Review

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A circadian rhythm-restricted diet regulates autophagy to improve cognitive function and prolong lifespan

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SUMMARY Diet and circadian rhythms have been found to have a profound impact on health, disease, and aging. Skipping breakfast, eating late, and overeating have adverse effects on the body's metabolism and increase the risk of cardiovascular and metabolic diseases. Disturbance of circadian rhythms has been associated with increased risk of atherosclerosis, Alzheimer's disease, Parkinson's disease, and other diseases. Abnormal deposition of amyloid β (Aβ) and tau proteins in the brain and impaired synaptic function are linked to cognitive dysfunction. A restrictive diet following the circadian rhythm can affect the metabolism of lipids, glucose, and amino acids such as branched chain amino acids and cysteine. These metabolic changes contribute to autophagy through molecular mechanisms such as adenosine monophosphate-activated protein kinase (AMPK), rapamycin (mTOR), D-β-hydroxybutyrate (D-BHB), and neuropeptide Y (NPY). Autophagy, in turn, promotes the removal of abnormally deposited proteins and damaged organelles and improves cognitive function, ultimately prolonging lifespan. In addition, a diet restricted to the circadian rhythm induces increased expression of brain-derived neurotrophic factor (BDNF) in the forebrain region, regulating autophagy and increasing synaptic plasticity, thus enhancing cognitive function. Consequently, circadian rhythm-restricted diets could serve as a promising non-pharmacological treatment for preventing and improving cognitive dysfunction and prolonging lifespan.

Keywords biological clock, intermittent fasting, metabolism, quality control, protein aggregation, sleep

1. Introduction

Cognitive impairment is a syndrome. Studies show that mild cognitive impairment affects 3–19% of adults over 65, and its prevalence increases with age. More than half of patients progress to dementia within five years (*1,2*). Reduced synaptic function, extracellular aggregation of amyloid β (Aβ), and intracellular tau protein aggregation are closely associated with cognitive impairment (*1,2*). Patients with cognitive dysfunction experience a gradual decline in memory, disorientation, and an inability to lead a regular life (*3*). While there are no specific medications available, most current clinical treatments serve to delay cognitive decline (*3*). Dietary habits strongly correlate with metabolic diseases, immunity, cognitive performance (attention, memory, executive function, *etc.*), and longevity (*4-6*). Disturbance of eating habits is a leading factor in endangering human health. Overeating increases the risk of obesity and metabolic diseases, while long-term restrictive diets can cause malnutrition and compromise the organism's immune system (*6-9*). Maintaining a balance in one's eating habits is essential to ensuring optimal health. Moreover, a rational and healthy diet decreases the risk of death from cardiovascular and cerebrovascular diseases, tumors, neurodegenerative diseases, respiratory diseases, and all-cause mortality (*10*). An intermittent restrictive diet is a cost-effective and widely applicable non-pharmacological therapy. This approach can help develop new healthy eating habits. The literature suggests that an intermittent restrictive diet regimen improves 24-hour glucose levels, modifies lipid metabolism and circadian gene expression, up-regulates autophagy, and has anti-aging action (*11*).

During a restricted diet, autophagy is stimulated by changes in the metabolism of glucose, amino acids, and fatty acids (*12-15*). Autophagy generates new energy sources through lysosomal degradation that contribute to the replenishment and maintenance of the organism and protection against external stressors (*16-19*). By eliminating abnormally accumulating proteins (such as Aβ and tau proteins) and damaged organelles, autophagy can positively influence health, cognitive

function, and disease recovery (*20-23*). The circadian rhythm is a natural phenomenon that regulates the process of autophagy in organisms when subjected to restrictive diets. Research has shown that following circadian rhythms with intermittent fasting can increase the expression of autophagy-related 1 (*ATG1*) and autophagy-related 8a (*ATG8a*), promote autophagy, and ultimately prolong lifespan, whereas disregarding circadian rhythms can negate these benefits (*22*). Implementing restrictive diets according to circadian rhythms can optimize health and increase longevity (*24*). The current work reviews the potential mechanisms by which a diet restricted to the circadian rhythm may affect autophagy and improve cognitive function. The mechanisms involved are outlined in Figure 1.

