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The influence of fasting periods on slowing brain aging and preserving cognitive functioning

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ABSTRACT

INTRODUCTION AND PURPOSE OF THIS WORK

Advanced age is a significant risk factor for the onset of cognitive decline. Nutritional interventions, including caloric restriction (CR) and intermittent fasting (IF), have garnered considerable attention for their potential neuroprotective effects. Emerging evidence suggests that these dietary approaches may attenuate age-related neurological deterioration. This review explores the mechanisms through which intermittent fasting may enhance cognitive function.

METHODS AND MATERIALS

For this review, we used the literature available in PubMed, searching the following keywords: “brain aging”, “cognition and diet”;”neuroprotection”;“caloric restriction”;“neuroplasticity”. The search results were limited to studies from 2005 to 2024, as well as key studies from earlier years. Authors took into consideration articles originally written in English. In the end, 25 articles were included in this review.

BRIEF DESCRIPTION OF THE STATE OF THE KNOWLEDGE

In recent decades, advancements in medical science and increased public awareness regarding health-promoting behaviors have contributed to a rise in life expectancy, leading to a growing elderly population. Consequently, the role of modifiable factors, such as dietary patterns, is proven to be an important elements which contributes to delaying brain aging.

CONCLUSIONS

The review indicates the evidence supporting the positive effects of intermittent fasting (IF) on cognitive function remains lacking. Nonetheless, numerous promising mechanisms have been identified but in short-term studies, suggesting potential benefits in mitigating cognitive decline. These findings underscore the necessity for longitudinal studies to comprehensively evaluate the long-term effects of IF on cognitive health.

KEY WORDS: “Intermittent fasting”; ”Brain aging”; ”Cognition and diet”; ”Neuroprotection”; ”Caloric restriction”; ”Neuroplasticity”

I) INTRODUCTION AND PURPOSE OF THIS WORK

The impact of lifestyle factors, particularly dietary habits, on cognitive function has become an increasingly significant area of research. Epidemiological evidence highlights that specific dietary patterns support brain health, with the Mediterranean diet being one of the most beneficial. Dietary strategies based on caloric restriction or alternating periods of fasting and food intake have also demonstrated positive effects on resilience against cognitive decline. Intermittent fasting (IF) is not a novel concept, it has historical roots in ancient civilizations, where it was practiced for both spiritual and health-related purposes. In recent years, there has been a resurgence of interest in IF. This review examines potential mechanisms by which cyclical periods of fasting and recovery (food consumption) may optimize brain function and enhance resilience across the lifespan. IF is thought to influence the brain through various direct and indirect pathways. The most extensively studied mechanisms connecting fasting to neuroplasticity and brain resistance to injury and disease include increased levels of brain-derived neurotrophic factor (BDNF), enhanced mitochondrial respiration, activation of autophagy (particularly in cortical and cerebellar neurons), and reduction of inflammation by down regulating pro-inflammatory gene expression or removing inflammatory agents from the brain. Furthermore, this review explores the microbiota-gut-brain axis, which has been identified as a critical mediator of the beneficial effects of IF on brain health, ultimately leading to improvements in cognitive function.

II) METHODS AND MATERIALS

For this review, we used the literature available in PubMed, searching the following keywords: “brain aging”;“cognition and diet”;”neuroprotection”;“caloric restriction”; “neuroplasticity”. The search results were limited to studies from 2005 to 2024, as well as key studies from earlier years. Authors took into consideration articles originally written in English. In the end, 25 articles were included in this review.

