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Understanding the susceptibility of dopamine neurons to mitochondrial stressors in Parkinson's disease

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Abstract

Mitochondria are undoubtedly changed in Parkinson's disease (PD), and mitochondrial functions are disrupted in genetic and pharmacologic models of PD. However, many of these changes might not truly drive neurodegeneration. PD is defined by the particular susceptibility of nigrostriatal dopamine (DA) neurons, but little is understood about the mitochondria in these cells. Here, we critically review the evidence that mitochondrial stressors cause PD. We then consider how changes in the intrinsic function of mitochondria and in their mass, distribution, and dynamics might synergize with an increased need for mitochondria and produce PD, and the importance of understanding how mitochondria contribute to its pathogenesis.

1. Introduction

Mitochondria are heavily disrupted in Parkinson's disease (PD), Alzheimer's disease, Huntington's disease, multiple sclerosis, and stroke. In these and other neurodegenerative and neurologic conditions, the enzymatic activity of respiratory chain enzymes is altered, mutations accumulate in mitochondrial DNA, and oxidative stress appears to be increased in affected brain areas at autopsy [1, 2]. Although mitochondrial morphology, behavior, and functions are disrupted in pharmacologic and genetic models of these diseases, the pathogenic role of mitochondria is unclear. Do changes in mitochondria initiate degeneration? If not, do they contribute to disease progression? Or are they simply epiphenomena that always accompany neuronal degeneration and death?

Among these conditions, perhaps only in those involving mutations in mitochondrial DNA can we be fully confident that primary changes in mitochondria actually cause disease. In most other diseases, changes in other cellular compartments have also been implicated in the pathophysiology. And even if mitochondrial changes cause these disorders, it is unclear which mitochondrial function or functions—such as loss of respiration, increased levels of reactive oxygen species (ROS), and impaired Ca^{2+} buffering—actually cause the degeneration.

In this review, we focus on mitochondria in PD, a neurodegenerative disease that is strongly linked to mitochondria. Indeed, the evidence for mitochondrial alterations in PD is as compelling as in any other neurodegenerative disorder. Support for a central pathogenic role of mitochondria is based on susceptibility to mitochondrial toxins, mitochondrial changes in autopsy tissue, genetic forms of PD caused by mutations in mitochondrial proteins, and model systems of PD. Here we evaluate the evidence that changes in mitochondria cause PD and consider how, specifically, mitochondria might be disrupted to cause PD.

2. Evidence That Mitochondrial Stressors Cause PD

2.1. Pharmacological evidence

DA neurons in the substantia nigra pars compacta (SN DA neurons) are uniquely vulnerable to specific mitochondrial stressors. The first direct evidence of this vulnerability was the discovery that the mitochondrial neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) preferentially kills SN DA neurons in humans [3]. MPTP proved to be toxic to DA neurons in primates and mice [4]. Its active metabolite, MPP^+, concentrates in mitochondria as a result of their negative membrane potential [5]. MPP^+ also weakly inhibits mitochondrial complex I [6], raising the possibility that this effect is responsible for the death of DA neurons. However, subsequent research revealed that MPP^+ likely produces death, at least in part, through mechanisms that are independent of its effects on complex I [7–12].

MPP^+ is a substrate for the DA transporter (DAT) and hence is preferentially imported into DA neurons [13, 14], likely resulting in higher cytosolic levels of MPP^+ than in other types of neurons. It is unclear whether this is truly the case and, if it is, how much higher the cytosolic levels are. Cytosolic MPP^+ is also sequestered in vesicles in DA neurons by the vesicular monoamine transporter 2 (VMAT2)[15, 16]. Therefore, the susceptibility to MPP^+ highlights how preferential uptake might lead to the selective death of DA neurons, but does not provide clear evidence that DA neurons themselves are intrinsically vulnerable to complex I or other mitochondrial stresses.

More compelling evidence for the intrinsic vulnerability of SN DA neurons to complex I inhibition comes from studies with rotenone, a potent complex I inhibitor [17, 18]. Systemically delivered rotenone selectively kills these cells in rats [19, 20], and exposure to rotenone also appears to increase the risk of developing Parkinson’s disease (PD) [21]. Moreover, sensitivity to complex I inhibition appears to be somewhat specific, as DA neurons are not preferentially susceptible to all mitochondrial toxins. For instance, the complex II inhibitors 3-nitropropionic acid and malonate are toxic to medium spiny neurons in the striatum [22–24] not DA neurons. This specificity further supports a specific vulnerability of DA neurons to complex I inhibition. Nonetheless, the data are inconclusive. Rotenone has never been directly proven to cause PD in humans, and it also inhibits microtubules and has other nonspecific effects. In addition, SN DA neurons are also relatively resistant to toxicity from deletion of the complex I subunit NDUFS4, although the extent of complex I dysfunction achieved in DA neurons *in vivo* was unclear [25, 26].

