alzheimer's research&therapy

REVIEW

Mitochondrial therapeutics in Alzheimer's disease and Parkinson's disease

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Abstract

In neurons, mitochondria serve a wide variety of processes that are integral to their function and survival. It is, therefore, not surprising that evidence of mitochondrial dysfunction is observed across numerous neurodegenerative diseases. Alzheimer's disease and Parkinson's disease are two such diseases in which aberrant mitochondrial activity is proposed to contribute to pathogenesis. Current therapies for each disease target various mechanisms, but few, if any, directly target improved mitochondrial function. Recent discoveries pertaining to mitochondrial dynamics reveal that regulation of mitochondrial fission and fusion may play a key role in the pathogenesis of these diseases and consequently could be novel future therapeutic targets.

Overview of mitochondrial function

Mitochondria are organelles serving a wide variety of actions critical to cellular function, several of which are of particular importance to neuronal survival. The primary function of mitochondria is to produce energy in the form of ATP via oxidative phosphorylation, in which electrons are transported down the electron transport chain (ETC) while generating a proton gradient. This gradient drives ATP synthase [1]. Mitochondrial function is particularly important to the central nervous system (CNS) since the CNS uses 20% of the body's resting metabolic energy, 95% of which comes in the form of ATP [1]. Neuronal ATP is essential to the function of the Na^+/K^+ and Ca^{2+} ATPases that maintain ion gradients [1,2]. Similarly, mitochondria play a prominent role in Ca^{2+} buffering by sequestering Ca^{2+} using ion transporters [1-3]. These actions of mitochondria are especially important to neurotransmission as well as synapse formation and remodeling [3-5]. However, critical roles for mitochondria go beyond ATP production since mitochondria also control cell signaling pathways and cell survival via apoptosis regulation [6]. Mitochondria are now also understood to be dynamic structures that undergo fission and fusion, and the relationships between mitochondrial dynamics and other 'classical' functions are a matter of intense investigation. For these reasons, mitochondria are commonly implicated in neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD).

Several neurodegenerative diseases show alterations in mitochondrial DNA (mtDNA) and genes that encode for mitochondria respiratory chain subunits [7]. Similarly, dysfunction of enzymes involved in mitochondrial respiration has been reported in neurodegenerative diseases [7,8]. Such deficits may lead to generation of excessive reactive oxygen species (ROS) and oxidative damage, clearly implicated in several neurodegenerative diseases, or to depletion of ATP [7,8]. Besides damaging tissues directly, ROS are thought to react with the nitric oxide (NO) produced by activated microglia, forming reactive nitrogen species (RNS) [7]. More recently, it has been demonstrated that mitochondrial dynamics likely plays a key role in AD and PD as proteins that regulate mitochondrial fission and fusion are altered in some neurodegenerative diseases [3,8]. Given the proposed role of mitochondrial dysfunction in AD and PD, restoration of mitochondrial function is a focus of therapeutic development.

This review will concentrate on mitochondrial involvement in AD and PD and emphasize current therapeutics that may directly or indirectly target mitochondria function. Potential roles of mitochondrial fission and fusion, at present a major area of active research, in AD and PD treatment also will be addressed.

1. Alzheimer's disease

1.1. Clinical presentation and pathology

AD is the most common neurodegenerative disease, contributing up to 70% of all cases of dementia, and has an exponentially increasing prevalence after the age of 65 [9]. Both common late-onset sporadic and rare autosomal

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dominant forms exist [10]. Biomarkers in cerebrospinal fluid or structural and functional neuroimaging are being used to assist in clinical classification of AD [11]. Pathologically, AD is characterized by the presence of neuritic plaques and neurofibrillary tangles, composed primarily of amyloid-beta (Aβ) and abnormal tau (respectively), which are found predominantly in cerebral cortex and other medial temporal lobe structures [9]. It is worth noting that, to date, most of the effective AD biomarkers are related to Aβ or tau species [11,12]. The earliest pathologic event occurring in AD is thought to be synapse loss, as several changes in proteins related to synaptic vesicles and membranes have been observed in AD brains [9,13]. It is hypothesized that soluble Aβ oligomers cause synaptic and neuronal dysfunctions that then lead to potentially interconnected processes of excitotoxicity, neuroinflammation, oxidative damage, insoluble protein accumulation, and neurodegeneration [9,14].

