Published in final edited form as:

Parkinsonism Relat Disord. 2009 December ; 15(10): 721–727. doi:10.1016/j.parkreldis.2009.09.010.

Parkin and PINK1 parkinsonism may represent nigral mitochondrial cytopathies distinct from Lewy body Parkinson's disease

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Abstract

Recent authors have concluded that Parkinson's disease (PD) is too heterogeneous to still be considered a single discrete disorder. They advise broadening the concept of PD to include genetic parkinsonisms, and discard Lewy pathology as the confirmatory biomarker. However, PD seen in the clinic is more homogeneous than often recognized if viewed from a long-term perspective. With appropriate diagnostic criteria, it is consistently associated with Lewy neuropathology, which should remain the gold standard for PD diagnostic confirmation. PD seen in the clinic has an inexorable course with eventual development of not only levodopa-refractory motor symptoms, but often cognitive dysfunction and prominent dysautonomia. This contrasts with homozygous parkin, PINK1 or DJ1 parkinsonism, characterized by young-onset (usually <40 years), and a comparatively benign course of predominantly levodopa-responsive symptoms without dementia or prominent dysautonomia. Parkin neuropathology is non-Lewy, with neurodegeneration predominantly confined to substantia nigra (and locus ceruleus), consistent with the limited clinical phenotype. Given the restricted and persistently levodopa-responsive phenotype, these familial cases might be considered "nigropathies". Based on emerging laboratory evidence linking parkin and PINK1 (and perhaps DJ1) to mitochondrial dysfunction, these nigropathies may represent nigral mitochondrial cytopathies. The dopaminergic substantia nigra is uniquely vulnerable to mitochondrial challenges, which might at least be partially attributable to large energy demands consequent to thin, unmyelinated axons with enormous terminal fields. Although sporadic PD is also associated with mitochondrial dysfunction, Lewy neurodegeneration represents a more pervasive disorder with perhaps a second, or different primary mechanism.

Keywords

Parkinson's disease; parkin; PINK1; DJ1; mitochondria; Lewy

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Financial Disclosure: Nothing to disclose.

This manuscript is based on the lecture delivered at the 4th Annual Meeting of the Genetic Epidemiology of Parkinson's disease (GEO-PD), University of Tübingen, Tübingen, Germany, July 8, 2009.

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Introduction

Parkinson's disease (PD) research is uncovering an ever-increasing array of potential causative or contributory factors. A myriad of environmental risk factors have surfaced, although the attributable risk for any one of these is no more than a few percent. Investigation of familial parkinsonism has generated multiple genetic clues, although Mendelian inheritance appears to account for little of the PD we see in the clinic. These broadened etiologic horizons have suggested to some investigators that major revisions of our diagnostic and pathological conceptualization of PD are necessary[1–4].

First, it has been argued that what we currently call Parkinson's disease actually represents many disorders, and that "...there is no single Parkinson's disease"[1]. While few would dispute the assertion that PD etiology is likely multi-factorial, this revised view proposes that PD represents many fundamentally different conditions; i.e., PD is actually many different parkinsonisms. This has major implications for epidemiologists investigating PD associations; the notion of multiple ill-defined parkinsonisms obviously complicates such studies.

Second, the long-standing assertion that Lewy neuropathology confirms PD has recently been questioned [2–4]. Previously, there was general acceptance that levodopa-responsive parkinsonism without clinical red flags was probably PD, but became definite with demonstration of Lewy pathology. The new revisionist view is primarily based on reports that parkin or LRRK2 parkinsonism has inconsistent Lewy pathology; thus parkinsonism due to either of these genotypes may or may not be associated with Lewy bodies/neurites. Thus, critics now "...challenge the common wisdom that Lewy bodies should be considered mandatory for the pathologic diagnosis of PD." [4] This view obviously complicates the study of PD if there is no gold standard confirmation of the diagnosis.

