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# REVIEW

# ABERRANT STRIATAL SYNAPTIC PLASTICITY IN MONOGENIC PARKINSONISMS

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**Abstract—In the recent past, the pathogenesis of Parkinson's disease (PD) has evolved from a neurodegenerative disorder considered entirely sporadic to a disease with an unequivocal genetic component. Indeed, different inherited forms of PD have been discovered and characterized, although the functional roles of the gene products identified are still under intense investigation. To gain a better understanding of the cellular and molecular pathogenic mechanisms of hereditary forms of PD, different animal models have been generated. Although most of the rodent models display neither obvious behavioral impairment nor evidence for neurodegeneration, remarkable abnormalities of dopamine-mediated neurotransmission and corticostriatal synaptic plasticity have been described, indicative of a fundamental distortion of network function within the basal ganglia. The picture emerging from a critical review of recent data on monogenic parkinsonisms suggests that mutations in PD genes might cause developmental rearrangements in the corticobasal ganglia circuitry, compensating the dopaminergic dysfunction observed both in mice and humans, in order to maintain proper motor function.**

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**Key words: Parkinson's disease, synaptic plasticity, striatum, animal model.**

Contents



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*Abbreviations:* DA, dopamine; DAT, DA transporter; LRRK2, leucine-rich repeat kinase 2; LTD, long-term depression; LTP, long-term potentiation; PD, Parkinson's disease; PET, positron emission tomography; SNCA, alpha-synuclein; SNPc, substantia nigra pars compacta; MSN, medium spiny neuron; 6-OHDA, 6-hydroxy-dopamine.

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Parkinson's disease (PD) is the most common movement disorder, affecting ~2% of individuals over age 60 years. The cardinal clinical features of PD include resting tremor, rigidity, bradykinesia, and postural instability, which are often accompanied by autonomic, cognitive, and emotional disturbances. The neuropathological hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The loss of dopaminergic input to the striatum is believed to lead to the appearance of the motor symptoms (Dauer and Przedborski, 2003). Although PD has long been regarded as a sporadic disorder, the identification of several gene mutations responsible for distinct forms of inherited PD provided strong evidence that genetic factors play a relevant role in the etiology of the disease. Monogenic parkinsonisms account for only a small fraction of PD cases, as only 20% of patients with an early onset and no more than 3–5% of those with a late onset have a clear familial etiology, exhibiting a classical recessive or dominant Mendelian mode of inheritance (Gasser, 2007). Linkage studies have identified about 15 loci and 11 genes associated with inherited forms of PD. Among these, five causative genes of PD have been better described: those that encode alpha-synuclein (SNCA/PARK1) and leucine-rich repeat kinase 2 (LRRK2/PARK8), also known as dardarin, which are responsible for the most common autosomal dominant forms of PD, and those that encode Parkin (PARKIN/PARK2), PTEN-induced kinase 1 (PINK1/PARK6), and DJ-1 (PARK7), which are linked to autosomal recessive forms (Klein et al., 2007; Gasser, 2007).

The lack of brain tissue specimens and the limited number of functional studies represent an obvious limitation to our progress towards a better understanding of the neural mechanisms involved in the pathophysiology of monogenic PD. An essential step forward has been represented by the generation of different animal models of monogenic parkinsonisms. Indeed, the big advantage of studying a genetic disorder with respect to a sporadic syndrome is that molecular approaches and transgenic animal models can be used to define pathological pathways (Dawson et al., 2010). For example, the study of proteins encoded by genes responsible for inherited forms of PD provided vital clues to understanding the molecular pathways linked to neurodegeneration, such as oxidative stress, intracellular inclusions of misfolded proteins, mito-

chondrial dysfunction, and alteration of the ubiquitin–proteasome pathway. The different mutations in genes associated with PD may act in series and/or in parallel pathways, ultimately converging on a molecular mechanism that leads to the loss of dopaminergic neurons (Cookson and Bandmann, 2010; Dawson et al., 2010).

Traditional animal models of PD, such as 6-hydroxydopamine (6-OHDA)-denervated or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned models, display neuropathological signs of degeneration of dopaminergic cells and express phenotypic motor abnormalities. Unlike these acute dopamine (DA) depletion models, most transgenic mice exhibit only subtle motor abnormalities without neuronal loss. Several lines of experimental evidence now suggest that these mutations are responsible for both dysfunction of DA neurotransmission in transgenic mice, as well as impairment of DA-dependent long-term plasticity at corticostriatal synapses (Goldberg et al., 2005; Kitada et al., 2007, 2009; Martella et al., 2009).