1.2. Mitochondrial involvement in Alzheimer's disease

Mitochondrial abnormalities have been associated with AD. Several enzymes involved in the Krebs cycle and ETC, including pyruvate dehydrogenase complex, ketoglutarate dehydrogenase complex, and cytochrome oxidase, are altered in the brains, platelets, and peripheral cells of AD patients [15-18]. Isolated mitochondria from AD patients also show decreased complex IV activity as well as elevated hydrogen peroxide production [19]. Indeed, oxidative damage to DNA, proteins, and lipids is elevated in AD patients compared with controls [20-22]. Aβ has also been linked to mitochondrial dysfunction in various studies. Aβ, especially the peptide that is 42 amino acids long, is toxic to cells *in vitro* [23] and decreases ETC complex IV activity [24]. Aβ or the Aβ precursor protein (APP) associates with mitochondria in the brains of AD patients, particularly with the translocase of the outer mitochondrial membrane (TOMM) 40 and the translocase of the inner mitochondrial membrane (TIMM) 23, suggesting possible mitochondrial translocation [19,25]. When a mutant form of human APP is overexpressed in mice, Aβ accumulates in mitochondria and, compared with controls, decreases Ca^{2+} buffering capacity, complex IV activity, and ATP levels and increases ROS production [26]. Two recent studies have found that Aβ induces abnormal mitochondrial transport within axons [27,28]. Therefore, elevated Aβ might contribute to mitochondrial dysfunction, ROS production, and stress to neurons in AD. An alternative hypothesis asserts that, in sporadic AD, mitochondrial function declines beyond a threshold level to activate a pathway yielding the pathologic hallmarks of AD, specifically overproduction of Aβ [29]. This would exacerbate mitochondrial dysfunction, leading to a reinforcing destructive cycle [29]. Key findings that support this hypothesis come from the use of cybrids (that is, cells with mitochondria derived from another cell). For example, mitochondria from fibroblasts and platelets of AD patients show decreased complex IV activity, a feature that remains consistent when cybrids are cultured over time, leading to elevated Aβ production and deposits [29,30].

1.3. Therapeutics and treatment

Current therapies for AD do not directly target mitochondria but may act through various mechanisms that can affect mitochondria (Table 1). One such mechanism is regulation of neuroinflammation [7]. When activated, microglia produce NO, which can interact with ROS (produced by mitochondria as a normal product of ETC activity) to generate RNS [7]. ROS and RNS can damage mitochondria as well as other organelles, leading to decreased ETC function, further ROS production, and decreased ATP production, resulting in neuron death [7]. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, which are approved by the US Food and Drug Administration (FDA) for AD treatment, may function through this manner as their use decreases markers of inflammation and improve AD symptoms [31,32]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease inflammation in a similar manner, but results from observational studies and clinical trials have not been consistent [31-33]. Another mechanism is by decreasing Ca^{2+} entry into neurons, as excessive intracellular Ca^{2+} can cause mitochondrial dysfunction, resulting in ATP depletion and excessive ROS generation [34]. Blocking Ca^{2+} influx decreases the amount of intracellular Ca^{2+} present in neurons, and this would decrease ROS generation by mitochondria. N-methyl-D-aspartate (NMDA) receptor antagonists (also FDA-approved for AD treatment) that suppress Ca^{2+} channel activity have been used with some success in treating AD [31,32]. A recent strategy that may affect mitochondria is decreasing Aβ load, and this may be achieved by decreasing Aβ production or enhancing its clearance [31,35]. Excessive levels of Aβ may be taken up by mitochondria, causing decreased complex IV activity, ATP production, and Ca^{2+} buffering, resulting in excessive ROS production and neuron death [19,23-26]. Aβ immunotherapy is an avenue being investigated to treat AD by reducing Aβ levels and has yielded some promising results [35]. An Aβ vaccine consisting of a synthetic Aβ peptide and an immune response booster was developed and tested in humans, but its trial was halted because of the development of aseptic meningoencephaitis and leukoencephalopathy (reviewed in [35]). Some follow-up studies indicated changes in biomarkers associated with AD, decreased Aβ load in plaques, and (in those who produced anti-Aβ

