JURNAL KESEHATAN
JURNAL ILMU-ILMU KEPERAWATAN, KEBIDANAN, FARMASI & ANALIS KESEHATAN
DOI : https://doi.org/10.52221/jurkes
JURKES
ISSN : 2089-3906

Impact of Intermittent Fasting on Genes Involved in Neurodegenerative Diseases

Rizky Amalia Siregar [1], Benedikta Diah Saraswati [2]
[1,2] Faculty of Medicine, IPB University, Bogor, Indonesia

Article Information
Revised: April 2025
Available online: April 2025

Keywords
Neurodegenerative Diseases, Intermittent Fasting (IF), Gene Expression

Correspondence
E-mail : rizkyamalia@apps.ipb.ac.id

ABSTRACT

Neurodegenerative diseases, characterized by progressive neuron loss, present a significant global health challenge. Recent research highlights the role of genetic expression in these diseases, with lifestyle interventions, such as dietary changes, shown to influence gene expression linked to neurodegeneration. One promising approach is intermittent fasting (IF), a dietary method alternating fasting and eating periods, which affects biological processes like cellular repair, inflammation, and metabolism. Emerging evidence suggests IF may also alter gene expression related to neurodegenerative diseases, potentially reducing risk and slowing progression. This review examines current studies on the impact of IF on gene expression in neurodegeneration, exploring its mechanisms and implications for new therapeutic and preventive strategies.

INTRODUCTION

Neurodegenerative diseases (NDDs) are a range of disorders that affect the central and peripheral nervous systems, causing a gradual loss of nerve cell structure and function. These diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and

multiple sclerosis (MS), are major contributors to global mortality and disability. Several factors are involved in the development of NDDs, including genetics, problems with cell signalling, cell death, inflammation, protein buildup, mitochondrial dysfunction, oxidative stress, aging, and environmental factors. Oxidative stress, caused by an excess of reactive oxygen and nitrogen species, plays a crucial role in damaging neurons and advancing these diseases. Unlike static damage from metabolic or toxic causes, NDDs are marked by the slow loss of specific groups of neurons. In 2019, NDDs were responsible for 10.06 million deaths and 349.22 million Disability-Adjusted Life Years (DALYs) worldwide, making them the second leading cause of death after cardiovascular diseases (excluding stroke).(Ayeni et al., 2022)(Shashikant et al., 2024)

Neurodegenerative disorders are expected to become a significant challenge for both medicine and public health in the coming years due to global demographic changes, with limited survival rates reported for most of these diseases. (Gadhave et al., 2024) In 2019, NDDs were responsible for 10 million deaths and affected 349.2 million individuals worldwide, ranking second in global prevalence. Alzheimer's disease (AD) accounted for the highest number of deaths, with 121,499 deaths in 2019, and is the 6th leading cause of death globally. Over 55 million people have dementia, with around 60% of them residing in low- and middle-income countries. Similarly, the global prevalence of Parkinson's disease (PD) exceeded 8.5 million people in 2019, leading to 5.8 million disability-adjusted life years (DALYs) and 329,000 deaths, reflecting a significant increase in the burden of PD since 2000. Multiple sclerosis (MS) affected over 1.8 million individuals globally in 2019, with 59,345 new diagnoses and 22,439 deaths. Amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) also contributed significantly to global mortality and disability. The burden of these diseases varies across regions, with reductions seen in South America, Asia, the Malay Archipelago, and much of Central Africa. Asia, with its rapidly aging population, has seen a rise in neurodegenerative diseases, contributing to the highest number of dementia cases globally, surpassing Europe and the Americas. In 2015, the World Alzheimer’s Report highlighted that Asia had the highest number of people with dementia (22.9 million), compared to 10.5 million in Europe and 9.4 million in the Americas. (Shashikant et al., 2024)(Turana et al., 2022)

Gene expression is essential in the development and progression of neurodegenerative diseases (NDDs), as it controls the function of proteins that regulate neuronal survival, inflammation, and repair processes. Some researches explore several facets of gene regulation in NDDs, including the creation of databases such as SCAD-Brain for Alzheimer’s disease (AD) and other conditions, the role of RNA modifications like m6A, and how genetic variations contribute to disease progression.(Muley, 2023)

