noted that the variability in model design (i.e. different background strains, influence of the endogenous LRRK2, random insertion of human/murine transgene) may influence the pathological features observed in these animals, therefore a critical approach in results interpretation is needed (Volta and Melrose, 2017).

A systematic review of evidence obtained in LRRK2 experimental models is out of our scope, and here we limit to show what we believe to be the most significant examples, addressing the reader to other excellent reviews for a more complete scenario (Mancini et al., 2020; Volta and Melrose, 2017).

Eight to nine-month-old G2019S LRRK2 transgenic mice exhibit hypoactivity without gross degeneration of nigrostriatal terminal. Whole-cell current-clamp recordings of DAns revealed a reduced spontaneous firing frequency, while amperometric recordings showed an impaired evoked dopamine release in the dorsolateral striatum (Chou et al., 2014).

Similarly, homozygous R1441C knockin (KI) mice do not exhibit dopaminergic neurodegeneration or alterations in striatal dopamine levels up to 2 years of age, but they show reductions in amphetamine-induced locomotor activity and impairment of dopamine D2 receptor function (Tong et al., 2009).

In corticostriatal slices from G2019S LRRK2 KI mice of less than 1 month of age, spontaneous glutamatergic activity onto SPNs of both direct and indirect pathways was significantly increased (Matikainen-Ankney et al., 2016; Volta and Melrose, 2017). The acute in vitro application of LRRK2 kinase inhibitors normalized the excitatory transmission, supporting that the alteration of corticostriatal function is kinase dependent (Matikainen-Ankney et al., 2016).

The same mice exhibited an age-dependent decrease of basal striatal dopamine levels, ascribable to a latent impairment of synaptic dopamine release (Yue et al., 2015). Another study hypothesized that striatal dopamine loss was due to altered regulation of dopamine release and/or nigral burst firing patterns in vivo, and not to impaired release or dopamine transporter reuptake (Volta and Melrose, 2017).

Human bacterial artificial chromosome (BAC) R1441G-LRRK2 mice showed a progressive and age-dependent hypokinesia, responsive to L-DOPA (Bichler et al., 2013; Li et al., 2009), while human BAC G2019S-LRRK2 animals displayed a paradoxical mild hyperactivity during young age, followed by progressive motor impairment and cognitive deficits (Melrose et al., 2010; Volta et al., 2015).

Human wild-type LRRK2 overexpressing mice have unaltered basal striatal neurotransmission, but display behavioral hypoactivity and recognition memory impairments. Glutamatergic short-term plasticity was altered, through augmented presynaptic dopamine D2 receptors signaling, despite a reduced dopamine tone (Beccano-Kelly et al., 2015).

LRRK2 BAC transgenic rats, expressing either G2019S or R1441C mutant or the wild-type forms of the entire human LRRK2 gene, developed progressive motor dysfunction, responsive to L-DOPA, and cognitive deficits, correlated to a reduction in SNpc DAns burst firing and altered striatal dopamine release, in the absence of neuropathology within the SNpc (Sloan et al., 2016).

The abnormalities of striatal dopaminergic transmission observed in different models may be ascribed to both presynaptic vesicle release and postsynaptic receptor function (Mancini et al., 2020).

A recent study performed on striatal tissues isolated from LRRK2 KO mice at 2 and 12 months of age described changes in nuclear and dendritic morphology of SPNs during aging (Chen et al., 2020a, 2020b). Similarly, R1441C and G2019S KI mice showed altered striatal synaptic structure and function, suggesting that LRRK2 mutations may accelerate the aging process and induce the deterioration of neuronal structures (Chen et al., 2020a, 2020b).

Given the influence of LRRK2 on both glutamatergic and dopaminergic synaptic transmission, impairment of long-lasting synaptic plasticity have been observed too.

A recent work showed that G2019S LRRK2 KI mice had an abnormal AMPA receptor response profile and, consequently, SPNs of both direct and indirect pathway were unable to express LTP (Matikainen-Ankney et al., 2018). Moreover, in G2019S LRRK2 transgenic mice, an impairment of corticostriatal LTD was described (Chou et al., 2014). The exact molecular mechanisms involved in this process are not completely understood, although it is assumed a critical interaction between LRRK2 and the vesicular transport protein Rab8a, which mediates AMPA receptors synaptic insertion (Steger et al., 2016), in addition to a link with PKA, involved in the modulation of LTD/LTP induction (Greggio et al., 2017; Parisiadou et al., 2014).