These experimental observations are in accordance with data obtained from PD patients carrying gene mutations, showing alterations of the dopaminergic pathway (Hilker et al., 2001; Eggers et al., 2010) and plastic changes in brain excitability (Buhmann et al., 2005; De Rosa et al., 2006; Bäumer et al., 2007; Schneider et al., 2008; van der Vegt et al., 2009).The aim of this brief survey is to provide an overview of experimental data from mouse models of familial PD, with a specific focus on the forms linked to mutations of *PINK1, DJ-1*, and *parkin* genes, characterized by DA dysfunction and plastic rearrangements in corticobasal ganglia network.

## MONOGENIC PARKINSONISMS

### Autosomal dominant forms of PD

In 1997, the discovery that an autosomal inherited mutation in the alpha-synuclein gene was unequivocally associated with a familial form of PD in a large Italian family (Polymeropoulos et al., 1997) paved the way to a new challenge for genetic studies and the understanding of molecular mechanisms underlying this disease.

Alpha-synuclein is a 140–amino-acid protein encoded by the SNCA gene, located on chromosome 4q, and abundantly expressed as a cytosolic lipid-binding protein in the vertebrate nervous system (McLean et al., 2000). The protein is mainly localized within presynaptic nerve terminals, where it is believed to participate in the regulation of vesicle trafficking and neurotransmitter release by promoting the assembly of the Soluble NSF Attachment Protein REceptor (SNARE) complex (Vekrellis et al., 2004; Burré et al., 2010; Darios et al., 2010). In addition to three missense mutations (A30P, E46K, A53T), also SNCA duplications or triplications have been identified in a handful of families affected by parkinsonism (Singleton et al., 2003). In general, point mutations are extremely rare and by far less frequent than SNCA multiplication events. For many SNCA-linked cases, the severity of the clinical phenotype appears to depend on gene dosage. Patients with duplications are often clinically indistinguishable from those affected by sporadic PD, in contrast to patients carrying triplications, who present a more severe phenotype characterized by earlier onset, faster disease progression, marked dementia, and frequent dysautonomia (Ross et al., 2008). The brain pathology of patients carrying either point mutations or multiplication events of SNCA is characterized by SNpc atrophy, and by alpha-synuclein- and ubiquitin-positive inclusions in the remaining monoaminergic neurons in the brainstem, cortical motor, and sensory areas (Spira et al., 2001; Zarranz et al., 2004; Obi et al., 2008). Overall, these observations support the notion that both overexpression and mutation-induced gain of function of alpha-synuclein can lead to neural damage. Although less frequent, the discovery of mutations in the gene coding for alpha-synuclein as the major component of Lewy body inclusions has been historically relevant.

On the other hand, the LRRK2 gene mutations are by far more common, suggesting that they might also represent a risk factor for the sporadic disease (Paisán-Ruíz et al., 2004). Autosomal dominant mutations in the LRRK2 gene, identified in the PARK8 locus on chromosome 12, were first described by two independent groups (Paisán-Ruíz et al., 2004; Zimprich et al., 2004) in a familial parkinsonism syndrome mimicking the clinical features of sporadic PD. The phenotype associated with LRRK2 mutations is similar to sporadic PD, with asymmetrical tremor, rigidity, bradykinesia, and a good response to levodopa treatment. Furthermore, a positron emission tomography (PET) study showed a reduction of presynaptic DA synthesis in the putamen, similar to the decrease observed in sporadic PD (Nandhagopal et al., 2008). However, the neuropathological features show a high heterogeneity, as nigral degeneration may be associated or not with brainstem or widespread Lewy bodies, and neurofibrillary tangles (Khan et al., 2005).

LRRK2 gene consists of 51 exons and encodes a multidomain protein, also named dardarin, that includes a Rho/Ras-like GTPase domain related to the mixed-lineage kinase (MLK) family, WD40-repeat, leucine-rich repeat (LRR), and C-terminal of ROC (COR) domains (Cookson, 2010). To date, nearly 80 missense mutations, located over the entire LRRK2 protein sequence and affecting all predicted functional domains, have been found, although the most common and best studied mutation is the glycine to serine substitution at position 2019 (G2019S). As for mutations at SNCA, penetrance is incomplete and age dependent, reaching approximately 70%. Pathogenic mutations are associated with a dysregulation of LRRK2 kinase activity; the most frequent G2019S mutation is associated with an increase in the kinase activity (Cookson et al., 2007), while mutations in the ROC domain (I1371V, R1441C, R1441G, R1441H) decrease GTPase activity (Deng et al., 2008), which modulates the kinase activity (West et al., 2005, 2007).

