Hypothesis

The Neuroscientist
Volume 15 Number 1
February 2009 28-35

10.1177/1073858408319974
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Etiopathogenesis of Parkinson Disease: A New Beginning?

Weidong Le, Shen Chen, and Joseph Jankovic

Parkinson disease (PD) probably represents a syndrome of different disorders and origins converging into a relatively uniform neurodegenerative process. Although clinical-pathological studies have suggested that the presymptomatic phase of PD may be relatively short, perhaps less than a decade, the authors postulate that the pathogenic mechanisms may begin much earlier, possibly even in the prenatal period. Thus, some patients with PD may be born with a fewer than normal number of dopaminergic (and nondopaminergic) neurons as a result of genetic or other abnormalities sustained during the prenatal or perinatal period; as a result of normal age-related neuronal attrition, they eventually reach the critical threshold (60% or more) of neuronal loss needed for onset of PD to become clinically manifest. The authors review the emerging evidence that genetic disruption of normal development, coupled with subsequent environmental factors (the so called multiple-hit hypothesis), plays an important role in the etiopathogenesis of PD.

Keywords: transcription factors; gene regulation; dopamine neuron development; environmental neurotoxins

Parkinson disease (PD) is a neurodegenerative disorder clinically characterized by bradykinesia, rigidity, resting tremor, postural instability, and a variety of other motor and nonmotor symptoms (Jankovic 2008). The pathological hallmark of PD is loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) with subsequent loss of dopamine (DA) in the nigrostriatal system and the presence of cytoplasmic inclusions, termed *Lewy bodies*. In addition, there is marked loss of non-DAergic neurons, particularly in the caudal brainstem, and these may become involved even before the DAergic neurons (Braak and others 2006). There is growing consensus among parkinsonologists that PD is probably not a homogenous disease but a syndrome of different disorders, caused by genetic, environmental, and other factors (Moore and others 2005; Klein and Schlossmacher 2007; Schapira 2008). Although the mechanism of neurodegeneration in PD is not clear, multifactorial causes representing different, although possibly converging, pathways have been proposed. The pathogenesis of PD has been postulated to result from a complex interaction between environmental and genetic factors leading to mitochondrial dysfunction, oxidative stress, inflammation, and excitotoxicity, eventually leading to nigral DAergic neuron degeneration (Moore and others 2005; Klein and Schlossmacher 2007; Schapira 2008). Impaired degradation of misfolded and aggregated proteins is being increasingly recognized as playing an important role in the pathogenesis of PD (Fig. 1). Besides the extensively studied ubiquitin-proteasome system, an autophagy-lysosome pathway has been receiving growing attention as an important machinery involved in the repair and removal of misfolded proteins (Hegde and Upadhya 2007; McNaught and others 2007; Pan and others 2008). Defects or dysfunction of certain genes, such as α-*synuclein* gene (PARK1), *parkin* gene (PARK2), *ubiquitin carboxyl-terminal hydrolases* (*UCHL-1*) gene (PARK5), *PINK1* (PARK6), *DJ-1* (PARK7), *LRRK2* (PARK8), and *Nurr1*, have been reported to be linked with familial PD (Le and others 2003; Moore and others 2005; Klein and Schlossmacher 2007). It is believed that mutations in the α-*synuclein* gene, *parkin* gene, and *UCHL-1* may result in the failure of degradation of misfolded proteins, leading to neurodegeneration (Moore and others 2005; Klein and Schlossmacher 2007; Fig. 1).

The adult brain contains more than 100 billion neurons with more than 10^{15} synapses, but only a small portion of the brain is affected in PD. It has been estimated that there are 400 000 DAergic neurons in the substantia nigra (SN), and 60% to 80% are lost before the first motor symptoms of PD begin to emerge (Leenders and others 1990). Because DAergic neurons in the SN are closely associated to PD, the molecular mechanism underlying their development and adult cellular properties has been the subject of intense investigations (Alavian and others 2008). Although PD is typically considered an age-related neurodegenerative disorder, with symptoms usually starting in or after the sixth decade of life, the biology of the disease may start decades prior to clinical manifestation (Fig. 2). Environmental factors acting early in

From the Department of Neurology, Baylor College of Medicine, Houston, Texas.

Writing of this article was supported by research grants from the National Institutes of Health (NS043567) and the Michael J. Fox Foundation (2005–2007).