2. A circadian rhythm-restricted diet

A circadian rhythm-restricted diet is defined as: restriction of food intake to a period of 4–12 hours from the beginning of breakfast to the end of the last meal of the day; fasting for more than 12 hours, with the fasting period coinciding with the circadian rhythm (*24-27*) (Figure 2). An article in Science by Francesco *et al.* classified fasting into four categories: caloric restriction, which entails consuming less than 15–40% of the usual daily intake; time-restricted feeding, in which food intake is limited to a specific 4–12 hour period; intermittent and periodic fasting, in which food intake is periodically reduced; and fasting-mimicking diets (FMD) (*25*). Current research on fasting has mainly focused on different forms of time-limited, intermittent, and periodic fasting, such as alternate-day fasting and the 5:2 diet (*28,29*). These types of fasting have been shown to provide significant health benefits by restricting either caloric intake or the timing of meals, which can enhance repair mechanisms and optimize cellular and organismal health. However, an important point worth noting is that skipping breakfast, having a late dinner, and fasting out of sync with the circadian rhythm can negatively impact the body to varying degrees. Breakfast is often considered the most important meal of the day (*30,31*). Studies suggest that consuming breakfast enhances cognitive abilities and academic performance in school-age children (*31,32*). However, skipping breakfast may increase the risk of atherosclerosis, cardiovascular disease, and mortality (*27,33*). Research also indicates that eating late at night increases the likelihood of obesity by inducing hunger and disrupting crucial pathways linked to lipid metabolism, such as p38 mitogen-activated protein kinase (MAPK) signaling, transforming growth factor-β (TGF-β) signaling, regulation of receptor tyrosine kinases, and autophagy. Consequently, this leads to lower lipolysis and elevated lipogenesis (*34*).

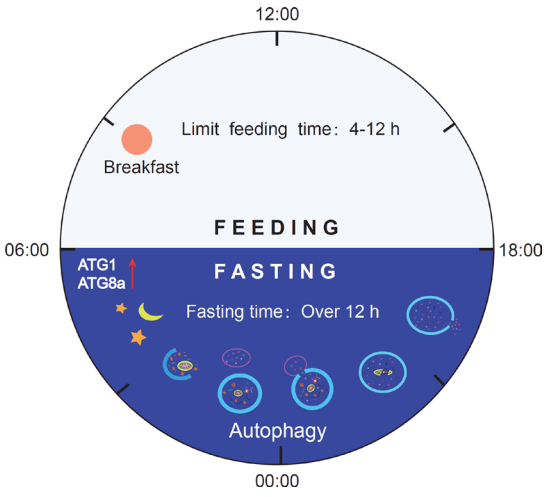

Figure 1. Diagram of a circadian rhythm-restricted dietary intervention. FEEDING: Breakfast within 2 hours of waking up; the day's dietary intake is completed within 4–12 hours after breakfast; FASTING: Fasting time > 12 hours, feeding and fasting with changes in one's circadian rhythm, and ensuring sleep at night to promote enhanced autophagy gene expression.

Circadian rhythms are an evolutionarily conserved timing system that coordinate behavioral control, hormonal fluctuations, physiological homeostasis, metabolism, and energy metabolism across the entire organism. This system includes sleep-wake cycles, feeding-fasting cycles, and activity-rest cycles. Long-term irregular circadian rhythms can lead to organismal dysfunction, resulting in an increased risk of developing many diseases (*35-37*). A clinical report examining the health effects of Ramadan fasting in Saudi Arabia indicated that evening hypercortisolism is associated with fasting during Ramadan and that disturbances to circadian rhythms result in reductions in liver enzymes, total bilirubin, total protein, and albumin as well as altered adipokine patterns, thereby increasing cardiometabolic risk (*38*). A clinical trial on a rhythmic time-restricted eating intervention in patients suffering from metabolic syndrome confirmed that limiting daily eating to 10 hours decreases body weight, blood pressure, and atherogenic lipid levels (*39*). In conclusion, a circadian rhythm of eating and fasting benefits an organism's health by inducing a "fasting physiology" during the fasting period. This process promotes repair, improved metabolism, and rejuvenation, consequently increasing resilience to the effects of undesirable factors. Conversely, an irregular eating pattern appears to be harmful to achieving a healthy metabolism (*24,40*).

3. Autophagy and a circadian rhythm-restricted diet

As a degradative system, autophagy is a crucial protective process of the cell that transports substances from the cytoplasm into lysosomes for degradation. It produces new building blocks and energy for cell renewal and homeostasis (*21*). There are three primary forms of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy

