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Review

Fasting, a Potential Intervention in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the onset of symptoms, typically occurring later in life, and significant deficits in cognitive functions including learning, memory, speech, and behavior. Ongoing research endeavors seek to explore methods for preventing and treating AD, as well as delving into the molecular mechanisms underlying existing and novel therapeutic approaches encompassing exercise, diet, and drug regimens for individuals with AD or those at risk of developing AD. Among these interventions, dietary interventions have garnered increasing attention due to their potential in addressing the disease. Eating is among the most fundamental of human daily activities, and controlled dietary practices, such as fasting, have gained prominence as essential clinical methods for disease prevention and treatment. Research findings indicate that fasting holds promise in effectively alleviating and improving the cognitive decline associated with age or as consequence of disease. The clinical efficacy of fasting in addressing AD and related disorders might be grounded in its influence on various molecular mechanisms, including neuroinflammation, glial cell activation, insulin resistance, autophagy regulation, nerve regeneration, the gut microbiome, and accumulations of amyloid-β and tau proteins. The present study reviews possible molecular mechanisms underpinning the therapeutic effects of fasting in patients with AD, as well as in models of the disorder, to establish a theoretical basis for using fasting as a viable approach to treat AD.

Keywords: fasting; Alzheimer's disease; neuroinflammation; insulin resistance; gut microbiome; brain-derived neurotrophic factor (BDNF); Aβ; tau protein

1. Introduction

Alzheimer's disease (AD), ranked as the fifth-leading global cause of mortality, represents a neurological disorder with a growing incidence among the elderly. Its prevalence has more than doubled since 1990, reached 43.8 million in 2016, and is expected to exceed 152 million by 2050 [1]. While advancements in science and technology have significantly extended human life expectancy, they have also contributed to the growing incidence of AD. The strategies for preventing and treating AD, as well as many other diseases, involve a combination of prescribed medications, exercise, and dietary regimens. Among these, a class of drugs known as anti-amyloid-β (Aβ) monoclonal antibodies (e.g., aducanumab and solanezumab) are currently used to target AD-related pathological factors and have demonstrated significant outcomes in clinical trials [2]. In contrast to exercise and drugs, dietary intervention offers a less stimulating, lower-risk, and more economically viable approach for individuals experiencing age-related AD. The effectiveness of dietary management might be associated with a relatively recent societal development. As the food supply in most nations has only gradually met human needs, diseases caused by long-term energy surplus in the body have become increasingly prevalent and significant. For instance, metabolic disorders such as obesity and diabetes significantly increase the risk of AD [3]. An increasing body of evidence underscores the beneficial effects of regulating dietary patterns, recommending it as an increasingly promising therapeutic method for treating various diseases. For instance, a 30-day intermittent fasting regimen significantly improved deoxyribonucleic acid repair, glucose and lipid metabolism, cytoskeletal remodeling, circadian rhythm, immune function, cognition, and vital regulatory proteins in healthy individuals [4]. A comprehensive review revealed that adherence to various structured dietary patterns, such as the Mediterranean diet, ketogenic diet, calorie restriction, intermittent fasting, methionine restriction, low-protein diet, and high-carbohydrate diet, exerts a significant positive influence on cognitive decline [5]. Studies investigating the molecular underpinnings of AD have indicated that fasting can mitigate disease severity, potentially through effects on glial cell activation [6], neuroinflammation [7], insulin resistance [8], mitochondrial quality [9], intestinal microbes [10], nerve regeneration [11], autophagy [12], Aβ plaques [13], and tau protein hyperphosphorylation [14]. However, it is important to note that most of these findings have been observed in non-human experiments. Intending to address this dearth in the literature and

provide insight into potential molecular targets for future human studies, the present review summarizes the diverse findings concerning the molecular mechanisms underlying the relationship between AD and fasting.

2. AD

In 1907, Alois Alzheimer made a significant observation regarding a 51-year-old woman who exhibited memory impairments and severe difficulties in reading and pronunciation. Upon examining brain tissue from this individual post-mortem, Alzheimer conducted silver staining and observed the presence of neural plaques and neurofibrils when examining the tissue under a microscope. These distinctive features later became the defining pathological characteristics of the newly identified disease, which was subsequently named AD [15]. AD is characterized by a progressive decline in cognitive function, including learning, memory, emotional regulation, and behavior, and the potential to lead to fatal outcomes [16]. Research has identified two main forms of AD; early-onset and late-onset, each associated with distinct genetic profiles. Early-onset AD is associated with mutations in the genes governing presenilin (PS)1/2 and amyloid precursor protein (APP) expression, while late-onset AD is associated with the presence of apolipoprotein E4. Regardless of the onset type, AD is characterized by Aβ deposition, neurofibrillary tangles, a reduction in neuronal numbers, and abnormal neuronal morphology.