III) CURRENT STATE OF KNOWLEDGE

BDNF as a neurotrophic result of IF

Brain-derived neurotrophic factor (BDNF) is a protein predominantly synthesized within the central nervous system, though it is also produced in skeletal muscle and other peripheral tissues. Increased BDNF expression in the brain has been observed as a response to intermittent fasting

(IF) [1,2,3]. Current evidence underscores the pivotal role of BDNF in neuronal survival, differentiation, and maintenance during brain development. It is particularly critical for the survival of newly formed neurons within the dentate gyrus of the hippocampus, a region intricately linked to learning and memory[4, 5]. BDNF is closely associated with long-term potentiation (LTP), a fundamental mechanism that drives neurogenesis and synaptic plasticity [2]. The process is initiated in the synaptic cleft, where BDNF binds to its high-affinity receptor, tropomyosin receptor kinase B (TrkB). This interaction activates intracellular signaling pathways, culminating in post- and presynaptic modifications that enhance synaptic communication. Such persistent synaptic strengthening translates into sustained and amplified signal transmission across neural networks. Alterations in BDNF expression are evident in key memory-associated brain regions, such as the hippocampus and parahippocampal areas, during aging, depression, and various neurological disorders. Notably, interventions like physical exercise, antidepressant therapies, and intermittent fasting have been shown to upregulate BDNF expression. Consequently, IF is hypothesized to augment synaptic plasticity by elevating BDNF levels, thereby facilitating protein synthesis and enhancing synaptic transmission, with potential improvements in cognitive function. Empirical studies further support the association between BDNF and cognitive resilience. For example, endurance training over three months has been shown to significantly increase BDNF levels in human participants compared to sedentary controls, as evidenced by blood sample analysis. In animal models, such as rodents, IF has been demonstrated to mitigate cognitive deficits by suppressing pro-inflammatory cytokines (e.g., IL-1β) and enhancing neurotrophic support [7]. Research by Vasconcelos et al. [6, 7] revealed that IF prevents reductions in hippocampal BDNF levels in lipopolysaccharide (LPS)-induced systemic inflammation in rats. These findings collectively indicate that both physical activity and IF can elevate BDNF concentrations, thereby explaining their positive effects on cognitive performance and neural plasticity.

IF and Oxidative Stress

Another critical mechanism associated with intermittent fasting (IF) is the enhancement of mitochondrial respiration. Mitochondria are integral to key metabolic pathways, particularly bioenergetic processes that are essential for maintaining intercellular signal transmission and overall cellular homeostasis [10]. Impairments in mitochondrial function are frequently observed in patients with neurological disorders and represent a natural consequence of aging. Intermittent fasting has been shown to enhance mitochondrial respiration, thereby conferring

neuroprotective effects [8, 9]. This process may support neuronal survival under conditions of oxidative stress through several potential mechanisms. Notably, IF reduces the mitochondrial production and release of reactive oxygen species (ROS) while simultaneously enhancing antioxidant defenses. These combined effects mitigate oxidative damage, thereby promoting the resilience and survival of neurons in the context of aging and neurodegenerative conditions.

IF promotes an increase of autophagy

Intermittent fasting (IF) has been observed to notably enhance autophagy, particularly in cerebral cortical and cerebellar neurons. These regions are critically associated with cognitive processes, including learning, memory, and overall cognitive function. Autophagy, a physiological response to fasting, serves to preserve cellular energy homeostasis by degrading and recycling cellular components [10, 12]. This process modulates the activity of the mammalian target of rapamycin (mTOR) protein kinase, a central regulator of cellular growth and metabolism. The mTOR signaling pathway is integral to neuronal proliferation, growth, maturation, and differentiation. Within the nervous system, mTOR plays a pivotal role in the development of neural cells and is crucial for processes such as learning and memory consolidation. Beyond its role in promoting cell growth and proliferation, mTOR activity also stimulates the synthesis of pro-inflammatory cytokines, which initiate immune responses. Given these mechanisms, IF appears to support the clearance of inflammatory stimuli including toxins, dysfunctional organelles, and cellular debris through enhanced autophagy. This process may underlie its neuroprotective effects by reducing neuroinflammation and maintaining neuronal integrity.