Notably, recent studies identified a functional interplay between alpha-synuclein and LRRK2. Transgenic overexpression of wild-type or G2019S LRRK2 in mice expressing A53T alpha-synuclein dramatically accelerated the neurodegenerative process in a dose-dependent manner, while the genetic deletion of LRRK2 ameliorated the phenotype (Lin et al., 2009; Tong and Shen, 2009). Moreover, loss of LRRK2

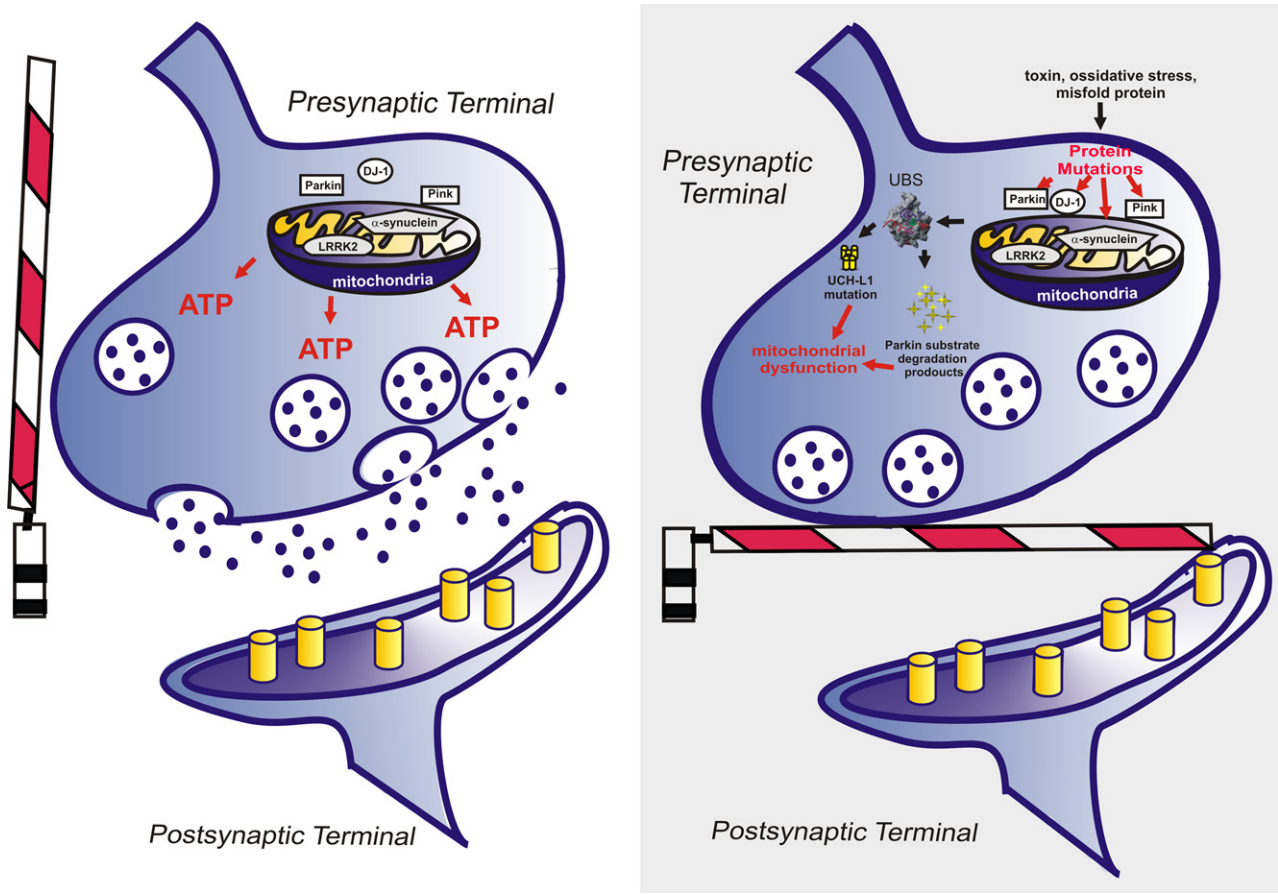


**Fig. 1.** PARK genes participate in common pathways underlying synaptic dysfunction. Pathogenic mutations in the PARK genes have been shown to cause mitochondrial dysfunction, oxidative damage, abnormal protein phosphorylation, and aggregation. Both LRRK2 and α-synuclein are associated with the mitochondrial outer membrane, whereas Parkin and DJ-1 are cytosolic proteins that can be translocated to the mitochondria. PINK1 can localize both to the cytosol and the mitochondria. An impairment of membrane trafficking and synaptic function has been demonstrated in different animal models of monogenic PD. All these proteins are apparently linked to each other and might act in a final common pathway leading to altered neurotransmitter release through dysregulation of synaptic vesicle mobilization or trafficking. Indeed, while in control conditions (left) a normal exocytosis ensures a physiological synaptic activity, in monogenic PD (right) the reduced vesicle mobilization and/or trafficking impairs transmitter release, thereby altering synaptic function.

