

Caloric Restriction and Intermittent Fasting: possible strategies for delaying brain aging in humans and animals

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ABSTRACT

Calorie restriction (CR) is the strategy that has demonstrated a significant impact on slowing the biological rate of aging and increasing both average and maximum longevity in a variety of animals. A diet plan known as intermittent fasting (IF) calls for eating habits that involve prolonged periods of low or no-calorie intake. The morphology, architecture, vasculature, and cognition of the brain are known to change as the organism ages. Oxidative stress plays a crucial role in the aging of the brain. The effects of oxidative stress include mitochondrial dysfunction, protein modification, membrane lipid peroxidation, nuclear DNA oxidation, and

mitochondrial and mitochondrial DNA oxidation. These effects hasten brain aging, neuronal loss, and cognitive impairment. Cognitive ability, long-term memory, and dementia are improved by CR and IF, which are beneficial for brain and neurodegenerative illnesses. The presented review article explores recent findings on how two dietary approaches, CR and IF, can support healthy aging and improve brain function. We will also explore how the most studied CR mimetics affect aging and how they might be used as treatments to promote neuroprotection.

Keywords Calorie Restriction, Intermittent fasting, aging, brain, oxidative stress

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INTRODUCTION

Aging is the gradual accumulation of changes induced by the ever-increasing risk of disease and mortality [1].

Since Harman's definition, an enormous amount of scientific attention has led to the broadening of the factors that contribute to aging. Genomic instability, telomere attrition, epigenetic changes, proteostasis loss, unregulated nutrient-sensing, mitochondrial failure, cellular senescence, stem cell fatigue, and altered intercellular communication are now recognized as hallmarks of aging [2].

Several anti-aging interventions have been extensively explored in the last few decades which have the potential to delay the onset of aging in different model organisms which are frequently used for aging research [3].

These possible strategies include calorie restriction (CR), hormonal therapies, antioxidant supplementation, autophagy induction, senolytic drugs, telomerase activation, epigenetic regulation, including drugs that modulate DNA methyltransferases, histone deacetylases, histone acetyltransferases, and noncoding miRNAs, as well as potential sirtuin activators [4].

Calorie restriction based on a calorie-restricted diet that maintains optimal nutrition is the only intervention that has shown a robust effect in reducing the biological rate of aging and extending both average and maximal longevity in several organisms. CR has been shown to slow the aging process and prolong the median and maximal lifespan in many models and species [5].

Long-term CR requires a significant amount of willpower, and the long-term adverse repercussions are unknown or less understood [6].

The CR paradox has led to the identification of substances that offer CR-like health and longevity effects without actually lowering calorie intake. CR mimetics (CRMs) are agents and/or interventions that allow people to get the biological benefits of CR without having to reduce their food intake [7].

Intermittent fasting (IF) is a dietary regimen that includes eating patterns in which subjects go for long periods (16–48 hours) with little or no-calorie intake, followed by periods of normal food intake [8].

This review explores how two dietary strategies, CR and IF, can promote healthy aging and enhance brain function by interfering with key metabolic and cellular signaling pathways.

CALORIE RESTRICTION

The discipline of caloric restriction (CR) involves lowering energy (food) intake without

going starving. It prolongs youth, reduces the onset of age-related illnesses, and prolongs the lifespan of animals from different phylogenetic groups. It has long been a popular concern in gerontology [9].

Although rodents were the subject of the initial studies of CR, a variety of other species—including fish, worms, spiders, flies, mice, and rats—have also been found to exhibit similar behaviours. The lack of appropriate data on the effects of CR in humans is a reflection of the challenges in conducting long-term caloric restriction studies, including methodological and ethical issues. In several regions of the world, naturally occurring CR episodes in human populations are widespread. It is crucial to keep in mind, though, that the majority of these populations are exposed to calorie-restricted diets that are low in protein and micronutrients [10].

Population studies can provide some useful information on the impacts of CR on malnutrition in people. The Danish people were compelled to restrict food consumption for two years during World War 1, yet with proper intake of whole-grain cereals, vegetables, and milk, the mortality rate was reduced by 34% [11].