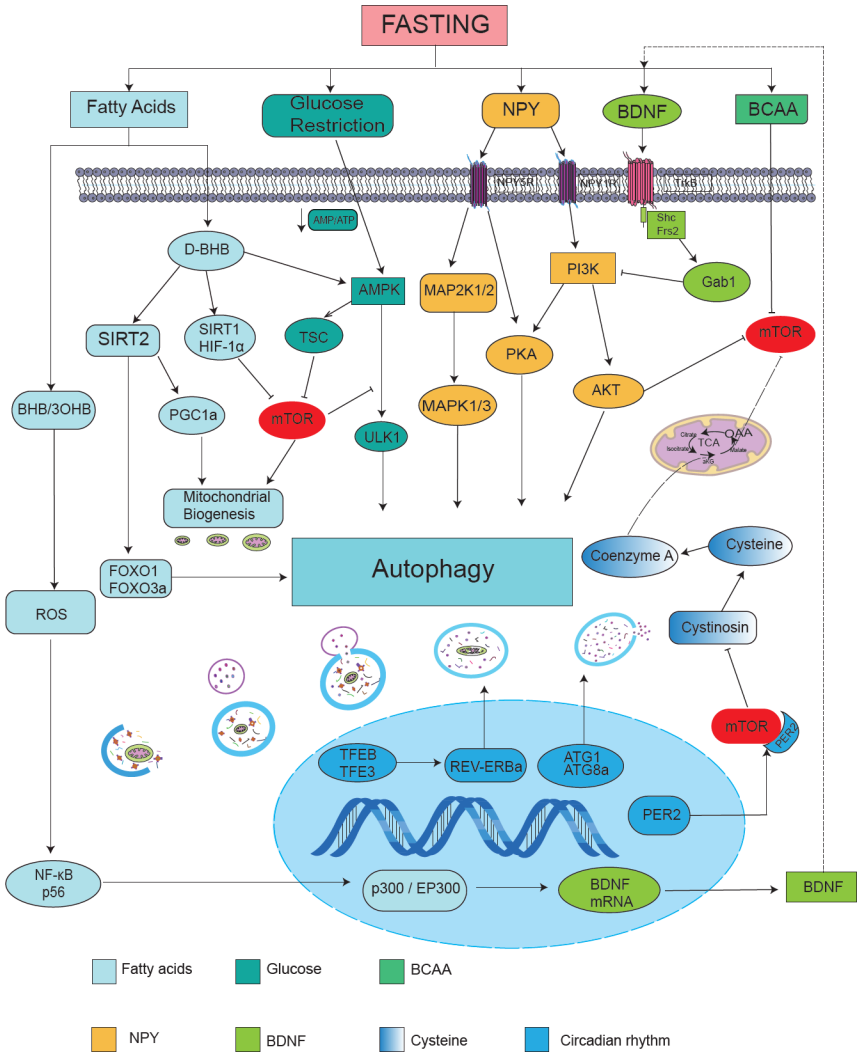

Figure 2. Diagram of the mechanistic role of fasting-mediated autophagy. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BHB/3OHB, β-hydroxybutyrate; FOXO3a, forkhead box O3; Gab1, Grb2-associated binder 1; HIF-1α, hypoxia-inducible factor-1α; MAPK, mitogen-activated protein kinase; NF-κB, Nuclear factor-κB; NPY, Neuropeptide Y; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1α; PI3K, Phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SIRT, sirtuin; mTOR, rapamycin; TCA, tricarboxylic acid cycle; TFs, transcription factors; TRKB, tropomyosin receptor kinase B ; TSC, tuberous sclerosis complex ; ULK1, uncoordinated 51-like kinase 1.

involves the formation of an autophagosome, which isolates a segment of cytoplasm and fuses with the lysosome for subsequent degradation of its contents. Microautophagy involves direct phagocytosis of a small portion of cytoplasm by the lysosome. Chaperone-mediated autophagy (CMA) is a degradation process where substrate proteins containing KFERQ-like pentapeptide sequences are recognized by heat shock cognate protein 70 (Hsc70) and auxiliary chaperone proteins in the cytoplasm. The proteins are then transported and bound to lysosomal lysosome-associated membrane protein-2 isoform A (Lamp-2A), translocated into the lysosomal lumen, and finally degraded (*21,41*). CMA degrades damaged or oxidized proteins during starvation to provide amino acids and aid in maintaining cellular quality control (*41*). Most current studies have focused on macroautophagy. Research has shown that during periods of starvation, the organism rapidly and vigorously induces the autophagy process in multiple tissues, leading to the degradation of its own components and providing new energy to sustain survival (*42-44*). Autophagy plays a critical role in intracellular quality control, including that of mitochondria and the endoplasmic reticulum, as well as in maintaining cellular homeostasis by degrading select proteins, organelles, and bacteria (*21,45*). A circadian rhythm-restricted diet can contribute to the induction of autophagy, thereby alleviating cognitive deficits by regulating organelle quality and degrading abnormally deposited proteins.

Mounting evidence suggests that autophagy is influenced by circadian rhythms. Transcription factor EB (TFEB) and transcription factor E3 (TFE3) serve as significant transcriptional regulators of lysosomal biogenesis and autophagy. Both TFEB and TFE3 experience circadian stimulation throughout the day.

During times of nutrient deprivation (in the light phase), these proteins translocate to the nucleus and bind to promoters at the E-Boxes/CLEAR locus, thus regulating the expression of autophagy-related genes (*46*). As a central inhibitory component of the cellular autonomic clock, Rev-erbα is also involved in regulating autophagy *via* its inhibitory action. Research has revealed that the dynamic balance between TFEB/TFE3 and REV-ERBα is responsible for regulating autophagy (*46-48*). The autophagy-related genes *ATG1* and *ATG8a* are regulated by circadian rhythms, and their expression increases at night during fasting. This increases the level of autophagic activity and can prolong lifespan. Knockdown of the genes *ATG1* and *ATG8a* counteracts this benefit of a prolonged lifespan (*22,49*). Research has demonstrated that the core clock protein, period 2, can suppress rapamycin (mTOR) complex activity through tuberous sclerosis complex 1 (Tsc1), which ultimately leads to the stimulation of autophagy (*50*). CMA interacts with the biological clock, facilitating the controlled degradation of clock mechanism proteins (selective temporal phagocytosis) and circadian reshaping of portions of the cellular proteome. However, the absence of a circadian clock eliminates the rhythmicity of CMA, resulting in notable alterations in the proteomes of CMA-dependent cells (*51*). In summary, autophagy is closely related to restrictive diets and circadian rhythms. Under a restrictive diet, starvation induces cell autophagy to promote the degradation of its own components and provide new energy. In addition, circadian rhythms regulate the expression of autophagy-related genes to control autophagy rhythms, as shown in Figure 1.