Address correspondence to: Joseph Jankovic, Professor of Neurology, Distinguished Chair in Movement Disorders, Director of Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, 6550 Fannin, Suite 1801, Houston; TX 77030; e-mail: josephj@bcm.tmc.edu; Web: www .jankovic.org.

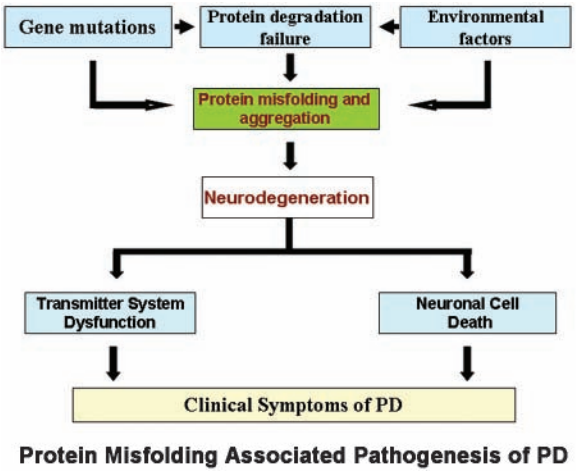

Figure 1. The common pathways of protein misfolding–mediated pathogenesis in Parkinson disease (PD). Mutations in α-*synuclein, Parkin, UCHL-1,* and possible other genes can cause the failure of the protein degradation system (ubiquitin-proteasome system and autophagy) or directly promote protein aggregation, which may lead to neurodegeneration and clinical phenotype of PD.

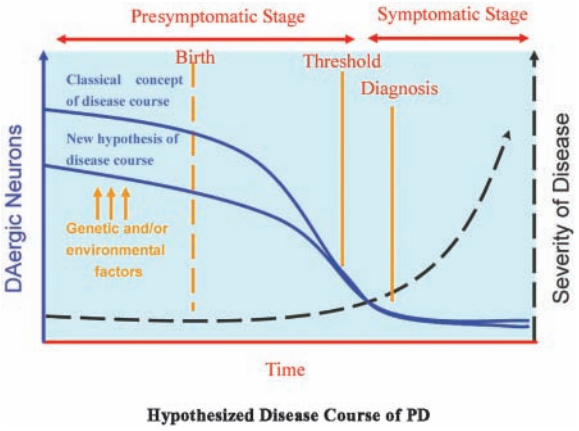

Figure 2. The hypothesized disease course of Parkinson disease (PD). The classical concept of PD is that the disease starts at the middle age and advances gradually. Our new hypothesis suggests that the disease starts at a very early age, perhaps even during the prenatal or perinatal period, so that the affected individual predisposed to develop PD starts with fewer than normal dopaminergic (DAergic) neurons. As a result of age-related neuronal attrition, a threshold of >60% loss occurs earlier than normal, and the progressive symptoms of PD emerge, usually in the sixth decade of life.

life or even before birth have been postulated to predispose some individuals to subsequently develop parkinsonism or other movement disorders (Scott and Jankovic 1996; Jankovic 2005; Carvey and others 2006; Barlow and others 2007; Wijemanne and Jankovic 2007; Fig. 2). Furthermore, inherited genetic defects or spontaneous gene mutations may result in a formation of mutated proteins that interfere with normal cellular viability because of either loss of function or gain of function. This in turn can lead to a cascade of events that initiates a progressive disease process with eventual loss of normal reserves and of compensatory mechanisms (Wijemanne and Jankovic 2007). Although many clinical-pathological studies have suggested that the presymptomatic phase of PD starts about 4 to 6 years prior to the onset of symptoms (Jankovic 2005), we hypothesize that some patients diagnosed with idiopathic PD may be born with a fewer than normal number of DAergic (and non-DAergic) neurons as a result of a nigrostriatal damage sustained in utero or during the perinatal period, and with the normal age-related neuronal attrition, they reach the critical threshold of 60% (or more) neuronal loss needed for onset of PD to become clinically manifest (Fig. 2). Thus, some patients with otherwise typical PD may not necessarily have a primarily age-related neurodegenerative disorder, but their symptoms may result from environmental or genetic disruption of normal development of DAergic (and non-DAergic) systems very early in life (Martyn and Osmond 1995). In this article, we will critically review the evidence for the notion that some forms of PD may represent a neurodevelopmental disorder. Although PD clearly involves DAergic as well as non-DAergic neurons, in this review, we will focus primarily on the DAergic system.