Intrinsic factors like aging, brain injury, and related neuroinflammation and oxidative stress, along with lifestyle choices such as high-sugar and high-fat diets, alcohol, and tobacco use, contribute to

neurodegeneration. However, several components in our diet, including polyunsaturated fatty acids, antioxidants like curcumin, resveratrol, blueberry polyphenols, sulforaphane, and salvionic acid, as well as caloric restriction and regular physical exercise, have the potential to promote healthier, longer lives· (Popa-Wagner et al., 2020) Intermittent fasting (IF), a form of caloric restriction, may promote neurodegenerative, neuroadaptive, and neuroprotective processes, leading to notable improvements in cognition and dementia. However, the complete effects of IF on the central nervous system are not yet fully understood. Potential factors driving these changes include modifications in energy metabolism, oxidative stress, insulin sensitivity, inflammation, and shifts in the activity of various neurotransmitters and hormones.(de Cabo & Mattson, 2019) Adopting a healthy lifestyle, including a balanced diet, physical activity, and intermittent fasting, may help protect against neurodegeneration and improve cognitive health, though further research is needed to fully understand these effects.

1. Neurodegenerative Diseases and the Role of Genetics

a. Overview

Neurons are essential for proper brain function, playing a critical role in communication throughout the body. While most neurons originate in the brain, they are found in other body regions as well. Neural stem cells produce most neurons during childhood, but this number decreases significantly in adulthood. Neurodegeneration, the progressive loss of neurons, their structure, or function, is central to several brain disorders and is a major health concern. It is associated with synaptic dysfunction, neural network disruption, and the accumulation of altered protein variants, such as tau, alpha-synuclein, and beta-amyloid. Diseases characterized by neurodegeneration, like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), result from complex interactions of genetic, environmental, and lifestyle factors. Genetic mutations, such as those in the APP, PSEN1, and PSEN2 genes in AD, and HTT in Huntington's disease, contribute to familial variants of these conditions. Additionally, many NDDs involve protein misfolding and aggregation, often exacerbated by environmental factors like toxic chemicals and oxidative stress, which damage neurons by creating an imbalance of reactive oxygen species and impaired mitochondria. (Lamptey et al., 2022)(Giri et al., 2024)

Neuroinflammation also plays a significant role in the progression of chronic NDs, contributing to neuronal deterioration and symptom intensification. Aging is another key risk factor, with the incidence of many NDs increasing with age. Researchers are also exploring potential links between viral infections and NDDs, as certain viruses have been connected to a higher risk of these conditions. Lifestyle factors, such as high-sugar and high-fat diets, alcohol, and tobacco use, contribute to neurodegeneration. Conversely, a diet rich in polyunsaturated fatty acids, antioxidants, and regular physical activity may help promote better brain health and longevity.(Lamptey et al., 2022)(Giri et al., 2024)

b. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive and irreversible form of dementia, marked by a gradual decline in memory and cognitive abilities. It is divided into two subtypes: early-onset AD (EOAD) and late-onset AD (LOAD). EOAD, which affects individuals under 65, represents 1-6% of cases and is often linked to specific genetic mutations such as PSEN1, PSEN2, and APP, which interfere with amyloid beta (Aβ) peptide processing. EOAD is usually inherited in an autosomal dominant pattern, with up to 13% of cases affecting multiple generations. In contrast, LOAD, the more prevalent form, typically occurs after 65, with age being the primary risk factor. Genetic factors, like mutations in the APOE ε4 allele, contribute to susceptibility, while sporadic AD is influenced by various factors such as gender, lifestyle, and environmental exposures. Both forms of AD result from a complex interplay between genetic predisposition and environmental factors. Although numerous theories, including amyloidogenesis, tauopathy, neuroinflammation, and oxidative stress, have been proposed to explain AD's development, the precise molecular mechanisms remain unclear. (Kamboh, 2003)(Andrade-Guerrero et al., 2023)

