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## Mitochondrial hyperactivity as a potential therapeutic target in Parkinson's disease

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### Abstract

Mitochondrial dysfunction is thought to contribute to neurodegeneration in Parkinson's disease (PD), yet the cellular events that lead to mitochondrial disruption remain unclear. Post-mortem studies of PD patient brains and the use of complex I inhibitors to model the disease previously suggested a reduction in mitochondrial activity as a causative factor in PD, but this may represent an endpoint in the disease process. In our recent studies, we identified a novel link between branched-chain amino acid metabolism and PD, and uncovered mitochondrial hyperactivity as a potential alternative mechanism of PD pathogenesis. Increased mitochondrial activity may occur in a subset of PD patients, or may be a more common early event that precedes the ultimate loss of mitochondrial function. Therefore, it may be that any imbalance in mitochondrial activity, either increased or decreased, could cause a loss of mitochondrial homeostasis that leads to disease. An effective therapeutic strategy may be to target specific imbalances in activity at selective stages of PD or in specific patients, with any efforts to reduce mitochondrial activity constituting a surprising new avenue for PD treatment.

### Keywords

Parkinson's disease; Hyperactive mitochondria; Mitochondrial homeostasis; Branched-chain amino acid metabolism

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Parkinson's disease (PD) is an age-associated neurodegenerative movement disorder for which there is currently no cure and the underlying mechanisms are still incompletely understood. PD is characterized by the progressive loss of dopamine-producing neurons in the substantia nigra (SN) and the aggregation of the protein  $\alpha$ -synuclein into pathological inclusions known as Lewy bodies [1]. Up to 15% of PD cases are inherited, including due to mutations and multiplications of the  $\alpha$ -synuclein gene, *SNCA*, whereas the remaining >85% of cases are sporadic and have no known cause [2]. Mitochondrial dysfunction has emerged

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Declaration of competing interest

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as a key player in dopamine neuron degeneration [2]. Several groups have reported post-mortem complex I deficiencies in brain tissue from sporadic PD patients, and these abnormalities are present in multiple brain regions including the SN [3,4]. Complex I activity is also reduced in peripheral tissues derived from PD patients, including platelets and skeletal muscle [5,6]. While these studies strongly suggest that mitochondrial function is disrupted in PD, the events leading ultimately to a loss of mitochondrial activity remain unknown.

The ability of complex I inhibitors to model aspects of PD in both humans and animals suggests that direct suppression of electron transport chain (ETC) activity may play a role in PD pathogenesis. The complex I inhibitor MPTP causes acute-onset parkinsonism and neurodegeneration of the SN in humans, a fact which was first discovered in drug users who inadvertently self-administered compounds contaminated with the toxin [7,8]. Since this discovery, MPTP has been extensively used to induce PD-like symptoms and neuropathology in animal models. Similarly, the pesticide rotenone is a complex I inhibitor that is often used to model PD motor deficits and dopaminergic cell death [9]. Loss of complex I activity from exposure to MPTP or rotenone is thought to cause neurodegeneration through production of reactive oxygen species (ROS) and decreased levels of ATP [2] (Fig. 1A).

While the use of complex I inhibitors has greatly contributed to our understanding of how mitochondrial bioenergetic failure can lead to neurodegeneration, it is unclear the extent to which these toxic insults model the etiology and progression of sporadic PD. Unlike PD, MPTP-induced models typically show acute degeneration that does not worsen over time [9]. Rotenone models are also limited in their ability to reproduce the progressive nature of PD, often due to high variability in the resulting phenotypes and low animal survival rates [10]. In both of these cases of complex I inhibitors, the rapid cell death and even animal death suggests that these models may primarily recapitulate endpoints in the disease process. It is therefore critical to investigate additional mechanisms that may lead to mitochondrial dysfunction in PD.

Recently, our lab discovered a metabolic link to PD that offers an alternative hypothesis for mitochondrial disruption in disease. Using a novel method that combines human GWAS with tissue-specific functional genetic networks in *C. elegans*, followed by rapid high-throughput screening of candidate disease genes, we identified the branched-chain amino acid (BCAA) transferase gene, *BCAT1*, as a new potential player in PD [11]. *BCAT1* expression is significantly decreased in the SN of sporadic PD patients, and RNAi-mediated knockdown of *bcat-1* in *C. elegans* causes an agedependent, progressive motor disorder and promotes dopaminergic neurodegeneration in worms expressing human  $\alpha$ -synuclein [11]. These findings demonstrate that dysfunctional BCAA metabolism can induce PD-like phenotypes and model the progressive nature of the disorder.