Neurotrophic effect of IF via the gut microbiota

A significant mechanism through which intermittent fasting (IF) impacts brain health and cognition is the microbiota-gut-brain axis (MGBA) [9, 10, 13]. The gut microbiome, encompassing the collective microorganisms residing in the gastrointestinal tract, is increasingly recognized as a key player in brain function. Evidence suggests that the composition and activity of the gut microbiome influence the brain via neural, endocrine, and immune pathways, forming the basis of the MGBA. The diversity of the gut microbiota is influenced predominantly by diet and dietary timing. Oscillations in microbiota abundance align with circadian rhythms, hormonal fluctuations, and the periods of feeding and fasting.

Notably, research indicates that microbiota oscillations are disrupted by Western dietary patterns, particularly by food intake during resting phases. These disruptions diminish microbiome diversity. In contrast, IF has been shown to restore microbiota oscillations, enhancing diversity even without alterations in overall nutritional intake. A landmark study by Thaiss et al. (2014) demonstrated time-of-day-specific microbial functionality in mice subjected to IF [13]. During the active dark phase, microbial activity centered on energy metabolism, cellular growth, and DNA repair. Conversely, during fasting periods, microbial functions emphasized detoxification and motility. These findings support the hypothesis that microbiota functionality oscillates within a 24-hour rhythm and adapts flexibly to feeding patterns.

IF and Cognitive Function in Diabetic Rodent Models

To explore the relationship between IF, gut microbiota, and cognitive function, a 2020 study by Zhigang Liu et al. [15] investigated diabetic mice with cognitive impairments. The study divided the animals into three groups: diabetic mice fed ad libitum (db/db), a non-diabetic control group (db/m), and diabetic mice on an IF regimen (db/db-IF). The experimental protocol included dietary monitoring, behavioral tests, and assessments of metabolic and gut parameters over 28 days.

Key findings include the following:

- Metabolic Improvements: IF significantly reduced fasting glucose levels by 54.8% and fasting insulin levels by 29.8% in diabetic mice, reflecting enhanced insulin sensitivity and reduced insulin resistance.
- Cognitive Benefits: The Morris water-maze test revealed decreased escape latency and increased time spent in the target quadrant among IF-treated diabetic mice, indicating improved spatial memory and cognitive function. Additionally, the elevated plus maze test showed reduced anxiety-like behavior and enhanced locomotor activity in the IF group.
- Gut Barrier Integrity: IF improved intestinal barrier function by increasing villi length, muscularis thickness, and the expression of tight junction protein claudin-1, which reduces gut permeability and prevents "leaky gut" syndrome.
- Microbiota Composition: While diabetes reduced the abundance of certain beneficial bacteria (e.g., *Allobaculum* and *Bifidobacterium*), IF increased the presence of *Lactobacillus* and butyrate-producing *Odoribacter*, while reducing harmful bacteria

such as *Enterococcus* and *Streptococcus*. These changes were linked to improved gut health and reduced inflammation.

Intermittent fasting exerts profound effects on the MGBA, influencing gut microbiota composition, intestinal barrier integrity, and systemic inflammation. These changes are associated with improved metabolic function, cognitive performance, and neuroprotection, particularly in conditions like diabetes-associated cognitive impairment. The flexibility and responsiveness of the gut microbiome to dietary timing underscore its critical role in mediating the health benefits of IF. Further research in human models is warranted to explore the therapeutic potential of IF in neurological and cognitive disorders

Caloric restriction

Caloric restriction (CR) and intermittent fasting (IF) represent distinct dietary strategies with differential impacts on physiology and cognition. CR typically involves a sustained reduction in daily caloric intake (approximately 20%) without inducing malnutrition [16]. In contrast, IF focuses on alternating periods of fasting and unrestricted eating without necessarily reducing overall caloric intake. Both strategies have been studied for their potential to improve lifespan, brain function, and behavior, though the underlying mechanisms and outcomes may differ [17, 18]

Effects of Caloric Restriction on Cognitive and Motor Function in Rats

The study by Singh et al., titled *"Late-onset intermittent fasting dietary restriction as a potential intervention to retard age-associated brain function impairments in male rats" [19]*,examined the effects of moderate CR on sensory, motor, and cognitive functions. The study utilized male albino rats aged 3 to 24 months, divided into two groups:

1. Dietary Restriction (DR): 21-month-old rats underwent an alternate-day fasting protocol (full-day fasting followed by ad libitum feeding) for three months.
2. Ad libitum (AL): 21-month-old rats that consumed food freely without fasting, serving as the control group.
3. Young Adult Rats**:** A positive control group consisting of 3-month-old rats.

