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AKADÉMIAI KIADÓ

The benefits of intermittent fasting: A review of possible mechanisms on central neurological disorders

W.W. Chen[1,2], L. Wang[1,2], A.J. Zhou[1,2], C. Fan[1,2], Y.D. Zhang[2], Z.P. Wang[2], S. Rong[2] and T. Wang[1,2,3]*

[1] Department of Pharmacy, College of Medicine, Institute of Advanced Pharmaceutical Technology, Wuhan University of Science and Technology, Wuhan 430065, China

[2] Academy of Nutrition and Health, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, Wuhan 430065, China

[3] Asia General Hospital, Wuhan 430065, China

REVIEW PAPER

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ABSTRACT

Intermittent fasting (IF) is a dietary strategy that involves alternating periods of abstention from calorie consumption with periods of *ad libitum* food intake and has been shown to have beneficial effects in many ways. Recent studies have shown that IF attenuates neurodegeneration and improves cognitive decline, enhances functional recovery after stroke as well as attenuates the pathological and clinical features of epilepsy in animal models. Furthermore, IF induced several molecular and cellular adaptations in neurons that overall enhanced cellular stress resistance, synaptic plasticity, and neurogenesis. In this review, the beneficial effects of IF on central neurological disorders are discussed. The information summarised in this review can be used to help contextualise existing research and better guide the development of future IF interventions.

KEYWORDS

intermittent fasting, cognition, central neurological disorders

* Corresponding author. E-mail: wt197391@wust.edu.cn

1. INTRODUCTION

Central neurological diseases are one of the leading causes of death and disability worldwide, and the incidence of neurological diseases is increasing year by year (Castillo et al., 2019). According to the Institute for Health Metrics and Evaluation, the number of people with neurological disorders exceeded 90 million until 2019 and the share of the total disease burden by cause is increasing every year (Roser et al., 2021). The three main types of common central neurological diseases are neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), cerebrovascular diseases including strokes, cerebral ischemia, cerebrovascular cognitive impairments, and psychiatric-related diseases (Fontana et al., 2021; Zhao et al., 2022). Although substantial research has been conducted to find possible treatments for brain-related diseases, treatment selection is still largely based on symptom relief and no cure has yet been found. Studies have shown that intermittent bioenergy challenges, such as intermittent fasting, exercise, and cognitive stimulation, better promote brain health throughout the life cycle (Mattson and Arumugam, 2018).

IF is a concept of a dietary pattern in which the timing of eating rather than the quantity or composition of food is restricted. There are many different types of IF, which can be divided into the following categories (Patterson et al., 2015; Gudden et al., 2021; Brocchi et al., 2022): Time-restricted Feeding (TRF), Alternate-day fasting (ADF), The 5:2 diet or periodic fasting (PF), and Fasting Mimicking Diet (FMD). TRF regulates the feeding/fasting window of the day without reducing the body's caloric and nutritional intake (Currenti et al., 2021). Alternate-day fasting (ADF) described alternating fasting days with free eating days in various schemes. The 5:2 diet or periodic fasting (PF) is characterised by fasting for 2 non-consecutive days in week and *ad libitum* eating for the other 5 days. Fasting Mimicking Diet (FMD) is similar to ADF but during fasting days a low-calorie intake is allowed (15–25% of the caloric needs). Additionally, religious fasting such as Ramadan Intermittent Fasting (RIF) is well represented in the fasting literature. (Figure 1) This review provides an overview of the effects of various IF modalities on central neurological disorders and discusses their possible mechanisms.