To investigate the mechanisms of neurotoxicity associated with reduction of *bcat-1*, we used a combination of neuronal transcriptional analysis, high-resolution metabolomics, and functional imaging approaches [12]. Surprisingly, we found that increased levels of mitochondrial activity - rather than decreased - underlie *bcat-1*-related PD phenotypes. We

found that reduction of mitochondrial respiration by treatment with a low dose of sodium azide significantly reduced PD-like motility defects in *bcat-1* RNAi-fed worms, without affecting overall levels of motor activity [12]. These results indicate that mitochondrial hyperactivity induces PD-like motor symptoms in *bcat-1* RNAi-fed worms. Moreover,  $\alpha$ -synuclein-expressing dopaminergic neurons had increased levels of carbonylated proteins upon *bcat-1* knockdown, suggesting that mitochondrial hyperactivity may be toxic because it causes oxidative damage [12].

Our finding that increased mitochondrial activity can lead to PD phenotypes was unexpected, given the reduction of mitochondrial ETC activity observed in post-mortem studies of brain tissue from sporadic PD patients [3,4]. It is possible that hyperactive mitochondria contribute to pathogenesis in a subset of PD patients that are not represented in these studies (Fig. 1B), particularly since some studies have focused on patients with known mutations in the complex I gene *MT-ND5* that are thought to be linked to loss of function [4]. An alternative possibility is that mitochondrial hyperactivity may be an early event in PD, causing oxidative damage and preceding the ultimate loss of mitochondrial function (Fig. 1C). Consistent with this, complex I itself was found to be oxidatively modified in PD brain, likely through auto-oxidation mechanisms [13]. An increase in mitochondrial respiration due to dysfunctional BCAA metabolism could potentially provide a local source of ROS that could mediate this damage. Oxidatively-damaged complex I may then have impaired function, as has been previously suggested [13], resulting in decreased levels of mitochondrial activity late in the disease process (Fig. 1C). The resulting neurodegeneration would then manifest in the form of motor symptoms and declining functional outcomes.

Therapeutic approaches that target mitochondria in PD are beginning to be explored, yet very few are aimed at directly modulating mitochondrial activity. Instead, the majority of the drugs tested are meant to stimulate mitochondrial biogenesis or act as antioxidant scavengers [2] (Fig. 2A). The most promising results thus far were obtained for exenatide, a glucagon-like peptide-1 receptor agonist, which improved motor symptoms in a small study of PD patients, potentially by promoting mitochondrial biogenesis [14]. Follow-up studies are necessary to validate these initial results and determine if exenatide modifies the disease course or simply provides symptomatic relief. Clinical studies with antioxidants have yielded mixed results [2]; for example, preliminary testing with N-acetyl-cysteine showed positive effects on clinical symptoms and dopamine transporter binding [15]. In contrast, there was no benefit from treatment with mitoquinone, an antioxidant that is targeted to mitochondria [16]. However, the lack of positive results with mitoquinone are potentially due to low statistical power and insufficient drug penetrance in the brain [2]. Despite these challenges, antioxidant therapies remain an attractive avenue to pursue, and may intervene at a point where pathological increases or decreases in mitochondrial activity may converge (Fig. 1).

In an effort to identify new potential therapies for PD, our lab developed a high-throughput screening platform using the *bcat-1* RNAi-induced *C. elegans* model of PD motor symptoms [17]. In a proof-of-concept screen of 50 FDA-approved drugs with diverse indications and mechanisms of action, the top candidate that improved motor function by 54% was the type 2 diabetes medication, metformin [17]. Follow-up testing revealed that metformin reliably

reduces motor deficits and rescues dopaminergic neurodegeneration induced by *bcat-1* knockdown [12]. Excitingly, these improvements were apparent even in aged worms, with administration post-disease onset, better modeling the timing of PD onset and clinical intervention in humans. Moreover, we found that metformin treatment decreased mitochondrial activity levels back down to those of age-matched controls [12], potentially through its ability to act as a complex I inhibitor [18]. These findings support the notion that reducing mitochondrial activity back to normal levels may in some contexts be protective against neurodegeneration in PD. To date, metformin has not been tested in PD patients without comorbid diabetes [19]. Metformin is therefore a promising new candidate for PD therapy (Fig. 2B).