causes age-dependent striking accumulation of endogenous alpha-synuclein in the kidney, further demonstrating a physiological role of LRRK2 in alpha-synuclein turnover (Tong et al., 2010).

### Autosomal recessive forms of PD

Three genes have been identified as responsible for autosomal recessive forms of PD: *parkin, PINK1*, and *DJ-1* (Fig. 1, Table 1).

The clinical phenotype of recessive forms of PD is usually characterized by an early onset, slow disease progression, a good response to levodopa treatment, occasionally associated with atypical features, such as dystonia as possible initial sign. However, mutations of these genes may also be responsible for a late-onset clinical phenotype indistinguishable from sporadic PD (Schiesling et al., 2008). A considerable percentage of both PD patients and non-manifesting individuals carry a single heterozygous mutation in PARK2, PARK6, or PARK7 genes, coding for Parkin, PINK1, and DJ-1 protein, respectively. The pathogenic role of heterozygous mutations in recessive genes is still controversial and remains a matter of investigation.

**Table 1.** Autosomal recessive forms of PD

| Gene | PARK locus | Putative function | Rodent model | Neuronal loss | Motor dysfunction | References |
|---|---|---|---|---|---|---|
| *parkin* | PARK2 | Ubiquitin E3 ligase, neuroprotective function | Parkin$^{-/-}$ mice | No | Yes | Goldberg et al., 2003; Kitada et al., 2009 |
| *PINK1* | PARK6 | Mitochondrial protein kinase, neuroprotective function | PINK1$^{-/-}$ mice | No | Yes | Kitada et al., 2007 |
| *DJ-1* | PARK7 | Chaperone, neuroprotective and antioxidant function | DJ-1$^{-/-}$ mice | No | Yes | Goldberg et al., 2005 |

Mutations of PARK2 gene, mapped on chromosome 6q, are the most common monogenic cause of early-onset parkinsonism (Kitada et al., 1998). The gene product, called Parkin, is an E3-ubiquitin ligase that participates in the proteasomal degradation of targeted proteins (Fig. 1, Table 1; Shimura et al., 2000). It has been shown that under physiological conditions Parkin is involved in the maintenance of mitochondrial integrity and might induce autophagy of dysfunctional mitochondria. Clinically, patients with Parkin mutations show early onset and slow progression of the disease, benefit from levodopa treatment, and may exhibit dystonia as presenting feature (Lohmann et al., 2003). Parkin mutations, spread across the entire gene, were identified in either homozygous, compound heterozygous, or heterozygous state in both familial and sporadic PD patients from different ethnic groups (Hedrich et al., 2004). Single heterozygous mutations have also been observed in non-manifesting individuals, which show subtle but consistent abnormalities in striatal dopaminergic neurotransmission, as shown by PET and single-photon emission computed tomography (SPECT) studies (Klein et al., 2007).

*PINK1* (PTEN-induced kinase1) was identified in 2001 by Unoki and Nakamura (2001) as a gene located on chromosome 1p whose transcription was activated by the tumor suppressor PTEN in carcinoma cell lines. Genetic analysis revealed that homozygous and compound heterozygous mutations in PINK1 are highly penetrant and are rather common among early-onset PD patients, while heterozygous mutations are present among late-onset PD cases at reduced penetrance (Valente et al., 2004). Patients with PINK1 mutations are often indistinguishable, both clinically and pathologically, from those affected by sporadic PD (Valente et al., 2002). PINK1 gene product is a putative serine/threonine kinase, located in the intermembrane mitochondrial space, and is involved in the mitochondrial response to cellular and oxidative stress (Fig. 1, Table 1). Most of the known mutations are localized within the serine/threonine kinase domain. Some mutations have been demonstrated to cause the loss of the mitochondrial potential in response to stress (Abou-Sleiman et al., 2006), suggesting that PINK1 inactivation may lead to neuronal dysfunction by affecting its interaction with cell death inhibitors, calcium homeostasis, reactive oxygen species production, mitochondrial respiration efficacy, and permeability of mitochondrial transition pores (Deas et al., 2009). It has been suggested that PINK1 and Parkin may be part of a common pathway, whose main function might be to regulate mitochondrial morphology and function in response to stressors (Park et al., 2009).