Differentiation of DAergic Neurons and the Multihit Hypothesis

Critical Determinants for DAergic Neuron Development

The development of the cortical, subcortical, and other parts of the central nervous system appears to be under separate regulatory mechanisms involving different transcriptional factors (Jankovic and others 2005; Bystron and others 2008). For example, the midbrain floor plate has been found to be a signaling center rich in radial glia-like cells that are neurogenic and give rise to midbrain DAergic neurons (Bonilla and others 2008). Throughout life, transcription factors determine the fate of this neuronal population and control essential processes such as localization in the ventral midbrain, their neurotransmitter phenotype, their target innervations, and synapse formation (Alavian and others 2008). Over the past decade, several transcriptional regulators, including *Nurr1, Lmx1a, Lmx1b, Msx1, Pitx3, SHH, Engrailed 1, Engrailed 2, Wnt-1, Wnt-3,* and *Wnt-5*, have been identified as responsible for the development and maintenance of midbrain DAergic neurons (Goridis and Rohrer 2002; Jankovic and others 2005; Andersson and others 2006; Abeliovich and Hammond 2007; Parish and others 2007; Fig. 3). Lmx1a and Msx1 have been found to be critical intrinsic DAergic neuron determinants, sufficient to trigger DAergic neuron differentiation (Andersson and others 2006). Early activity of Lmx1a is necessary to induce the expression of Msx1, complementing Lmx1a by inducing the proneural protein Ngn2 and subsequent neuronal differentiation (Andersson and others 2006). Some

neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial-cell-derived neurotrophic factor (GDNF), and transforming growth factor (TGF) also participate in DAergic neuronal development (Jankovic and others 2005; Park and others 2006). Another factor important in the development of midbrain DAergic neurons is TGF-α; in TGF-α, knockout mice SN contains 50% fewer DAergic neurons than that in control animals (Blum 1998). The homeobox transcription factors Engrailed 1 and Engrailed 2 are also involved in the regulation of the development of DAergic neurons (Alberi and others 2004). In double mutants null for both genes, these neurons are lost by E14 earlier than in any other described genetic model system for PD (Alberi and others 2004). Furthermore, gene silencing of *Engrailed 1* and *Engrailed 2* in the postmitotic neurons by RNA interference activates caspase 3 and induces apoptosis in less than 24 h (Alberi and others 2004). This rapid induction of cell death in DAergic neurons suggests that the Engrailed genes participate directly in the regulation of apoptosis and may contribute to the presymptomatic neuronal loss in PD. Of note, the heterozygous null mice deficient of these two genes have an adult phenotype that resembles key pathological features of PD, showing a slow progressive degeneration of nigral DAergic neurons, especially during the first 3 months of their lives (Sgado and others 2006). Intriguingly, α-synuclein, a gene recently linked to familial forms of PD, is regulated by Engrailed 1 and Engrailed 2 (Sgado and others 2006).

The Role of Nurr1 in PD: Neuronal Maturation and Development

Transcription factors of the Nur and retinoid X receptor subgroups have been found to play an important role in DA-mediated functions, particularly neuroadaptation (Levesque and Rouillard 2007; Maden 2007). The Nurs are part of the nuclear hormone receptor family, defined as the *NR4A* subgroup, which includes *Nur77* (also known as *NR4A1* and *NGFI-B*), *Nurr1* (*NR4A2*), and *Nor1* (*NR4A3*; Jankovic 2005; Levesque and Rouillard 2007). Nurr1, a member of the orphan nuclear receptor gene superfamily, is a critical genetic factor regulating the development and maintenance of midbrain DAergic neurons (Zetterstrom and others 1996; Jankovic and others 2005). This transcription factor is a product of immediate-early genes whose expression and activity are regulated in a cell-specific manner by a variety of extracellular mitogenic, apoptotic, and differentiation stimuli. A few Nurr1-regulated genes have so far been identified. For example, Nurr1 has been found to regulate the expression of tyrosine hydroxylase (*TH*), aromatic L-amino acid decarboxylase (*AADC*), and vesicular monoamine transporter-2 (*VMAT2*) in DA cell lines (Schimmel and others 1999; Hermanson and others 2003). Recently, Volpicelli and others (2007) reported that BDNF is a downstream target of Nurr1 transcription factor in rat midbrain neurons. Mice lacking the orphan nuclear receptor *Nurr1*, which is normally expressed in developing neurons, fail to generate midbrain DAergic neurons (Zetterstrom and others 1997). In homozygous *Nurr1*-deficient mice (*Nurr1*–/–), DAergic neurons are absent in the SN and ventral tegmental area (VTA) but are preserved in other regions (Le, Conneely, Zou, and others 1999). Heterozygous animals (*Nurr1*+/–) have reduced DA levels and