2.2 Evidence from PD mutations

Autosomal-recessive PD—Genetic mutations associated with rare familial forms of PD provide near-definitive evidence that primary deficits in mitochondrial function cause PD. In particular, the finding that mutations in the serine/threonine-protein kinase PINK1 cause an autosomal-recessive form of PD [27, 28] is particularly compelling evidence that DA neurons are intrinsically susceptible to mitochondrial stressors. PINK1 is a mitochondria-targeted protein that regulates mitochondrial turnover (mitophagy) [29], complex I function [30], mitochondrial dynamics, [31] and mitochondrial transport [32]. Although it localizes to mitochondria and its effects on mitochondria are believed to be critical to its functions, PINK1 has functions outside of the mitochondria [33, 34], and a subset of PINK1 is cytosolic [35–37]. The relative significance of mitochondrial versus non-mitochondrial functions in PD pathogenesis is unknown.

Other recessive PD genes further support the unique vulnerability of SN DA neurons to mitochondrial stressors. In particular, the E3 ubiquitin ligase Parkin associates with mitochondria, especially damaged mitochondria, where it promotes the turnover of damaged mitochondria and decreases mitochondrial motility in axons through PINK1-dependent mechanisms [29, 32, 38]. Moreover, loss of PINK1 severely disrupts the morphology and function of mitochondria in *Drosophila* flight muscles, and these deficits are rescued by overexpression of Parkin [39, 40]. Thus, PINK1 and Parkin act in the same pathway to influence mitochondria.

Just as PINK1 inhibits complex I independently of Parkin [30], Parkin also influences mitochondria through pathways that are seemingly unrelated to PINK1. For instance, Parkin inhibits the transcriptional repressor Paris. When Parkin is absent, Paris accumulates and represses the expression of peroxisome proliferator–activated receptor-gamma coactivator 1-alpha (PGC-1α), a central regulator of mitochondrial biogenesis and functions [41]. In addition, the autosomal recessive PD protein DJ-1 decreases oxidative stress in mitochondria and also influences mitochondrial morphology and bioenergetics [42–45]. Interestingly, DJ-1 complements the mitochondrial effects of other PD proteins, including PINK1, Parkin, and α-synuclein [42, 46, 47]. Nonetheless, like PINK1, Parkin and DJ-1 have mitochondria-independent effects [48–52], and the relative contributions of mitochondrial versus non-mitochondrial pathways to degeneration in PD have not been established.

Autosomal-dominant PD—The evidence that mitochondrial dysfunction causes sporadic PD was strengthened by the discovery that typical adult-onset PD can be caused by mutations in the autosomal dominant gene *CHCHD2* [53], which encodes a small protein localized to the mitochondrial intermembrane space. CHCHD2 binds to cytochrome c oxidase and maintains its level and activity [54, 55], and loss of CHCHD2 may compromise mitochondrial respiration. Like recessive PD genes, however, CHCHD2 also appears to have non-mitochondrial functions [54], and it is not known whether these functions also contribute to its role in PD pathogenesis.

Proteins causing other autosomal dominant forms of PD have been linked to mitochondria. In particular, a fraction of the central PD protein α-synuclein interacts with mitochondria,

and α-synuclein promotes mitochondrial fragmentation and disrupts the function of mitochondrial complex I [47, 56–59]. The effects of α-synuclein may represent a toxic gain of function that is distinct from the proposed physiologic roles of α-synuclein in regulating synaptic vesicle release [60]. Increasing evidence, including evidence from human neurons, also shows that LRRK2 influences mitochondrial functions and movement [61–65]. However, both α-synuclein and LRRK2 are primarily cytosolic and have other biologic functions, and hence the role of their interactions with mitochondria in producing neurodegeneration in PD remains to be clarified.

2.3. Significance of PD genetics in understanding how mitochondria contribute to sporadic PD

In assessing the relevance of mitochondrial changes in genetic forms of PD to sporadic PD, we must consider the possibility that the pathophysiology of recessive PD differs from that of the sporadic and autosomal dominant forms of the disease [66]. If the disorders are truly distinct, establishing a causative role for mitochondria in recessive PD might not help us understand the role of mitochondria in the more common sporadic forms. However, the evidence that autosomal recessive PD is indeed distinct is limited. For example, although autosomal recessive PD usually begins at a younger age than sporadic PD, disease onset in the 50s or later has been reported [67, 68]. Furthermore, in a large proportion of early-onset cases, there is no clear familial inheritance, and no mutations were found in a panel of PD-associated genes (*α*-synuclein, Parkin, PINK1, DJ-1, LRRK2, with or without glucocerebrosidase) in ≈85–90% of patients with an age of onset of 30–50 years, and in ≈60–85% with onset at less than 30 years of age [69, 70]. Hence, younger patients are more likely to have genetic mutations, but the age of onset itself does not indicate a distinct pathophysiology.