2. ALZHEIMER'S DISEASE (AD)

AD is characterised by the deposition of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau proteins, representing the most frequent type

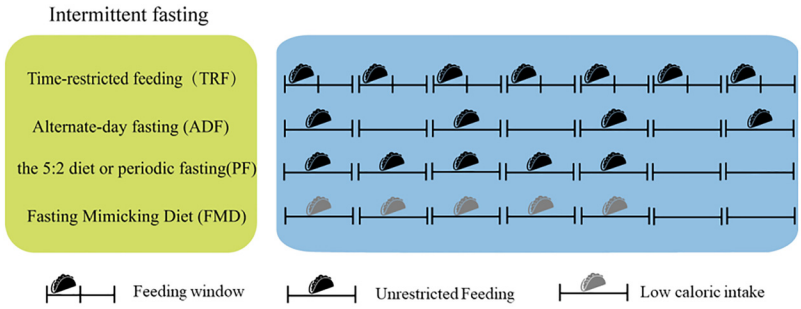

Fig. 1. Different forms of intermittent fasting

of dementia worldwide (Scheltens et al., 2021). The excessive accumulation of Aβ peptide and the hyperphosphorylation of tau proteins trigger neuroinflammation, blood-brain barrier (BBB) dysfunction, and cognitive decline (Bhaskar et al., 2010; Nasaruddin et al., 2020).

In humans, IF from dawn to sunset for 30 consecutive days has been shown to reduce blood amyloid precursor protein (APP), the precursor of Aβ, and upregulated key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodelling, immune system, and cognitive function in fourteen healthy subjects (Mindikoglu et al., 2020). Ooi and colleagues found that three years of IF training enhanced cognitive function in older adults with mild cognitive impairment, compared with age-matched adults who did it irregularly or not (Ooi et al., 2020). Studies have shown that in AD model mice, Alternate-day fasting (ADF) can improve cognitive impairment by down-regulating aquaporin 4 (AQP4) M1 subtype in the cerebral cortex of APP/PS1 mice, reducing the ratio of AQP4-M1/M23, restoring the polarity of AQP4 and increasing the clearance of Aβ (Zhang J.Z. et al., 2017). Liu's study showed that in the $APP^{NL\text{-}G\text{-}F}$ knock-in mouse of AD, ADF increased γ-aminobutyric acid (GABA) synaptic activity through the mitochondrial protein deacetylase sirtuin 3 mediated hippocampal neuronal network, limited Aβ-induced neuronal hyperexcitability, enhanced hippocampal synaptic plasticity, and improved spatial learning and memory deficits (Liu et al., 2019). The 6-week Fasting-mimicking diet (FMD) intervention attenuated cognitive deficits, amyloid pathological changes, and microglia reactivity compared to the *ad libitum* fed PDAPP-J20 transgenic mice (Gregosa et al., 2019). In a model of paraquat-induced neuronal toxicity, ADF contributes to proteostasis and neuronal protection by improving autophagic flux, reducing oxidative damage, and enhancing APP clearance through chaperone-mediated autophagy and robust engagement induced by mega autophagy (Ntsapi and Loos, 2021). It is argued that IF can decrease and/or prevent AD-related neuropathology and cognitive decline by upregulating neuronal stress resistance pathways and suppressing inflammatory processes through decreased activity of the mammalian target of the rapamycin (mTOR) pathway (Mattson et al., 2018).

3. PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) pathogenesis is distinguished by the aggregation of α-synuclein Lewy vesicles and the death of dopaminergic neurons in the substantia nigra (SN). Mitochondrial malfunction, oxidative stress, and selective neuronal death all contribute to the pathophysiology of Parkinson's disease, which manifests clinically as motor control issues, depression, anxiety, and cognitive impairment (Tysnes and Storstein 2017; Neth et al., 2021; Weintraub et al., 2022). Fasting mimicking diet (FMD) alleviates the degeneration and loss of SN dopaminergic neurons in PD mice induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), reshapes the composition of the intestinal microflora, restores the balance of astrocytes and microglia in SN through signalling effects of metabolites, and alleviates the inflammatory response in PD mice (Zhou et al., 2019). In an animal model of early brainstem autonomic nervous system dysfunction in PD, Alternate-day fasting (ADF) improved abnormal autonomic control of the heart, elevated resting heart rate, and impaired cardiovascular stress response, associated with reduced parasympathetic activity and accumulation of alpha-synuclein in the brainstem (Griffioen et al., 2013).