Table 1. Current treatments for Alzheimer's disease

Therapy	Results	Mitochondrial involvement?
Cholinesterase inhibitors	Improves AD symptoms and decreases markers of inflammation	May decrease nitric oxide produced, leading to decreased RNS and ROS
NMDA receptor antagonists	Improves AD symptoms and decreases ROS production	May decrease amount of ROS produced due to excessive intracellular Ca^{2+}
Enhanced clearance of Aβ	May improve cognition	May decrease Aβ-induced mitochondrial dysfunction and ROS generation
NSAIDs	No consistent results	May reduce inflammation and ROS
Antioxidants	No consistent results	Can reduce ROS
Herbal/Natural products	No consistent results	Potentially decreases Aβ, inflammation, and ROS generation

Aβ, amyloid-beta; AD, Alzheimer's disease; NMDA, N-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug; RNS, reactive nitrogen species; ROS, reactive oxygen species.

antibodies) decreased rate of cognitive decline [36]; however, others reported that clearance did not prevent progressive neurodegeneration [37]. Current trials that are in various phases and that use passive immunization against Aβ (that is, anti-Aβ antibodies) are being evaluated, but further studies are clearly needed [35]. Aβ-binding alcohol dehydrogenase (ABAD), an enzyme present in neuronal mitochondria, has been shown to coimmunoprecipitate and colocalize with Aβ in human tissue, with increased precipitation in AD patients [38]. Data from mouse models of AD support inhibiting Aβ-ABAD interaction as a possible therapeutic strategy for AD [38,39]. Other treatments such as antioxidants, vitamins, statins, natural products, and hormone therapy have been studied but do not give consistent results [31-33].

2. Parkinson's disease

2.1. Clinical presentation and pathology

PD is a progressive neurodegenerative disease with an average age of onset of between 55 and 60 years of age and a 2% lifetime risk [40]. As with AD cases, a small fraction of PD cases (5% to 10%) are due to autosomal dominant or recessive forms of disease, whereas the majority of PD cases are sporadic [40]. PD is diagnosed clinically by a constellation of motor symptoms, including resting tremor, rigidity, postural instability, and slowness of movement (bradykinesia) [40,41]. The most prominent changes in PD are loss of dopamine (DA)-producing neurons that project from the substantia nigra pars compacta (SNpc) to the striatum [40,41] and accumulation of eosinophilic intraneuronal protein inclusions called Lewy bodies [34,40,41]. Lewy bodies are composed primarily of α-synuclein, parkin, ubiquitin, and neurofilaments [34,41]. Currently, it is thought that one of the proximal events leading to DA neuron death is the formation of α-synuclein fibrils from misfolded α-synuclein [34]. These fibrils can continue to aggregate misfolded proteins, leading to the formation of larger inclusions with the eventual formation of Lewy bodies and ultimately neuron death [34,41].