There is strong evidence in favour of a pathophysiological interplay between α-syn and LRRK2 (Kuhlmann and Milnerwood, 2020). Indeed, Lin and Colleagues illustrated that, while overexpression of LRRK2 alone is not sufficient to cause neurodegeneration, co-expression of wild-type, G2019S, or kinase domain-deletion LRRK2 with A53T α-syn proves to be toxic for neurons, accelerating the progression of neuropathological abnormalities. Thus LRRK2 may modulate the accumulation of α-syn (Lin et al., 2009).

Besides the main cytoplasmatic localization, LRRK2 also resides at mitochondria, where it interacts with several mitochondrial fission/fusion regulators (Niu et al., 2012; Wang et al., 2012). Compelling evidence assigns a mitochondrial regulatory role for this protein, since it has been demonstrated that the expression of mutant LRRK2 causes negative effects at the mitochondrial level (reviewed in Singh et al., 2019). Skin biopsies from patients with LRRK2-G2019S-PD show decreased mitochondrial membrane potential and total intracellular ATP levels (Mortiboys et al., 2010). Also fibroblast from G2019 carriers are characterized by fragmented and dysfunctional mitochondria (Grünewald et al., 2014).

There is also evidence that LRRK2 regulates mitochondrial dynamics. Before the onset of mitophagy, mitochondrial motility halts to favour the sequestration of damaged mitochondria, a process mediated by removal of the Miro protein from the mitochondrial surface. LRRK2 acts at this level, through a complex with Miro, triggering the PINK1/Parkin-dependent degradation (Hsieh et al., 2016). In fact, LRRK2 G2019S mutation prevents the interaction with Miro, delaying the arrest of damaged mitochondria and, consequently, the initiation of mitophagy. Impaired mitochondrial trafficking has also been observed in neuronal cultures from patients with idiopathic PD (Hsieh et al., 2016).

Mutant LRRK2 also impairs PINK1/Parkin-dependent mitophagy via other mechanisms. The increased kinase activity of LRRK2-G2019S mutants is able to disrupt the interactions between Parkin and Drp1 and their mitochondrial targets early in mitophagy (Bonello et al., 2019). Moreover, LRRK2 controls the activity of RAB10, a small GTPase at mitochondrial sites regulating intracellular membrane trafficking. Under oxidative stress, through a pathway involving PINK1 and Parkin, LRRK2 phosphorylates RAB10 and induces its accumulation on depolarized mitochondria. Here, RAB10 recruits the autophagy receptor optineurin to induce mitophagy (Scorziello et al., 2020). LRRK2-G2019S and R1441C mutations enhance RAB10 phosphorylation, which inhibits the interaction of RAB10 with optineurin, thus reducing the accumulation of PINK1/Parkin on the depolarized mitochondria and impairing the autophagic clearance (Wauters et al., 2020).

Of note, different LRRK2 mutant models show an enhanced susceptibility to ROS and environmental stressors. In this regard, Tozzi and coworkers recently described abnormally high fragmented

mitochondria in G2019S Lrrk2-expressing SH-SY5Y cells exposed to rotenone (Tozzi et al., 2018). Also G2019S KI LRRK2 mice appeared more vulnerable to the toxic effects of the complex I inhibitor compared to wild-type, LRRK2 kinase-dead, and LRRK2 KO mice, suggesting that the G2019S LRRK2 mutation predisposes to enhanced striatal susceptibility to environmental mitochondrial stressors and that LRRK2 kinase domain seems to be involved in this process (Tozzi et al., 2018b).

In conclusion, numerous evidence points towards the potential role of LRRK2 in the modulation of mitochondrial activity and striatal synaptic transmission, although the scenario seems extremely complex. Indeed, LRRK2 expression in peripheral immune cells (i.e. B-cells, T-cells, and monocytes) is markedly upregulated in PD, hence it has been implicated in the regulation of immune-related pathways that may contribute to PD pathogenesis (Cook et al., 2017).

Similarly to other PD genetic models, the study of transgenic LRRK2 mouse models has reinforced the idea that the initial stage of PD is characterized by a potentially reversible synaptopathy, and that LRRK2 should be explored as a molecular target to counteract neurodegeneration. The investigation of the molecular pathways influenced by this multidomain protein will be particularly of interest, also given the relatively high frequency of LRRK2 mutations in both familial and sporadic PD.