Cognitive deficits appear to develop and progress more slowly in patients with mutant Parkin than in age-matched patients with sporadic PD [71]. However, this difference does not prove a distinct pathophysiology. Indeed, patients with mutant PINK1 and Parkin often develop cognitive deficits and other nonmotor changes that are indistinguishable from those in many patients with sporadic PD [28, 72, 73]. This substantial overlap of clinical features occurs because sporadic PD itself is clinically heterogeneous, and the motor changes, their responsiveness to levodopa [74], and the type and severity of nonmotor features, such as cognitive deficits, vary considerably [74, 75]. Moreover, patients with triplication of α-synuclein (a protein firmly linked to sporadic PD) develop disease at a younger age than those with duplication and can have a much more aggressive form of parkinsonism (that sometimes manifests as diffuse Lewy body disease) [76–78]. Thus, at least in this case, a greater dose of the same insult (rather than a distinct pathophysiology) leads to an earlier and more severe disease onset.

Finally, recessive PD has been proposed to have a distinct pathophysiology: patients with Parkin mutations usually do not have α-synuclein inclusions. However, some Parkin patients have Lewy bodies [79, 80], and the only PD patient with mutant PINK1 to come to autopsy also had typical Lewy bodies [81]; no autopsy data have been reported for DJ-1. Therefore, there is no evidence that most forms of recessive PD lack Lewy bodies. Conversely, despite

having similar clinical presentations, some patients with autosomal dominant PD caused by mutations in LRRK2 also lack α-synuclein inclusions (in some cases having tau deposition instead), and others in the same family have typical Lewy bodies [82, 83]. Indeed, the clinical diagnosis of PD requires movement deficits, which result from the dysfunction or loss of SN DA neurons and can develop in the absence of Lewy bodies [82–84]. Moreover, Lewy bodies and Lewy neurites appear to develop in various regions, including the hippocampus, without causing significant neuronal death [85–88]. Lewy bodies can even accumulate at high levels in SN DA neurons in the absence of extrapyramidal symptoms (i.e., incidental Lewy bodies)[89].

Importantly, although PD is a heterogeneous disorder, SN DA neurons likely have a shared susceptibility that underlies its many different causes and forms. Mitochondria likely contribute to this shared pathogenesis, but the extent and nature of the contribution may differ markedly between different disease variants. Ultimately, autosomal recessive forms of PD may prove to have greater pathophysiologic overlap with subtypes of sporadic PD characterized by fewer cognitive deficits and greater responsiveness to levodopa than they do with other subtypes.

2.4. Evidence from sporadic PD

Do changes in mitochondria cause sporadic PD? The extensive mitochondrial changes in sporadic PD strongly suggest an important role for mitochondria in its pathogenesis, regardless of the indirect evidence from genetics and environmental toxins discussed above. These changes include decreased function of mitochondrial complex I in the SN [90, 91] and platelets [92, 93], decreased expression of PGC-1α and PGC-1α-regulated mitochondrial genes in DA neurons in PD[94, 95], as well as increased accumulation of mutations in the mitochondrial DNA of SN DA neurons with age and PD [96].

Nonetheless, it remains unclear which, if any, of these changes cause neurodegeneration. Definitive answers may require substantial technical advances, for instance new methods to longitudinally and simultaneously track mitochondrial functions and disease progression in susceptible neurons in patients, as well as new approaches to specifically correct the mitochondrial deficits and determine whether degeneration is blocked. Meanwhile, our understanding of whether and how changes in different mitochondrial functions cause sporadic PD depends heavily on insights from genetic and pharmacologic models.

Of particular importance to understanding mitochondria in sporadic PD is α-synuclein. Indeed, α-synuclein and mitochondria have important parallels. Changes in either α-synuclein or mitochondria can cause PD, and both α-synuclein and mitochondria are changed in sporadic PD. As reviewed in depth [59], increased α-synuclein influences mitochondria in several respects, including making them more fragmented [47, 56], inhibiting mitochondrial complex I function [57, 58], increasing transfer of Ca^{2+} from the endoplasmic reticulum (ER) to mitochondria [97], increasing mitophagy [98, 99], and modulating PGC-1α expression [100]. Endogenous α-synuclein also sensitizes mice to mitochondrial toxins [101, 102] and influences mitochondrial dynamics [47, 103], while endogenous PGC-1a protects against the toxicity of a-synuclein oligomers [104], suggesting that α-synuclein-mitochondria interactions also have physiologic roles. However,

a central question about all physiologic and pathologic interactions between α-synuclein and mitochondria remains unanswered: Which, if any, of these changes actually contribute to neurodegeneration?

3. Pathophysiology of Mitochondrial Insufficiency in PD

Overwhelming evidence suggests that DA neurons are particularly vulnerable to specific mitochondrial stressors and that this susceptibility underlies certain rare genetic forms of PD. Furthermore, PD caused by mitochondrial insults can be clinically indistinguishable from sporadic PD, and mitochondrial insults in all likelihood contribute to the pathophysiology of at least some forms of sporadic PD. However the mechanisms governing this selective vulnerability are poorly understood. What is clear, however, it that the presence of DA alone cannot explain this susceptibility to mitochondrial insults. Indeed, DA neurons in the SN are more susceptible than DA neurons in the medial aspect of the immediately adjacent ventral tegmental area (VTA) [105, 106], and DA neurons in the hypothalamus are largely spared [107]. Furthermore, in sporadic PD, specific populations of nonDA neurons also die, including noradrenergic neurons in the locus coeruleus [108] and cholinergic neurons in the dorsal motor nucleus of the vagus [109] and in the nucleus basalis of Meynert [105, 110]. However, the extent to which neurons in these other susceptible areas degenerate and die varies considerably [78, 80]. How, then, do mitochondrial insults produce PD, and in what way are mitochondrial functions first disrupted in PD?