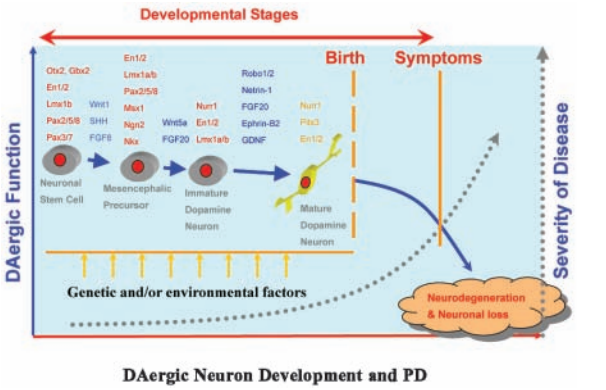

Fig. 3. Gene regulation of dopaminergic (DAergic) neuron development and Parkinson disease (PD). The development and maturation of mesencephalic DAergic neurons before birth is a complex process that requires the participation of numerous genes and factors, including *Otx, Shh, En1, En2, Pax-2, Pax-5, Lmx1-b, Pitx-3, Wnt, FGF, Msx1*, and *Nurr1*. Abnormalities or dysfunction of any stage during the development of DAergic neurons are hypothesized to be linked with PD. It is suggested that some PD may have fewer DAergic neurons or decreased DAergic function even at birth. The progressive loss of DAergic neurons or decline in DAergic function may result in clinical PD.

are more susceptible to the effects of 1,2,3,6-methyl-phenyl-tetrahydropyridine (MPTP) than wild animals (Le, Conneely, He, and others 1999). Although the *Nurr1*–/– animals die within 1 day after birth because of an inability to suck milk, the *Nurr1*+/– mice appear otherwise normal, although they tend to exhibit slowness of movement with age as compared with wild animals (Le, Conneely, He, and others 1999; Jiang and others 2005). *Nurr1* is highly expressed in the SN, VTA, olfactory bulb, hippocampus, and other subcortical areas (Saucedo-Cardenas and others 1998). *Nurr1* is down-regulated in the brains of aged individuals and in patients with PD (Chu and others 2002). Furthermore, the level of *Nurr1* in the SN appears to decrease with age and seems to correlate with disease progression (Chu and others 2006).

The human analog of the murine *Nurr1* and rat *RNR-1* genes is *NR4A2* (previously called *NOT* for nuclear receptor of T cells) gene, localized on 2q22-q23 (Mages and others 1994). Studies are currently under way to determine if mutations in this gene affect the development of the DAergic system and increase predisposition to PD. Indeed, at least three point mutations have been found in the *NR4A2* gene in patients with PD (Le and others 2003; Grimes and others 2006; Jacobsen and others 2008). We initially reported that mutations in exon (-291Tdel and -245T→G sequence variation in 5′ untranslated region) in familial PD cases and a homozygous polymorphism in intron 6 of the Nurr1 were associated with typical PD (Xu and others 2002; Le and others 2003). A third novel mutation (heterozygous C-to-G transversion resulting in serine-to-cysteine substitution) in the translated region of exon 3 was found in a nonfamilial PD, resulting in a change of p. Ser125Cys adjacent to the ERK1/2 phosphorylation site and subsequently leading to a marked reduction of *Nurr1*-induced transcriptional activation (Grimes and others 2006; Jacobsen and others 2008). Zheng and others (2003) found that a

heterozygous, rather than homozygous, single base pair insertion in intron 6 (NI6P) in the *Nurr1* gene was associated with a greater risk of PD. These mutations are rare and may be race and region restricted because other reports have not been able to find mutations in the *Nurr1* gene among their PD patients (Ibanez and others 2004; Nichols and others 2004; Tan and others 2004; Healy and others 2006). In addition, quantitatively measuring the level of Nurr1 mRNA in human peripheral blood lymphocytes has revealed a significant decrease of *Nurr1* expression in patients with PD (58% reduction vs non-PD healthy controls and 39% reduction vs neurological disease controls; Le et al, 2008). Thus, the expression of *Nurr1* may be a reliable biomarker for PD and its progression.

