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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