The rarest cause of autosomal recessive forms of PD is determined by mutations in the *DJ-1* gene (PARK7), located on chromosome 1p and identified for the first time in a Dutch family with multiple consanguinity (Bonifati et al., 2003). The clinical features of DJ-1 parkinsonism are similar to those of other autosomal recessive forms of PD. DJ-1 belongs to the peptidase C56 family of proteins. In addition to its function of positive regulator of androgen receptor-dependent transcription, DJ-1 also acts as a redox-sensitive chaperone, as a sensor for oxidative stress, and it apparently protects neurons against oxidative stress and cell death (Fig. 1, Table 1; Cookson, 2003). Mutation analysis revealed homozygous, compound heterozygous, as well as single heterozygous missense mutations in the *DJ-1* gene. As previously discussed for *parkin*, also *DJ-1* heterozygous mutations were found in non-manifesting individuals.

Recently, DJ-1 has been suggested to be part of an E3-ligase complex together with Parkin and PINK1 (Xiong et al., 2009). Indeed, several findings are in line with a possible converging role in mitochondrial and dopaminergic dysfunction of mutations in *parkin, PINK1*, and *DJ-1* genes, suggesting a common molecular pathway in recessive parkinsonisms.

Both Parkin and PINK1-null Drosophila flies show a similar mitochondrial phenotype, and overexpression of Parkin can rescue PINK1 deficiency (Clark et al., 2006; Yang et al., 2006). PINK1-kinase activity is required for the translocation of Parkin to depolarized mitochondria prior to selective clearance of damaged organelles by mitophagy (Geisler et al., 2010; Kim et al., 2008). The exact role of DJ-1 is less known, yet, but its deficiency activates an oxidative stress pathway, causing loss of polarization and fragmentation of mitochondria, which can be rescued by overexpression of Parkin (Krebiehl et al., 2010).

## ALTERATIONS OF STRIATAL SYNAPTIC ACTIVITY IN AUTOSOMAL DOMINANT FORMS OF PD

Both *SNCA* and *LRRK2* gene mutations have been reported to impair synaptic activity and plasticity in a variety of different brain regions. In particular, studies using alpha-synuclein null- and overexpression models have indicated that alpha-synuclein plays a role in the modulation of synaptic activity at nigrostriatal, corticostriatal, and hippocampal synapses (Abeliovich et al., 2000; Steidl et al., 2003; Gureviciene et al., 2009; Watson et al., 2009).

Electrophysiological studies have shown differential effects on short-term synaptic plasticity depending upon the absence or the overexpression of alpha-synuclein. It has been reported that the overexpression of alpha-synuclein may induce paired-pulse facilitation in the dorsolateral region of the striatum, whereas such synaptic facilitation was not recorded in striatal slices from alpha-synuclein knockout ($SNCA^{-/-}$) mice (Watson et al., 2009). In dentate gyrus-perforant pathway from A30P alpha-synuclein mutant mice, the accumulation of mutated protein leads to a long-term depression (LTD) of synaptic plasticity after a stimulation protocol that in normal condition induces long-term potentiation (LTP) (Gureviciene et al., 2009). At corticostriatal synapses, the overexpression of alpha-synuclein leads to a presynaptically mediated LTD after high-frequency stimulation, whereas LTD was not observed in wild-type mice. The striatal synaptic plasticity impairment has been attributed to the overexpression of alpha-synuclein at presynaptic level, that might cause a decrease in glutamate release from corticostriatal terminals, thereby

impairing long-term synaptic transmission between cortex and striatum (Watson et al., 2009). More recently, abnormalities in striatal DA signaling and impaired corticostriatal LTD were detected only in aged A53T alpha-synuclein–overexpressing mice, whereas a physiological synaptic plasticity was recorded in younger animals (Tozzi et al., in press). These data suggest an age-dependent alteration of the striatal synaptic plasticity linked to overexpression of alpha-synuclein, related, at least to some extent, to a defect in DA signaling consisting in a progressive reduction in DA receptor responses (Kurz et al., 2010). The seemingly conflicting results obtained from alpha-synuclein models on the changes of short- and long-term plasticity have been related to the different experimental models used, the different brain regions analyzed, and complexity of the modulation of synaptic plasticity (Watson et al., 2009; Cheng et al., in press). However, several studies support the concept that one common mechanism underlying the effect of alpha-synuclein on synaptic plasticity might reside in an altered neurotransmitter release determined by dysregulation of synaptic mobilization and/or trafficking from the reserve pool to the readily releasable pool (Cheng et al., in press).