4. Mechanisms of autophagy activated by a circadian rhythm-restricted diet

Targeting autophagy could be an effective intervention for improving cognition, slowing aging, and extending lifespan (*52-54*). According to one study, a restricted diet induces astrocyte autophagy, reducing amyloid buildup and memory deficits in mice with Alzheimer's disease (AD) (*53*). A limited diet can affect the metabolism of lipids, glucose, and amino acids (including branched-chain amino acids (BCAAs) and cysteine) and facilitate autophagy through molecular mechanisms such as adenosine monophosphate-activated protein kinase (AMPK), D-β-hydroxybutyrate (D-BHB), mTOR, and neuropeptide Y (NPY). These mechanisms function to eliminate abnormally accumulating proteins and damaged organelles, resulting in enhanced cognitive performance. However, a restricted diet results in augmented brain-derived neurotrophic factor (BDNF) expression in the forebrain area and hinders autophagy by impacting the PI3K/AKT pathway. As a consequence, this results in enhanced synaptic plasticity and improved cognitive functionality.

4.1. AMPK / mTOR

During a restricted diet, autophagy is activated by AMPK and inhibited mTOR activity, leading to the degradation of misfolded proteins and damaged cellular organelles, which in turn reduces cognitive dysfunction. AMPK serves as an objective sensor of cellular energy levels and is activated by a decrease in the AMP:ATP ratio in response to energy depletion. The activated AMPK in turn activates the uncoordinated 51-like kinase 1 (ULK1) complex, initiating autophagy as well as phagocytosis of damaged organelles and protein degradation *via* lysosomal fusions (*55,56*). mTOR serves as a regulator of cell growth by integrating signals from growth factors and nutrients. It can detect and integrate various signals, including amino acids, glucose, growth factors, and energy, while participating in the regulation of cellular metabolism, mitochondrial function, and cellular growth through the autophagy pathway (*57*). Studies have indicated that during glucose starvation, AMPK activates UIK1 by phosphorylating Ser317 and Ser777 to encourage autophagy. In addition, AMPK inhibits the mTOR complex by phosphorylating tuberous sclerosis complex 2 (TSC2) and Raptor. In nutrient-limited settings, mTOR complex activity is curtailed, resulting in decreased translation, a reduced growth rate, and enhanced autophagy. However, minimal mTOR complex activity is critical to encouraging lysosomal biogenesis, which is necessary to sustain autophagic degradation required for survival. Dietary restrictions might impede mTOR complex activity and boost autophagy, which sustains basic survival by recycling nutrients from organelles and cytoplasm to provide internal nutrient storage (*58*). Fasting has been shown to boost AMPK activity in agouti-related peptide (AgRP) neurons, inducing spinogenesis and synaptic plasticity and ultimately enhancing cognitive performance (*59*). A study on AD found that downregulation of the mTOR signaling pathway can activate autophagy. Autophagy degrades misfolded proteins and damaged cell organelles, which inhibits the progression of AD and ameliorates cognitive dysfunction (*60*). AMPK and mTOR complex function as controllers of energy and nutrition. Their interaction regulates autophagy, which contributes to enhanced cognitive function (Figure 1).

4.2. Ketone bodies

Ketone bodies can increase autophagy, facilitate the expression of BNDF, increase neuronal synaptogenesis, and enhance cognitive brain function while serving as an alternative source of energy. They act as a crucial metabolic fuel option and primary energy source for many tissues, including the brain, during restricted energy intake. They participate in cellular metabolism, homeostasis, and signaling in various physiological and pathological conditions (*13,61*). When the diet is