2.2. Mitochondrial involvement in Parkinson's disease

Mitochondrial dysfunction has been repeatedly associated with PD. Complex I of the ETC is decreased in the SNpc of PD patients when compared with controls, leading to excessive ROS formation [42]. Oxidative damage to lipids, proteins, and nucleic acids is also elevated in PD brain tissue [43-45]. Toxicants recapitulating most aspects of human PD also implicate mitochondrial dysfunction in PD pathogenesis, particularly through complex I inhibition. These toxicants include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone [46]. MPTP was discovered when a drug abuser who synthesized and injected himself with MPTP-contaminated meperidine analog presented with parkinsonism; this patient later showed damage to the DA system in the SNpc at autopsy [47]. Other drug abusers subsequently presented with clinical symptoms of PD due to MPTP exposure [46]. MPTP is metabolized to 1-methy-4-penylpyridium (MPP^+), which enters DA neurons via the DA transporter. MPP^+ binds to and inhibits complex I of the ETC, leading to DA neuron death and PD symptoms [46]. Rotenone also acts by inhibiting complex I. Although rotenone is highly lipophilic and can cross the plasma membrane, it causes selective DA neuron degeneration with elevated oxidative stress, indicating that DA neurons may be particularly susceptible to mitochondrial dysfunction [48].

Studies on two genes that are mutated in inherited forms of PD, PINK1, and parkin further implicate mitochondria in PD. In Drosophila, ablation of either gene causes flight muscle degeneration, and mitochondria appear enlarged and swollen with fragmented christae [49-51]. Whereas parkin expression in a PINK1 knockout reverses this phenotype, PINK1 expression in a parkin knockout does not, indicating that parkin acts downstream of PINK1 to affect mitochondria [49-51].

Table 2. Current treatments for Parkinson's disease

Therapy	Results	Mitochondrial involvement?
Levadopa and DA agonists	Improves PD symptoms	May improve mitochondrial function in neurons by restoring nigrostriatal signaling
MAO-B inhibitors	Blocks oxidative deamination	May improve mitochondrial function in neurons targeted by DA and may decrease ROS produced by mitochondria
COMT inhibitors	Blocks catechol metabolism	May improve mitochondrial function in neurons by restoring nigrostriatal signaling
Anticholinergic drugs	Most effective in alleviating tremor and rigidity	May improve mitochondrial function in striatal neurons by balancing the DA and acetylcholine
NMDA receptor antagonists	Can suppress dyskinesia	May decrease amount of ROS produced due to excessive intracellular Ca^{2+}
Coenzyme Q_{10}	Less disability develops in patients given Coenzyme Q_{10} compared with placebo in one study [59]	May increase electron flow in electron transport chain and decrease ROS production
Creatine	Not rejected as futile in a phase II futility clinical trial [58]	May increase high-energy phosphate pool and decrease ROS production

COMT, catechol-O-methyltransferase; DA, dopamine; MAO-B, monoamine oxidase B; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; ROS, reactive oxygen species.

DA neuron degeneration in PINK1- and parkin-deficient Drosophila also has been observed [51,52] along with sensitivity to compounds that model PD and generate ROS [49]. One hypothesis is that loss of these PD-related genes that help regulate mitochondrial function leads to increased sensitivity to neurotoxic insults and DA neuron death.