4. STROKE

Stroke is a neurological deficiency that occurs suddenly as a result of a disruption in blood flow, resulting in the brain, spinal cord, or retinal infarction. The majority of strokes are ischemic, including neuron death, neuroinflammation, neural network remodelling, and neuron functional reconfiguration (Sacco et al., 2013; Feigin et al., 2021). The overall positive effects of prophylactic IF to protect brain tissue against excitotoxicity, oxidative stress, and inflammation in the management of brain injury during ischemic stroke involved the coordinated upregulation of multiple neuroprotective proteins including neurotrophic factors (*e.g.* BDNF and BFGF), protein chaperones (*e.g.* Hsp70 and GRP78), antioxidant enzymes (*e.g.* SOD and HO-1), down-regulation of pro-inflammatory cytokines (*e.g.* TNF-α, IL-1β, and IL-6), and suppression of inflammasome activation at the site of brain injury in mouse models of ischemic stroke (Arumugam et al., 2010; Fann et al., 2014).

Mice fed Time-restricted Feeding (TRF) for three months prior to middle cerebral artery occlusion (MCAO) have improved neurogenesis in the hippocampus and subventricular zones, as well as infarcts that are less than half the size of those reported in mice fed *ad libitum*, and TRF also prevents a drop in post-MCAO circulating leptin levels (Manzanero et al., 2014). Changes in leptin levels or sensitivity indicate a potential mechanism for neuroprotection in IF mice, given earlier studies revealing that exogenous leptin lowers infarct size (Zhang F. et al., 2007; Zhang J.Y. et al., 2013) and leptin receptor-deficient animals exhibit greater damage and more widespread cell death following ischemia (Vannucci et al., 2001). Furthermore, rats fed Time-restricted Feeding (TRF) for three months before and 70 days after global cerebral ischemia show persistent improvements in spatial memory compared to non-fasting controls (Roberge et al., 2008). Compared to *ad libitum* fed mice, C57 mice treated with MCAO for three months after alternate-day fasting (ADF) intervention showed increased levels of brain-derived neurotrophic factor (BDNF) and basic fibroblast growth factor (BFGF), which were associated with the promotion of neuronal survival and plasticity and reduction in brain infarct size, as well as reduced levels of TNF-α and IL-6 associated with neuroinflammation in the cortex and striatum, leading to a reduction in ischemic brain injury (Arumugam et al., 2010).

5. EPILEPSY

Epilepsy is a neurological disorder characterised by recurrent bursts of abnormal excessive neuronal activity, known as seizures, in which motor control and consciousness are often lost (Duncan et al., 2006.). There is mounting evidence that IF has antiseizure and antiepileptogenic benefits in animal models due to metabolic and biochemical effects such as reduced blood glucose levels, suppression of mTOR signalling, decreased inflammatory markers, increased Adenosine 5′-monophosphate-activated protein kinase (AMPK) signalling and autophagy.

Mice on Time-restricted Feeding (TRF) have a longer latency to seizure generation and a lower severity and frequency of seizures than mice fed *ad libitum*. More importantly, the TRF intervention group increased the AMPK protein level and decreased the protein kinase B level (Landgrave-Gómez et al., 2016). A study on an epileptic state animal model showed that activation of AMPK has a protective effect on brain damage caused by an epileptic state (Han et al., 2011). Activation of AMPK also reduces the epithelial chloride secretion mediated by cyclic adenosine monophosphate (cAMP), thereby reducing the inflammatory response and thus affecting seizures (Walker et al., 2003).

Meanwhile, the Time-restricted Feeding (TRF) intervention group increased the concentration of the endogenous inhibitor β-hydroxybutyrate (β-HB) of histone deacetylase (HDAC) in the hippocampus (Landgrave-Gómez et al., 2016). There are many reports that β-HB is associated with improved seizure control. High blood β-HB concentration was strongly positively correlated with prolonged seizure latency and negatively correlated with seizure severity scores (Yum et al., 2012; Yuen and Sander, 2014). The possible mechanism for the role of β-HB could be mediated by increasing the equilibrium transfer of glutamate to the aspartate-glutamate-transaminase reaction, thereby making more glutamate available for the glutamic acid decarboxylase reaction to produce more γ-amino-butyric acid (GABA). In addition, β-HB also reduced the expression of GABA transaminase and GABA transporter genes in cultured astrocytes, thus providing an additional antiepileptic mechanism by inhibiting GABA degradation in astrocytes (Suzuki et al., 2009). TRF can produce acetylation epigenetic modifications on two lysine residues of histone 3, which are epigenetic tags associated with the transcriptional activation of genes (Landgrave-Gómez et al., 2015). The increase in these post-translational modifications may be mediated primarily by inhibiting histone deacetylase activity throughout β-HB (Shimazu et al., 2013). The benefits of a two-month modified TRF regimen in six epileptic children with an inadequate response to a ketogenic diet were explored in a human trial, with four of the six children experiencing modest improvements in seizure control (Hartman et al., 2013).