Short stature, delayed reproductive maturity [12], reduced baseline gonadal steroid production in adults [13], suppressed ovarian function [14], decreased lactation performance [15], impaired fecundity [16], and impaired immunological function are frequently related with CR in these people. Such diet, however, was likewise of poor quality and resulted in several negative psychological repercussions.

Insulin–insulin-like growth factor-1 (IGF-1), Mammalian Target of Rapamycin (mTOR), ROS, AMP-activated protein kinase (AMPK), sirtuin activation (SIRT6), and p53 act as core stimulators of metabolic control, linking aging to the pathways that lead to neurodegenerative disorders [17].

The CR effect on lifespan is mediated by the nutrition-sensing signaling pathways (mTOR/insulin), which increase the activation of genes encoding protective and repair functions. This slows down aging and prolongs the period of survival [18].

There are four possible target pathways for CR; these pathways serve as a link between nutritional status and the longevity-promoting effect: IGF-1 signaling, suppression of mTOR, SIRT6, and AMPK (Fig 1). These are some of the key CR mechanisms, all of which govern cell proliferation, mitochondrial function, and autophagy directly or indirectly [4].

At certain ages, calorie restriction combined with consistent exercise can lead to healthy weight loss. Yet, CR can have several negative effects by affecting several mechanisms at

a young age. CR has a considerable preventative effect on the onset of age-related illnesses in middle and old age [19].

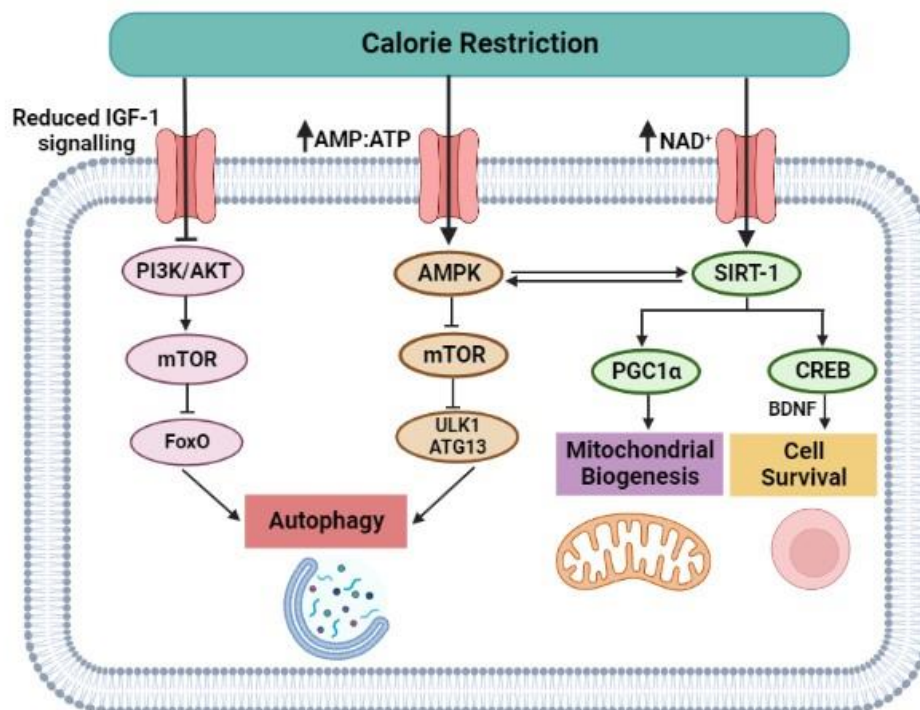


Figure 1. Molecular mechanism underlying the effects of Calorie Restriction. By activating the SIRT1 and AMPK pathways and suppressing the IGF-1 and mTOR signals, CR may lower the risk of developing neurodegenerative disorders and brain aging. SIRT1 activation brought on by CR may promote AMPK and inhibit mTOR activity. For sirtuin to have neuroprotective effects, other nutrition-sensitive proteins that are activated by CR, like AMPK and PGC-1 α , must also be involved. The CREB protein family can be activated by a variety of external and internal stimuli, including nutrition, hormones, and growth factors. This has a significant impact on the expression of BDNF, which mediates the survival, growth, differentiation, and plasticity of neurons.