3.1. Insufficient mitochondrial function

Intrinsic mitochondrial function—The initial mitochondrial insult may involve a defect in one or more intrinsic mitochondrial functions—many of which have been implicated in PD pathogenesis, in particular changes in respiration, Ca^{2+} buffering, and the production of reactive oxygen species (ROS), as briefly discussed below. However, mitochondria are also important in apoptotic pathways and in lipid and neurotransmitter metabolism [111, 112], and changes in these functions may also contribute to degeneration in PD. Not surprisingly, many of the mitochondrial changes are closely related, and primary changes in one function may alter other functions. As a result, it is often difficult to discern which change occurs first and which changes drive degeneration. Thus, determining which mitochondrial function is affected first in PD and which mitochondrial functions are critical to degeneration is an extremely challenging (but very important) task.

Energy failure: As discussed earlier, a potential role for complex I dysfunction in PD pathogenesis has been proposed, largely because of the association of complex I toxins with PD and the decreased activity of complex I in the SN of PD patients. Disruptions in complex I or other parts of the respiratory chain may occur for several reasons. Mutations in mitochondrial DNA might accumulate in PD and with age [96, 113, 114]. Mitochondrial turnover and quality control might be impaired, as may occur with mutations in Parkin or PINK1[29, 38]. And mutant PINK1 [30] or environmental toxins, such as rotenone, might directly inhibit mitochondrial complex I.

Any disruption in complex I or other components of the respiratory chain may lead to “energy failure,” defined here as insufficient ATP to maintain normal cellular functions.

Although energy failure has long been implicated in the pathophysiology PD and other neurodegenerative disorders, it is not known whether it truly occurs in dying neurons in PD [115]. We have shown that disruptions in complex I function or in mitochondrial fission can produce energy failure in hippocampal axons [116, 117]. It will be important to determine whether SN DA neurons are particularly susceptible to energy failure and, if so, why. If respiration is impaired in DA neurons in PD, it will also be important to know whether it is sufficient to impair function and produce degeneration.

Oxidative damage from excessive mitochondrial ROS: Respiration is closely tied to other mitochondrial functions, including ROS production. A small proportion of electrons escapes from the respiratory chain and reduce molecular oxygen to form superoxide, and ROS are also produced by certain enzymes in the mitochondrial matrix [118]. The extent of this electron leak can increase when the respiratory chain is blocked at key sites, including complex I [119, 120]. The mechanisms of changes in ROS production are often poorly understood [118]. Furthermore, just as the respiratory rate can influence ROS production, the converse is also true, as primary changes in ROS levels can compromise respiration [121]. Therefore, although the effects of mitochondria on ROS and respiration can be dissociated under certain circumstances[122], it is often challenging to identify the initiating factor when both are altered.

In PD, there is considerable evidence for weakened antioxidant defenses (e.g., less glutathione [123]) and increased oxidative damage [124–127], and the potential contribution of ROS to the pathophysiology of PD has been reviewed extensively [128, 129]. There are three key points to emphasize here.

First, DA neurons may produce and be exposed to more ROS, in part because the degradation of DA produces ROS [130, 131]. However, DA neurons likely have intrinsic defenses against ROS. For instance, they express VMAT2, which maintains low levels of cytosolic DA by sequestering it in vesicles [15, 132], although, SN DA neurons may have less capacity to do this than VTA DA neurons[133]. DA neurons also express tetrahydrobiopterin which, in addition to functioning as a cofactor for tyrosine hydroxylase in catecholamine synthesis, also functions a free radical scavenger [134, 135], and cultured embryonic DA neurons appear to maintain lower levels of superoxide than other mesencephalic neurons [9]. On the other hand, compelling evidence indicates that SN DA neurons in slices and in postnatal cultures have a higher level of oxidation than adjacent VTA DA neurons [43, 136], and its unclear whether these seemingly discrepant findings reflect differences in the culture paradigms or in the specificity of the probes studied (e.g., hydroethidine to measure superoxide[134] versus mito-roGFP to assess oxidation state [43]). Therefore, it is unclear whether DA neurons are exposed to higher ROS levels than non-DA neurons, especially *in vivo*, where differences in neural activity and environment (e.g., increased iron levels in the midbrain [137]) are also likely to influence ROS levels.

Second, although mitochondria are thought to be the major source of ROS in most cell types, their contribution to total ROS levels in DA neurons, versus other sources of ROS (e.g., NADPH oxidase [138] and the metabolism of DA itself [130, 131]) are not known [118, 139]. However, as the oxidation state of mitochondria in DA neurons depends on DJ-1

and mitochondrial Ca^{2+} uptake [43, 45], mitochondria do at least appear to contribute significantly to mitochondrial ROS levels. Whether changes in mitochondrial ROS levels initiate or contribute to degeneration in PD is still unclear.

