Proceedings of ICMMGH 2025 Workshop: Computational Modelling in Biology and Medicine
DOI: 10.54254/2753-8818/90/2025.GU20452

The Impact of Mitochondria on Neurodegenerative Diseases

Ruibo Liu[1,a,*]

[1]*School of Chemistry and Life Sciences, Beijing University of Technology, Beijing, 100124, China*
a. b20040423@emails.bjut.edu.cn
**corresponding author*

Abstract: Neurodegenerative diseases (NDDs) include Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), which are defined by the progressive deterioration of neurons in the central nervous system and functional decline. The pathogenesis of these diseases is complex and there is currently no effective treatment. For example, the failure rate of clinical trials for AD treatment strategies is as high as 99.5%. Research indicates that elements such mitochondrial malfunction, oxidative stress, excitotoxicity, inflammation, and apoptosis are closely related to the onset of NDDs, especially mitochondrial dysfunction, which is considered to be one of the core mechanisms of NDDs. Mitochondria are not only the main production site of ATP, but also participate in key processes such as metabolite synthesis and reactive oxygen generation. Due to the high energy demand of brain neurons and their high dependence on mitochondrial function, abnormal mitochondrial function may lead to serious neuronal structural and functional disorders. In addition, neurons also need to maintain local activities such as synaptic transmission and axonal transport through the precise transport and distribution of mitochondria. Therefore, abnormalities in mitochondrial dynamics and function may become early characteristics and potential pathogenic factors of NDDs. By reviewing the mechanism of mitochondrial abnormalities in AD, PD, and HD and their potential therapeutic strategies.This article seeks to investigate mitochondria as a prospective target for the prevention, early detection, and treatment of NDD.

Keywords: Neurodegenerative Disease, Parkinson's disease, Alzheimer's disease, Huntington's disease.

1. Introduction

NDDs are caused by the gradual loss of neurons, a process called neurodegeneration. Neuronal damage may eventually lead to their death. NDDs include PD, AD and HD. The WTO predicts that 55 million individuals globally experienced dementia in 2019, with projections indicating that figure will rise to 139 million by 2050 [1]. However, there is currently a lack of effective treatments. For example, in clinical trials of AD, the failure rate of stable and effective AD treatment strategies is 99.5% [2]. Recent studies indicate that mitochondrial malfunction, oxidative stress, excitotoxicity, inflammation, and apoptosis can all contribute to neuronal loss. Although there are many causes of NDDs, The primary characteristics of the major NDDs are either mitochondrial malfunction or decreased brain metabolism. Abnormal mitochondrial metabolism has been significantly linked to

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DOI: 10.54254/2753-8818/90/2025.GU20452

neurodegenerative diseases. The findings indicate that mitochondrial dysfunction may be pivotal in the etiology of NDDs.

Eukaryotic cells contain multiple structures known as mitochondria. Mitochondria are semi-autonomous organelles with their own genetic system and protein synthesis system. Mitochondria serve as the principal source of ATP for cellular energy and are also integral to the manufacture of essential metabolites, as well as in the processes of cell apoptosis and ferroptosis. The brain constitutes a minor portion of the body's weight, although it accounts for approximately 20 percent of energy expenditure. Their restricted glycolytic capability and dynamic metabolic characteristics are the cause. Neurons in the cerebral cortex are energy-intensive cells that necessitate meticulous upkeep of mitochondrial function. Abnormal mitochondrial function may significantly affect neurons. In addition, as highly differentiated and complex extension processes, In order to supply energy and store Ca2+, neurons also require timely and adequate transport as well as distribution of mitochondria. Synaptic transmission, axonal transport and synaptic vesicle circulation are all supported by it [3]. It can be seen that abnormal mitochondrial function will have serious effects on. Abnormal mitochondrial function significantly impacts the overall structure and functioning of neurons.

Therefore, this article reviews the role of various mitochondrial abnormalities in the pathogenesis of NDDs, taking AD, HD as well was PD for examples, and explores possible treatments.

2. Mitochondrial Dynamics

2.1. Mitochondrial Fission and Fusion

Mitochondrial fission and fusion are important factors in maintaining mitochondrial quality. This mechanism allows damaged mitochondria to disintegrate and maintain the balance of mitochondrial components. Neurons have high energy demands and therefore rely heavily on healthy mitochondria to maintain their normal function. Mitochondrial fission is divided into two pathways: intermediate zone fission and peripheral fission. Intermediate zone fission is an important indicator of mitochondrial health, and no adverse changes occur when it occurs. Peripheral fission usually occurs at one pole of the mitochondria when the membrane potential decreases or ROS increases. After fission, the larger product retains its original function while the smaller product will undergo apoptosis. The activation of the same protein is the basis of both central and peripheral fission, with central fission involving attachment to the endoplasmic reticulum and peripheral fission involving the binding anchor of the lysosome [4]. According to previous studies, the ER-mitochondrial contact site (EMCS) is where the ER contacts the mitochondrial outer membrane (OMM) during the initial stage of mitochondrial fission, which results in mitochondrial constriction. Then, some mitochondrial-binding proteins, including FIS1, MFF, and MiD, which act as “membrane-anchored adaptors”, help the oligomeric form of Drp1 to be recruited to the EMCS. In the end, Drp1 bound to mitochondria forms a ring structure., which strengthens the neck that already has mitochondrial constriction and eventually induces fission [5].

