MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATIVE DISEASES: FROM ENERGY FAILURE TO NEURONAL DEATH

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Abstract

Neuroplasticity enables the brain to adapt structurally and functionally after injury. Following stroke, traumatic brain injury, and other neurological insults, synaptic remodeling, axonal sprouting, cortical reorganization, and glial responses contribute to functional recovery. Rehabilitation, neuromodulation, brain-computer interfaces, and emerging AI-based approaches aim to enhance these adaptive processes. This review summarizes key mechanisms of post-injury neuroplasticity and current therapeutic strategies for improving neurological recovery.

Keywords: Neuroplasticity, Brain injury, Stroke, Synaptic plasticity, BDNF, Neurorehabilitation, Brain-computer interface

1. Introduction: Neuronal Dependence on Oxidative Metabolism

Neurons are uniquely vulnerable to metabolic perturbations owing to their non-mitotic nature, highly polarized cytoarchitecture, and exceptional basal bioenergetic demands (Johri & Beal, 2012). Representing only two percent of total body mass, the human brain accounts for approximately twenty percent of resting systemic glucose and oxygen consumption (Wang et al., 2019). This intensive metabolic expenditure primarily powers plasma membrane repolarization via Na+/K+-ATPase activity, sustains synaptic vesicle priming and endocytosis, and supports neurotransmitter synthesis (Johri & Beal, 2012). Because mature neurons exhibit restricted glycolytic capacity due to continuous proteasomal degradation of PFKFB3, they rely almost exclusively on mitochondrial oxidative phosphorylation (OXPHOS) for adenosine triphosphate (ATP) generation (Wang et al., 2019). Consequently, maintaining

mitochondrial inner membrane potential (ΔΨm) and electron transport chain efficiency is crucial; even minor impairments rapidly precipitate bioenergetic failure, synaptic disconnect, and neurodegeneration (Klemmensen et al., 2024).

2. Pathophysiological Axis of Mitochondrial Dysfunction

Mitochondrial decay in neurodegenerative disorders represents a multi-faceted collapse of organellar quality control and bioenergetic cascades. Structural lesions within electron transport chain (ETC) complexes—most notably Complexes I, III, and IV—impair proton pumping and cause electron leakage to molecular oxygen, generating superoxide radicals ($O_2^{\bullet-}$) and downstream reactive oxygen species (ROS) (Wang et al., 2019; Wen et al., 2025). Excessive ROS generation causes lipid peroxidation, damages mitochondrial DNA (mtDNA), and oxidizes respiratory enzymes, initiating a self-propagating cycle of oxidative stress (Wen et al., 2025). Concurrently, mitochondrial dynamics are severely altered: pathological shifting toward GTPase Dynamin-related protein 1 (Drp1)-mediated fission, combined with down-regulation of fusion proteins Mitofusin-1/2 (Mfn1/2) and Optic Atrophy 1 (OPA1), causes mitochondrial fragmentation and structural collapse (Klemmensen et al., 2024). Furthermore, severe dysregulation of mitochondrial calcium (Ca^{2+}) buffering leads to matrix overload, while impairment of PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy prevents the autophagic degradation of damaged mitochondria, ensuring the persistent accumulation of neurotoxic, ROS-emitting organelles (Fivenson et al., 2017; Williamson et al., 2023).

3. Role in Neurodegenerative Diseases: Disease-Specific Vulnerabilities

While mitochondrial dysfunction is a primary driver across major neurodegenerative conditions, distinct primary triggers govern specific disease pathologies. In Alzheimer's disease, soluble oligomers of amyloid-beta (Aβ) and hyperphosphorylated Tau accumulate within neuronal mitochondria (Pantiya et al., 2020). Aβ directly inhibits Cytochrome c oxidase (Complex IV) and interacts with Cyclophilin D, whereas hyperphosphorylated Tau disrupts mitochondrial anterograde transport along microtubules by compromising kinesin motor activity (Klemmensen et al., 2024). In Parkinson's disease, dopaminergic neurons of the substantia nigra pars compacta exhibit heightened susceptibility to Complex I deficiency and oxidative damage (Gao et al., 2022). Familial PD mutations in PINK1, PRKN (Parkin), LRRK2, and SNCA (α-synuclein) converge on impaired mitophagy, defective organelle transport, and bioenergetic collapse (Williamson et al., 2023). In amyotrophic lateral sclerosis, aggregates of mutant superoxide dismutase 1 (mSOD1), TDP-43, and C9orf72 dipeptide repeats associate with outer mitochondrial membranes in motor neurons, impairing calcium buffering, destabilizing ETC complexes, and blocking axonal organelle transport to distal neuromuscular junctions (Zhao et al., 2022). In Huntington's disease, mutant huntingtin (mHTT) binds directly to the outer

mitochondrial membrane in striatal medium spiny neurons, suppressing PGC-1α-driven mitochondrial biogenesis and lowering the threshold for calcium-induced permeability transition (Johri & Beal, 2012; Pantiya et al., 2020).