Although no specific studies on long-term synaptic plasticity have been performed, thus far, on mice models carrying LRRK2 mutations, extensive data are available on the relationship between LRRK2 and dopaminergic neurotransmission. In both R1441C LRRK2 homozygous knockin (Tong et al., 2009) and in R1441C LRRK2 BAC transgenic mice (Li et al., 2009), functional impairment in nigrostriatal dopaminergic innervation and degeneration of the nigrostriatal projections have been reported, respectively. Furthermore, deficiencies in striatal DA release, with detectable reduced extracellular DA levels in the striatum, were found in either mutant G2019S (Melrose et al., 2010) or R1441C (Li et al., 2010) BAC transgenic mice. These reports are in agreement with the evidence of a deficit in DA release observed in chromaffin cells derived from R1441C homozygous knockin mice (Tong et al., 2009), and in murine G2019S slices (Li et al., 2010).

Membrane hyperpolarization and cell firing inhibition are typical responses of nigral neurons mediated by somatodendritic D2 autoreceptors. In line with a deficit in DA signaling, electrophysiological recordings from dopaminergic nigral neurons from LRRK2 knockin mice, the response to D2 agonists were significantly shorter in duration, supportive of a reduced sensitivity of D2 receptors to endogenous DA (Tong et al., 2009).

## DOPAMINE DYSFUNCTION AND ABNORMALITIES IN CORTICOSTRIATAL SYNAPTIC PLASTICITY IN MOUSE MODELS OF RECESSIVE PARKINSONISM

Multidisciplinary studies performed in rodent models of autosomal recessive PD (Parkin knockout ($^{-/-}$), PINK1$^{-/-}$, and DJ-1$^{-/-}$ mice) demonstrated that they share a common alteration of DA signaling, without overt abnormalities in the number, cellular morphology, or projections of nigral dopaminergic neurons (Table 1; Goldberg et al., 2005; Kitada et al., 2007, 2009). In these animal models, DA release evoked from SNpc neurons was reduced as compared to wild-type mice (Goldberg et al., 2005; Kitada et al., 2007, 2009). Consistent with these results, total catecholamine release and quantal size were reduced also in dissociated chromaffin cells derived from PINK1$^{-/-}$ and Parkin$^{-/-}$ mice. An altered DA signal may result from changes in either DA release from vesicles or its reuptake by DA transporter (DAT). Additional amperometric measurements performed in the presence of DAT blockers revealed that in both PINK1$^{-/-}$ and Parkin$^{-/-}$ mice the reduction of evoked DA overflow was attributable to a decrease in exocytotic DA release rather than an increase in reuptake. Accordingly, while the DA reuptake inhibitor nomifensine greatly enhanced the evoked DA overflow in normal striatum, it had no significant effect in PINK1$^{-/-}$ and Parkin$^{-/-}$ mice. Conversely, the blockade of DA reuptake restored a normal evoked DA overflow in the striatum of DJ-1$^{-/-}$ animals, suggesting that in these mice an enhanced DA reuptake primarily accounts for the reduction in evoked DA. Moreover, in DJ-1$^{-/-}$ mice a reduced sensitivity of nigral neurons to both DA and D2 receptor agonists was also demonstrated, suggesting a partial impairment in D2 receptor-mediated activities. Somatodendritic D2-like autoreceptors regulate the membrane potential of nigral dopaminergic neurons through the modulation of the conductance of neuronal G protein-gated inward rectifying potassium channels. Upon DA binding, activation of D2 autoreceptors causes a membrane hyperpolarization and suppression of firing activity (Lacey et al., 1987). The autoreceptor-mediated response, that is absent in D2 receptor knockout mice, is reduced in DJ-1$^{-/-}$ mice suggesting a partial impairment of D2 receptor function (Mercuri et al., 1997; Goldberg et al., 2005).

Dopaminergic signaling in the striatum plays a critical role in the control of motor activity, reward, and cognition, and in the pathogenesis of PD (Obeso et al., 2000; Calabresi et al., 2007). Indeed, DA is an essential requirement for both forms of long-term plasticity at corticostriatal synapses (LTD and LTP), which are believed to represent the cellular correlate of motor learning (Pisani et al., 2005).