11. GBA

Besides monogenic forms of PD, some genetic risk factors have been recently discovered (González-Pérez et al., 2009). Among this, heterozygous mutations of the GBA1 gene, encoding the lysosomal enzyme GCase, represent the major genetic risk for the development of PD, accounting for 5–7% of PD cases, while homozygous mutations cause Gaucher's disease (GD), a recessive lysosomal storage disorder (Goker-Alpan et al., 2004; Lwin et al., 2004; Migdalska-Richards and Schapira, 2016; Sidransky and Lopez, 2012).

The clinical features of GBA1-PD are similar to that of sporadic PD, except for an earlier onset and a higher prevalence of cognitive impairment and non-motor symptoms (Mata et al., 2016). Different GBA1 mutations have been identified; the two most frequent mutations associated with PD are N370S and L444P. Mutations lead to a decrease in GCase activity in the lysosome, resulting in the accumulation of glucosylceramide. The phenotypic variability among individuals is partly related to the severity of the underlying mutations (Avenali et al., 2020).

Of note, GCase deficiency has also been observed in sporadic PD patients, suggesting a crucial involvement of this enzyme in PD pathogenesis (Alcalay et al., 2015; Gegg et al., 2012).

The well documented lysosomal dysfunction associated with PD (Alvarez-Erviti et al., 2010; Dehay et al., 2010) has directed much of the GCase research towards the autophagy lysosome pathway and the α-syn pathology. It has been demonstrated that the reduced enzymatic function of GCase impairs α-syn degradation, favouring the toxic accumulation of α-syn fibrils (Cullen et al., 2011; Schöndorf et al., 2014). Moreover, the accumulation of glycosphingolipids impairs the autophagy-lysosome system, further promoting α-syn aggregation (Mazzulli et al., 2011).

The induction of endoplasmic reticulum stress, mitochondrial dysfunction and neuroinflammation are also potentially involved in the pathogenesis of GBA1-PD (Burbulla et al., 2017; Rocha et al., 2015; Ron and Horowitz, 2005). It has also been speculated that GBA1 mutations increase the risk for PD through the loss or gain of a yet undiscovered GCase function. Therefore, the molecular mechanism by which GBA1 mutations induce susceptibility to PD is still a matter of debate.

In this regard, mouse models have proven to be a useful tool. To date, several homozygous GBA1 mouse models have been generated and originally used to study GD, while heterozygous mice have been less frequently studied (Farfel-Becker et al., 2019). The homozygous GBA mouse bearing L444P mutation shows biochemical and phenotypic abnormalities similar to Gaucher patients (Ginns et al., 2014), while heterozygous mice have a milder reduction in GCase activity associated with increased α-syn accumulation and impaired neuronal autophagy and mitophagy, in the absence of nigrostriatal neurodegeneration and a PD-like phenotype (Migdalska-Richards et al., 2017; Yun et al., 2018), thus being more representative of the susceptibility of GBA1 mutation carriers to developing PD.

Loss of GCase activity results in loss of mitochondrial function, as reported both in primary fibroblast derived from GD patients and in GD mouse models. Fibroblasts from patients with homozygous L444P mutation showed reduced mitochondrial membrane potential, increased ROS, mitophagy activation and impaired autophagic flux (de la Mata et al., 2015). Inhibition of GCase in vitro or loss of function in a GD KO mouse model caused dysfunctional fragmented mitochondria, and a reduction in respiratory enzyme activities, membrane potential and consumption of oxygen (Cleeter et al., 2013; Osellame and Duchen, 2013).

Mitochondrial impairment in GD models may be attributed to dysfunction in the autophagy-lysosome pathway, altered sterol metabolism, neuroinflammation, dysregulation in calcium homeostasis or a combination of the above (reviewed in Gegg and Schapira, 2016).

Recently, it has been described that dopaminergic iPSC-derived neurons harbouring mutant GBA1 have prolonged mitochondria-lysosome contacts, due to defective modulation of the untethering protein TBC1D15, with altered mitochondrial distribution and function, which could be rescued by GCase modulators increasing enzyme activity (Kim et al., 2021).