Behavioral Assessments:

- Rotarod Test: Evaluated motor coordination and balance. DR rats displayed improved performance, with fewer falls and increased time spent on the rotating rod compared to AL rats, suggesting enhanced motor skills and adaptability.

- Morris Water Maze Test: Assessed spatial memory. DR rats demonstrated better escape latency, increased time spent in the target quadrant, and higher platform crossings compared to AL rats, indicating superior spatial memory and learning. AL rats exhibited greater deficits, especially when compared to young controls.

The findings suggest that moderate late-onset dietary restriction can delay age-related declines in motor coordination and cognitive function, supporting its potential as a neuroprotective intervention.

Contrasting Effects of Severe Food Deprivation

While moderate dietary restriction shows promising benefits, studies on severe food deprivation highlight potential drawbacks, particularly in humans. Severe caloric deficits are associated with negative physiological and psychological outcomes, including lethargy, irritability, depression, and cognitive impairments [19, 20]. Human participants in long-term food restriction studies have reported difficulties with concentration, memory, and reduced overall intellectual functioning. These observations underscore the importance of balance in dietary interventions to optimize benefits while minimizing adverse effects. Moderate dietary restriction, as demonstrated in animal studies, enhances motor and cognitive performance, potentially by promoting neuroplasticity and reducing age-related neural decline. However, the adverse effects of extreme caloric deprivation in humans caution against overly restrictive diets. These findings emphasize the need for tailored dietary strategies that consider individual metabolic and cognitive responses to achieve optimal outcomes for brain and body health.

Additive antidepressant-like effect of fasting

The effects of intermittent fasting (IF) on mood have been a focal point of research in recent years, with numerous studies highlighting its potential benefits [4]. Emerging evidence from animal models suggests that IF may exert a positive influence on mood, particularly in mitigating symptoms of anxiety and depression. In addition to its well-documented benefits on body composition, insulin sensitivity, and physical health, IF appears to improve behavioral markers associated with mental health. A study by Li et al. [21, 22] explored the antidepressant potential of acute 9-hour fasting in mice. This investigation assessed locomotor activity using the forced swimming test and measured levels of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) and its precursor (pre-CREB) in the brain. Mice underwent fasting for durations of 3, 9, and 18 hours, with comparisons drawn to a non-fasting

control group. Additionally, the study evaluated the interaction of fasting with imipramine, a tricyclic antidepressant, and DOI, a 5-HT2A/2C receptor agonist, to explore the potential involvement of 5-HT2 receptors. The findings revealed that 9-hour fasting significantly reduced immobility time in the forced swimming test compared to the control group, indicating an antidepressant-like effect. Fasting for 18 hours resulted in a slight reduction in locomotor activity but failed to alter immobility time, suggesting that prolonged fasting may be overly strenuous for the animals. Conversely, 3-hour fasting was insufficient to produce a measurable impact. Administration of imipramine during the 9-hour fasting period further reduced immobility time, demonstrating an additive effect. This additive antidepressant effect was partially reversed by DOI, suggesting the involvement of 5-HT2 receptors in mediating the observed behavioral changes. The study also examined the effects of fasting, imipramine, and DOI on the pre-CREB/CREB ratio in the brain. A 9-hour fasting period significantly increased the pre-CREB/CREB ratio, a mechanism associated with the action of many antidepressants. Co-administration of fasting and imipramine further amplified this effect, while DOI partially attenuated the increase, leading to a prominent decrease in the pre-CREB/CREB ratio compared to the fasting group alone. Importantly, no significant changes in the pre-CREB/CREB ratio were observed in the non-fasting control group. In conclusion, this study demonstrated that 9-hour fasting exerts an antidepressant-like effect, likely through mechanisms involving the modulation of 5-HT2 receptors and the enhancement of pre-CREB/CREB signaling. The combination of fasting with imipramine resulted in synergistic antidepressant effects, which were partially reversed by a 5-HT2 receptor agonist. These findings suggest that IF not only holds intrinsic antidepressant potential but may also potentiate the effects of traditional antidepressant therapies such as imipramine in animal models.