INTERMITTENT FASTING

IF is a dietary strategy complementary to CR. A range of eating patterns that alternate between fasting and feeding times fall under this broad class. Across the world and in many different religious traditions, including Islam, Christianity, Judaism, and Hinduism, people observe the ancient custom of fasting in several distinct ways (20). Intermittent fasting (IF) is a dietary strategy in which eating time is restricted rather than the amount or composition of food consumed [21]. Elevated glucose, insulin, obesity-related illnesses, and neurodegenerative and cardiovascular disorders are the main aging-related factors whose effects can be reduced in humans by fasting; rodents also exhibit comparable alterations [22].

Alternate-day fasting (ADF) and time-restricted eating (TRF) are two types of IF diets. The key differences between them are the varied times spent fasting and spent without restriction [23]. ADF implies feeding on one day and fasting

the next day which maintains an alternate pattern of feeding and fasting observed in repeated cycles, whereas the TRF mechanism allows feeding within a limited duration in a day of relatively 8-12 hours and total abstinence from food for the rest of the day.

Frequent fasting can have positive physiological effects on the body, including decreased inflammation, enhanced circadian rhythmicity, improved autophagy, and stress resistance, and altered gut flora [24].

During fasting, some energy biosensors sense the energy-depleted state and thereby, switch on and off the bioenergetics sensors which help maintain health during this state. The AMPK (AMP-activated protein kinase) is activated during fasting which maintains the energy status of the cell. Activation of AMPK turns off mTOR (Mammalian Target of Rapamycin) therefore, autophagy is promoted during fasting, a crucial factor regulating several beneficial effects of fasting. The Sirtuins maintain overall stress resistance and mitochondrial

biogenesis during fasting [25].

However, it has been observed that as time-restricted feeding is dependent on the circadian cycle, any disruption in the timing of food intake disturbs the circadian rhythm of the organism which may become a cause of impairment in metabolic health like increased oxidative stress, and deregulation of hormonal levels and insulin sensitivity [26].

In individuals on antidiabetic drugs that can cause hypoglycemia, the most apparent concern of intermittent fasting is the potential occurrence of hypoglycemia [27,28]. If patients are not aware of maintaining an appropriate protein diet on eating days when on long-term IF, protein deficiency needs to be an issue. Malnutrition of vitamins and minerals can also happen [28].

EFFECT OF CR AND IF ON BRAIN AGING

Up to 40% of neurological illnesses could be prevented or delayed by altering lifestyle habits. It has been demonstrated that various dietary intervention techniques can alter the IGF-1, AMPK, and mTOR nutrient-sensing systems in cells, which increase longevity and protect against aging-related disorders in both humans and animals [29].

The aging brain experiences a wide range of changes. Several studies contend that the hippocampus is the area of the brain that ages the most, even though the prefrontal cortex and striatum show the most alterations [30]. The temporal cortex, thalamus, accumbens, and putamen are the other areas that change with age. The occipital cortex is the area that is least influenced [31,32].

The loss of brain function that comes with aging is caused by many factors. A significant factor in the aging brain is oxidative stress [33]. Redox control and the equilibrium of reactive oxygen and nitrogen species (ROS and RNS) are essential for preserving healthy brain homeostasis. Along with the immune system and inflammation, they can also influence synaptic plasticity, learning, and memory [34].

Oxidative stress causes mitochondrial malfunction, protein modification, membrane lipid peroxidation, nuclear DNA, and mitochondrial DNA oxidation, which accelerate brain aging, neuronal loss, and cognitive impairment [35].

In the central nervous system, neurogenesis is essential for neural plasticity, brain homeostasis, and maintenance. It also plays a significant role in sustaining cognitive function and repairing damaged brain cells brought on by aging and brain trauma. Adult neurogenesis can be negatively impacted by lifestyle factors like high-fat and high-sugar diets, alcoholism, and opioid addiction in addition to internal factors like aging,

neuro-inflammation, and traumatic brain injury [36].

