Exploring the Potential Mitochondrial Mechanisms by Which Intermittent Fasting Ameliorates Neurodegenerative Diseases (Postprint)

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Abstract

With the intensification of global population aging, the incidence of neurodegenerative diseases, for which aging is the primary risk factor, is steadily increasing. Research has shown that intermittent fasting (IF) can prevent or delay neurodegenerative diseases by regulating metabolic pathways. Mitochondria participate in key metabolic pathways, and IF can regulate mitochondrial function and homeostasis, while studies have indicated that mitochondrial dysfunction is an early hallmark of brain aging and neurodegeneration. These findings suggest a close association among IF, mitochondria, and neurodegenerative diseases. This article reviews four aspects from both positive and negative perspectives: the ameliorative effects of IF on neurodegenerative diseases, the crucial role of mitochondria in neurodegenerative diseases, the regulatory effects of IF on mitochondrial function, and the impact of excessive caloric intake on neurons and mitochondria, aiming to explore the possibility that IF improves neurodegenerative diseases by modulating mitochondrial function, and hoping to provide novel insights for investigating the specific mechanisms through which IF ameliorates neurodegenerative diseases.

Full Text

Preamble

Possible Mechanism of Intermittent Fasting-Induced Changes in Mitochondria for Improving Neurodegenerative Diseases

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Abstract: As global population aging intensifies, the incidence of neurodegenerative diseases—where aging represents the primary risk factor—continues to rise. Intermittent fasting (IF) has been investigated for its ability to prevent or delay neurodegenerative diseases through metabolic pathway modulation. Mitochondria participate in key metabolic pathways, and IF can regulate mitochondrial function and homeostasis, while mitochondrial dysfunction has been identified as an early hallmark of brain aging and neurodegeneration. These findings suggest a close association among IF, mitochondria, and neurodegenerative diseases. This review examines four complementary perspectives: (1) the therapeutic effects of IF on neurodegenerative diseases, (2) the critical role of mitochondria in neurodegenerative disease pathogenesis, (3) IF' s regulatory effects on mitochondrial function, and (4) the detrimental impacts of excessive caloric intake on neurons and mitochondria. By exploring these dimensions, we aim to investigate whether IF may improve neurodegenerative diseases through mitochondrial functional modulation, potentially providing novel insights into the specific mechanisms underlying IF' s neuroprotective effects.

Keywords: Mitochondria; Intermittent fasting; Neurodegenerative diseases; Review

Introduction

According to recent statistics, the global population aged 65 and older reached 727 million in 2020, with projections indicating this number will more than double over the next three decades [1]. This demographic shift introduces new challenges, as increased longevity among older adults often comes at the cost of poor health status and rising disability rates. Indeed, the development of chronic degenerative diseases has become a primary factor affecting quality of life in older adults, with neurodegenerative diseases being the most common. Neurodegenerative diseases (ND) are characterized by progressive decline in motor and/or cognitive functions resulting from selective neuronal loss within the central nervous system, with Alzheimer' s disease (AD), Parkinson' s disease (PD), Huntington' s disease (HD), and multiple sclerosis (MS) being the most prevalent forms [2]. Within the central nervous system, neurons rely predominantly on mitochondria for adequate energy supply to support survival and excitability, making mitochondrial dysfunction particularly likely to cause neuronal injury or death [3]. Multiple studies have confirmed that mitochondrial

dysfunction constitutes a major feature of neurodegeneration and plays a critical role in the onset and progression of neurodegenerative diseases [4, 5].