6. VASCULAR COGNITIVE IMPAIRMENT

Vascular cognitive impairment (VCI) was created to describe all forms of cognitive impairment associated with cerebrovascular pathology (O'Brien et al., 2003.; Iadecola et al., 2019), and decreased cerebrovascular health is rapidly becoming recognised as a major marker of age-related cognitive decline (Tarantini et al., 2017; Sweeney et al., 2018). Excess superoxide reacts with nitric oxide (NO) in endothelial cells to form peroxynitrite, a highly reactive oxidant that mediates the harmful effects of oxidative stress in many blood vessels. This includes cytotoxicity, mitochondrial malfunction, and pro-inflammatory pathway overexpression. Excess free radical production can exacerbate vascular inflammation and lead to age-related cognitive dysfunction. Administration of Time-restricted Feeding (TRF) has been reported to reduce reactive oxygen species production and improve endothelial function (Headland et al., 2018), which may indicate cerebrovascular protection for age-related cerebral blood loss harmonisation and the development of VCI. Recent preclinical studies in rodents suggest that TRF may exert vascular protective effects by attenuating pro-inflammatory processes (Hatori et al., 2012; Chaix et al., 2014; Sutton et al., 2018). Thus, TRF-induced improvements in endothelial function may reverse age-related decline in endothelial-dependent NO bioavailability, thereby improving cerebral microvascular function and cerebral bloodstream perfusion.

7. MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) is one of the most prevalent mental disorders and interferes with mood, motivation, cognitive function, sleep, work, diet, and quality of life in general (Manchishi et al., 2018). A meta-analysis including 11 studies and 1,436 participants found that the Ramadan fasting group showed lower levels of anxiety and depression evaluated with the Beck Depression

Inventory and Depression Anxiety Stress Scale compared to the control group (Berthelot et al., 2021). Time-restricted Feeding (TRF) improved depression-like behaviour characterized by reduced activity and lack of pleasure and reduced enhanced anxiety-like behaviour on absentee trials in a model of depression and anxiety exposed to shift work. More importantly, TRF reduced microglia activation in the Cornu Ammonis 3 (CA3) region of the hippocampus, increased the number of glial fibrillary acidic protein and ionised calcium-binding adaptor molecule-1(IBA-1) positive cells in the prefrontal cortex and basolateral amygdala, and reduced neuroinflammation in brain regions associated with emotion regulation (Guerrero-Vargas et al., 2021).

Current first-line medications for treating MDD are selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (Gałecki et al., 2018; Faquih et al., 2019). Meanwhile, an increasing number of studies have discovered a relationship between serotonin (5-HT) and depression treatment (Lipsky et al., 2022). Increased availability of brain tryptophan (precursor of 5-HT) and 5-HT has been found after IF in rats (Dhahbi et al., 2004). Li et al. (2014) have reported that TRF has an additive antidepressant effect with imipramine in mice through the modulation of 5-HT receptors. Similarly, another study found that acute fasting (9 h) exerted antidepressant-like effects and suggested that the antidepressant-like effects may be mediated via the 5-HT receptor and particularly sensitive to neural activity in the prefrontal cortex as well as mediated by cAMP response element binding protein (CREB) and BDNF pathway in the hippocampus and frontal cortex (Cui et al., 2018). In addition, CREB and BDNF pathways have been extensively studied in depression (Kuwatsuka et al., 2013; Li et al., 2014; Manchishi et al., 2018). Thus, the antidepressant effect of TRF may be related to 5-HT and the CREB-BDNF pathway in the frontal cortex and hippocampus.