It has been observed that long-term energy restriction improves verbal memory, recognition memory, and working memory [37]. Increased grey matter volume in the inferior frontal gyrus and hippocampus, as well as improved resting-state functional connections from the hippocampus to parietal areas, have been linked to improved recognition memory [38].

In particular, CR was observed to up-regulate glutamatergic synaptic currents and down-regulate GABAergic inhibition in the neocortical pyramidal neurons, which can both be signs of age-related changes in synaptic transmission. Old wild-type mice's neocortical neurons' long-term synaptic plasticity was therefore rescued by CR [39]. Additionally, by minimizing neuroinflammation, CR stimulates the gene Foxo3, improving adult neurogenesis [40,41].

In older mice, CR of 40% maintains long-term memory, energy production, and white matter integrity [42]. Calorie restriction affects human memory and learning capacity as well. Dementia has been proven to be controlled by CR in elderly people [43]. According to several findings, CR boosts memory in healthy, older (average age: 60.5 years), and overweight to normal-weight adults [44]. The association between CR and transcriptional reprogramming in the brain was discovered through DNA microarray analysis of mouse brain tissue. Genes associated with stress and immunological responses were not induced when CR was present [45].

The outcomes are consistent with research that suggests CR mice's brains had less oxidative stress and autoimmune [46].

Although the precise mechanism of CR is not fully understood, evidence suggests that it enhances mitochondrial function, activates the anti-inflammatory response, and stimulates neurogenesis and synaptic plasticity to slow down the aging process of the brain [30].

Several animal models for human disorders, obtained either through experimental or genetic manipulation, have been used to explore the potential therapeutic effects of dietary restriction on degenerative diseases. Animals previously treated to dietary restriction through intermittent fasting showed a reduction in both the loss of nigro-striatal dopaminergic neurons and the motor impairments in a rat model of Parkinson's disease, i.e. mice injected with the dopaminergic toxin MPTP [47].

Regarding animal models of Alzheimer's disease, long-term dietary restriction significantly lowered the risk of the condition in transgenic mice expressing human-mutated forms of the β -amyloid precursor protein, which causes the progressive development of amyloid plaques in the cortex and hippocampus [48,49].

Following 24-36 hours of fasting, when the blood glucose is lowered to the level that it cannot provide sufficient energy to the brain, the body enters a state of ketosis where ketone bodies are produced to serve as the fuel source for the brain. Beta-hydroxybutyrate (BHB) serves as the main source of ketone for the brain during periods of prolonged fasting. This intermittent metabolic switch from glucose to ketones confers fasting-induced protection by transcription of Brain-derived neurotrophic factors (BDNF) which induces several beneficial effects on the brain. BDNF signaling stimulates mitochondrial biogenesis and synaptic plasticity protects degenerating neurons and provides resistance to stress, injury, and disease [50].

Glucose is essential to fulfilling the energy requirement of the brain even when the brain derives energy from ketone bodies. Glucose consumption by the brain helps maintain antioxidant status through the production of reduced glutathione [51]. This helps in reducing the oxidative stress in the brain of rats during aging.

ADF in rats has shown increased expression of BDNF, heat-shock protein 70, FGF2, glucose-regulated protein (GRP 78), and hemeoxygenase in the cortex and striatum [52]. These proteins protect the neurons against degeneration and dysfunction. These proteins activate several different signaling pathways that play important role in conferring stress resistance and neuronal plasticity. IF also reduces levels of pro-inflammatory cytokines IL-6, TNF- α , and IL-1 β . IF promotes synapse formation and the generation of new neurons, a process termed neurogenesis [50].

Mitochondrial dysfunction has been identified as an early sign of neurodegeneration and aging in the brain [34,53]. The physiological and molecular mechanisms of IF in brain aging and neurodegeneration include the activation of adaptive cellular stress responses as well as signaling and transcriptional pathways, which improve mitochondrial function by boosting energy metabolism and lowering oxidant production (Fig 2) [54].