Current clinical management of neurodegenerative diseases remains primarily symptomatic, with numerous trial drugs failing to prevent or halt disease progression. Intermittent fasting (IF) represents a dietary pattern involving cyclical alternation between normal energy intake and energy restriction, with compelling clinical evidence demonstrating its potential to improve human cognitive function [6]. Furthermore, numerous preclinical studies have shown that IF exerts neuroprotective effects by modulating metabolic pathways, thereby preventing and slowing damage associated with aging and neurodegenerative diseases, though the specific mechanisms remain under investigation and are not yet fully elucidated [7, 8]. Mitochondria are key participants in cellular metabolic pathways, and emerging research indicates that IF can enhance neuronal mitochondrial function and cellular stress resistance, altering brain metabolic capacity by regulating or augmenting mitochondrial bioenergetics [9]. These findings suggest a potential close relationship among IF, mitochondria, and neurodegenerative diseases. Therefore, based on existing clinical and preclinical evidence, this review analyzes four complementary perspectives: (1) IF' s therapeutic effects on neurodegenerative diseases, (2) the critical role of mitochondria in neurodegenerative disease pathogenesis, (3) potential mechanisms through which IF regulates mitochondrial function, and (4) the detrimental effects of excessive caloric intake on neurons and mitochondria. By examining these dimensions from both positive and negative angles, we aim to explore the possible mechanisms by which IF may prevent and delay neurodegenerative diseases through mitochondrial functional modulation, hoping to provide new insights for investigating the specific mechanisms underlying IF' s neuroprotective effects.

1. IF' s Therapeutic Effects on Neurodegenerative Diseases

Since the dawn of recorded history, the influence of nutritional intake on aging, health, and longevity has been widely recognized. IF is rooted in evolutionary biology, as animals must develop adaptive behavioral and metabolic pathways to survive periods of food scarcity while minimizing bodily damage [10]. Alternate day fasting (ADF) and time-restricted feeding (TRF) represent the two primary forms of IF. ADF is defined as 36 hours of complete energy abstinence followed by 12 hours of ad libitum feeding, though less stringent protocols permit 25% of caloric intake on fasting days [11]. TRF restricts daily food consumption to an 8–10 hour window or shorter [12].

Clinical studies on IF intervention have demonstrated promising results. Mindikoglu et al. [13] found that after four weeks of IF, subjects exhibited significantly decreased expression of the amyloid precursor protein gene in serum proteins, which accumulates extensively in cerebral vessels of AD patients, suggesting a protective effect of IF against AD. Ooi et al. [6] conducted a three-year study on IF' s impact on cognitive function in elderly patients with mild cognitive impairment, revealing that long-term IF improved

cognitive function compared to controls, with patients returning to better cognitive performance at 36-month follow-up. Similarly, an Italian nutritional intervention study in older adults reported a positive correlation between TRF and improved cognitive function [14]. Numerous preclinical studies have also investigated IF in animal models of neurodegenerative diseases. Experiments in AD and PD animal models demonstrated that alternate-day fasting could delay disease onset and progression, with reports indicating that dietary interventions using nutritional fortifiers and adjusted feeding times could reduce neuropathy risk [15]. In an ovariectomized AD (AD OVX) rat model, four weeks of IF intervention alleviated cognitive deterioration, impaired energy metabolism, and dyslipidemia associated with estrogen deficiency, suggesting that IF could improve memory function by enhancing hippocampal insulin signaling and subsequently inhibiting Aβ deposition [16]. Similarly, other dietary restriction patterns, such as three cycles of fasting mimicking diet (FMD), completely reversed disease progression in an MS mouse model [17]. Neurodegenerative diseases may also be closely linked to neuronal energy metabolism, as early caloric restriction (CR) intervention in mice enhanced cerebral metabolic efficiency and maintained this level over extended periods, with these metabolic changes potentially playing a key neuroprotective role [18].

In summary, IF and related dietary restriction patterns can effectively ameliorate pathological changes in various neurodegenerative diseases, improve brain tissue metabolic efficiency, and thereby alleviate corresponding functional deficits.

2. The Critical Role of Mitochondria in Neurodegenerative Diseases

The most common neurodegenerative diseases, including AD, PD, HD, and MS, are intimately associated with alterations in mitochondrial morphology, structure, and function.