The electrophysiological analysis of striatal medium spiny neurons (MSNs) recorded from PINK1$^{-/-}$, Parkin$^{-/-}$, and DJ-1$^{-/-}$ mice showed no significant changes in the intrinsic membrane and synaptic properties as compared to their respective wild-type littermates (Table 2; Goldberg et al., 2005; Kitada et al., 2007, 2009; Martella et al., 2009). However, significant alterations of long-term synaptic plasticity were found in PINK1$^{-/-}$, Parkin$^{-/-}$, and DJ-1$^{-/-}$ mice. Both in PINK1$^{-/-}$ and Parkin$^{-/-}$ LTD and LTP were impaired. Consistent with the neurochemical data showing a reduced striatal DA content, exogenous DA supply could rescue plasticity processes in both genotypes. The findings that amphetamine, but not nomifensine, restored synaptic plasticity are in support of a selective impairment in DA release (Kitada et al., 2007, 2009). Characterization of striatal plasticity in DJ-1$^{-/-}$ mice revealed a similar defect in DA release, although only

**Table 2.** MSN membrane and synaptic properties

| Patch-clamp recordings | DJ-1/$^{++}$ | DJ-1$^{-/-}$ | PINK1/$^{++}$ | PINK1$^{-/-}$ | Parkin/$^{++}$ | Parkin$^{-/-}$ |
|---|---|---|---|---|---|---|
| RMP (mV) | −84±3.2 | −83±3.5 | −81±4.2 | −80±3.3 | −82±3.7 | −80±2.9 |
| Input resistance (MOhm) | 80.11±1.7 | 83.56±2.3 | 81.24±2.8 | 80.26±2.2 | 81.41±1.9 | 80.37±1.6 |
| Firing elicited by depolarizing current injection | Tonic | Tonic | Tonic | Tonic | Tonic | Tonic |
| Action potential amplitude (mV) | 74.3±3.3 | 73.2±2.9 | 75±3.4 | 73.6±3.5 | 74.1±2.9 | 73±3.1 |
| Width at half amplitude (ms) | 1.48±0.1 | 1.36±0.3 | 1.33±0.1 | 1.50±0.2 | 1.44±0.2 | 1.45±0.2 |
| Spontaneous glutamatergic activity (Hz) | 5.65±1.4 | 7.25±1.69 | 5.11±0.43 | 5.03±0.87 | 5.01±0.5 | 5.33±0.39 |
| Spontaneous glutamatergic activity (pA) | 15±0.38 | 17.26±1.66 | 10.98±0.21 | 11.02±0.09 | 10.00±0.1 | 11.03±0.18 |
| Spontaneous GABAergic activity (Hz) | 1.45±0.26 | 1.85±0.1 | 1.46±0.53 | 1.63±0.40 | 1.40±0.04 | 1.52±0.29 |
| Spontaneous GABAergic activity (pA) | 27.5±3.1 | 26.34±3.24 | 28.96±0.21 | 24.81±0.46 | 27.30±0.34 | 28.20±0.29 |

LTD was impaired, whereas LTP was preserved. Consistent with prior reports showing that corticostriatal LTD requires D2 receptors, whereas corticostriatal LTP induction depends on the selective activation of D1 receptors (Centonze et al., 2001), D2 receptor agonists restored LTD in DJ-1$^{-/-}$ MSNs.

## HOMEOSTATIC CIRCUIT REORGANIZATION

The striatum is the major input area of the basal ganglia, subserving a central role in motor function, through a rich interplay among different neurotransmitters (Lovinger, 2010). In PD, the loss of nigrostriatal dopaminergic fibers induces a profound rearrangement in the functional neuroanatomy of the basal ganglia. Such reorganization is thought to account, at least in part, for the generation of motor symptoms, although endogenous processes that compensate for the loss of DA should also be taken into account (Pisani et al., 2011). One of the most consistent observations is represented by the evidence that the corticostriatal glutamatergic activity increases, an evidence supported by *in vivo* studies showing an elevation in striatal glutamate content in 6-OHDA-denervated rats (Meshul et al., 1999) as well as by electrophysiological recordings from striatal MSNs, demonstrating a substantial increase in glutamate-mediated synaptic currents (Calabresi et al., 1993; Picconi et al., 2002). However, contrarily to what was measured in the 6-OHDA-denervated striatum, no significant alteration in spontaneous glutamate-mediated synaptic events could be recorded in the knockout mice (Martella et al., 2009), suggesting that, compared to the acute denervation of nigrostriatal fibers observed in the 6-OHDA model, in these genetic models of PD the gene mutation produces early adaptive changes that lead to a compensation across development.