There is an emerging body of evidence suggesting that a cross-talk between *Nurr1* and several other transcriptional factors and neurotrophic growth factors may exist in different development and maturation stages of mensencephalic DAergic neurons (van den Munckhof and others 2003). *Pitx3* is the bicoid-related homeodomain-containing transcription factor that is expressed only in mesencephalic DAergic neurons (Smits and Smidt 2006; Smidt and Burbach 2007). Although the expression of *Pitx3* is independent of *Nurr1*, *Nurr1* may be critical for the maintenance of *Pitx3* in the late stages of DAergic neuron development (Saucedo-Cardenas and others 1998). *Pitx3* is highly expressed in DAergic neurons of the SNc and ventral VTA (Smits and Smidt 2006). Many studies have found a close association of *Pitx3* with *TH* expression during development and adulthood (Hwang and others 2003; Nunes and others 2003; Smits and Smidt 2006; Smidt and Burbach 2007), indicating that DAergic neurons in the SNc are specifically regulated by *Pitx3*. *Pitx3*-deficient *aphakia* mice failed to develop the nigrostriatal pathway, showing a complete loss of DAergic neurons in the SNc, the main region of degeneration in PD, whereas DAergic neurons in the VTA were less affected (Hwang and others 2003; Nunes and others 2003). Furthermore, variants in the regulatory regions of the *Pitx3* gene may be associated with PD (Bergman and others 2008; Fuchs and others 2008). Overexpression of *Pitx3* in stem cells has been used to enhance DAergic neuron differentiation aiming at providing cell replacement therapy for PD (Chung and others 2005; Martinat and others 2006). Moreover, overexpression of *Pitx3* up-regulates the expression of *BDNF* and *GDNF* in SH-SY5Y cells and in primary DAergic neuron cultures (Peng and others 2007), demonstrating that Pitx3 is important not only in regulating DAergic neuron phenotype but also in the production of growth factors to promote the survival of DAergic neurons. Therefore, Pitx3 might be a potential therapeutic target for the treatment of PD.

Neuronal development is largely dependent on proper orchestration and control of gene expression, largely regulated by newly discovered microRNAs (miRNAs; Gao 2008). Recently, a miRNA, miR-133b, has been identified that is specifically expressed in midbrain DAergic neurons and is deficient in midbrain tissue from patients with PD (Kim and others 2007). This miRNA regulates the maturation and function of midbrain DAergic neurons, possibly by regulating *Pitx3*. In fact, abnormal regulation of certain genes, such as the *fibroblast growth factor 20* (*FGF20*) on 8p21.3-22, has been suggested as a novel mechanism of individual susceptibility to the development of PD (Wang and others 2008). The risk allele (rs12720208) of the gene *FGF20*, another development-related gene of midbrain DAergic neurons, disrupts a binding site for miRNA-433, which correlates with increased α-synuclein expression (Wang and others 2008). In addition, Nurr1 also interacts with *Wnts*, a family of glycoproteins that regulates cell proliferation and differentiation (Castelo-Branco and others 2003). Another factor with which *Nurr1* interacts is *p57kip2*, a kinase inhibitor of the CIP/KIP family, whose expression in postmitotic differentiating midbrain DAergic neurons partly depends on *Nurr1* (Castelo-Branco and others 2003). *Nurr1* also interacts with the *GRIK5* gene, which codes for kainate-preferring glutamate receptor subunit KA2 (Chew and others 1999).

Gestational Environmental Factors in Initiation and Development of PD

Multihit Hypothesis in DAergic Neurons

There are many examples of disorders caused by an insult in utero or in the perinatal period that remain static until later in life, when the symptoms begin to progress (Scott and Jankovic 1996; Wijemanne and Jankovic 2007). Although the mechanism of conversion from the silent stage to a progressive course is not often readily apparent, a failure of normal compensatory mechanisms or second insult has been proposed as an explanation for this phenomenon. In addition, silent toxicity has been proposed for persistent morphological and/or biochemical injury without clinical manifestation (Reuhl 1991; Clarke and others 2000; Barlow and others 2007). During this period, however, the system has an increased vulnerability to a variety of secondary environmental insults. Toxic exposures in early development could determine long-term pathology in the central nervous system.