This revisionist rethinking of PD as clinically and pathologically amorphous should itself not go unchallenged. In this manuscript, we will review evidence suggesting that: (1) the routine PD we see in the clinic is actually fairly homogeneous if considered over the course of the lifetime; (2) when contemporary rigorous diagnostic criteria are applied, PD diagnosed in the clinic does indeed have consistent Lewy neuropathology; (3) although LRRK2 pathology can be heterogeneous, so can the associated LRRK2 clinical phenotypes, some of which are inconsistent with PD; (4) familial parkinsonism linked to parkin, as well as PINK1 and DJ1 are all similar, but quite distinct from PD, perhaps meriting separate classification. Finally, as an extension of this last assertion, one might propose that these parkin, PINK1, and perhaps DJ1 cases may represent limited "nigropathies"; i.e., neurodegenerations primarily confined to the substantia nigra (and locus ceruleus). In fact, increasing evidence allows speculation that the pathogenic substrate for parkin, PINK1 and possibly DJ1 may be via mitochondrial mechanisms, i.e., mitochondrial cytopathies.

Lewy pathology remains the gold standard for PD confirmation

The rationale for abandoning Lewy neuropathology relates to LRRK2 or parkin parkinsonism associated both with and without Lewy pathology[1–4]. Indeed, if these familial disorders are clinically interchangeable with routine PD, then Lewy pathology is not necessary. However, the story is a bit more complex.

LRRK2 neuropathology

LRRK2 parkinsonism generally has a phenotype that closely resembles sporadic PD and the pathology is usually Lewy[5]. However, there are cases of other neuropathologies, including tau [6–8], Marinesco bodies[8,9] or absence of distinctive neuropathology[6,8].

On the other hand, not only is there neuropathological heterogeneity, but also well-documented phenotypic variability. Thus, in one well studied LRRK2 kindred (so-called Family A) clinical manifestations included amyotrophy, as well as Meige dystonia syndrome[5,9]. Supranuclear gaze palsy has also been documented in another kindred[5], whereas in yet others, the phenotype has been primary progressive aphasia or corticobasal syndrome[10]. Given the pathologic and phenotypic heterogeneity, it has been proposed that LRRK2 dysfunction is not a proximate cause of these neurodegenerative disorders, but reflects a mechanism more upstream in the pathogenic sequence[5]. Thus, LRRK2 function may be more fundamental to neurodegeneration in general, rather than simply to PD.

Parkin neuropathology

Homozygous parkin mutations cause an autosomal recessive form of parkinsonism. Among the half-dozen of these cases undergoing autopsy, four were genetically-confirmed[11–14], whereas two predated genetic testing[15,16]. The neuropathologic findings have been consistent: no Lewy pathology and neuronal loss primarily confined to the substantia nigra and locus ceruleus, which is fundamentally different from routine PD. Moreover, the clinical phenotype of parkin also substantially differs from PD, as detailed below.

Taking exception, two additional familial parkin cases were indeed found to harbor Lewy pathology[17,18]. However, the family pedigrees in both cases necessarily indicate that some other crucial PD susceptibility factor must have been present. Thus, in one family, the affected son of the proband had only a hemizygous deletion[17]. In the other family, most of the 25 affecteds had no, or heterozygous parkin mutations[18]. Hence, parkinsonism in these two families cannot be solely attributed to parkin mutations.

Lewy pathology is linked to alpha-synuclein

Lewy bodies accumulate a variety of cell products, but especially alpha-synuclein[19,20], which is currently regarded as a crucial factor in PD pathogenesis. Alpha-synuclein immunohistochemistry is universally employed as the specific histological marker of Lewy pathology. Alpha-synuclein mutations have been associated with parkinsonism that is a good phenotypic fit with sporadic PD[21,22]. Moreover, extra genetic copies of wild-type alpha-synuclein also result in a Parkinson's disease phenotype[23–28], and there is a dose-related effect, with genetic triplications causing more aggressive disease than duplications[26,28].