Mitochondrial fusion consists of two integral processes. In mammalian cells, Mfn1 and Mnf2–dynein-like GTPases that have conserved catalytic domains guarantee OMM fusion, OPA1 and mitochondria-specific cardiolipin (CL) play a crucial role in mediating the fusion of the intermitochondrial membrane (IMM) [5].

2.2. Mitochondrial Transport

Compared with other cell types, the most important morphological features of neurons are extreme polarity and long axons. The diameter of the neuron cell body ranges from 5 to 100 μm, while the axon can be up to 1 m long. For the stability of the axon, it is important to have a way to transport cargo from the cell body to the axon. Axonal transport undertakes this function. It is not only

DOI: 10.54254/2753-8818/90/2025.GU20452

responsible for the supply of cargo (proteins, RNA, organelles) to the nerve terminal, but also for the recycling of folded proteins and abnormal organelles.

The transport of mitochondria can be divided into two main modes: anterograde transport and retrograde transport. The former is responsible for transporting newly synthesized mitochondria to supplement the mitochondrial deficiency at the distal end of the axon, while the latter can participate in mitochondrial autophagy by transporting autophagosomes formed by damaged mitochondria to the cell body [5]. The two transport modes coordinate with each other to maintain the homeostasis of neurons [6,7]. The axonal motor system consists of motor proteins, microtubules, cargo, and their adaptors. Microtubules that run through axons act as conduits for the axonal transport system. Motor proteins, including dynein and kinesin, are the source of power for axonal transport. One end of dynein binds to microtubules, which act as tracks as they run through axons. The other end binds to cargo. Both dynein and kinesin are ATP-dependent proteins that can obtain energy by hydrolyzing ATP. They mediate reverse transport and forward transport, respectively. Adapters are responsible for connecting cargo and dynein [8].

2.3. Mitophagy

The complete clearance of the entire mitochondria in lysosomes is achieved by mitochondrial autophagy, the only known cellular pathway. Thus, mitophagy is instrumental in ensuring the quality and quantity of mitochondria.

Three major mechanisms can lead to mitophagy after mitochondrial damage: ubiquitin-mediated mitophagy, OMM receptor-mediated mitophagy, and lipid-mediated mitophagy. The mitophagy pathway that is most extensively studied involves PTEN-induced putative kinase protein 1 (PINK1). Mitochondrial membrane potential loss ($\Delta\psi m$) leads to accumulation of PINK1 on the OMM, which recruits and activates the E3 ubiquitin ligase Parkin through ubiquitin phosphorylation. Parkin ubiquitinates numerous OMM proteins and then initiates the ubiquitin-proteasome system (UPS) to eliminate them. This causes autophagic machinery to be recruited, which leads to damaged mitochondria being engulfed by phagocytic vacuoles or isolation membranes. Thereby forming mitophagosomes and clearing them through the lysosomal system. Other E3 ubiquitin ligases can regulate mitophagy independently of Parkin. MUL1 shares similar substrates with Parkin and directly interacts with GABAA receptor-associated proteins to promote autophagy.

Receptor-mediated mitophagy: Numerous autophagy receptors are affixed to the OMM, like FK506 binding protein 8. These receptors can associate with LC3 on the phagophore to direct defective mitochondria for autophagy. Lipid-mediated mitophagy: The translocation of cardiolipin from the inner mitochondrial membrane to the outer membrane triggers mitophagy by direct interaction with LC3 [9]. Neurons have a high energy demand and therefore the quality of their mitochondria is of great importance. Mitochondrial fission and fusion, mitophagy, and mitochondrial transport are important components of mitochondrial maintenance. Mitochondrial dynamics can be disrupted if disorders of the neuronal system occur. Mitochondrial fragmentation in neurons is found in most neuronal NDDs.