restricted, the liver transforms fatty acids into ketone bodies. The brain mitochondria then metabolize these ketone bodies into acetyl-CoA, an energy source that supplants glucose (*61*). Studies have revealed that D-BHB, a ketone body, stimulates autophagy by increasing FOXO1 and FOXO3a expression through SIRT2. In addition, it promotes mitochondrial biogenesis through PGC-1α (*62*). Moreover, research suggests that D-BHB activates the autophagy-lysosome pathway by activating AMPK and TFEB-mediated lysosomal biogenesis (*62*). Ketone bodies have displayed the potential to activate SIRT1 and HIF-1α, hence inhibiting the mTOR complex and leading to the promotion of autophagy in brain neurons. This process facilitates the breakdown of damaged mitochondria and protein aggregates, playing an important role in the improvement of cognitive function (*63-65*). Moreover, 3-hydroxybutyrate (3OHB), a ketone body, actively stimulates the production of reactive oxygen species. This process further activates the transcription factor NF-κB and the histone acetyltransferase p300/EP300, leading to an induced expression of the BNDF gene. This process promotes neurogenesis, synapse growth, and synaptogenesis (*66*). When energy intake is restricted, fatty acids are transformed into ketone bodies, which stimulates brain-derived neurotrophic factor expression and induces autophagy. This is beneficial to brain health by improving cortical neuron function, helping to restore brain function, and helping to alleviate cognitive dysfunction and neurodegenerative diseases (*56*,*67-70*).

4.3. Cysteine

When the diet is restricted, cysteine intake is restricted. Hence, the body undergoes autophagic degradation of lysosomes to release cysteine. This results in heightened cysteine levels, assists in acetyl-CoA metabolism, and constrains the activation of mTOR. Consequently, autophagy is sustained and the life of the organism is prolonged. Cysteine plays a crucial role in regulating hypoxia-inducible factor (HIF), promoting neurogenesis and tRNA thiolation, and providing anti-inflammatory and antioxidant benefits (*71-73*). Research has revealed that taking supplements of cysteine or its modified molecules can help buffer cellular oxidative stress and inhibit inflammatory reactions (*74*). In contrast to many amino acids that promote protein synthesis by increasing mTOR complex activity, cysteine can actually inhibit mTOR complex activity, which can delay the aging process (*14,75*). During starvation, the autophagy mechanism releases cystine in the cell lysosomes, which then increases cytosolic cysteine levels, ultimately inhibiting the activation of mTOR complex signaling and continuously inducing autophagy (*76,77*). If, however, long-term fasting surpasses the threshold for mTOR complex activation, it may harm the body's metabolic balance and pose a risk to health (*76*). A study found that restricting sulfur-containing amino acids in the diet, like cysteine, may boost the expression of cystathionine γ-lyase (CGL) in the transsulfuration pathway (TSP). This can lead to the production of hydrogen sulfide in the body, which provides protection against ischemia/reperfusion injury (IRI) and extends an animal's lifespan (*78*).

4.4. BCAAs

The physiological and molecular mechanisms through which BCAAs maintain metabolic balance are intricate. Studies have shown that restricting the consumption of BCAAs during a restricted dietary reduces mTORC1 activity *in vivo*, leading to improved cognition, a prolonged lifespan, and other benefits attributed to the promotion of autophagy (*57,79,80*). BCAAs are leucine, isoleucine, and valine, which are essential amino acids and the most prevalent amino acids in protein. They have been linked to cognitive decline, aging, frailty, obesity, and diabetes (*81,82*). Studies have shown that BCAAs suppress hepatic autophagy induced by lipids, boost hepatocyte apoptosis, prevent hepatic FFA/triglyceride conversion, and worsen hepatic lipotoxicity by activating the mTOR pathway in hepatocytes (*83*). Prolonged exposure to a diet high in BCAAs could result in hyperphagia, obesity, and a shorter lifespan (*84*). Notably, astrocytic biotinylation and increased BCAAs accumulate in the aging cerebral cortex, which may be related to the inhibition of autophagy and overactivation of the mTOR complex (*85*). However, restricting BCAAs intake has been shown to promote metabolism, delay aging, and prevent disease (*86*). Moreover, Weaver *et al.* suggested that limiting consumption of BCAAs, and particularly isoleucine, may induce starvation and result in a prolonged lifespan by influencing histone acetylation in the brain (*87*). To sum up, restricting BCAAs as part of a diet promotes autophagy, enhances cognition, and delays aging by regulating mTOR.

4.5. NPY

NPY plays a crucial role in maintaining bodily homeostasis. The increased release of NPY during a restricted diet promotes autophagy in hypothalamic neurons, resulting in improved memory and delayed aging by protecting synapses. NPY is a potent biologically active peptide primarily produced by the hypothalamus, and it is involved in diverse physiological and pathological processes (*88*), including learning, memory, feeding behavior, and anxiety (*89,90*). Moreover, NPY can regulate both innate and adaptive immune responses by altering cytokine secretion and megakaryocyte chemotaxis. Studies have confirmed that NPY boosts p62/SQSTM1-mediated autophagy and NRF2 antioxidant signaling pathways in giant cells, which are crucial for the host's inflammatory