c. Parkinson's disease

Parkinson's disease (PD) is a common, incurable neurodegenerative condition that impacts 1% of people over 65 years old. It is clinically identified by its characteristic motor symptoms and, on a pathological level, by the loss of neurons in the substantia nigra and the presence of Lewy bodies. While the exact molecular mechanisms driving neurodegeneration in PD remain uncertain, genetic factors are increasingly understood to play a key role in the disease's complex development. More than 23 loci and 13 genes, including LRRK2, SNCA, GBA1, PRKN, PINK1, and PARK7/DJ-1, have been linked to inherited forms of Parkinsonism. Research on these gene products has highlighted potential pathways of neurodegeneration shared by both Mendelian and sporadic forms of the disease, such as synaptic, lysosomal, mitochondrial, and immune-related mechanisms. (Lesage & Trinh, 2023)(Funayama et al., 2023)

d. Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative condition caused by the expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat in the huntingtin (HTT) gene on chromosome 4, leading to a mutant huntingtin protein (HTT) with an excessive glutamine (polyQ) sequence, which is harmful to cells. Recent advances in genetic research have identified several genes, known as HD genetic modifiers, that regulate HTT gene expression. Notably, at least three loci on chromosomes 8 and 15 have been associated with the age at which motor symptoms begin in HD. Genes such as MTMR10, FAN1, and the pseudogene HERC2P10 on chromosome 15, along with RRM2B and UBR5 on chromosome 8, play roles in DNA repair and impact the pathogenicity of the CAG repeats. Overexpression of the FAN1 gene, which encodes a DNA repair enzyme, has been linked to delayed onset and slower

progression of HD. (Gonzalez Rojas et al., 2022)(Gatto et al., 2020)

e. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive degeneration of motor neurons in the brain and spinal cord, leading to muscle atrophy and death within 3-5 years of symptom onset. While the exact causes of ALS are not fully understood, approximately 10% of cases have a genetic basis. Since the discovery of the first familial ALS gene, SOD1, in 1993, more than 40 ALS-related genes have been identified. Recent research has uncovered additional genes associated with ALS, such as ANXA11, ARPP21, CAV1, C21ORF2, CCNF, DNAJC7, GLT8D1, KIF5A, NEK1, SPTLC1, TIA1, and WDR7, which help improve our understanding of the disease and offer potential avenues for developing better treatments. Some of these ALS-related genes, including CCNF and ANXA11, have also been linked to other neurological disorders like frontotemporal dementia (FTD). ALS can be categorized into familial (FALS), which accounts for 5-10% of cases, and sporadic (SALS), where genetic factors still contribute significantly. The number of ALS-related genes continues to grow, with over 130 genes and loci now identified. Some of these genes are involved in modifying disease progression, influencing clinical outcomes and survival time for patients.(Wang et al., 2023)(Su et al., 2022)

2. Intermittent Fasting (IF) and Its Effects on Cell Biology

Intermittent fasting (IF) has become increasingly popular in recent years, involving cycles of fasting and eating periods with several different methods. These methods include alternate-day fasting (ADF), where individuals alternate between eating normally one day and consuming fewer than 500 calories the next; the 5:2 diet, which involves eating normally for five days and fasting for two; and time-restricted fasting (TRF), where eating is confined to an 8-12 hour window each day.(Cubeles-Juberias et al., 2024; Diab et al., 2024)

Intermittent fasting (IF), including time-restricted eating (TRE) and alternate-day fasting (ADF), has become popular for weight loss, resulting in 1–12% weight reduction over 2–12 months. TRE limits food intake to a designated window, usually between 4–10 hours per day, while ADF alternates between fasting days (0–500 calories) and feast days. These methods help reduce pro-inflammatory gene expression and decrease chronic inflammation. Fasting also initiates a coordinated shift in metabolic and gene expression processes that impact neurons, leading to a metabolic state that improves neuronal energy use, adaptability, and stress response, which in turn helps maintain or enhance cognitive performance. Within 12–36 hours of fasting, the body enters ketosis, marked by reduced blood glucose, depleted liver glycogen, and the production of ketones from fat, which become the brain's primary energy source. Both the liver and brain astrocytes generate ketones, which, within a few days, supply up to 70% of the brain's energy needs. Ketones are a more efficient energy source, potentially boosting

cognitive function and bioenergetics, as demonstrated in rodents that exhibited improved learning and memory after a five-day ketone ester regimen.(Mulas et al., 2023; Phillips, 2019)