3. Calcium Homeostasis

Calcium ions (Ca 2+) play a crucial role in energy production and cellular signalling, influencing cell fate by initiating or inhibiting apoptosis. Therefore, calcium homeostasis is very important for maintaining normal cell function. Mitochondria are one of the key factors in calcium regulation, and calcium ions also affect mitochondrial metabolism. Mitochondrial Ca 2+ (m Ca 2+) promotes ATP synthesis, which is induced by the activation of Krebs cycle enzymes and oxidative phosphorylation. This function is accomplished by physiological Ca 2+ signals, enabling cells to modulate ATP

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synthesis in accordance with demand. Ca 2+ furthermore induces the generation of ROS from many sources. The intake of calcium by mitochondria can trigger the activation of dehydrogenases, enhance mitochondrial respiration, and lead to mitochondrial hyperpolarization. Elevated mitochondrial membrane potential results in an increased likelihood of electron leakage and ROS generation within mitochondria. When calcium ion content is too high, excessive ROS produced by mitochondria triggers the opening of mPTP, resulting in loss of mitochondrial membrane potential and cell death [10].

4. NNDs

4.1. AD

AD is the most common neurodegenerative disorder globally, characterized by a deterioration in memory and cognitive function due to the progressive death of brain neurons. Two significant characteristics of ADare the hyperphosphorylation of tau protein and the presence of amyloid beta plaques.

Studies have found that α-synuclein coexist, pathogenic tau and Aβ plaques in the brains of people with NDDs, and α-synuclein plays a role in connecting Aβ plaques and tau. The research additionally revealed a specific relationship between Drp1 and tau protein, which makes it easier for Drp1 and Aβ to bind. These congestions are expected to induce aberrant mitochondrial division and result in excessive mitochondrial fragmentation [5].

In addition to abnormal mitochondrial morphology, mitochondrial distribution in the brain and brain of AD patients is also disrupted: the number of mitochondria in the neuronal processes of susceptible pyramidal neurons in patient AD is reduced. The forward and reverse transport of mitochondria can substantially influence the ratio of healthy mitochondria and their distribution. Studies have found that Aβ affects mitochondrial axonal transport. Aβ results in decreased expression of the orthodromic protein KIF5A. In terms of retrograde transport, oligomeric Aβ interferes with the motor protein intermediate chain and disrupts motor protein-Snapin coupling, which may affect mitochondrial transport. Overexpression or phosphorylation of Tau also affects mitochondrial movement. Studies have found that overexpression of tau disrupts kinesin-dependent mitochondrial transport by enhancing microtubule binding. At the same time, studies have found that tau phosphorylated at the AT8 site inhibits mitochondrial movement in PC12 cells. Phosphorylated tau at the AT8 site will damage the spacing of microtubules and disrupt mitochondrial transport [11]

Mitochondria are primary targets of autophagic breakdown in the brains of Alzheimer's disease patients. Although the specific mechanism leading to mitochondrial abnormalities is still unclear, the strong correlation between mitophagy and AD is beyond doubt. It can be seen that abnormal mitochondrial function will have serious effects on the Neuronal structure and function. Therefore, this article reviews the role of various mitochondrial abnormalities in the pathogenesis of NDDs, taking AD, PD, and HD as examples, and explores possible treatments.

4.2. PD

PD is characterized by degeneration of the central nervous system and is marked by involuntary tremors, bradykinesia, rigidity, sadness, anxiety, exhaustion, and dementia. The condition results from the gradual degeneration of dopaminergic neurons in the substantia nigra and the accumulation of Lewy bodies containing α-synuclein within neurons. Due to the fact that dopaminergic neurons necessitate 20 times more energy than other neurons, Parkinson's disease may be the neurodegenerative disorder most closely associated with mitochondrial dysfunction.

Researchers identified abnormalities in mitochondrial respiration, pyruvate oxidation, and the activities of complexes, as well as in mitochondrial transcription factor A in patients with Parkinson's

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disease. On the one hand, The diminished functionality of the electron transport chain in Parkinson's disease may result in decreased ATP production and promote vesicular dopamine buildup. It may also affect mitochondrial dynamics such as axial transport and fusion of mitochondria. Conversely, various PD cell models exhibit heightened mCa 2+ uptake and decreased output, resulting in mCa 2+ overload. Excessive sodium ions can result in mitochondrial hyperpolarization, reactive oxygen species production, mitochondrial DNA damage, and cellular apoptosis [10].

Mitochondria fragmentation in nerve cells is one of the distinctive features of PD. Mutated α-synuclein mislocalizes to mitochondria, interacting with Spectrum to facilitate Drp1 translocation, resulting in mitochondrial fragmentation. Pathogenic leucine-rich repeat kinase 2 mutants were also found to cause mitochondrial fragmentation in a Drp1-dependent manner. Recent studies have shown that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) can cause mitochondrial fragmentation. The metabolite of MPTP, MPP+, tilts the balance of mitochondrial fusion and fission toward excessive fission in a Drp1-dependent manner, Leading to mitochondrial fragmentation and mitochondrial dysfunction, which ultimately leads to death of neurons [12].

4.3. HD

HD is a NDDs that is primarily hereditary and is incurable. IT is induced by mutations resulting in CAG triplet repeats within the polyQ domain of the huntingtin protein (Htt). HD is marked by a gradual decline in the capacity to regulate movement, cognitive function, and emotional expression, along with other additional symptoms. Neurodegeneration predominantly transpires in the striatum and cerebral cortex.