More than a century has passed since the initial discovery of AD, yet its specific pathogenesis remains controversial. Currently, there are several prevailing theories, namely the Aβ cascade hypothesis [17], the cholinergic hypothesis [18], and the tau protein abnormal phosphorylation hypothesis [19]. The Aβ cascade hypothesis suggests that the production and circulation of Aβ in the brain induces neurotoxic effects that disrupt neuronal function, leading to the formation of "senile plaques". These plaques, in turn, cause neuronal tangles and loss, contributing to the development and progression of AD. The Aβ cascade depends on the activity of APP [20]. APP is a protein comprising 39–43 amino acids that is produced from the proteolytic activity of β- and γ-secretase from various tissue cell types and participates in several physiological functions. Of all isoforms of APP in the human body, Aβ40 and Aβ42 are the most common forms, with Aβ42 being more toxic.

The cholinergic hypothesis posits that AD is linked to a reduction in cholinergic neurons and changes in the activity of acetylcholine transferase and cholinesterase. These pathological changes result in decreased acetylcholine levels, a neurotransmitter crucial for synaptic transmission, learning, memory, and other advanced cognitive functions. The tau protein abnormal phosphorylation hypothesis proposes that the hyperphosphorylation of tau protein leads to the formation of neuronal tangles. Tau protein plays a vital role in stabilizing microtubules within neurons. Dysregulation of protease activity, including protein kinases and protein phosphatases, causes tau to malfunction, resulting in tangle formation [21] and impaired axonal transport. The resulting loss of communication and neuronal death might cause and aggravate AD development.

In addition to these theories, a deeper understanding of AD has given rise to other hypotheses, including the neuroinflammation hypothesis [22], metal ion disorder hypothesis [23], mitochondrial cascade hypothesis [24], and oxidative stress hypothesis (Fig. 1) [25]. The presence of multiple theories suggests that the pathogenesis of AD is multifaceted and cannot be attributed to a single mechanism. These theories, while addressing AD symptoms and informing potential therapeutic strategies, might collectively contribute to an intricate mechanism whose dominant pathogenic factor, if one such exists, remains uncertain [26–29]. Currently, the clinical diagnosis of AD involves a battery of behavioral, learning, and memory assessments, along with evaluations of blood and cerebrospinal fluid biomarkers, brief mental state examinations, brain magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography [30]. As mentioned earlier, prevention and treatment strategies for AD encompass a combination of exercise, drug, and dietary interventions.

3. Fasting in Mild Cognitive Impairment (MCI) and AD

Fasting represents a type of calorie restriction involving the subjective reduction or temporary suspension of specific or partial food intake. It has been demonstrated to yield favorable health outcomes when incorporated into routine clinical care and strategies for disease prevention. Additionally, fasting simulates the patterns of reduced material and energy intake that humans encountered during evolution. Importantly, scientific evidence, both at the molecular and clinical levels, supports fasting as a catalyst for improving health [31]. Across diverse cultures and influenced by various religious beliefs and lifestyle choices, fasting has evolved into distinct established modes. These include time-restricted eating, which involves limiting daily eating to a 6–8 h window (often achieved by skipping breakfast or dinner) with meal intervals of less than 8 h. Alternate-day fasting entails fasting every other day, with fasting periods exceeding 36 h. Periodic fasting involves maintaining minimal energy intake on two consecutive or intermittent days per week. Long-term fasting extends for more extended durations, surpassing 2 days and even weeks with reduced caloric intake. Additionally, fasting mimetics, such as metformin, spermidine, and rapamycin, replicate the effects of fasting [31–34]. In large number of healthy and overweight individuals, long-term fasting has exhibited positive outcomes, including a longer lifespan, enhanced quality of life, weight management, and potential benefits in countering cognitive decline [35–37].