4. Molecular Mechanisms of Neuronal Injury and Death

The convergence of bioenergetic failure, chronic ROS production, and matrix Ca2+ accumulation ultimately activates programmed neuronal cell death pathways. Prolonged matrix Ca2+ overload induces the opening of the high-conductance mitochondrial permeability transition pore (mPTP) in the inner membrane (Wang et al., 2019; Wen et al., 2025). Opening of the mPTP causes collapse of ΔΨm, uncouples oxidative phosphorylation, prompts influx of water, and causes matrix swelling with subsequent outer membrane rupture (Wang et al., 2019). This event releases pro-apoptotic intermembrane space proteins, including Cytochrome c and Second Mitochondria-derived Activator of Caspases (Smac/DIABLO), into the cytoplasm (Wang et al., 2019). Cytosolic Cytochrome c binds Apoptotic Protease Activating Factor-1 (Apaf-1) and dATP to assemble the apoptosome, which cleaves and activates initiator Caspase-9 and executioner Caspases-3 and -7 (Wang et al., 2019). Parallel to apoptotic cascades, leaked mitochondrial damage-associated molecular patterns (DAMPs), such as oxidized mtDNA, trigger cytosolic NLRP3 inflammasome assembly, activating Caspase-1 and driving neuroinflammatory cell death (Wen et al., 2025). Finally, impaired mitochondrial axonal transport starves synaptic terminals of local ATP, inducing a "dying-back" degeneration of axons (Zhao et al., 2022).

5. Therapeutic Perspectives and Conclusion

Targeting mitochondrial integrity offers a vital strategy for slowing or arresting neurodegenerative progression. Mitochondria-targeted antioxidants, such as MitoQ and Szeto-Schiller (SS) peptides, concentrate selectively at the inner membrane to neutralize ROS at their primary source (Apostolova & Victor, 2015). Strategies aimed at enhancing biogenesis through PGC-1α activators or nicotinamide adenine dinucleotide (NAD+) boosters, such as nicotinamide riboside, restore cellular energy status and promote Sirtuin activity (Fivenson et al., 2017; Wen et al., 2025). Additionally, small-molecule inhibitors of deubiquitinases such as USP30 promote PINK1/Parkin-independent mitophagy, facilitating the clearance of damaged organelles (Williamson et al., 2023). However, translating these approaches to clinical efficacy faces substantial hurdles, including poor blood-brain barrier permeability, off-target toxicity, and narrow therapeutic windows. Early intervention before irreversible synaptic loss remains essential for mitochondrial therapy to achieve clinical success in treating neurodegenerative disorders.

References

1. Apostolova, N., & Victor, V. M. (2015). Molecular strategies for targeting antioxidants to mitochondria: Therapeutic implications. Antioxidants & Redox Signaling, 22(8), 686–729.

2. Fivenson, E. M., Lautrup, S., Sun, N., Scheibye-Knudsen, M., Stevnsner, T., Nilsen, H., Bohr, V. A., & Fang, E. F. (2017). Mitophagy in neurodegeneration and aging. Neurochemistry International, 109, 202–209.

3. Gao, X.-Y., Yang, T., Gu, Y., & Sun, X.-H. (2022). Mitochondrial dysfunction in Parkinson's disease: From mechanistic insights to therapy. Frontiers in Aging Neuroscience, 14, 885500.

4. Johri, A., & Beal, M. F. (2012). Mitochondrial dysfunction in neurodegenerative diseases. The Journal of Pharmacology and Experimental Therapeutics, 342(3), 619–630.

5. Klemmensen, M. M., Borrowman, S. H., Pearce, C., Pyles, B., & Chandra, B. (2024). Mitochondrial dysfunction in neurodegenerative disorders. Neurotherapeutics, 21(1), e00292.

6. Pantiya, P., Thonusin, C., Chattipakorn, N., & Chattipakorn, S. C. (2020). Mitochondrial abnormalities in neurodegenerative models and possible interventions: Focus on Alzheimer's disease, Parkinson's disease, Huntington's disease. Mitochondrion, 55, 14–47.

7. Wang, Y., Xu, E., Musich, P. R., & Lin, F. (2019). Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. CNS Neuroscience & Therapeutics, 25(7), 816–824.

8. Wen, H., Deng, H., Li, B., Chen, J., Zhu, J., Zhang, X., Yoshida, S., & Zhou, Y. (2025). Mitochondrial diseases: From molecular mechanisms to therapeutic advances. Signal Transduction and Targeted Therapy, 10, e20443.

9. Williamson, M. G., Madureira, M., McGuinness, W., Heon-Roberts, R., Mock, E. D., Naidoo, K., et al. (2023). Mitochondrial dysfunction and mitophagy defects in LRRK2-R1441C Parkinson's disease models. Human Molecular Genetics, 32(18), 2808–2821.

10. Zhao, J., Wang, X., Huo, Z., Chen, Y., Liu, J., Zhao, Z., et al. (2022). The impact of mitochondrial dysfunction in amyotrophic lateral sclerosis. Cells, 11(13), 2049.