Similar findings were also detected in the heterozygous L444P KI mouse model, characterized by inhibited autophagy and mitochondrial priming; moreover, postmortem brain tissue from PD patients carrying heterozygous GBA mutations showed mitochondria oxidative stress and impaired autophagy, too (Li et al., 2019).

The accumulation of α-syn may also have an impact on mitochondrial function in GD models. A preferential mitochondrial localization of α-syn aggregates has been reported in cerebral cortical neural cells of GD D409H mice (Xu et al., 2014).

Compelling evidence supports that the loss of GCase activity not only impairs the autophagy-lysosome pathway, but also the dopaminergic transmission. Indeed, in a pharmacological GD model, Ginns and colleagues demonstrated that a subtle GCase deficiency, induced by the subchronic exposure to conduritol β epoxide (CBE), a GCase inhibitor, significantly impairs nigrostriatal function causing a reduction of striatal evoked dopamine release and altered synaptic plasticity markers (Ginns et al., 2014).

This evidence is in line with clinical studies demonstrating a striatal presynaptic dopaminergic dysfunction (Goker-Alpan et al., 2012) and alterations in functional connectivity of the striatocortical circuits (Sezgin et al., 2021) in asymptomatic carriers of GBA1 mutations.

GBA mutations in asymptomatic patients have been linked to aberrant neuroinflammatory responses, occurring early before neurodegeneration (Mullin et al., 2021). In fact, GBA is expressed in immune cells, including monocytes/macrophages and lymphocytes. The enzyme activity is found to be reduced in monocytes of PD patients compared with controls, and to be inversely correlated with motor severity (Hughes et al., 2021).

GCase is increasingly taking center stage in PD research. There are still many unanswered questions around the pathobiological mechanisms underlying the link between GCase deficiency and the development of PD. However many doors are open, and it is not excluded that diminished GCase activity could also affect synaptic function, although only a better characterization of GBA1 models could help clarifying this point.

Finally, in addition to the well characterized monogenic forms of PD, other PD-linked genes have emerged as possibly linked to mitochondrial and synaptic dysfunction. We provide some additional hints in Table 1.

12. Conclusion

The number of patients diagnosed with PD is destined to increase in the next decades, which makes this disease at risk of becoming a public health issue in the future (Tolosa et al., 2021). Despite the availability of many symptomatic therapies, to date no treatments able to block or slow down the underlying neurodegenerative process exist (Connolly and Lang, 2014; Lang and Espay, 2018).

The development of potential effective therapeutic strategies closely depends on a better comprehension of the underlying pathogenetic processes of the disease.

It is well recognized that the etiology of PD is multifactorial, depending on a complex interplay of both genetic and environmental factors (Kalia and Lang, 2016; Ascherio and Schwarzschild, 2016), and engaging multiple different biological mechanisms.

A large body of evidence converges to confirm that mitochondrial dysfunction plays an important role in PD pathogenesis (Borsche et al., 2021; Schapira and Gegg, 2011; Trinh et al., 2021; Trist et al., 2019). Indeed, several PD preclinical models based on neurotoxins or bearing PD-associated mutations directly involved in mitochondrial function have been developed. Each model has its own advantages and limitations. The firsts better allowed us to study the neuropathology and the functional basis of the late stage of PD, reproducing a typical phenotype. The second ones rarely show significant nigral degeneration or overt motor dysfunction, but helped in the identification of early mechanisms and pathophysiological processes (Blesa and Przedborski, 2014; Chia et al., 2020; Terzioglu and Galter, 2008).

Translating results from PD animal models brought out that mitochondrial dysfunction is a key point already in the early phase of the disease, thus representing an attractive target for the development of neuroprotective interventions.

Mitochondrial and synaptic dysfunctions seem to affect each other, in a vicious circle. In this scenario, we hypothesize that strategies designed to target mitochondria and oxidative stress may represent a promising approach also to counteract synaptic dysfunction, which is an early event characteristic of a prodromal stage of PD.

Advancing our understanding of the role of these aberrant processes occurring in the earliest phase of PD is an urgent need in view of the development of potential disease-modifying treatments.

Declaration of interest

None.

CRediT authorship contribution statement

Paola Imbriani: Conceptualization, Writing – original draft, Writing – review & editing. **Giuseppina Martella:** Writing – original draft. **Paola Bonsi:** Writing – review & editing. **Antonio Pisani:** Conceptualization, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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