Definite clinical PD predicts Lewy pathology

One further argument in favor of Lewy pathology is the consistent association with well-defined PD in the clinic. In this modern era when specific diagnostic criteria are applied, the clinical phenotype positively predicts Lewy pathology close to 100% of the time[29,30]. Thus, when the clinician recognizes definite clinical PD with the diagnosis maintained over several years, and without diagnostic red flags, the pathology is almost always Lewy.

PD in the clinic is characterized by a natural inexorable history

Lewy pathology ties together a clinically heterogeneous assortment of PD patients, ostensibly suggesting more than a single condition[1]. This heterogeneity, however, should not be an argument to discount the significance of the Lewy body. If one takes a step back and reviews the temporal course of PD, it is clear there is a consistent natural history. Thus, while there may be many causes, they may work through one final common pathway of Lewy pathology. The pattern becomes apparent as patients are followed over the course of two or more decades. Breaking this down into early, intermediate and late, one can see the following patterns, which are also influenced by older ages that facilitate progression.

Early PD

Initially, patients are highly responsive to levodopa therapy, as evidenced by very low UPDRS scores in treatment trials of newly diagnosed patients. These early patients also experience the levodopa benefit with “long-duration” pharmacodynamics[31]: this long-duration anti-parkinsonian effect gradually builds up over approximately a week, then plateaus, and is not influenced by occasional skipped doses. Not only motor, but also many non-motor problems respond, such as anxiety, bradyphrenia and insomnia.

Intermediate PD

After several or more years, the response to even maximal doses of levodopa and related drugs may be less complete, suggesting non-dopaminergic substrates. This is evident in clinical treatment trials of advancing PD, where the UPDRS scores are now worse than among early patients, despite aggressive medication dosing. Moreover, levodopa dynamics transition to “short-duration” responses[31], where the benefit is tied to each dose, lasting a few hours or less; these may be associated with dyskinesias. Finally, more levodopa-refractory non-motor symptoms begin to develop, such as depression, mild cognitive impairment and so on.

Late PD

Well beyond ten years, levodopa-refractory symptoms increase still further, albeit to variable degrees. Thus, the UPDRS scores are now much higher, even though dopaminergic replacement therapy is pushed to the point of maximum benefit. Short-duration responses (motor fluctuations) and dyskinesias increasingly become of lesser concern and tend to be overshadowed by gait failure that does not respond to levodopa. Thus, gait freezing or imbalance with falls may eventually require gait aids and ultimately a wheel chair. Moreover, often keeping company with these motor problems are cognitive deficits, dementia.

Dysautonomia follows a similar pattern. Mild autonomic symptoms are present early in PD and may predate the motor symptoms (e.g. constipation[32]). In certain late PD patients, some of the most troublesome problems are autonomic, such as symptomatic orthostatic hypotension or urinary incontinence (neurogenic bladder).

This evolution of PD is inexorable but also somewhat variable. Thus, while dementia tends to be late, mild cognitive impairment may be seen in around 20–30% of early PD cases[33–35]. Similarly, some early PD cases may have an incomplete levodopa response and experience substantial residual symptoms, despite maximum treatment. Regardless, the course of PD seen in the clinic is progressive over years.

The substrate for advanced PD remains Lewy pathology

Most recent studies have confirmed that PD evolving to dementia represents proliferation of the Lewy neurodegenerative process, ascending beyond the midbrain to limbic cortex and neocortex[30,36,37]. Although cortical neuronal loss and Lewy body counts may not be profound, widespread alpha-synuclein aggregation in cortical terminals has been documented in DLB[38], and by extension, PD-dementia. Similarly, levodopa-refractory motor symptoms appear to have this same substrate, reflecting proliferation of Lewy pathology[37].