Third, ROS changes may be particularly critical in DA axons. However, very little is known about ROS levels in DA axons in PD or in cellular or animal models of PD. Therefore, it is unclear whether mitochondria-derived ROS contribute significantly to neurodegeneration in PD.

Mitochondrial Ca^{2+} buffering and ER–mitochondria contacts: Mitochondrial Ca^{2+} buffering is another intrinsic mitochondrial function that may be disrupted in PD. Cytosolic Ca^{2+} crosses the outer mitochondrial membrane freely and is transferred across the inner mitochondrial membrane into the mitochondrial matrix by the mitochondrial calcium uniporter [140, 141]. Its capacity to import Ca^{2+} depends primarily on the electrochemical gradient defined by the mitochondrial membrane potential and the Ca^{2+} gradient between the cytosol and the mitochondrial matrix[140, 142–144]. Indeed, mitochondrial Ca^{2+} buffering and respiration are closely tied, and respiration is regulated by both cytosolic and mitochondrial Ca^{2+} levels—a potentially important mechanism for cells, particularly neurons, to upregulate energy production to meet energy needs [145, 146]. Although not fully understood, this complex process includes both the upregulated transfer of metabolites into the mitochondrial matrix by cytosolic Ca^{2+}-sensitive transporters [147] and direct activation by mitochondrial Ca^{2+} of enzymes involved in energy metabolism and oxidative phosphorylation, including α-ketoglutarate, isocitrate, and pyruvate dehydrogenases [148, 149].

Besides stimulating respiration, increased cytosolic Ca^{2+} is also predicted to increase energy consumption by increasing the energy needed to restore normal Ca^{2+} levels [150]. Nonetheless, increased Ca^{2+} has an overall positive effect on respiration and ATP levels in cortical neurons [146, 151]. It is not known whether this beneficial effect on the energy level also applies to axons, which are more susceptible to energy depletion from neural activity [116, 117], or to SN DA and other neurons, which may have both a greater Ca^{2+} burden and fewer mechanisms to buffer Ca^{2+} [152]. Furthermore, at excessively high levels, mitochondrial Ca^{2+} depolarizes mitochondria and inhibits respiration, increases mitochondrial ROS production, and triggers apoptotic pathways [153–156]. Excessive mitochondrial toxicity may contribute, for instance, to PINK1-based PD, as PINK1-deficient neurons have increased mitochondrial Ca^{2+} from decreased mitochondrial Ca^{2+} efflux by the Na^{+}/Ca^{2+} exchanger [157].

Of particular interest is Ca^{2+} transfer from the ER (the main calcium storage organelle) to the mitochondria at the areas of apposition between the two organelles known as mitochondria-associated membranes (MAMs) [158, 159]. Basal transfer of Ca^{2+} at MAMs appears to be required for normal bioenergetics [159, 160], and several PD proteins, including α-synuclein [97, 161], DJ1 [162] and Parkin [163], disrupt MAM function or ER-Ca^{2+} transfer—and may have important and convergent roles in neurodegeneration. MAMs also participate in functions other than Ca^{2+} transfer, including lipid transfer, cell signaling,

autophagy, and apoptosis[159]. It is not known whether these processes contribute to neurodegeneration in PD.

Mitochondrial mass (biogenesis, turnover)—The primary mitochondrial deficit in certain forms of PD might not be impaired mitochondrial function. Rather, it might be a decrease in the number of functional mitochondria as a result of decreased synthesis or decreased turnover of dysfunctional mitochondria. Indeed, the decreased level of PGC-1α-responsive genes in DA neurons in sporadic PD [94], the association of PGC-1α pathway activation with a decreased incidence of PD[164], and the finding that Parkin provides critical support for PGC-1α activity[41] suggest that mitochondrial biogenesis is impaired, perhaps leading to a decrease in mitochondrial mass. Consistent with this possibility, deletion of Parkin produces a decrease in mitochondrial content specifically in human DA neurons and not in non-DA neurons[165]. Conversely, impaired mitophagy due to defects in Parkin or PINK1 [29, 38] might increase mitochondrial mass, but with a greater proportion of dysfunctional mitochondria (i.e., intrinsic dysfunction as described above). Thus, it is surprising that mitochondrial mass is normal in brain lysates from PINK1- and Parkin-knockout mice [166–168], although it will be important to learn whether mitochondrial mass changes specifically in DA neurons *in vivo*.

SN DA neurons have lower mitochondrial mass at the cell body and dendrites than VTA DA and other non-DA midbrain neurons [169]. It will be important to determine whether this is also the case in humans and whether SN DA neurons in patients with genetic or sporadic PD have any changes in mitochondrial mass, especially in axons, which degenerate before the cell body. Moreover, mitochondrial turnover is complicated, and although the entire organelle can be degraded at once, multiple processes also regulate the turnover of individual compartments. Indeed, proteins in the matrix and inner and outer membranes appear to be degraded at different rates, as can specific proteins in the same compartment [170–172]. Disruption of Parkin differentially affects the turnover of mitochondrial compartments [171]. Therefore, the biosynthesis or turnover of mitochondrial components may be deficient in PD, even if the total mass of mitochondria proves to be unchanged.