2.3. Therapeutics and treatment

As with AD, a majority of current PD treatments (Table 2) do not target the mitochondria directly, although mitochondrial protection is more common in PD than AD. The current gold standard to restore DA signaling is the DA precursor levodopa (L-DOPA), which crosses the blood brain barrier, combined with a peripheral decarboxylase inhibitor such as carbidopa, which minimizes the gastrointestinal and cardiovascular side effects of DA [53,54]. Treatment may also include a selective inhibitor of monoamine oxidase B (MAO-B) or catechol-O-methyltransferase (COMT) to decrease DA metabolism [53,54]. DA agonists also have been used but appear less effective than L-DOPA [53,54]. Unfortunately, the effectiveness of L-DOPA therapy often is limited and can be associated with debilitating side effects [54]. L-DOPA has been hypothesized to enhance neurodegeneration [54] since DA metabolism by MAO-B generates ROS [55]. In theory, this oxidative stress would cause mitochondrial dysfunction and further ROS production. MAO-B inhibitors may decrease the amount of oxidative damage potentially caused by DA metabolism [53,54]; however, data from some clinical investigations do not support this hypothesis [56]. Regulation of Ca^{2+} influx shows a slight effect in alleviating dyskinesia in PD patients [53,54]. While regulation of intracellular Ca^{2+} to prevent ROS production is a potential therapeutic target in PD, NMDA receptor antagonists that block Ca^{2+} entry have shown minimal benefits in treating PD [53,54]. A more promising strategy may be to supplement mitochondria with molecules that improve their function. In this case, not only would ATP production improve, but ROS production by mitochondria might be decreased [53,54,57-59]. Coenzyme Q_{10} and creatine both may act through such a mechanism, with Coenzyme Q_{10} improving electron flow and creatine improving high-energy phosphate reservoirs [53,54,57-59]. Any approach that suppresses ROS production might also impact Lewy body formation since ROS can modify α-synuclein, increasing its tendency to aggregate and possibly form Lewy bodies [34,40].

3. Mitochondrial dynamics: new direction of mitochondrial research and potential therapeutics

Although mitochondrial dysfunction is extensively associated with AD and PD, direct effective mitochondrial therapy is very limited. A new area of mitochondrial research, known as mitochondrial dynamics, may provide new opportunities for mitochondrial therapies in AD and PD. Accumulating evidence suggests that mitochondrial morphology and transport can be regulated by fission and fusion, with fusion regulated primarily by mitofusins (Mfn) 1 and 2 and optic atrophy 1 (OPA1) and fission regulated primarily by Fis1 and dynamin-related protein 1 (Drp1) [60]. Several observations support the involvement of mitochondrial dynamics in neurodegeneration. Mutations in Mfn2 lead to Charcot-Marie-Tooth disease and peripheral neuropathy, and mutations in OPA1 lead to autosomal dominant optic atrophy and loss of optic nerve fibers