8. SLEEP

Sleep disorder is a wide risk factor for the onset of mental illness. The Baha'i Fast (BF) is a religious fast of fasting and abstaining from food and drink during daylight hours for 19 consecutive days every year in March (Mähler et al., 2021). Ring's research suggests that Bahá'í fasting appears to enhance participants' mindfulness and well-being, lower stress levels, and reduce fatigue. Some of these effects lasted for more than three months after fasting (Ring et al., 2022). Another pilot study demonstrated that 8 days of modified fasting promoted the quality of sleep and daytime performance in non-obese subjects (Michalsen et al., 2003). Kesztyüs et al. (2020) reported that subjects with 12 weeks of 9 h TRE intervention had a significant increase of 10 points (from 65 to 75) in their sleep quality score evaluated by the Visual Analogue Scale rating. Although the evidence suggests that intermittent fasting may be beneficial for sleep disorders, further research is needed to confirm these results.

9. CONCLUSIONS

Based on relevant prior studies, we summarised the effects of IF on a variety of prevalent neurological illnesses. The beneficial effects of IF on central neurological disorders mainly include improving cell bioenergetics, enhancing neurotrophic factor signalling, reducing the oxidative stress, and decreasing neuroinflammation (Hamrick and Stranahan, 2020) (Fig. 2). Eventually IF can improve cognitive impairment by promoting neurogenesis and increasing

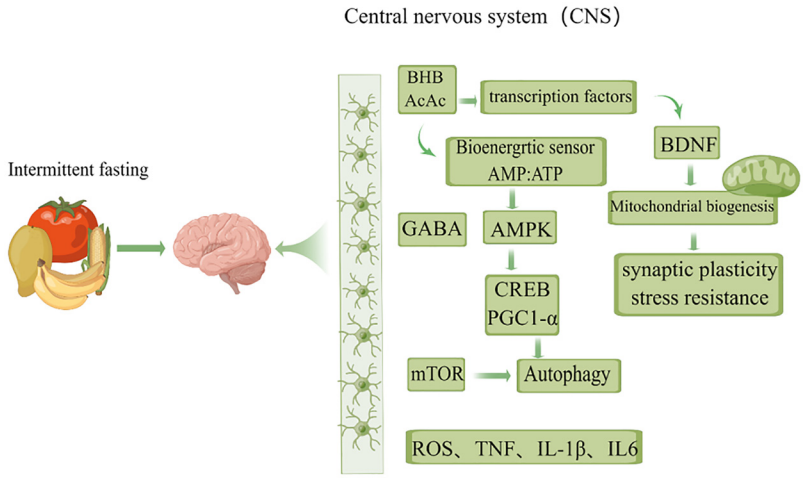

Fig. 2. The mechanisms and signalling pathways of IF on the central neurological disorders. Hepatic glycogen stores are depleted during intermittent fasting, and through a process called lipolysis, lipids (triacylglycerols and diacylglycerols) are converted into ketones such as acetoacetate (AcAc) and beta-hydroxybutyric acid (BHB). BHB and AcAc are transported from the blood to the brain and then to neurons. The reduced glucose supply and elevated ketone bodies reduce the ratio of AMP:ATP in neurons, which activates AMPK and stimulates autophagy by activating CREB and PGC1α. In addition, lower glucose levels during fasting reduce the activity of the mTOR pathway, leading to autophagy. BHB also upregulates the expression of brain-derived neurotrophic factor (BDNF), which may promote mitochondrial biogenesis, synaptic plasticity, and cellular stress resistance. Fasting suppresses inflammation, reducing the expression of pro-inflammatory cytokines such as interleukin 6 (IL6) and tumor necrosis factor α (TNFα)

synaptic plasticity (Yoon and Song 2019; Currenti et al., 2021). Although there is evidence that IF is beneficial in a variety of neurological conditions, further studies should distinguish whether this protective effect is established, taking into account age, the presence of obesity, total calorie intake, and the timing and intake of specific nutrients.

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