This process at least generally fits with the Braak staging scheme[39–41], although not necessarily via the precise neuroanatomically-contiguous ascending pattern proposed by Braak and colleagues. While exceptions to this scheme have been well-documented[42–50], clinical-

pathological studies of most PD and incidental Lewy pathology cases appear consistent with this general ascending/proliferating pattern[42–46,49].

Long-term studies

Clinicians are well-aware of this PD evolution and several recent prospective studies have documented such long-term outcomes in defined PD cohorts. Thus, cognitive impairment (dementia or MCI) was documented in 85% of a surviving PD cohort from Sydney, Australia by 15 years[51], whereas a 60% dementia prevalence was noted in a Norwegian PD cohort by 12 years of followup (with dementia increased to 80–90% by age 90)[52]. Although only 25% of a United Kingdom cohort were demented by 14 years, more than ¾ of the original group was deceased and half of the survivors were lost to followup[53]. The Sydney study also confirmed increasing levodopa-refractory motor symptoms that became the primary sources of disability, with 81% of the surviving cohort experiencing falls, and 65% reaching Hoehn-Yahr stages 4–5 by 15 years of followup[51].

Conclusions

PD seen in the clinic relentlessly progresses, resulting in levodopa-refractory motor symptoms, cognitive impairment and dysautonomia, with progression of the Lewy degenerative process as the primary substrate[30,36,37]. The general experience in the clinic suggests this occurs in all patients developing PD at typical ages, albeit to different extents. Age is a major factor, with older PD patients experiencing more of these problems earlier, whereas some never experience much disability if other fatal medical conditions intervene.

Phenotypic exception: no progression beyond the midbrain dopaminergic nigra

Case history

A patient from the 1969 Mayo Clinic levodopa trial continues to be regularly followed. Parkinsonism began around age 19 and he was started on levodopa at age 27. After approximately 4 decades on primarily levodopa therapy, he continues to live an independent life, but with an hourly levodopa requirement complicated by dyskinesias. In 2008 when last evaluated in the Clinic (J.E.A.) he was nearly normal in his full levodopa on-state, except for prominent dyskinesias.

Although rare, PD specialists recognize this pattern, although not often with this length of followup (40 years). Most clinicians would suggest genetic testing, which in his case was offered but declined. This pattern is typical of the PD consistently documented in autosomal recessive parkinsonism associated with homozygous mutations in parkin, PINK1 and DJ1.

Parkin, PINK1 and DJ1 appear to represent unique disorders

Arguments for abandoning the unitary concept of Parkinson's disease and discarding Lewy pathology have especially been based on parkin, PINK1 and DJ1 phenotypes, plus heterogeneous parkin pathology[1–4]. These genetic parkinsonisms now deserve further consideration.

The parkinsonisms of homozygous parkin[54–58], PINK1[55,56,59] and DJ1[56,60–62] are phenotypically similar, yet they are distinctly different from the course of sporadic PD, outlined above. Consistent features in the parkin, PINK1, DJ1 phenotype include:

- Onset in most cases before age 40;
- A much more benign course despite decades of parkinsonism;

- Symptoms primarily referable to dopaminergic substrates with well-preserved levodopa responsiveness (but levodopa dyskinesias and motor fluctuations);
- No substantial cognitive decline (although psychiatric symptoms may occur);
- Minimal dysautonomia (confined to urinary urgency, male impotence and autonomic symptoms attributable to medications).

Although parkin, PINK1 and DJ1 parkinsonism are often lumped with PD[2–4], these are clearly distinctive. Not only is the course in stark contrast to what is described above for PD, but onset-age also is unusual. For example, compare the 202 incident-PD cases ascertained in Olmsted County, Minnesota over 20 years (1976–1995), none had onset before age 40 years (youngest, age 41)[63].

Comparative dopaminergic brain-imaging also distinguishes PD from parkin[64,65], as well as PINK1[66,67], although the differences were slight in one study[68]. Finally, as discussed above, parkin neuropathology is non-Lewy, although admittedly, there have been only a few autopsied cases.