Mitochondrial distribution in axons—Yet another possibility is that the function and total mass of mitochondria are normal, but their subcellular distribution is disrupted and may lead to regional energy failure or regional deficits in other key mitochondrial functions. As discussed above, SN DA neurons have unusually large axonal arbors and, hence, could be more susceptible to a disruption in axonal transport or localization. Indeed, PINK1 directly modulates mitochondrial movement in axons through effects on Miro in a Parkin-dependent manner[32]. Other PD proteins, including LRRK2 and α-synuclein, also affect mitochondrial transport [173, 174]. Interestingly, deletion of PINK1 does not affect the morphology of synaptic mitochondria [175]. However, it is unclear whether the mass or distribution of axonal mitochondria changes in PD or in models of PD, or whether any such changes in distribution would produce areas of insufficient energy [116, 176] or deficiency in other mitochondrial functions. To answer these questions, we might need more sensitive analyses of different models systems of PD (including those in which there is clear neurodegeneration), as well as a systematic examination of mitochondria in DA synapses in

patients with PD. There is also very little information on whether or how mitochondrial distribution in dendrites is altered in PD.

Mitochondrial dynamics—Changes in mitochondrial dynamics—the balance between the fusion and fission of mitochondria—are yet another potential initial insult in PD. Such changes could affect respiration [117, 177], mitochondrial mass and turnover [178, 179], mitochondrial transport, or other intrinsic mitochondrial functions [180]. Indeed, nigrostriatal DA neurons are more susceptible to loss of mitochondrial fission than other midbrain DA neurons [179] and seem to have a similar (albeit less severe) preferential susceptibility to loss of the mitochondrial fusion protein Mfn2 [180]. Although a specific mitochondrial fusion or fission protein has not been implicated in classic PD, recent data suggest that mutations in Opa1 manifest as parkinsonism in the absence of clinically significant optic atrophy [181]. Furthermore, Parkin and PINK1 have both been proposed to act as mitochondrial fission proteins in *Drosophila*, likely by degrading Mfn [182]. In addition, increased α-synuclein causes the fragmentation of mitochondria independent of Drp1, likely by interacting directly with the mitochondrial membrane [47, 56]. In a PD mouse model, inhibition of DRP1 reduces neurotoxicity and synaptic transmission deficits [175]. This finding raises an important question: Is manipulating mitochondrial dynamics an effective therapeutic strategy[175]?

Secondary mitochondrial dysfunction due to non-mitochondrial causes—Mitochondrial insults likely initiate several some forms of genetic and sporadic PD. In other forms, the primary insult is probably non-mitochondrial. For instance, primary changes in the extent or pattern of synaptic transmission [183], ER-to-Golgi transport [184], and lysosomal function [185] may also initiate certain forms of PD. Are mitochondria disrupted in these non-mitochondrial cases? If so, do these disruptions occur early enough to contribute to the initiation or progression of degeneration, or are they simply epiphenomena to the primary processes of degeneration? These questions cannot be answered until the pathophysiologic subtypes of PD have been better defined.

3.2. Increased need for mitochondria

Insufficient mitochondrial function might result from impaired, insufficient, or misdistributed mitochondria. However, it might also result from excessive demand for mitochondrial functions. Here we consider this possibility from the perspective of energy levels, but the same principle might also apply to other mitochondrial functions.

Intrinsic pacemaking and Ca^{2+} buffering—There are several reasons—none of them proved—why SN DA neurons may theoretically have greater metabolic needs than other neuron types. First, their intrinsic pacemaking function may entail greater overall neural activity than is required by other types of neurons. Supporting synaptic transmission produces the greatest energy demand in the brain [186], and increased neural activity predisposes axons to energy failure when mitochondria are compromised [116, 117]. SN DA neurons may also be particularly susceptible because they are enriched in L-type Ca^{2+} channels ($Ca_V1.3$) [43, 187], rather than Na^+ channels used by most other pacemaking neurons, including adjacent DA neurons in the VTA, which are relatively resistant in PD

[150, 187]. Indeed, pacemaking supported by Ca^{2+} influx may be especially demanding energetically because Ca^{2+} must be removed from the cell against a steep concentration gradient [150]. SN DA neurons in PD also have more K-ATP channels, which may facilitate burst firing and further increase Ca^{2+} levels [188, 189], and the activity of SN DA neurons further increases in pharmacologic and certain genetic models of PD [190–195].

Vulnerable SN DA neurons also have low levels of the Ca^{2+}-binding protein calbindin [108, 152] and a low overall capacity for intrinsic Ca^{2+} buffering [196]. Other vulnerable neuronal populations in PD besides SN DA neurons are also spontaneously active and tend to have lower Ca^{2+} buffering capacity[150]. Nonetheless, it has not been established that Ca^{2+} pacemaking and decreased buffering place SN DA neurons under greater metabolic stress. Indeed, very little is known about the energy status of DA neurons, and both cytosolic and mitochondrial Ca^{2+} can also stimulate respiration. Therefore, it is not known whether Ca^{2+} influx also stimulates respiration in SN DA neurons and, if so, whether the extent of increase compensates for the increased energy demands that the influx may impose. A better understanding of the balance between energy production and consumption in DA neuron subtypes—including the relative contributions of different Ca^{2+} channels, intrinsic pacemaking, and Ca^{2+}-binding mechanisms—will help clarify the intrinsic vulnerability of this neuronal population.