The multihit model explores the possibility that early damage to the DAergic system could result in cell loss or high vulnerability to a second environmental factor, which may lead to critical loss of DAergic neurons and subsequent development of PD symptoms (Thiruchelvam and others 2003). This multihit hypothesis has been tested in several models of PD (Eells and others 2002; Jiang and others 2005). For example, changes in locomotor activity, thought to be related to decreased mesolimbic and mesocortical DA levels without obviously altered striatal DA levels, have been reported in adult, phenotypically normal Nurr1+/– mice when exposed to MPTP (Eells and others 2002). Furthermore, old *Nurr1*+/– mice (>15 mo) displayed a significant decrease in the rotarod performance and locomotor performance compared with the normal *Nurr1*+/+ mice and adult Nurr1+/– mice (Jiang and others 2005). The reduction of rotarod and locomotor performance correlated with decreased striatal DA and *Nurr1* mRNA levels in an age-dependent manner (Jiang and others 2005). In contrast, overexpression of *Nurr1* in mouse neuronal stem cells has been found to have neuroprotective effects against neurotoxin MPTP-induced cell death (Lee and others 2002). Thus, we postulate that various transcriptional factors are important not only in the early development of the DAergic system but also in mediating compensation during the silent stage and that as a result of prenatal, perinatal, or

postnatal environmental or genetic hits, a critical threshold is reached, after which the course becomes progressive (Fig. 3).

Bacteriotoxin Lipopolysaccharide

One possible cause of PD is some prenatal event or process that predisposes some individuals to start with fewer DAergic neurons at the time of birth (Jankovic 2005; Logroscino 2005). Several studies have provided evidence in support of this hypothesis. For example, in utero exposure to some toxins, such as lipopolysaccharide (LPS), may reduce the number of normal DAergic neurons at birth. The loss of DAergic neurons found in rats born to mothers exposed to LPS during pregnancy mimics the progressive pattern of cell loss seen in human PD (Thorsen and others 1998; Carvey and others 2006). Prenatal LPS exposures decreased striatal DA concentration and the number of DAergic neurons in both the SNpc and VTA to a similar degree (~25%) in 3-wk-old offsprings (Ling and others 2004). Furthermore, the DAergic neuron loss is accompanied by reduction in striatal DA, increases in DA activity, and increases in production of the proinflammatory cytokine tumor necrosis factor alpha, which is present in the brains of PD patients (Mogi and others 1994).

Paraquat and Maneb

Another study suggested that prenatal or early postnatal exposure to certain toxins, such as the herbicide paraquat and the fungicide maneb, both of which adversely affect DA systems, may reduce the number of DAergic neurons in the SN in early development and enhance vulnerability to these toxins when administered subsequently in adulthood (Barlow and others 2004). Experimental animals exposed to maneb prenatally and to paraquat in adulthood show a dramatic decrease (95%) in activity associated with decreased levels of striatal DA and selective reduction in TH-positive neurons in the SNpc (Barlow and others 2004). Furthermore, paraquat and maneb exposure during critical periods of development could permanently change the DA system and enhance its vulnerability to subsequent neurotoxin challenge (Thiruchelvam and others 2003). Mice exposed early in life to two neurotoxins, paraquat and maneb, and subsequently exposed again as adults presented with the most severe damage, showing a 70% reduction in motor activity 2 wk after the last toxic dose (Thiruchelvam and others 2003). Striatal DA levels were reduced by 37% after only the developmental exposure to paraquat plus maneb compared with a 62% reduction after adult reexposure, which suggests that the exposure during the development stage produced a state of masked toxicity that was revealed after adult reexposure and that the toxic effect may be enhanced (Thiruchelvam and others 2003). Besides paraquat and maneb, there are many other neurotoxins, such as other pesticides, metals, and organic solvents, that are known to affect the developing brain (Grandjean and Landrigan 2006). These studies are consistent with the multiple-hit hypothesis (Sulzer 2007).