Nigropathies

The clinical phenotypes of parkin, PINK1 and DJ1 are very similar and primarily characterized by levodopa-responsive parkinsonism without substantial development of levodopa-refractory symptoms. This is consistent with neuronal loss largely confined to the dopaminergic substantia nigra, and fits with the neuropathology described above for parkin homozygotes. Although the neuropathology of homozygous PINK1 or DJ1 parkinsonism has not been documented, the phenotypic similarity to parkin suggests that they may well share this pattern of predominant nigral degeneration. Arguing from this premise, one might characterize these three genetic parkinsonisms as “nigropathies”; i.e., selective nigral degenerations. Obviously, this concept of nigropathy should encompass the contiguous dopaminergic ventral tegmental area, as well as the locus ceruleus, which also degenerates in parkin cases.

The evidence suggesting that parkin, PINK1 and possibly DJ1 represent nigral mitochondrial cytopathies

Common features allow evidence-based speculation as to the pathogenesis possibly shared by parkin, PINK1 and possibly DJ1. Specifically, two lines of evidence suggest that these nigropathies may represent circumscribed mitochondrial cytopathies:

1. The dopaminergic substantia nigra is uniquely susceptible to mitochondrial toxins, most notably, rotenone and MPTP.
2. All three genes, parkin, PINK1 and DJ1, have been linked to mitochondrial dysfunction, especially parkin and PINK1.

Background

Mitochondria are obviously fundamental to aerobic metabolism but are vulnerable organelles. They have their own DNA, which is highly susceptible to damage from oxidative phosphorylation, generating potentially toxic oxyradicals; they also lack protective histones and have limited DNA repair mechanisms[69,70].

To offset these threats to cellular/neuronal survival, multiple mitochondria are contained within each cell and each mitochondrion has multiple copies of its own DNA[71]. Moreover, mitochondria are constantly being remodeled through fission and fusion processes that can

eliminate dysfunctional mitochondrial segments that are not only sources of oxyradicals, but also capable of releasing substrates that initiate apoptosis[71].

Parkin

Parkin is an ubiquitin ligase and an integral component of the ubiquitin proteasome system (UPS), which degrades cellular/neuronal proteins. The UPS was initially suggested as an important PD pathogenic component with the discovery of not only parkin, but also a second UPS protein linked to familial parkinsonism, UCHL1[72]. Thus, with PD being regarded as an alpha-synucleinopathy, impaired UPS protein degradation of alpha-synuclein was a logical extension of this conceptual framework. More recent evidence, however, suggests that impaired UPS degradation of alpha-synuclein is probably not a central feature of PD pathogenesis. Thus, wild-type alpha-synuclein is predominantly degraded by chaperone-mediated autophagy, which is disrupted by pathogenic alpha-synuclein mutants[73,74]. Moreover, alpha-synuclein aggregates and misfolded proteins, in general, are primarily degraded by simple autophagy (macroautophagy)[75]. Hence, with alpha-synuclein processing predominantly occurring in lysosomes, the perceived role of the UPS in these neurodegenerative processes was diminished.

Recent evidence now points to a crucial role for parkin beyond the UPS, in maintaining mitochondrial morphology and function. Thus, parkin is recruited to dysfunctional mitochondria and targets them for autophagy, presumably by ubiquitination[76,77]. This may occur in conjunction with mitochondrial fission proteins (e.g. Drp1) promoting deletion of impaired regions of mitochondria, which then undergo autophagy. Thus, parkin-deficient mice [78], as well as *Drosophila*[79] have deficient oxidative phosphorylation and reduced respiratory capacity; dysmorphic mitochondria become apparent[79]. Conversely, parkin overproduction protects against at least some mitochondrial toxins, in vitro[80]. Finally, fibroblasts from homozygous parkin patients have reduced mitochondrial complex I activity, reduced ATP production and dysmorphic mitochondria[81].