In summary, while the link between mitochondrial dysfunction and PD is well-established, the precise sequence of events leading to mitochondrial disruption remains to be fully elucidated. Our finding that defects in BCAA metabolism result in PD-like phenotypes through mitochondrial hyperactivity offers a new potential mechanism for PD pathogenesis, either in a subset of patients or as a more common early event that precedes loss of mitochondrial function later in the disease. *bcat-1* expression decreases during normal aging in worms, fish, and mice [20], suggesting a plausible mechanism by which BCAA metabolism may become naturally impaired with age, and consistent with aging being the greatest risk factor for developing PD. Genetic defects might also contribute to BCAA dysfunction, since PD GWAS have associated the BCAA pathway genes *MCCC1* and *BCKDK* with disease risk [21]. It is possible that a personalized medicine approach may be required for patients harboring genetic variants in BCAA-related genes, and/or those who might exhibit biomarkers of hyperactive mitochondria (i.e. potentially in blood or muscle). Possible approaches may include reducing mitochondrial activity, potentially with metformin, and/or targeting BCAA metabolism. For example, high-intensity interval training (HIIT) was recently shown to improve motor and cognitive symptoms in PD [22,23], and rats exposed to HIIT had significant alterations in plasma levels of BCAAs [24], consistent with a protective effect on BCAA metabolism. Moreover, different therapeutic strategies targeting BCAA metabolism or mitochondrial activity may be necessary at different stages of PD, such that specific imbalances are corrected rather than exacerbated, and mitochondrial homeostasis is restored.