Research has demonstrated that mutant HTT (mHTT) induces mitochondrial problems. mHTT not only fails to activate autophagy due to its aberrant interaction with ULK1 and BECN1, but also leads to diminished recruitment of LC3-II to mitochondria owing to the loss of mHTT's interaction with two critical receptors, OPTN and CALCOCO2, as well as other auxiliary receptors. Consequently, the detrimental effects of mHTT manifest concurrently at several stages of the mitochondrial autophagy process [13]. Treatment of Neurodegenerative Diseases

4.4. Drug Treatment

4.4.1. Mitochondrial Fission Inhibitors

Mitochondrial fragmentation is found in most NDDs. Excessive mitochondrial fission and dysregulated fusion are one of the causes of this phenomenon. Modulating mitochondrial fission by disrupting the formation of Drp1 filaments in the constricted regions of mitochondria can alleviate associated symptoms. A Drp1-derived peptide, P110, has been developed in the quest to identify compounds that might repair abnormal mitochondrial fragmentation. P110 selectively targets Drp1, inhibiting its enzymatic activity and association with the mitochondrial adaptor protein mitochondrial fission 1 (Fis1). In addition, the method of promoting mitochondrial fusion by stimulating MFN fusion activity is also expected to correct mitochondrial dynamics defects [14].

4.4.2. Drugs to Improve Axonal Transport

Aβ protein deposition and tau phosphorylation are the main pathologies associated with AD. They both hinder mitochondrial transport. Therefore, by inhibiting Aβ protein deposition and tau phosphorylation, mitochondrial transport can be restored, healthy mitochondria can be replenished, and abnormal mitochondria can be recycled.

KIF5A expression can be restored by inhibiting Aβ protein deposition, and the coupling of motor protein-Snapin can be restored. β-secretase inhibitors, γ-secretase inhibitors, and α-secretase

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modulators can inhibit the production of Aβ protein. Drugs that interfere with Aβ aggregation, such as curcumin, can inhibit the deposition of Aβ protein. It is also possible to reduce the precipitation of Aβ protein by enzyme-mediated degradation of Aβ protein. Enkephalinase and insulin degrading enzyme can degrade Aβ protein.

The same method for tau phosphorylation and precipitation can restore mitochondrial transport. Excessive tau phosphorylation by kinases, especially GSK3, correlates with the impairment of microtubule function. Inhibitors can be designed to diminish kinase activity. Insoluble aggregation of tau protein results in the loss of tau functionality, subsequently causing microtubule instability and impairing transport. Consequently, treatment approaches aimed at diminishing microtubule instability are crucial. Administration of paclitaxel in tau transgenic mice improves axonal transport and performs various additional activities[15].

4.5. Mitochondrial Transplantation Therapy

Compared to improving the quality of mitochondria by protecting and promoting mitochondrial transport through drugs, mitochondrial transplantation aims to transplant functional exogenous mitochondria into cells with mitochondrial defects to restore or prevent mitochondrial diseases. The effect of each drug is relatively single, but the causes of mitochondrial abnormalities are very complex, so the efficacy of the drug is relatively single. Mitochondrial transplantation may be more direct and thorough to replace the old engine with a new one to restore its function. Numerous recent research have proven the efficacy of mitochondrial transplantation in treating neurological disorders. Furthermore, to enhance the efficacy of mitochondrial delivery, increasingly sophisticated methods have been employed. A study showed that the use of peptide-mediated delivery can enhance the delivery and functionality of allogeneic exogenous mitochondria by combining with the cell-penetrating peptide Pep-1.

5. Conclusion

This article discusses mitochondrial dynamics, calcium homeostasis and their relationship with NDDs. The dynamic processes of mitochondrial fission and fusion, transport and autophagy are crucial for maintaining the normal function of neurons. The dysregulation of these mechanisms, such as excessive mitochondrial fission, calcium instability and mitochondrial autophagy, not only impairs the energy metabolism of neurons, but also leads to oxidative stress and cell death, thus playing an important role in NDDs such as AD, PD and HD. Although the specific mechanism of mitochondrial dysfunction leading to NDDs has not yet been fully elucidated, more and more studies have demonstrated that mitochondrial defects can influence neuronal survival and function via multiple pathways. Based on the pathological mechanism of mitochondria, drug treatment strategies targeting mitochondrial fission, fusion, autophagy and calcium homeostasis show good prospects. Mitochondrial fission inhibitors, ROS scavengers, calcium homeostasis regulators, etc. have all achieved positive results in animal models or preclinical studies. With the in-depth study of mitochondrial dynamics and function, mitochondria are expected to become an important target for prevention, early diagnosis and treatment.

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