On the other hand, both an impaired DA neurotransmission and alterations of corticostriatal synaptic plasticity are similarly observed either in 6-OHDA or in genetic models of PD. It is plausible that the latter changes reported in Parkin-, PINK1-, and DJ-1–deficient mice may not be sufficient to cause overt behavioral alterations, as even in humans the symptoms manifest only after a substantial degeneration of dopaminergic cells. This observation would suggest that an altered DA signaling, together with the disruption of synaptic plasticity, might represent an endophenotype to monogenic PD.

Recent neurophysiological and functional imaging studies on parkinsonian patients and mutation carriers further support a compensatory circuit rearrangement induced by PD gene mutation. TMS studies reported abnormalities in corticospinal excitability in Parkin patients, likely explained by an altered excitability of pyramidal neurons (De Rosa et al., 2006; Schneider et al., 2008). This functional analysis disclosed different alterations in patients and carriers; while central motor conduction time was increased in patients, asymptomatic carriers had increased motor thresholds and reduced short interval intracortical inhibition (Schneider et al., 2008). Moreover, asymptomatic Parkin mutation carriers also show impaired short-interval afferent inhibition after digital stimulation (Bäumer et al., 2007). Overall, these data suggest that adaptive changes, presumably requiring long-term synaptic modifications, might take place in the corticobasal ganglia circuitry to compensate for the mild dopaminergic dysfunction in carriers.

Functional MRI (fMRI) studies provided evidence for a compensatory redistribution of neuronal activity within the motor system in non-manifesting carriers of PINK1 or Parkin mutations (Buhmann et al., 2005; van Nuenen et al., 2009). According to these findings, preclinical deficit of dopaminergic neurotransmission in the striatum of these individuals alters cortical processing during motor tasks. Particularly, Parkin and PINK1 mutation carriers displayed a stronger activation of the rostral supplementary area (pre-SMA) and dorsal premotor cortex (PM-d), compared to healthy controls without mutations. These activity changes may represent an adaptive redistribution of neuronal activity in rostral motor cortical areas in attempt to maintain motor function, in the contest of a mild chronic dysfunction of the nigrostriatal dopaminergic pathway (van der Vegt et al., 2009).

Both PET and SPECT have been used to map the functional impact of monogenic parkinsonism mutations on dopaminergic neurotransmission at pre- and postsynaptic level in manifesting and non-manifesting mutation carriers (Piccini and Whone, 2004). In accordance to animal model data, several PET studies have provided converging evidence for a moderate chronic dysfunction of the nigrostriatal dopaminergic pathway induced by the mutation. Of interest, the entity of the dopaminergic dysfunction was related to the carrier phenotype. Manifesting mutation car-

riers show a peculiar bilateral reduction of both presynaptic uptake and striatal DAT. While the rostrocaudal gradient of presynaptic dopaminergic impairment is similar to sporadic PD (Varrone et al., 2004; Hu et al., 2006; Eggers et al., 2010), the progression rate of this dysfunction is significantly slower (Khan et al., 2002, 2005), consistent with a more benign clinical course in recessive parkinsonisms. Interestingly, neuroimaging analysis of non-manifesting carriers has shown subtle but consistent decrease in striatal DAT binding. This mild alteration in heterozygous carriers in the absence of striatal [18F]-DOPA uptake alterations might represent a marker of the subclinical loss of nigrostriatal afferents (Adams et al., 2005).

## CONCLUSIONS

The past decade has witnessed a significant advance in our knowledge on the pathogenesis of PD, which has been favored, at least in part, by extensive work on rodent models. Studies of these models have produced experimental data that, to some extent, lead in different directions. Nevertheless, they provided fundamental information that finds confirmation in clinical observations, such as the prominent role of DA signaling.

Overall, the neurochemical and electrophysiological data obtained in models of monogenic PD are in support of a possible developmental disorder, in which rearrangement of the basal ganglia circuitry occurs, probably in the attempt to compensate for the alterations induced by gene mutation. It is plausible that either exposure of predisposing genotypes to environmental stressors (Shen and Cookson, 2004; Frank-Cannon et al., 2008), or the protraction over time of the dopaminergic deficits, might overwhelm the compensatory mechanisms and trigger the clinical symptoms. Identifying the link between the gene products and the functional rearrangement of motor circuit is of primary importance for a better understanding of both sporadic and monogenic PD, and might help finding novel targets for pharmacological intervention.

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