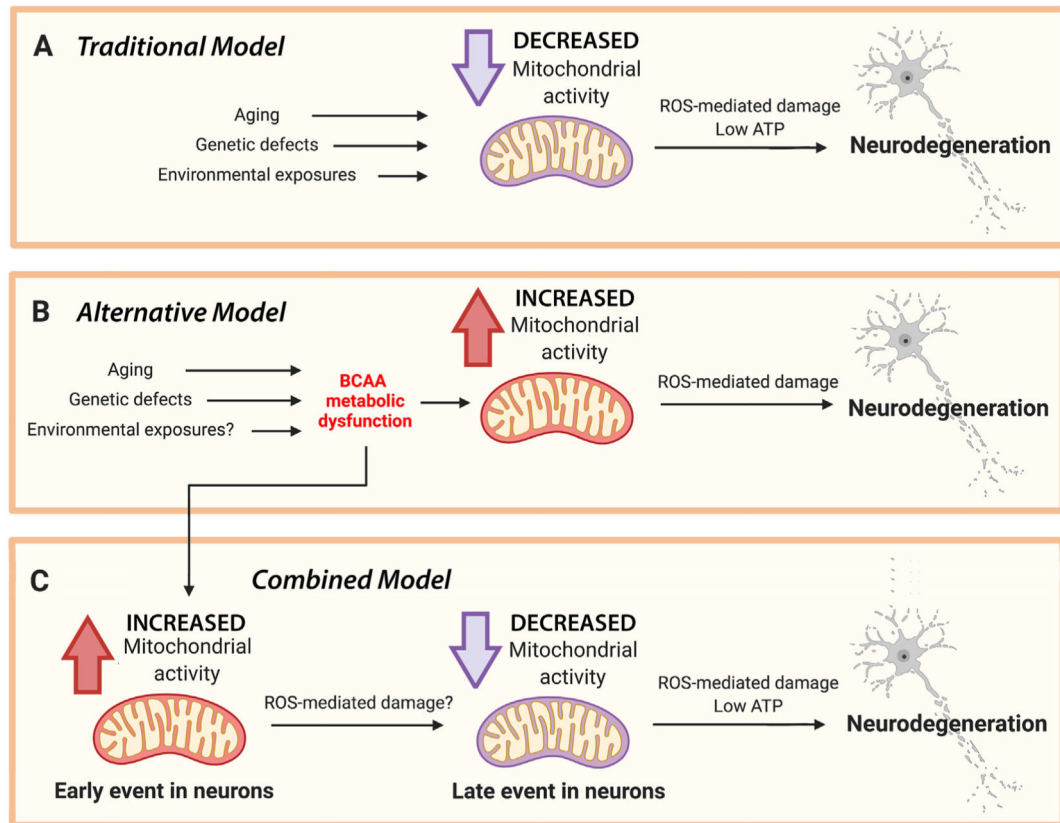
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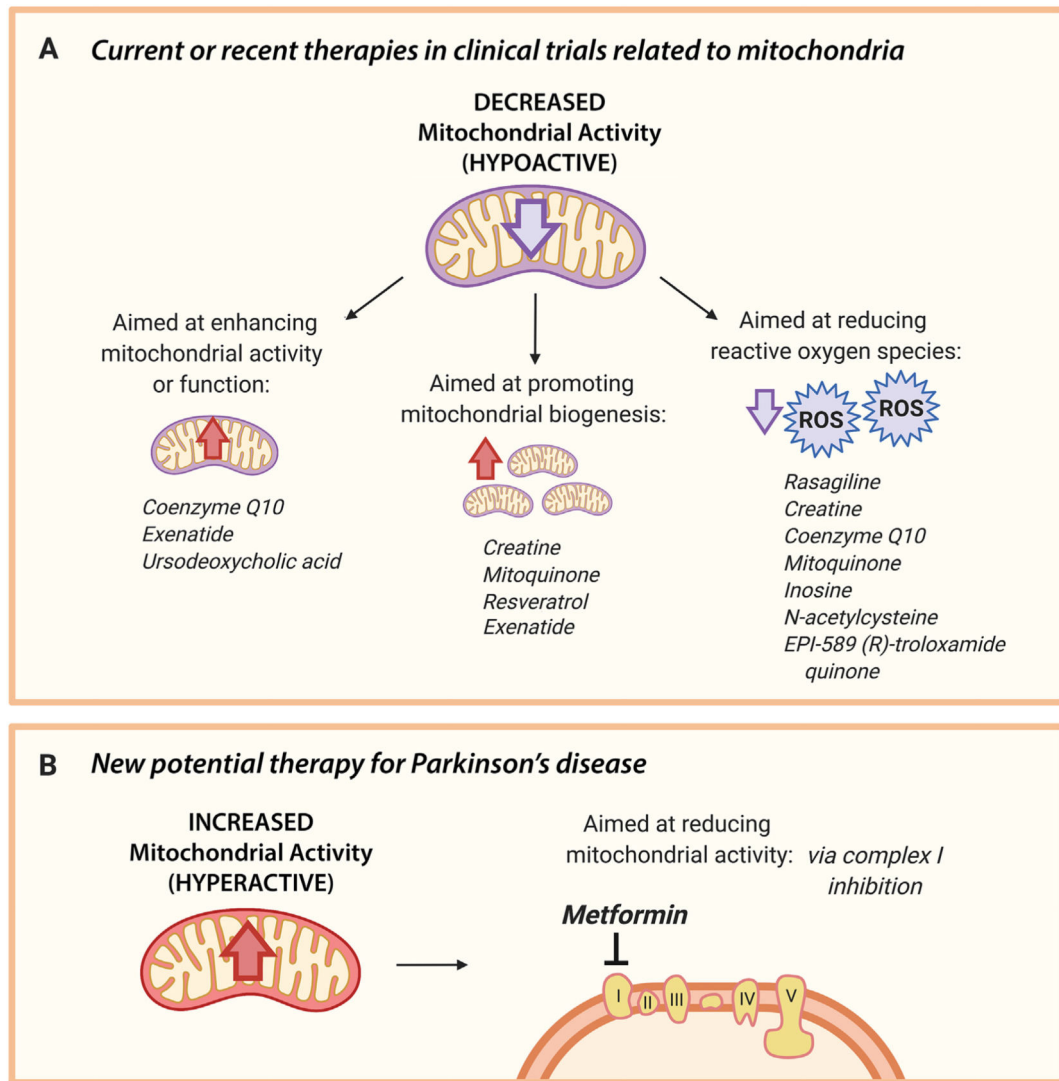
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**Fig. 1. Possible scenarios for mitochondrial activity levels driving neurodegeneration in PD.** (A) Aging, genetic defects, and/or exposure to environmental toxins such as the complex I inhibitors MPTP or rotenone may cause a reduction of mitochondrial activity levels. This may lead to neurodegeneration through ROS production and consequently oxidative damage, as well as decreased ATP. (B) In a subset of PD patients, BCAA metabolic dysfunction due to aging, genetic defects, or potentially environmental exposures may instead cause increased mitochondrial activity, with consequent ROS-mediated damage inducing neurodegeneration. (C) A third possibility is that deficits in BCAA metabolism may increase mitochondrial activity levels early in PD neurons, and the resulting oxidative damage may drive an ultimate loss of mitochondrial function later, eventually leading to neuronal cell death.





**Fig. 2. Therapeutic strategies aimed at improving mitochondrial function in PD.**

(A) Potential treatments currently or recently tested in clinical trials, with intended effects on mitochondria indicated. For detailed review, see Ref. [2]. (B) Metformin as a new potential therapy for PD, via complex I inhibition.