PINK1

PINK1 protein is localized to mitochondria, and also appears crucial to mitochondrial function. In vitro, PINK1 down-regulation/knock-down results in impaired oxidative phosphorylation, reduced mitochondrial membrane potential and abnormal mitochondrial morphology[82–84]. These abnormalities can be reversed with wild-type, but not with mutant PINK1[82]. Fibroblasts from PINK1 patients also have abnormal mitochondrial morphology and oxidative metabolism[85]. Recent reports indicate that PINK1 promotes mitochondrial fission, critical to maintenance of mitochondrial function and morphology[86,87]. Also, PINK1 deficiency is associated with abnormal mitochondrial calcium fluxes, possibly pathogenic[88,89].

Parkin and PINK1 function in a common mitochondrially-related pathway

In vitro, the abnormal mitochondrial function and morphology from PINK1 downregulation can be rescued with wild-type, but not mutant parkin[82]. In *Drosophila*, evidence supports parkin and PINK1 interacting in a common biologic pathway; thus, parkin overexpression rescues PINK1 mitochondrial phenotypes[90–92]. Since parkin rescues PINK1 but not vice versa, it is suggested that parkin functions downstream of PINK1 in this biologic pathway [90–92]. Translocation of parkin to mitochondria is promoted by PINK1[93]. The primary role of this pathway may be to facilitate mitochondrial fission, which is crucial to overall mitochondrial function and integrity[86].

DJ1

In general, DJ1 is thought to play a role in mitigating neuronal oxidative stress, which can be generated by mitochondrial oxidative phosphorylation, as well as from other sources. However, the precise role DJ1 plays in cellular function has yet to be elucidated. The primary reason for including DJ1 in this discussion is the clinical phenotypic similarity to parkin and PINK1. In view of this clinical overlap, a similar mitochondrial pathogenic substrate is plausible.

In an experiment of nature, two young parkinsonian sisters have been reported who each carried a single DJ1 and a single PINK1 pathogenic mutant allele as the explanation for their condition [94]. Parkinsonism resulting from a compound digenic heterozygotic state suggests a common pathogenic mechanism for DJ1 and PINK1.

Currently, there is only limited laboratory evidence linking DJ1 with mitochondrial function, in contrast to parkin and PINK1. DJ1 appears to translocate to mitochondria during oxidative stress, suggesting a neuroprotective effect in the oxyradical microenvironment of mitochondria [95–98]. Other studies have reported a general localization of DJ1 in mitochondrial fractions of both mice [99] and humans [100] (although also present in other subcellular compartments). In contrast to parkin and PINK1, DJ1-deficient models have not documented abnormal mitochondrial morphology or function. However, DJ1 knockout mice have an increased sensitivity to the mitochondrial toxin, MPTP, and neurons *in vitro* from these animals had an increased sensitivity to oxidative stress, including the mitochondrial toxin, rotenone [101]. *Drosophila* DJ1- knockouts are also significantly more sensitive to mitochondrial toxins (e.g. rotenone) and other sources of oxidative stress (e.g. H₂O₂), but not to toxins acting via other mechanisms [102]. *In vitro*, DJ1 over-expression increased resistance to oxidative stress, including the mitochondrial toxin, rotenone, whereas DJ1 down-regulation had the opposite effect [97]. Experimental oxidative stress up-regulated endogenous DJ1 *in vitro* [97].

Summary: familial nigral mitochondrial cytopathies

Parkinsonism due to homozygous parkin mutations is clinically and pathologically associated with degeneration primarily restricted to the dopaminergic substantia nigra (plus locus ceruleus). The nigra is uniquely susceptible to mitochondrial toxins and parkin function appears crucial to maintenance of mitochondrial health. Similar arguments can be made for PINK1, and with less conviction for DJ1, although the neuropathologies of homozygous PINK1 and DJ1 remain unreported.