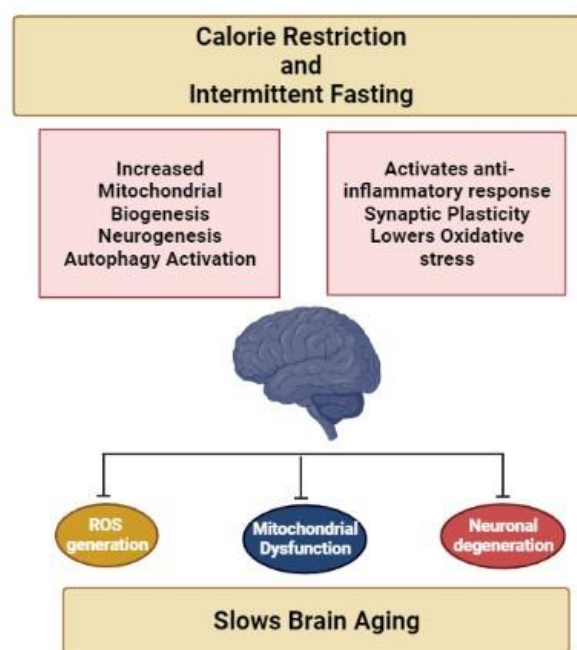


Figure 2 Effect of dietary restriction interventions on brain aging. CR and IF stimulate mitochondrial biogenesis which protects against neuronal degeneration and induces neurogenesis and stress resistance.

The transcription factor peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α) is also expressed as a result of fasting. PGC1 α is thought to be the major accelerator for mitochondrial biogenesis, which enhances neuron bioenergetics and promotes synaptic plasticity [55].

In animal models of neurological trauma like stroke as well as neurodegenerative illnesses

like Parkinson's disease and Huntington's disease, IF regimens have been shown to alleviate and reduce neuronal damage and enhance functional outcomes. Although the exact method by which IF exerts its neuroprotective effects is unknown, it has been noted that IF stimulates the synthesis of brain-derived neurotrophic factor (BDNF), which in rats and mice is linked to an increase in hippocampus

neurogenesis [56].

The ketogenic diet (KD), is a very high-fat, low-carbohydrate diet that induces ketosis in the body by having a fasting-like effect. KD has positive impacts on improving cellular metabolism and mitochondrial activity. In older persons with Alzheimer's disease, it is linked to better cognitive function [57].

Many studies in animal models have shown that reducing food intake leads to longer longevity [58]. Reduced age-related methylation changes in the brain, greater adult neurogenesis, improved cognitive performance, and protection against age-related neurodegenerative illnesses like dementia are some of the additional positive outcomes [59]. IF improves neurons' resistance to dysfunction and deterioration in neurological illnesses such as Huntington's disease, Alzheimer's disease, Parkinson's disease, and neuroinflammation [43].

Alzheimer's disease is caused due to the accumulation of beta-amyloid plaques that show a decline in cognitive abilities. IF is known to reduce neuronal death and cognitive decline by activating the stress resistance pathways in the brain and by suppressing inflammation by inhibiting the mTOR pathway. Parkinson's disease is characterized by motor control problems due to the loss of dopaminergic neurons. However, fasting-mimicking diets (FMD) introduced in PD mouse models showed an increase in BDNF levels. Therefore, FMD confers neuroprotection in PD mouse models due to BDNF which reduces the loss of dopamine from neurons and regulates motor control problems [60].

Bidirectional interactions between the central nervous system, the enteric nervous system, and the gastrointestinal tract (the so-called "gut-brain axis") connect the brain and the gut. Microbiota homeostasis is required for the regulation of cognitive functions such as blood-brain barrier permeability, brain energy homeostasis, brain development, and ultimately behavior [61].