response (*91*). Research has suggested that NPY plays a significant role in maintaining energy homeostasis as the primary regulator of feeding (*92*). NPY levels in the arcuate nucleus (ARC) decrease mainly when energy is overconsumed (*93*). A study has found that AGRP neurons secrete the neurotransmitter NPY during fasting, which enhances an organism's attraction to food odors and which contributes to the hunger drive (*94*). Another study has shown that levels of NPY in the ARC increase significantly in response to fasting while energy balance is maintained by increasing food intake (*95*). When energy intake is restricted, increased NPY release in the paraventricular hypothalamic nucleus (PVH) induces hepatic autophagy (*12*). An increase in hypothalamic NPY by caloric restrictions can further induce autophagy in hypothalamic neurons by inducing the activation of neuropeptide Y receptor Y1 (NPY1R) or neuropeptide Y receptor Y5 (NPY5R) intracellular pathways (*96*). AKT and protein kinase A (PKA) signaling pathways are activated by NPY1R in a PI3K-dependent manner, while NPY5R activation increases MAPK/extracellular regulated kinase (ERK) and PKA phosphorylation (*96*). Research in a cell culture medium mimicking heat restriction has shown that autophagy can be stimulated in rat cortical neurons and that it is blocked by NPY or ghrelin receptor antagonists (*97*). Research has indicated that a restricted diet is associated with stimulation of autophagy through inhibition of PI3K/AKT/mTOR and activation of ERK1/2-MAPK by NPY and ghrelin, leading to alleviation of age-related disease (*98*). Impaired autophagy is a key aspect of aging. NPY protects against age-related hypothalamic damage and slows aging by activating NPY, which synergistically stimulates the PI3K, MEK/ERK, and PKA signaling pathways (*99*). There is mounting evidence that NPY plays a significant role in the aging process and an extended lifespan (*96,100*). Aging is associated with a decrease in both autophagy and NPY levels in the hypothalamus (*99,101*). Replenishing NPY can lessen age-related brain alterations by impacting six of the nine cellular aging criteria: mitochondrial dysfunction, dysregulated nutrient sensing, cellular senescence, loss of protein homeostasis, stem cell failure, and altered intercellular communication (*100*). On the whole, NPY protects against neurodegenerative diseases (*102*). In addition, a study found that NPY enhances hypothalamic autophagy, resulting in increased progerin clearance, decreased DNA damage, mitigation of cellular senescence, and other benefits (*103*). Thus, it slows down aging and alleviates cognitive dysfunction (*96*). Impaired neuron autophagy results in decreased memory and learning abilities, particularly during aging. However, neuropeptides can inhibit synaptic degeneration and alleviate memory impairment. Levels of transcription of the NPY family members (sNPF) are regulated by autophagy, and in turn, sNPF can prevent synaptic aging through autophagy (*104*). Metabolism can affect neuronal function and plasticity through autophagy. Restrictions on diet trigger the production of endogenous neuropeptides in the hypothalamus, stimulating autophagy *via* activation of the downstream pathways NPY1R or NPY5R (Figure 1). This protective mechanism preserves synapses, improves cognitive function, and prolongs lifespan.

4.6. BDNF

During nutrient deprivation, BDNF is reported to promote autophagy, but its inhibition of autophagy has also been documented. Moreover, fasting has been shown to upregulate the expression of BDNF, resulting in the activation of autophagy in various regions of the brain, such as the hypothalamus, cortex, and hippocampus. In mice that were older than three months, however, the expression of BDNF induced by fasting produced inconsistent results in the cortex and hippocampus, while neuronal autophagy was suppressed in these areas (*105*). As a member of the neurotrophic factor family, BDNF is essential for neuronal survival and differentiation during development (*106*), and it plays a critical role in regulating learning and memory formation (*107*). BDNF can influence synapse formation in three major ways: increasing the sprouting of axons and dendrites, initiating the formation of axonal and dendritic branches, and consolidating existing synapses (*108*). Nikoletopoulou *et al.* found that BDNF inhibits autophagy *in vivo* through the mediation of the myosin receptor kinase B (TrkB) and phosphatidylinositol-3'kinase (PI3K)/AKT pathways. Moreover, the prevention of autophagy by BDNF during fasting is necessary for improved synaptic plasticity and enhanced memory (*105,109*). BDNF regulates structural plasticity in the suprachiasmatic nucleus of the hypothalamus (SCN) through the BDNF/TrkB signaling pathway in a circadian-dependent manner (*110,111*). Restricted diets trigger BDNF signaling, which boosts peripheral energy metabolism, neuronal bioenergetics, and overall brain health (*111,112*).