2.1 Alzheimer' s Disease

AD represents one of the world' s most prevalent neurodegenerative diseases, characterized by progressive and selective neuronal loss in the forebrain and other regions, manifesting primarily as deteriorating cognitive and memory functions that lead to severe disability over time [19]. AD pathological features include [20]: (1) extracellular deposition of Aβ forming senile plaques (SP) and intracellular abnormal phosphorylation of Tau protein leading to neurofibrillary tangles (NFTs) visible under light microscopy; and (2) neuronal degeneration in the hippocampus, entorhinal cortex, frontal cortex, and other structures related to cognition, as well as brain regions involved in emotional behavior, including the amygdala, prefrontal cortex, and hypothalamus. To date, extensive research has demonstrated widespread mitochondrial abnormalities in AD brains, consistent with clinically observed impairments in energy metabolism, with mitochon-

drial dysfunction confirmed as a prominent early disease feature [19].

Clinical studies have revealed significantly reduced oxygen metabolism rates in the frontal, temporal, and parietal cortices of early-stage AD patients, which correlates significantly with dementia severity [21]. Additional research has shown decreased mitochondrial metabolism, impaired activities of pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and cytochrome oxidase, and altered mitochondrial morphology in AD patients, suggesting that mitochondrial dysfunction may be an initial triggering factor [22]. Swerdlow et al. [22] first proposed the mitochondrial cascade hypothesis for AD, positing that mitochondrial dysfunction may exist independently of Aβ or upstream of Aβ deposition, at least mediating and possibly initiating pathological molecular cascades in AD. Pradeepkiran et al. [23] argued that defective mitophagy triggers Aβ and p-Tau accumulation in both early-onset and late-onset AD, leading to synaptic dysfunction and cognitive deficits, and suggested testing currently available mitophagy enhancers in preclinical animal models to identify potential future AD therapies.

Collectively, these findings indicate that AD onset and progression are closely associated with morphological and functional alterations in neuronal mitochondria, which may represent a key factor initiating AD pathological molecular cascades.

2.2 Parkinson' s Disease

PD is an incurable chronic degenerative disease affecting nearly 2% of individuals over 50, characterized by preferential loss of dopaminergic neurons in the substantia nigra, leading to progressive motor system dysfunction. While its pathology remains unclear, nearly all cases show misfolded protein aggregation forming Lewy bodies, primarily composed of α-synuclein [24]. Evidence indicates that α-synuclein is a lipophilic protein localized to mitochondria and connected to the endoplasmic reticulum via mitochondrial-associated membranes; overexpression of α-synuclein in PD patients can suppress normal function of mitochondrial membrane-anchored respiratory chain complexes in substantia nigra neurons [25]. Furthermore, Luth et al. [26] demonstrated that mitochondrial α-synuclein overexpression disrupts intraneuronal Ca^{2+} homeostasis, causing mitochondrial membrane potential changes and NADH oxidation. In current PD research, mitochondrial dysfunction undoubtedly participates in pathogenesis, mediated by both genetic mutations and environmental factors.

Several studies have identified defects in the mitochondrial respiratory chain in PD patients. Monzio Compagnoni et al. [27] found impaired mitochondrial complex I (MCI) function in the substantia nigra, skeletal muscle, platelets, and leukocytes of PD patients. Recent reports show that selective disruption of MCI function in mouse dopaminergic neurons is sufficient to cause progressive Parkinsonism-related motor deficits, with different types of motor impairment (gross and fine motor function) correlating with dopamine release in different

regions (striatum and substantia nigra) [28]. Mitochondrial gene mutations also represent important pathogenic factors in PD. PD can be caused by dominant or recessive mutations in genes encoding proteins closely related to mitochondrial function and quality control, with PINK1 and Parkin together forming the molecular basis for a regulatory pathway ensuring mitochondrial quality control. During PD progression, mutations in PINK1, Parkin, and related proteins affect α-synuclein clearance pathways, leading to α-synuclein accumulation as Lewy bodies and potentially causing selective neurodegeneration in the substantia nigra [27].

In summary, mitochondria may play a more prominent role in PD, with respiratory chain activity—particularly MCI impairment—and mutations in mitochondria-related genes (PINK1 and Parkin) causing mitochondrial dysfunction that is closely linked to pathological α-synuclein accumulation. While mitochondrial dysfunction is clearly implicated in the pathological mechanisms of neurodegenerative diseases identified to date, it likely represents only one component of a complex network leading to neuronal degeneration or death, with specific mechanisms requiring further investigation.