Relevance to routine Parkinson's disease seen in the clinic

Whereas parkin, PINK1 and perhaps DJ1 function are linked to mitochondria, the pathogenic substrate for PD remains unknown. However, mitochondrial dysfunction, primarily complex I, has been consistently documented in PD, and in a variety of cells: platelets [103,104], muscle [105], lymphocytes [104], as well as in the substantia nigra [106]. In fact, the impairment in leukocyte mitochondrial complex I activity is nearly identical in routine PD patients and parkinsonian patients homozygous for parkin mutations [107].

Dual pathogenic processes in routine Parkinson's disease?

Lewy body disease is obviously more pervasive and extensive than the restricted nigropathies of parkin or PINK1. Moreover, it is not necessarily inextricably linked to nigral degeneration. Note that most cases of Lewy body dementia (DLB) and Parkinson's disease with dementia (PDD) are pathologically and clinically nearly identical [108,109], except for the early development of dementia in DLB. These might arguably represent opposite ends of a disease spectrum [110]. LBD, however, sometimes is not associated with parkinsonism [111], and may spare or partially spare the substantia nigra on pathological examination [48,111,112]. The fact

that the Lewy pathologic process can be dissociated from dopaminergic nigral degeneration suggests there may be two fundamentally different pathogenic mechanisms operative in diffuse Lewy body disorders. Thus, mechanisms in typical PD might include: (1) a primary Lewy pathogenic condition with currently unknown biological mechanisms, but likely linked to alpha-synuclein; (2) a secondary challenge to the nigra, vulnerable because of huge mitochondrial energy demands due to nigral neuronal morphology and other factors.

Why is the dopaminergic substantia nigra susceptible to mitochondrial challenges?

The vulnerability of the nigra to mitochondrial insults could at least partially relate to the unique morphology of nigral neurons. Thus, Braak and colleagues have noted that PD-susceptible neurons of all types (i.e., not just dopaminergic) have long, thin, poorly myelinated axons with high energy expenditures[40]. However nigral dopaminergic neurons are unique well beyond that. As documented in rats, they have enormous terminal projection fields. A single rat nigral neuron gives rise to an axon and terminal field up to a total 78 cm in length (around 3 times the length of a rat)[113]. A single rat nigral neuron gives rise to approximately 170,000–400,000 synapses within the striatum, orders of magnitude greater than, for example, the 2,000 synapses of an external globus pallidus neuron, or striatal medium spiny neurons, which give rise to around 300 synapses[114]. Thus, a single dopaminergic nigral neuron directly influences about 75,000 striatal neurons[113]. This extremely large terminal field must place huge energy demands upon these nigral neurons. An unanswered question is whether the spared dopaminergic nuclei (e.g. A8) have substantially smaller terminal fields.

Evidence of challenged nigral mitochondria is suggested in gene expression profiling studies in rats[115]. Also, the mitochondrial mass in dopaminergic nigral neurons of mice appears to be substantially less than in adjoining non-dopaminergic somata and dendrites[116]. Thus, the mitochondrial energy demands of dopaminergic nigral neurons may be on the margins of adequate compensation. In humans, mitochondrial DNA deletions have been shown to accumulate in nigral neurons with age and PD[117,118]; this may further predispose to later-onset sporadic PD.

Summary

The genetic parkinsonisms (parkin, PINK1, DJ1) are providing crucial clues to neurodegenerative parkinsonism. However, they are distinct from Lewy body PD and deserve separate classification. A working hypothesis suggests mitochondrial dysfunction as the primary substrate for the parkinsonism of parkin, PINK1 and perhaps DJ1. In Lewy body PD, however, a more pervasive neurodegenerative process appears to be at work, but nonetheless implicating mitochondrial dysfunction.

Acknowledgments

Funding/Support: This work was supported by the Morris K. Udall Parkinson's Disease Research Center of Excellence grant (P50 NS40256).

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