5. Associations among circadian rhythm, a restricted diet, autophagy, and cognitive dysfunction

Autophagy is closely correlated with cognitive impairment. A restricted diet can activate autophagy, increasing the expression of BNDF and NPY, clearing Aβ and tau protein plaques, and ameliorating cognitive dysfunction. Mounting evidence indicates a link between cognitive impairment and autophagy-lysosomal pathway damage, which results in misfolded proteins and abnormal intracellular aggregation of dysfunctional mitochondria (*45,113-116*). Research has demonstrated that mutations in *PSEN1* and *PSEN2* disrupt the autophagy-lysosomal pathway, resulting in protein aggregation and neuronal death that significantly contribute to the development of early-onset familial

AD (*114*). Mouse models of AD have shown that abnormal autolysosomal acidification causes autophagic accumulation of Aβ, leading to the production of senile plaques (*117*). Dysregulated mitochondrial autophagy is a prominent neuronal hallmark of AD and Parkinson's disease (PD) (*118,119*), leading to cognitive dysfunction. Autophagy has the ability to improve cognitive function by modifying neuronal metabolism and eliminating damaged organelles and harmful substances. A model of AD revealed that enhanced autophagy decreased Aβ plaque formation and alleviated cognitive impairment (*120,121*). The activation of autophagy by peroxisome proliferator activated receptor alpha (PPARA) lessened Aβ deposition and alleviated cognitive decline in AD (*122*). A restricted diet has been reported to alleviate cognitive impairment by increasing astrocyte autophagic flux and attenuating amyloid pathology in transgenic mice (*53*). A circadian rhythm-restricted diet reduces mitochondrial oxidative stress, promotes mitochondrial biogenesis, enhances autophagy, promotes neuroplasticity, and aids cognition and memory (*29,123,124*). A model in older mouse demonstrated that a regular diet mimicking fasting promoted multisystem regeneration, hippocampal neurogenesis, and improvement in cognitive performance while reducing insulin-like growth factor 1 (IGF-1) levels and PKA activity with an increase in NeuroD1 (*54*). A clinical trial examining the dietary habits of adults in southern Italy indicated that consuming a limited diet was correlated with cognitive status and had a likely impact on brain health (*125*). A clinical study involving obese adults showed that a limiting feeding schedule within a 24-hour window improved glucose control, induced autophagy, increased the level of BNDF, and delayed aging (*11*). Another study of elderly obese patients with mild cognitive impairment (MCI) showed that intentional dietary restrictions significantly improved cognition (*126*). In Huntington's disease, increased autophagy induced by fasting facilitates the elimination of Huntington's protein (mHTT) (*127*). Adopting a circadian rhythm-restricted diet with augmented mitochondrial autophagy gene expression retards the progression of PD (*128*). Preclinical and clinical studies have shown that a circadian rhythm-restricted diets affect amino acid, glucose, and lipid metabolism as well as NPY and BDNF, which regulate intracellular autophagy. This process eliminates abnormal proteins and defective mitochondria, enhances synaptic function, and improves cognitive function, as listed in Table 1.

6. Limitations of restricted diets

There are, however, limitations to restrictive diets due to their potential adverse effects on blood glucose levels, reproductive function, and immune system. A clinical trial on fasting in adults revealed that all types of fasting increased the incidence of hypoglycemic reactions in patients with type 2 diabetes while they were receiving glucose-lowering medications (*135*). Moreover, research has indicated that restrictive diets may disrupt reproduction in young rats *via* the hypothalamic-pituitary-gonadal axis (*136*). Research has demonstrated that 72 hours of intense fasting upregulates signalling upstream of autophagy and it activates essential pathways, thereby promoting autophagy. That said, fasting can inhibit apoptosis by decreasing the expression of pro-apoptotic genes and increasing leukocyte viability, leading to the restructuring of human immune function. Fasting has been found to significantly enhance immune function, and particularly innate immunity, by increasing peripheral neutrophil production and cytokine secretion (*137*). Fasting induces a change in leukocyte migration that extends the lifespan of monocytes and alters disease susceptibility. When the diet is restricted, T cells are recruited from secondary lymphoid organs to the bone marrow, B cells leave Peyer's patches, and the number of circulating monocytes decreases in mice and humans as their mobilization from the bone marrow is prevented (*9*). The effects of fasting on the immune system depend on its duration and form, as well as the purpose of intermittent fasting, so additional research is required. Rough intermittent fasting can lead to lower blood pressure and low levels of cholesterol and triglycerides, but these effects gradually diminish over several weeks following the resumption of a normal diet (*138*). Long-term fasting may cause weakness, hunger, dehydration, headaches, difficulty concentrating, low blood pressure, or fainting, so it is not advisable for pregnant or nursing women, frail elderly individuals, people with immune deficiencies, or people with or at risk for eating disorders to engage in intermittent fasting. The impact of the body's blood glucose, the timing of fasting, and the body's state during a restricted diet or fasting should be considered.