Ramadan IF

Ramadan intermittent fasting (RIF) is a central religious practice in Islam, observed by healthy Muslims who abstain from food and fluid intake from dawn to sunset for approximately 30 consecutive days. The fasting period typically lasts about 10 hours but can extend up to 18 hours depending on geographical and seasonal variations. While RIF has traditionally been associated with spiritual benefits, recent studies have revealed a complex interplay of positive and negative effects on mental health, coping mechanisms, and cognitive functions [23, 24]. One noteworthy study by Alabed et al. investigated the subjective impact of RIF on physical, mental, and social activities, as well as fatigue levels [25]. Using a structured questionnaire, they found that daytime fasting significantly decreased mental, physical, and social activity

levels compared to control conditions. These reductions were attributed to the metabolic and behavioral shifts inherent to Ramadan fasting, including altered sleep patterns, changes in eating habits, and modifications in physical activity. These changes collectively influence metabolism and may underlie the observed negative effects of RIF on certain cognitive functions. The metabolic and lifestyle disruptions caused by RIF appear to play a central role in its impact on mental health. Altered sleep patterns, particularly a reduction in total sleep duration and quality, are common during Ramadan due to late-night meals (suhoor) and early morning prayers (fajr). Changes in eating habits, such as the concentration of food intake during non-fasting hours, may also influence energy availability and neurocognitive processes. Reduced physical activity during fasting hours further compounds these effects, potentially contributing to fatigue and diminished cognitive performance. Despite these findings, the relationship between RIF and mental health remains nuanced. Some evidence suggests that the practice of Ramadan fasting may enhance resilience and promote positive coping strategies in certain individuals, potentially due to the spiritual and communal aspects of the observance. Further research is required to elucidate the conditions under which RIF may exert beneficial versus adverse effects on cognitive and psychological well-being

IV) CONCLUSIONS

In conclusion, dietary interventions such as intermittent fasting (IF) and caloric restriction (CR) significantly influence brain function, particularly in the context of aging. IF exerts direct metabolic effects on the brain by enhancing the production of brain-derived neurotrophic factor (BDNF), promoting autophagy, and improving mitochondrial respiration. Additionally, IF indirectly benefits brain health by modulating the gut microbiome, emphasizing the intricate relationship between diet and cognitive function through the microbiota-gut-brain axis. Animal model studies have provided compelling evidence of cognitive and behavioral benefits associated with IF, including improvements in cognition, motor skills, and spatial memory. However, the majority of these studies are short-term, highlighting the need for longitudinal research to better understand the long-term consequences and potential benefits of IF on brain health. Current research has also identified promising mechanisms by which IF influences brain function, such as the modulation of microbiome diversity and rhythmic fluctuations, which are associated with enhanced cognitive outcomes and overall brain health. Preclinical studies further suggest that IF may have a beneficial effect on mood, as demonstrated by its antidepressant-like properties in animal models. Mechanistic studies reveal that IF enhances the pre-CREB/CREB ratio, a pathway implicated in antidepressant activity, and can potentiate the

effects of pharmacological antidepressants. However, findings from human studies are more complex, with reports of long-term caloric restriction being associated with impaired cognitive performance, including reduced sustained attention. This underscores the variability in outcomes based on dietary patterns, individual differences, and study conditions. Despite the promising findings from animal research, there remains a critical need for detailed, unified, and longitudinal studies in humans to validate these benefits and better elucidate the mechanisms by which IF and CR influence cognitive function and mood. Such research will be essential to objectively determine the long-term implications of dietary interventions on brain health and to guide future therapeutic applications.

V) DATA

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