Genetic Defect Models and Latent Period

The recent discovery of specific genes (α-*synuclein*, *parkin*, *DJ-1*, *Pink1*, *Nurr1*, and most recently *LRRK2*) that cause familial forms of PD has contributed to the development of novel genetic mouse models of PD. These models offer the opportunity to examine the possibility that a gene defect may be a promoter signal of neuronal degeneration, which could be enhanced by late environmental factors and lead to development of disease. Several transgenic mouse lines including α-synuclein knockout or overexpression of human α-*synuclein* (wild-type, A30P, A53T, or A30P+A53T), *parkin* knockout, *DJ-1* knockout, and *LRRK2* knockout have been generated (Fleming and others 2005; Melrose and others 2006). Although these transgenic mouse lines have subtle neurophysiological abnormalities, they are not associated with a loss of nigrostriatal DAergic neurons, the pathological hallmark of PD (Fleming and others 2005; Melrose and others 2006). It is believed that these mice models may represent the early stages of the disease or that they act as susceptibility to the disease, but when coupled with environmental risk factors, including neurotoxins, they can lead to marked neuorodegeneration (Oliveira and others 2003). For example, in mice expressing human α-synuclein, combined exposure to two neurotoxins, paraquat and maneb, markedly enhanced neurotoxicity (Thiruchelvam and others 2003). Interestingly, only a specific mutant presents enhanced vulnerability to neurotoxins, which suggests a specific gene-environment interaction could be an early signal of DAergic neuron degeneration in animal models and in humans. Intriguingly, transgenic *Drosophila* models overexpressing both α-*synuclein* and *LRRK2* mutant genes are associated with a selective loss of DAergic neurons, locomotor dysfunction, and early mortality, whereas knock out of *Pink1*, *Parkin*, and *DJ-1* genes mostly causes severe mitochondrial abnormalities of muscle and spermatid defects, without marked striatonigral degeneration (Dodson and Guo 2007; Liu and others 2008; Trinh and others 2008). Because most of the PD-causing genes are expressed in the embryonic or early postnatal stages, it is quite possible that defects in these genes may adversely affect the development of nigral DAergic neurons and other neuronal networks involved in PD.

On the other hand, defects in genes important for the nigral DAergic neuron development and survival lead to severe nigrostriatal DAergic neuron agenesis and abnormal motor and behavioral function (Fleming and others 2005; Jankovic and others 2005; Riaz and Bradford 2005). For example, in *Nurr1* knockout mice, DAergic neurons showed age-dependent degeneration, which is associated with deterioration in motor function and increased vulnerability to MPTP and rotenone compared with the wild type (Le, Conneely, He, and others 1999; Jiang and others 2005). Furthermore, *Pitx*3-aphakia mice, heterozygous *Engrailed* mutant mice, *Lmx1*α deficient mice, and *Ngn2* knockout mice provide good models to study the mechanisms of developmental DAergic neuronal loss and ways to prevent it (Sgado and others 2006; Smits and Smidt 2006).

The possibility that prenatal toxin exposure may contribute to the development of a neurodegenerative disease of the aged population raises interesting new pathogenic questions and draws attention to the possibility that in utero exposure to neurotoxins may represent a heretofore unrecognized cause of PD (Barlow and others 2004; Cory-Slechta and others 2005; Barlow and others 2007). This is also supported by the finding that the Y chromosome–linked, male-determining gene *Sry* is specifically expressed in the SN of

the adult male rodent in TH-expressing neurons (Dewing and others 2006). Just like estrogen may be neuroprotective in females, *Sry* may be neuroprotective in males, and the deficiency in the *SrY* gene in males may lead to development of PD (Dewing and others 2006). Toxic exposures that occur early in development could determine long-term pathology in the central nervous system.

Conclusion

There is emerging evidence that PD is not a single disease but a syndrome of different disorders in which genetic, environmental, and other factors converge into a common final pathology. Although traditionally viewed as an age-related disorder, PD may have an early, possibly even prenatal, onset as a result of disruption of neuronal development, making the nigrostriatal system vulnerable to subsequent insults. Although in this review we focused on the midbrain DAergic system, the other source of DAergic cells, namely the subventricular zone, is also affected in the brains of patients with PD (Curtis and others 2007). The multiple-hit, gene-environment hypothesis, discussed here, is gaining support from various animal models and should be regarded as a possible pathogenic mechanism for PD. Further studies are needed to determine whether the various development-related genes, such as *Nurr1* and *Pitx3*, interact with known PD-causing genes that lead to nigrostriatal DAergic and non-DA dysfunction, resulting in PD-related pathology, including misfolding and aggregation of proteins and formation of Lewy bodies (Balch and others 2008). Advances in understanding the role of developmental genes and their interaction with early and subsequent environmental insults should provide insight into the etiopathogenesis of PD and assist in planning future neuroprotective strategies.

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