3. IF' s Regulatory Effects on Mitochondrial Function

As previously discussed, IF and related dietary restriction patterns can effectively ameliorate pathological changes in various neurodegenerative diseases. In these conditions, mitochondrial structural damage and dysfunction represent important pathological mechanisms. Conversely, normal mitochondrial metabolism not only maintains neuronal activity but also protects neurons by reducing oxidative damage. Interestingly, research indicates that IF can regulate mitochondrial function by modulating mitochondrial dynamics, the respiratory chain, and associated oxidative stress [29]. Therefore, this section explores potential mechanisms through which IF may ameliorate neurodegeneration by regulating mitochondrial function.

3.1 IF' s Effects on Mitochondrial Energy Metabolism

Research shows that during fasting, expression of carnitine palmitoyltransferase-1 (CPT-1)—the primary regulator of mitochondrial fatty acid oxidation—increases. Correspondingly, endogenous fatty acid synthesis increases with extended oxidation periods, potentially shifting metabolism from glucose to fatty acids during fasting states, utilizing free fatty acids and producing ketone bodies [30, 31]. β-hydroxybutyrate (β-OHB), a major ketone body, can restore impaired mitochondrial respiration and neuronal metabolic dysfunction. Importantly, β-OHB concentration is a critical factor: at high concentrations, β-OHB can suppress glucose metabolism, while at low concentrations it reduces reactive oxygen species production by modulating the NAD^+/NADH ratio and improves mitochondrial metabolic efficiency, thereby enhancing mitochondrial function [32]. Preclinical evidence demonstrates that ketogenic therapy has neuroprotective effects, improving mitochondrial respiration, suppressing pro-inflammatory

cytokine release, and reducing Aβ deposition [33]. Specifically, β-OHB can also bind to G protein-coupled receptor 109a, protecting hippocampal mitochondrial respiratory function from Aβ toxicity.

Additionally, ADF can reduce insulin resistance in obese patients, which represents an early symptom in AD patients and is associated with exacerbated Aβ accumulation and glucose transport dysfunction. Insulin resistance is closely linked to systemic metabolic dysfunction, primarily due to mitochondrial dysfunction. Shin et al. [16] reported that IF can regulate energy metabolism in rats and improve memory function by enhancing hippocampal insulin signaling and reducing Aβ deposition. Therefore, we hypothesize that dietary restriction interventions such as ADF may improve pathological status in AD patients by ameliorating insulin resistance and promoting mitochondrial functional recovery.

In summary, IF may beneficially impact energy metabolism dysfunction in neurodegenerative diseases by increasing β-OHB levels and improving insulin resistance, thereby influencing mitochondrial metabolism and bioenergetics.

3.2 IF' s Effects on Mitochondrial Oxidative Damage

Mitochondrial-derived oxidants and radicals participate in cellular signal transduction under physiological conditions; however, under pathological conditions, excessive reactive oxygen species (ROS) production in neurons causes mitochondrial dysfunction by damaging mtDNA and reducing mitochondrial bioenergetics [34]. Oxidative stress is also implicated in the pathogenesis of many neurodegenerative diseases, leading to pathological product accumulation and synaptic dysfunction. Wegman et al. [35] found that in a 10-week crossover clinical trial, IF intervention caused a modest increase in SIRT3—a mitochondrial protein deacetylase that plays a positive role in preventing oxidative stress. Other studies have shown that IF, unlike other restrictive dietary interventions, exhibits complexity and tissue specificity in promoting mitochondrial bioenergetics and tissue redox status: IF partially restored certain brain antioxidant enzymes and reduced oxidative pathological product accumulation in aged animals, whereas short-term IF in young animals significantly increased protein carbonyl signals (protein oxidation) in rat brains without measurable changes in mitochondrial function. For cardiac tissue, IF intervention rapidly affected cardiac redox status, preventing glutathione oxidation and protein carbonylation [36].