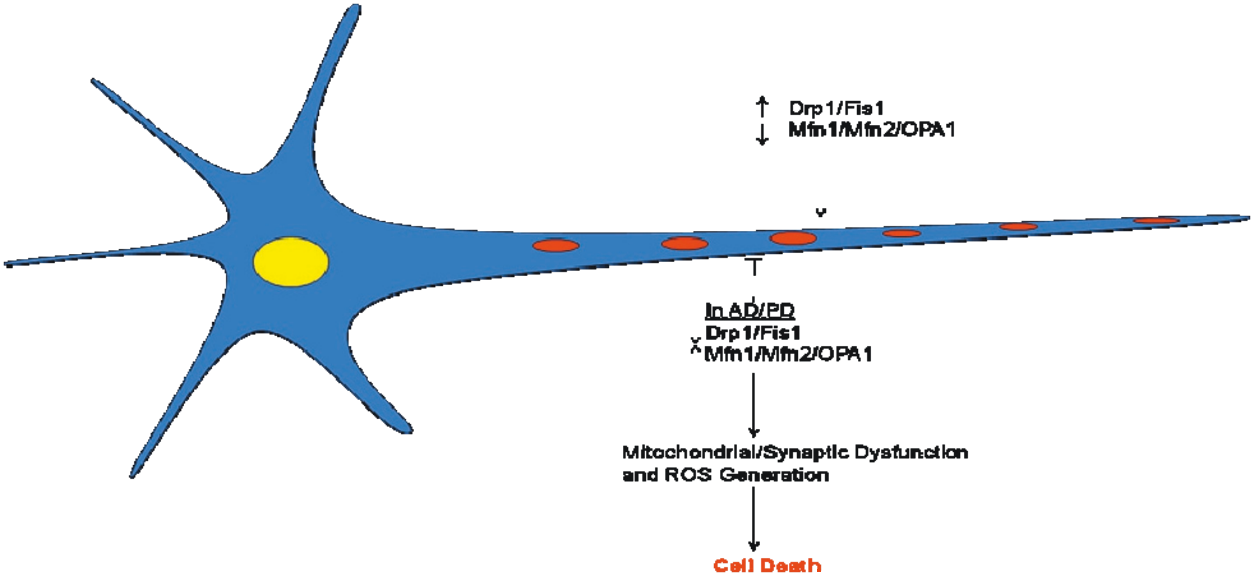

Figure 1. Synaptic function is dependent on proper trafficking of mitochondria to synapses. Mitochondrial trafficking down a neurite to a synapse can be promoted by increased fission (Drp1 or Fis1) or decreased fusion (Mfn1/2 or OPA1). Alterations in the levels of these proteins can lead to synaptic and mitochondrial dysfunction, neurodegeneration, and AD/PD pathogenesis. AD, Alzheimer's disease; Drp1, dynamin-related protein 1; Mfn, mitofusin; OPA1, optic atrophy 1; PD, Parkinson's disease.

[3,8,60]. More recently, Drp1, Mfn1, Mfn2, and OPA1 levels were shown to be decreased in brain tissue from AD patients whereas Fis1 levels were increased [5]. When these changes were mimicked in primary neurons using RNAi (RNA interference) or gene overexpression, mitochondria were decreased in neurites and dendritic spines, indicating that such changes may play a role in AD [5]. This study also showed that Drp1 overexpression in primary cultures protected neurons against neurotoxic insult, suggesting that increased fusion may be a neuroprotective strategy [5]. In a separate study, Drp1 was genetically ablated in Drosophila with a resulting loss of synaptic mitochondria, perhaps due to defects in axonal transport [61], an aspect of neuronal function affected in neurodegenerative diseases [62]. Using the neuromuscular junction (NMJ) to study synaptic actions of Drp1, the same group observed defects in Ca^{2+} buffering and neurotransmission during prolonged stimulation of the NMJ [61]. In a study of PINK1 and parkin in Drosophila, mitochondrial size and shape and muscle degeneration phenotypes observed in knockout Drosophila were reversed when Drp1 was overexpressed or Mfn2 or OPA1 function was decreased, again showing that increased fission or decreased fusion may be protective [50]. Although this is a relatively recent area of research, these results suggest that loss of fission or increased fusion could play a role in AD or PD. A proposed connection of mitochondrial fission and fusion to AD and PD is diagrammed in Figure 1. Mitochondrial dynamics also may alter mitophagy (elimination of dysfunctional mitochondria) [63], a topic beyond the scope of this review. Regulating mitochondrial dynamics is a new and emerging topic that may provide new targets for therapy.

Conclusions

Mitochondrial dysfunction is a feature of AD and PD. Mitochondria can affect neuronal function not only through ATP production but also through regulation of ion homeostasis (especially Ca^{2+}), synapse function, ROS generation, cell signaling, and survival. Current therapies for AD and PD might influence mitochondrial function indirectly, but few specifically target mitochondrial function. Regulating mitochondrial dynamics might provide new targets for mitochondria-directed therapy in AD and PD.

Abbreviations

Aβ, amyloid-beta; ABAD, amyloid-beta-binding alcohol dehydrogenase; AD, Alzheimer's disease; APP, amyloid-beta precursor protein; CNS, central nervous system; DA, dopamine; Drp1, dynamin-related protein 1; ETC, electron transport chain; FDA, US Food and Drug Administration; L-DOPA, levodopa; MAO-B, monoamine oxidase B; Mfn, mitofusin; MPP, 1-methy-4-penylpyridium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartate; NMJ, neuromuscular junction; NO, nitric oxide; OPA1, optic atrophy 1; PD, Parkinson's disease; RNS, reactive nitrogen species; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors participated in planning, writing, and revising this manuscript and read and approved the final version.

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