CALORIE RESTRICTION MIMETICS IN BRAIN AGING

Even though CR extends human life, enforcing long-term CR in humans is challenging. As a result, developing a method or chemical that reproduces the effect of CR without reducing the amount of food consumed is preferred [62]. The putative CRM under investigation works on the same signaling cascades as CR, including the insulin pathway, AMPK activation, autophagy stimulus, alpha-lipoic acid, and other antioxidants [36]. The following categories are included in the classification of CRMs: Glycolytic inhibitors: (2-Deoxy-d-glucose, 3-bromopyruvate, d-allulose, d-

glucosamine, mannoheptulose, astragaloside, chrysin, genistein, etc), Polyamines (Putrescine, spermidine, spermine, etc), and Polyphenols (Curcumin, quercetin, resveratrol, gallic acid, etc., others include hydroxycitric acid, salicylic acid, NAD⁺ precursors, etc.) [9].

The anti-diabetic medication metformin (dimethyl biguanide hydrochloride), a well-studied CR-mimetic, has been shown to improve spatial and recognition memory in elderly animals and to control gene expression in reactive astrocytes in the mouse model of Parkinson's disease (39). Metformin has been shown to have several metabolism-related anti-aging effects in both animal models and human patients, most commonly in the scenario of age-associated neurodegenerative disorders where diabetes is a complicating factor [63,64].

In the rat brain, fisetin may have offered neuroprotection against oxidative stress, apoptotic cell death, neuro-inflammation, and neurodegeneration brought on by aging. As a result, the use of fisetin as a possible CRM may be taken into consideration as a therapeutic candidate for the treatment of neurological illnesses associated with aging [65].

In recent decades, there has been a lot of research and reporting on the neuroprotective potential of natural polyphenols. Resveratrol has been one of the most researched polyphenols for its neuroprotective properties [66,67]. In rats with angiotensin II (Ang-II)-induced early Alzheimer's disease, Lin et al. investigated the link between resveratrol administration, reduced reactive oxygen species (ROS), and cognitive impairment [68].

Resveratrol medication over a prolonged period greatly enhances cognitive function in elderly people. The hippocampus's functional connectivity increased in the resveratrol-treated group, which may indicate that the hippocampus's integrity and functionality have improved. The memory improvement was connected with this increase in functional connectivity in the hippocampus's resting state. Resveratrol appears to boost glucose metabolism as seen by a reduction in glycated hemoglobinA1c (HbA1c), a measure of glucose management. The researchers hypothesized that resveratrol might, by this route, have protective effects on neuronal activity and, subsequently, on cognition, as the hippocampus is considered to be susceptible to perturbations in glucose supply [38].

Rapamycin is another CRM whose ability to protect neurons has garnered much attention. In a mouse model of early-stage Alzheimer's disease - type tau pathology, systemic rapamycin treatment protected against tau-induced neuronal loss, synaptotoxicity, reactive microgliosis, and astrogliosis, indicating that rapamycin has a positive effect on tau, the hallmark of Alzheimer's disease (AD) [69].

CONCLUSION FOR FUTURE PERSPECTIVE

The study and knowledge of aging biology have led to the discovery of pharmaceutical and nutritional therapies that slow the aging process and prevent a variety of age-related diseases. As a result, it is possible that therapeutic approaches that slow down the aging process could be employed to cure and prevent dementia and brain aging. The current review attempts to condense the most pertinent information from studies that aim to illustrate and characterize the positive effects of long-term calorie restriction on brain aging and age-related neurodegenerative disorders.

However, it is unclear whether a CR mimetic would be a practical medicine to develop, especially given that our understanding of the processes by which CR exerts its protective benefits is still inadequate, and the underlying principles are proving to be extremely complex. In this review, we drew particular attention to a few CRMs that may slow down brain aging and possess neuroprotective effects. CRM offers intriguing possibilities for cutting-edge preventive and therapeutic measures. Before they can be incorporated into our way of life to delay aging and prevent or decrease the progression of age-related disorders, there is still a long way to go. It is also important to consider the psychological effects of food consumption in higher, more introspective species like humans. Future studies must be driven to find clinically significant improvements in metabolic health rather than only concentrating on body weight. The study populations should be expanded to include younger and older people and those with other conditions as several previous studies have focused on obese but otherwise healthy individuals.

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Conflicts of interest

The authors have no conflict of interest.

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