Large axonal arbors and axonal mitochondria—To understand how changes in mitochondria contribute to PD, we must also focus on axons. SN DA neurons have remarkably extensive axonal arbors, which almost certainly contain the majority of mitochondria. A single rat SN DA neuron may form synapses with some 75,000 striatal target neurons, and make up to 245,000 synapses [197, 198]. In contrast, adjacent VTA DA neurons that project to the nucleus accumbens and other areas in the ventral striatum may form synapses with fewer than 30,000 target neurons, and the axons of other key neuronal types in the basal ganglia may give rise to fewer than 5000 synapses. Remarkably, in humans, SN DA neurons are even larger: they are estimated to form up to 2.4 million synapses and average 4.5 meters in length [198]. Since support for neural activity is the greatest consumer of energy in the brain [186, 199], it seems likely that neurons with larger axonal arbors and more synaptic connections will have proportionally greater energy requirements.

SN DA neurons and susceptible non-DA neurons are unmyelinated or only lightly myelinated [200, 201]. Thus, they may be more susceptible to energy stressors because of increased energy demands—myelin decreases the energy required for synaptic transmission [202], but it is not known whether the energy savings exceeds the costs of myelin synthesis and maintenance [199]—and a decreased supply of energy precursors such as lactate to underlying axons [110, 203] (Fig. 1). Axons are also where key disease proteins such as α-synuclein and tau accumulate and, importantly, where neurodegeneration begins in PD, Alzheimer’s disease, Huntington’s disease, and other neurodegenerative diseases and in most mitochondrial models of neurodegeneration [19, 180, 204–208].

3.3 Intrinsic vulnerability and Aging

Aging is the strongest risk factor for PD [209]. Hence it is important to consider whether aging interacts with mitochondria to produce degeneration and, if so, how. One likely possibility is a progressive decline in key intrinsic mitochondrial functions with age [210], such that the level of mitochondrial function in DA neurons drops below the threshold for normal function and survival. In addition, dysfunctional mitochondria may in some cases produce damaging byproducts that accumulate over time. For instance, oxidative damage from mitochondrial ROS is thought to accumulate with age [211], and may make neurons more susceptible to the toxicity of disease processes. The increase in mitochondrial DNA mutations with age may also predispose neurons to degeneration by impairing respiration and compromising other mitochondrial functions [212, 213]. Chronic energy deficiency may well have other long-term adverse effects on a multitude of cellular functions, including protein synthesis [214], neurogenesis, and synaptic integrity [215, 216]. However, very little is known about these relationships.

The energy requirements of the brain may also change with age, although this remains controversial. A number of studies have found that total brain glucose consumption decreases with age, which could reflect decreased energy requirements, decreased substrate availability at the brain or neuron level, or a decreased capacity to produce energy [217]. It is not known if energy requirements of individual neurons change with age. Interestingly, during postnatal development in mice, SN DA neurons increasingly rely on L-type $Ca_V1.3$ Ca^{2+} channels to support autonomous pacemaking, which may place mature DA neurons under greater oxidative and energetic stress [187]. It is not known whether similar changes occur in older adults and influence energy requirements.

Summary of mitochondrial pathophysiology in PD—Mitochondria may be chronically stressed by multiple mechanisms in PD. The stressors can be broadly classified into those resulting from insufficient mitochondrial function and those resulting from excessive demand. Insufficient mitochondrial function might reflect a defect in an intrinsic function of the mitochondria or a change in their number, distribution, or dynamics. Finally, mitochondrial functions are often intertwined—making it particularly challenging to determine their relative contributions to degeneration.

4. Significance/Rationale for Understanding Disease Pathophysiology

Why do we need to understand how mitochondria cause and contribute to PD? Certainly, understanding how changes in mitochondria cause PD would provide important insights into mitochondrial metabolism and selective neuronal vulnerability. But would it also lead to new disease-modifying therapies? Can mitochondria be targeted therapeutically for neurologic diseases? These questions are important, as therapies to boost mitochondrial functions, including creatine [218] and coenzyme Q10 [219], have failed to slow PD progression in large clinical trials.

These failures likely resulted largely from an inadequate understanding of how, exactly, mitochondria contribute to the disease and a consequent lack of basic science evidence that the therapies would be beneficial. Indeed, although creatine failed for PD, it is an effective

disease-modifying therapy for guanidinoacetate methyltransferase deficiency, where there is a defect in creatine biosynthesis [220, 221]. Similarly, CoQ10 is an effective disease-modifying therapy for primary CoQ10 deficiency [222, 223]. Another successful energy-based therapy for neurologic disease, a ketogenic diet for glucose transporter type 1 deficiency, appears to help by providing an alternate fuel source when glucose import into the brain is impaired [224, 225].