Furthermore, mitochondrial DNA (mtDNA) is particularly vulnerable to oxidative damage due to its proximity to oxidant production sites and lack of protective proteins. Consequently, mitochondrial homeostasis imbalance accompanied by inflammatory responses in neurons exacerbates mtDNA oxidative damage. In turn, mtDNA damage affects respiratory chain function, enhances oxidative stress and inflammatory responses, induces apoptosis, and causes further cellular dysfunction and tissue damage, creating a vicious feedback loop [37]. Liu et al. [38] found that IF intervention in a mouse model of cognitive impairment

improved mitochondrial bioenergetic metabolism and increased hippocampal mtDNA levels to enhance mitochondrial mass. Additionally, IF intervention increased gut microbial metabolites such as 5-HT, which can protect against dopamine-induced oxidative damage in mitochondria and synaptosomes.

In summary, IF may ameliorate neurodegenerative diseases by increasing SIRT3 levels, modulating mitochondrial enzyme activities, and inhibiting mtDNA damage to reduce oxidative stress injury.

3.3 IF' s Effects on Mitochondrial Quality Control

Neuronal mitochondrial quality control requires participation throughout the entire mitochondrial life cycle, encompassing biogenesis, fusion, fission, and autophagy. Mitochondrial biogenesis is triggered to meet increased cellular energy demands, requiring co-expression of nuclear DNA and mtDNA, as well as involvement of transcription factor A (TFAM), nuclear respiratory factors 1 and 2 (NRF1 and NRF2), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), sirtuins, and AMPK. PGC-1α and AMPK serve as important regulators of mitochondrial biogenesis, with their activity declining with age [39].

Serrano et al. [40] demonstrated that fasting triggers AMPK activation and upregulates PGC-1α protein content, which plays a central role in regulating mitochondrial biogenesis, thereby enhancing mitochondrial energy supply efficiency through the AMPK/PGC-1α pathway.

Following mitochondrial synthesis, fusion and/or fission maintain relative equilibrium; promoting or inhibiting either process alone cannot improve mitochondrial dysfunction or adapt to fluctuating cellular energy demands. Proteins such as DRP1 and FIS1, derived from the mitochondrial outer membrane, are essential for mitochondrial fission. Research indicates that blood-brain barrier damage in neurological diseases such as AD and PD may depend on DRP1-FIS1-mediated mitochondrial dynamics disruption [41]. Interestingly, Khraiwesh et al. [42] analyzed ultrastructural changes in mouse hepatocyte mitochondria after six months of 40% CR intervention, finding that fission/fusion markers and mitochondrial fission-related proteins (FIS1 and DRP1) increased with CR duration, while three fusion proteins (MFN1, MFN2, and OPA1) showed no changes.

Mitophagy is a physiological process in healthy cells that selectively removes damaged or dysfunctional mitochondria, which could otherwise damage cells through excessive ROS production or pro-apoptotic signal release [43]. Hood et al. [44] found that dietary energy restriction combined with exercise can suppress mTOR pathway activation and stimulate mitophagy, thereby improving brain function and increasing neuronal resistance to oxidative stress.

In summary, we hypothesize that IF may exert positive effects on neurodegenerative diseases by maintaining mitochondrial quality control system balance and remodeling mitochondrial homeostatic networks.

4. Effects of Excessive Caloric Intake on Neurons and Mitochondria

The evidence presented above suggests that IF' s therapeutic effects in neurodegenerative diseases may be achieved through regulating mitochondrial energy metabolism, reducing mitochondrial oxidative stress damage, promoting mitochondrial biogenesis, balancing mitochondrial fusion/fission stability, and facilitating mitophagy. Conversely, the detrimental effects of excessive dietary caloric intake on the nervous system may also result from interference with normal mitochondrial structure and function.