3. The Effect of Intermittent Fasting on Gene Expression in Neurodegenerative Diseases

Intermittent fasting (IF) is increasingly recognized as a valuable non-drug approach with significant influence on gene expression linked to neurodegenerative conditions. Current research highlights that IF impacts various molecular and cellular processes involved in disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and dementia. One of the core mechanisms behind IF's benefits is its ability to trigger adaptive stress responses like autophagy, lower inflammation, and regulate neurotrophic pathways, all of which contribute to supporting neuron health and function(Dong et al., 2024; Jeevitha et al., 2024; Szegő et al., 2025)

In Parkinson's disease models, especially in mice, IF has been found to reduce the buildup of α-synuclein, a protein closely associated with PD, by stimulating autophagy to clear harmful protein clumps. Transcriptomic studies from these models show that IF alters the expression of inflammation- and glia-related genes, such as CCL17 and IL-36RN, pointing to its role in regulating inflammatory pathways at the genetic level. These gene expression changes are linked to better motor coordination, preservation of dopamine-producing neurons, and stronger synaptic connections. (Szegő et al., 2025)

The benefits of IF go beyond Parkinson's, offering protection for the aging brain in general. During fasting, the body produces ketone bodies like beta-hydroxybutyrate (BHB), which not only fuel the brain but also serve as signalling molecules that stimulate the production of brain-derived neurotrophic factor (BDNF). BDNF is crucial for processes like memory formation, synaptic strength, and learning. IF has been shown to boost BDNF levels in brain regions like the hippocampus and cortex, indicating a genetic basis for its positive effects on cognition.(Dong et al., 2024)

Additionally, IF affects multiple cellular pathways involved in neurodegeneration by decreasing the expression of inflammatory genes (e.g., IL-6, TNF-α) and increasing protective genes, including those for fibroblast growth factor and AMPK. These effects help improve resistance to cellular stress, support mitochondrial function, and encourage the growth of new neurons. IF also downregulates components of the mTOR pathway, which is associated with aging and cell proliferation, further reinforcing its protective and longevity-enhancing effects.

IF's ability to reduce neuroinflammation is driven by both brain-specific and whole-body mechanisms. It improves gut-brain signalling, regulates adipokine levels, and boosts insulin sensitivity, all of which indirectly shape brain function and gene expression in neurons and glial cells. Altogether, these findings suggest that IF not only helps prevent the onset of neurodegenerative diseases but may also slow their progression by targeting gene networks across multiple systems [6]

CONCLUSION

Intermittent fasting (IF) emerges as a promising and practical non-pharmacological intervention for reducing the burden of neurodegenerative diseases (NDDs). Through its influence on gene expression, IF modulates several critical biological processes, including inflammation, oxidative stress, mitochondrial function, and neuronal survival. In particular, ketone bodies generated during fasting, especially beta-hydroxybutyrate (BHB), play an essential role in enhancing the expression of neuroprotective genes like brain-derived neurotrophic factor (BDNF), which supports synaptic plasticity, memory formation, and overall cognitive function.

In models of Alzheimer's and Parkinson's disease, IF has demonstrated the ability to downregulate genes associated with neuroinflammation while upregulating those involved in autophagy and cellular repair. These gene-level changes contribute to improved neuronal resilience and reduced accumulation of pathological proteins. Additionally, IF impacts systemic functions such as insulin sensitivity and gut-brain axis communication, which further shape neural health and gene activity in both neurons and glial cells.

Overall, the current body of research indicates that IF may not only delay the onset of neurodegenerative disorders but also slow their progression through sustained genetic and metabolic adaptations. Although further clinical studies are necessary to establish its long-term safety and effectiveness in humans, IF holds significant potential as a complementary strategy to conventional therapies. Its ability to target multiple mechanisms through gene regulation positions IF as a compelling candidate for future dietary-based interventions in the prevention and management of neurodegenerative diseases.

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