In all of these examples, a specific therapy was used to target a specific metabolic defect. However, as mitochondrial therapies for PD have not been based on a solid foundation of mechanistic understanding, it isn't surprising that they failed. Nevertheless, our understanding of the mechanistic basis for mitochondrial therapies has advanced, a new line of therapeutic approaches has emerged. For instance, PINK1-mediated PD is likely caused by a loss of kinase activity [226], and efforts to boost kinase activity [227] might be expected to help at least the small subset of patients with PD caused by PINK1 mutations. Strategies to boost Parkin function carry a similar rationale [228], and it will be important to discover whether these approaches are beneficial in treating sporadic forms of PD. Another promising approach targets an intrinsic susceptibility of SN DA neurons by blocking L-type Ca^{2+} channels, an intervention that protects against mitochondrial inhibitors and oxidative stress in PD model systems [43, 187, 229]. Important caveats for this and other approaches targeting sporadic PD, however, are the heterogeneity of sporadic PD and the risk that a therapy that helps only a subset of sporadic forms of PD may not be recognized. Nonetheless, these and other approaches give reasons for optimism about the future of mitochondria-based therapies for PD. They also highlight the need for concerted research efforts to deepen our understanding of how, exactly, mitochondria contribute to the various genetic and sporadic forms of the disease.

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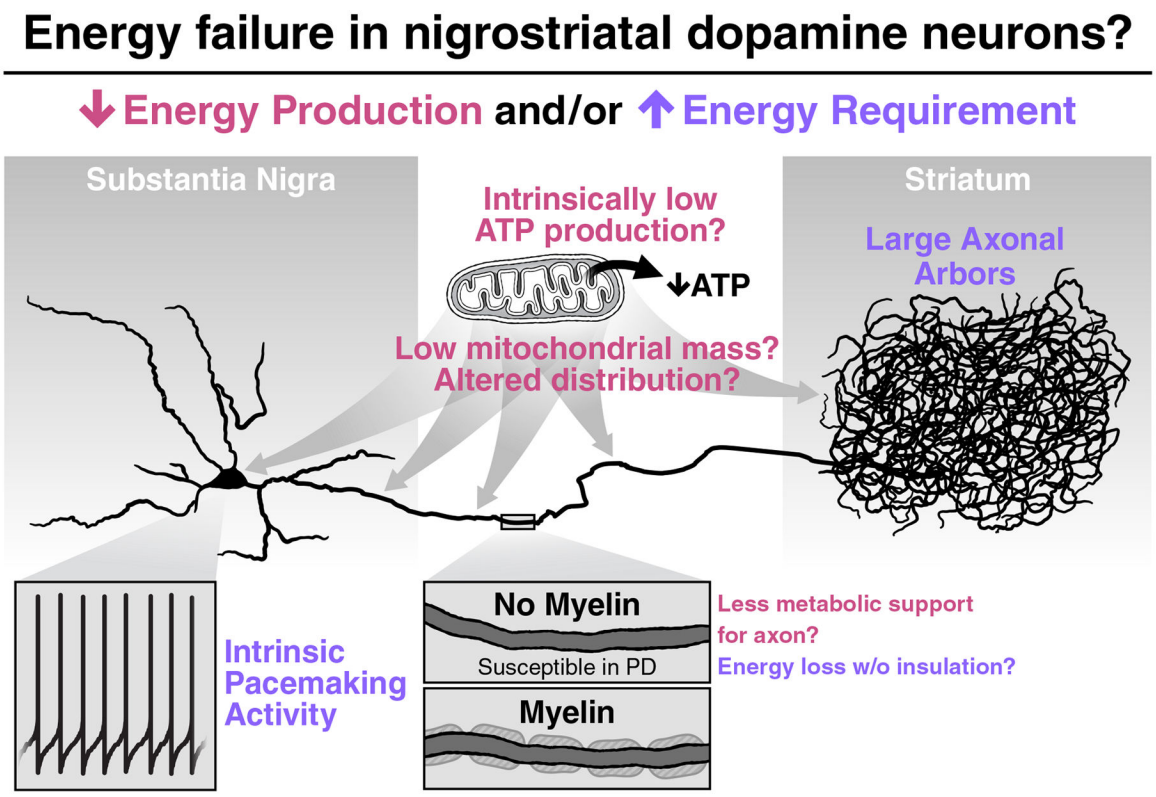

Fig. 1.

SN DA neurons may be susceptible to energy failure if they cannot produce enough energy to meet normal demand or have increased energy requirements. The former might result if their mitochondria have less capacity to make ATP or if they have fewer or misdistributed mitochondria, especially in their axons, which degenerate first in PD. SN DA axons also lack myelin, which may mean they have a decreased abundance of energy substrates to support energy production. Increased energy requirements might result if DA neurons require significantly more energy to support intrinsic pacemaking and their massive axonal arbors, which project to the striatum. If SN DA neurons are indeed more energetically challenged, they could be predisposed to the toxicity of additional bioenergetic and other mitochondrial insults, which may underlie their unique susceptibility to mitochondrial stressors in PD.