7. Importance of the circadian rhythm

The circadian rhythm plays an essential role in regulating numerous physiological and cognitive functions in the body. The suprachiasmatic nucleus (SCN) in the hypothalamus controls this inherent 24-hour cycle, which is calibrated by external stimuli such as exposure to light. Disrupting the circadian rhythm may result in detrimental consequences for human health, impairing both cognitive and physical performance and elevating the risk for illnesses such as sleep disorders, metabolic disorders, atherosclerosis, AD, PD, and cancer. Therefore, maintaining a stable circadian rhythm is fundamental to maintaining overall health and well-being. A frequent cause of circadian disturbance is shift work, resulting in a desynchronization between one's internal clock and external cues. Other factors that may adversely affect the circadian rhythm are exposure to artificial light at night, inconsistent sleep patterns, and

Table 1. Different types of fasting to modulate autophagy for cognitive function, lifespan

Authors, Year *(Ref.)*	Study subjects	Cytokines	Type of fasting	Circadian rhythm	Autophagy	Results
Whittaker *et al*. 2023 (*129*)	APP23 TG mice	N/A	Fasting for 18 hours, feeding for 6 hours	Circadian modulation	N/A	Reduces amyloid deposition, increases Aβ42 clearance, and improves sleep and memory
Ulgherait *et al.* 2021 (*22*)	Flies	*ATG1, ATG8a*	Fasting for 20 hours, feeding for 28 hours	Constant circadian rhythm	Induces the autophagy process	Delays aging and extends life span
Currenti *et al.* 2021 (*125*)	Humans	N/A	Time-restricted feeding for 10 hours	Constant circadian rhythm	N/A	Improves cognition and has beneficial effects on brain health
Ferreira-Marques *et al.* 2021 (*98*)	Rat cortical neurons	NPY	Caloric restriction	N/A	Stimulates autophagy	N/A
Leclerc *et al.* 2020 (*130*)	Humans	N/A	25% caloric restriction	N/A	N/A	Improves working memory
Wilkinson *et al.* 2020 (*39*)	Humans	N/A	Time-restricted feeding for 10 hours	Constant circadian rhythm	N/A	Weight loss, improves body metabolism and sleep
Jamshed *et al.* 2019 (*11*)	Humans	N/A	Time-restricted feeding at 8 AM and 2 PM	Constant circadian rhythm	Increases autophagy	Enhances circadian clock gene expression and has anti-aging action
Gregosa *et al.* 2019 (*53*)	Mice	N/A	Restricted feeding for 5 days (60% of intake), then ad libitum for 9 ays	N/A	Induced astroglial autophagy	Mitigates cognitive deficits, amyloid pathology, and microglial reactivity
Nikoletopoulou *et al.* 2017 (*105*)	Mice (3–4 month-old male)	BDNF	Fasting for 12, 24, or 48 hours	N/A	Suppresses autophagy in the forebrain	Synaptic plasticity
Kong *et al.* 2016 (*59*)	Mice	AMPK	Fasting for 24 hours	N/A	N/A	Induces spinogenesis and excitatory synaptic activity
Alirezaei *et al*. 2010 (*131*)	Mice (6–7 week-old male)	mTOR	Fasting for 24 or 48 hours	N/A	Increased neuronal autophagy	Neuroprotective effect
Witte *et al.* 2009 (*132*)	Humans	N/A	30% caloric restriction	N/A	N/A	Improves memory function
Davis *et al.* 2008 (*133*)	SD rats	D-BHB	Fasting for 24 hours	N/A	N/A	Improves cognitive function
Lee *et al.* 2002 (*134*)	Mice (two-month-old male)	BDNF	Fasting on alternate days	N/A	N/A	Promotes the survival of newly generated neurons

Abbreviations: Aβ, amyloid β; AMPK, adenosine monophosphate-activated protein kinase; ATG1, autophagy-related 1; ATG8a, autophagy-related 8a; BDNF, brain-derived neurotrophic factor; D-BHB, D-β-hydroxybutyrate; mTOR, rapamycin; N/A, not accessible; TG, transgenic.

lifestyle choices such as drinking and smoking (*139,140*). Prolonged disruption of circadian rhythms increases the likelihood of cardiovascular disease, dementia, and type 2 diabetes; these conditions in turn interfere with sleep, further exacerbating circadian disruption (*141-143*). A study investigating the link between sleep parameters and subclinical atherosclerosis in asymptomatic middle-aged individuals found that reduced sleep duration and fragmented sleep were independently associated with an increased risk of subclinical multiregional atherosclerosis (*141*). Shokri-Kojori *et al.* found that one night of sleep deprivation resulted in a significant increase in Aβ accumulation in the right hippocampus and thalamus (*144*). Elevated norepinephrine levels related to deprivation of rapid eye movement (REM) sleep may impact neuronal autophagy, destabilizing neuronal integrity and homeostasis and leading to altered brain function and associated diseases such as AD and PD (*145*).

8. Conclusion

Currently, preclinical and clinical studies have demonstrated that adhering to a circadian rhythm-restricted diet can modify body metabolism, improve cognitive function, and increase life expectancy. Although the mechanisms are not entirely understood, autophagy is vital to this process. A circadian rhythm-restricted diet triggers autophagy, which clears anomalous protein deposits, engulfs impaired organelles, and improves cognitive performance through its effects on energy, lipid, and amino acid metabolism. In the forebrain, BDNF helps increase synaptic plasticity and improve cognitive function. A circadian rhythm-restricted diet has been found to be critical to maintaining and improving mental health and cognitive function in older adults. Therefore, a circadian rhythm-restricted diet may offer a novel approach to prevent and alleviate cognitive impairment.

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