Overnutrition can impair cellular stress resistance and neuroplasticity, adversely affecting brain neurons. Carneiro et al. [45] demonstrated that individuals chronically exposed to high-fat diets (HDF) exhibit reduced cognitive performance across various domains, including working and spatial memory and emotional regulation. Similarly, high-sucrose diets negatively impact cognition. Animal studies have also shown that hyperglycemia and obesity induced by HDF exacerbate amyloid pathology and cognitive impairment in AD transgenic mice [46].

Correspondingly, imbalanced dietary intake and caloric excess have been shown to alter mitochondrial energetics. Emelyanova et al. [47] found that mice fed a lard-based diet exhibited reduced functional activity of mitochondrial complexes I and III, increased mitochondrial superoxide production, and oxidative stress damage in cardiomyocytes compared to standard diet-fed controls. Additionally, substantial evidence from clinical and preclinical studies indicates that chronic excessive alcohol consumption enhances oxidative stress and alters mitochondrial function by limiting translation of protein complexes such as NADH dehydrogenase (complex I), cytochrome b-c1 (complex III), cytochrome oxidase (complex IV), or ATP synthase (complex V), thereby restricting mitochondrial oxidative phosphorylation [48].

In summary, excessive high-calorie dietary intake exerts detrimental effects on cognitive function and neuroplasticity, likely through enhanced mitochondrial oxidative stress damage and mitochondrial dysfunction.

Summary and Outlook

In conclusion, IF can improve neurodegenerative diseases, mitochondrial dysfunction constitutes an important feature of neurodegenerative diseases, IF can regulate mitochondrial function, and excessive caloric intake damages neuronal and mitochondrial function. Therefore, IF may improve neurodegenerative diseases through mitochondrial functional modulation.

However, IF' s effects on the nervous system and mitochondria are likely multifactorial. This review has not detailed the complete mechanistic pathways of IF' s action on mitochondria, such as energy metabolism sensors, specific signal transduction pathways, and mechanisms for inhibiting apoptosis, oxidative

stress, and inflammatory responses—all requiring further refinement in future research.

In an era of rising neurodegenerative disease incidence and escalating healthcare costs, IF represents a low-cost, easily implementable, and effective dietary therapy with significant potential for clinical promotion. However, considering that neurodegenerative disease patients are predominantly elderly, statistics indicate that 12.6–59.8% of AD patients and 17.2–40% of PD patients may be at risk for malnutrition alongside neurological symptoms [49, 50]. Therefore, we propose that before implementing IF as a clinical adjunctive therapy, comprehensive nutritional assessment protocols and standardized implementation criteria must be established. Only after meeting these standards should personalized fasting protocols be developed, thereby enhancing IF safety and ensuring ethical compliance. Additionally, the strict caloric restriction required by IF poses a major challenge for clinical compliance. We believe future research must further investigate the specific mechanisms through which IF improves neurodegenerative diseases and the precise signaling pathways underlying metabolic transitions in the nervous system. This would enable determination of optimal intervention timing and development of more targeted pharmacological alternatives that could mimic IF effects without requiring patients to substantially alter their dietary habits, thus facilitating clinical translation.

Therefore, future research must not only explore personalized IF promotion protocols through additional clinical trials and animal experiments but also investigate specific mechanisms to identify alternative therapeutic targets that simulate IF effects and overcome poor patient compliance. This review, examining IF' s potential mechanisms for improving neurodegenerative diseases from a mitochondrial functional perspective, aims to contribute to future research on IF-based alternative therapies and promote their clinical implementation.

Literature Search Strategy: We searched PubMed, Medline, Web of Science, and Sci-Hub using the English keywords "mitochondria, intermittent fasting, alternate day fasting, time-restricted feeding, neurodegenerative diseases, Alzheimer' s disease, Parkinson' s disease." Chinese databases including CNKI, Wanfang Data, VIP, and SinoMed were searched using Chinese keywords "线粒体, 间歇性禁食, 隔日禁食, 限时禁食, 神经退行性疾病, 阿尔茨海默病, 帕金森病." The search period covered database inception to May 25, 2022. Inclusion criteria: published literature. Exclusion criteria: articles with insufficient data, duplicate publications, unavailable full text, or poor quality.

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Note: Figure translations are in progress. See original paper for figures.