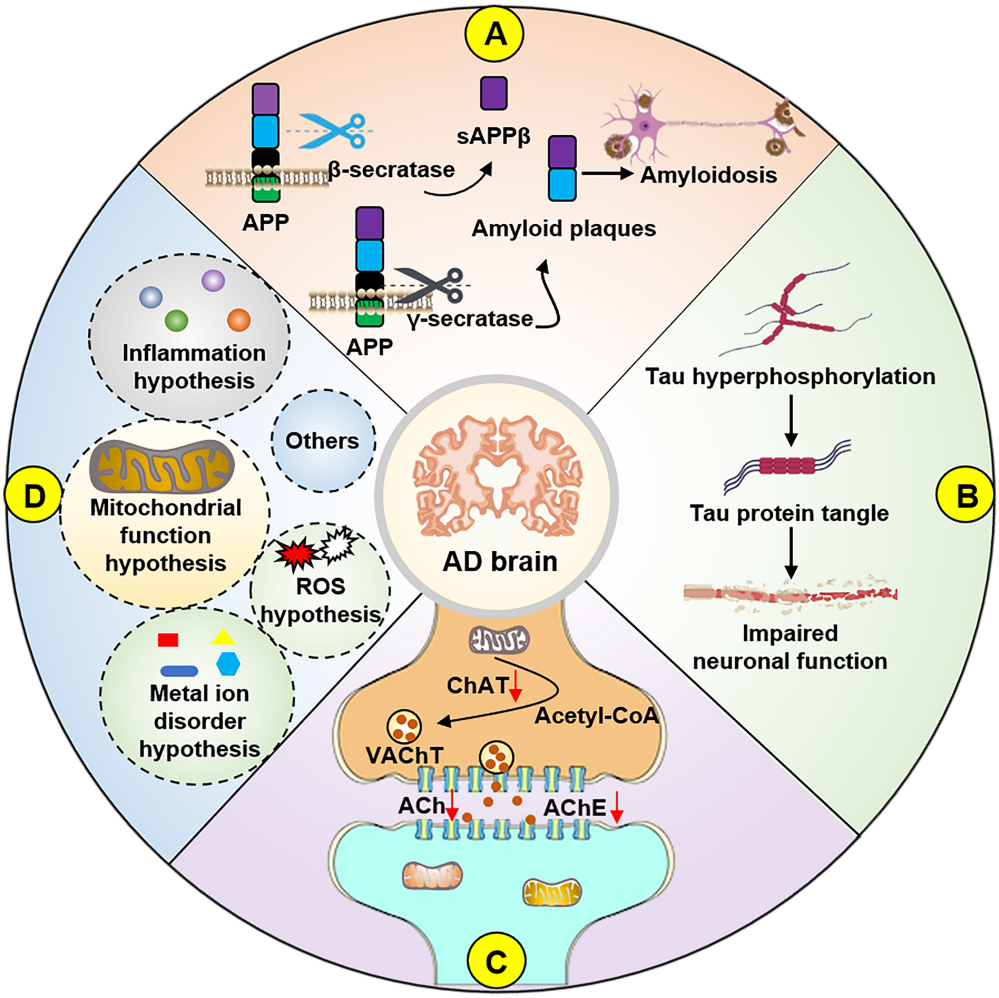

Fig. 1. Hypotheses for the pathogenesis of AD. (A) APP is cleaved by β- and γ-secretase to yield amyloid proteins, including Aβ42, that aggregate into plaques that compromise neuronal function, (B) neurofibrillary tangles form after tau is hyperphosphorylated by dysfunctional protein kinases and protein phosphatases, (C) increase in cholinesterase activity and decrease in acetylcholine transferase decrease acetylcholine levels in nerve synapses and diminish synaptic function, (D) increase in neuroinflammation and the ROS levels, as well as abnormalities in the metal ion activity and concentration accelerate the onset and progression of AD. ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; APP, amyloid precursor protein; ChAT, choline acetyltransferase; CoA, coenzyme A; sAPPβ, ROS, reactive oxygen species; sAPPβ, soluble peptide APPβ; VAChT, vesicular acetylcholine transporter.

Mild cognitive impairment (MCI) is a state of progressive memory and cognitive function decline that does not significantly effect daily life functioning and does not meet the diagnostic criteria for dementia. Given the heightened prevalence of AD within the MCI population, it is often considered a pre-AD manifestation. Timely implementation of fasting can be a beneficial intervention for preventing cognitive decline and the onset of AD [5]. This relationship might be closely associated with the regulation of material energy intake. An associated study revealed that the proportion of MCI cases in the elderly population with high nutritional status was significantly higher than those with good nutritional status [38]. Numerous human studies have demonstrated the positive impact of intermittent dietary interventions on cognitive performance in older adults with symptoms of MCI [39,40]. Furthermore, fasting has proven effective in improving cognitive impairment associated with various conditions, including radiotherapy [41], cognitive impairment caused by chronic cerebral hypoperfusion [42], cognitive dysfunction caused by hyperglycemia [43], and cognitive impairment caused by traumatic brain injury [44]. These findings collectively underscore the favorable role of dietary intervention in the prevention and amelioration of MCI.

As the condition of individuals with MCI continues to decline, there is a substantial likelihood of progression to AD. A study involving older adults who practiced time-restricted fasting revealed a significant positive association between caloric restriction and cognitive ability [45]. Additionally, it was observed that daily extended fasting

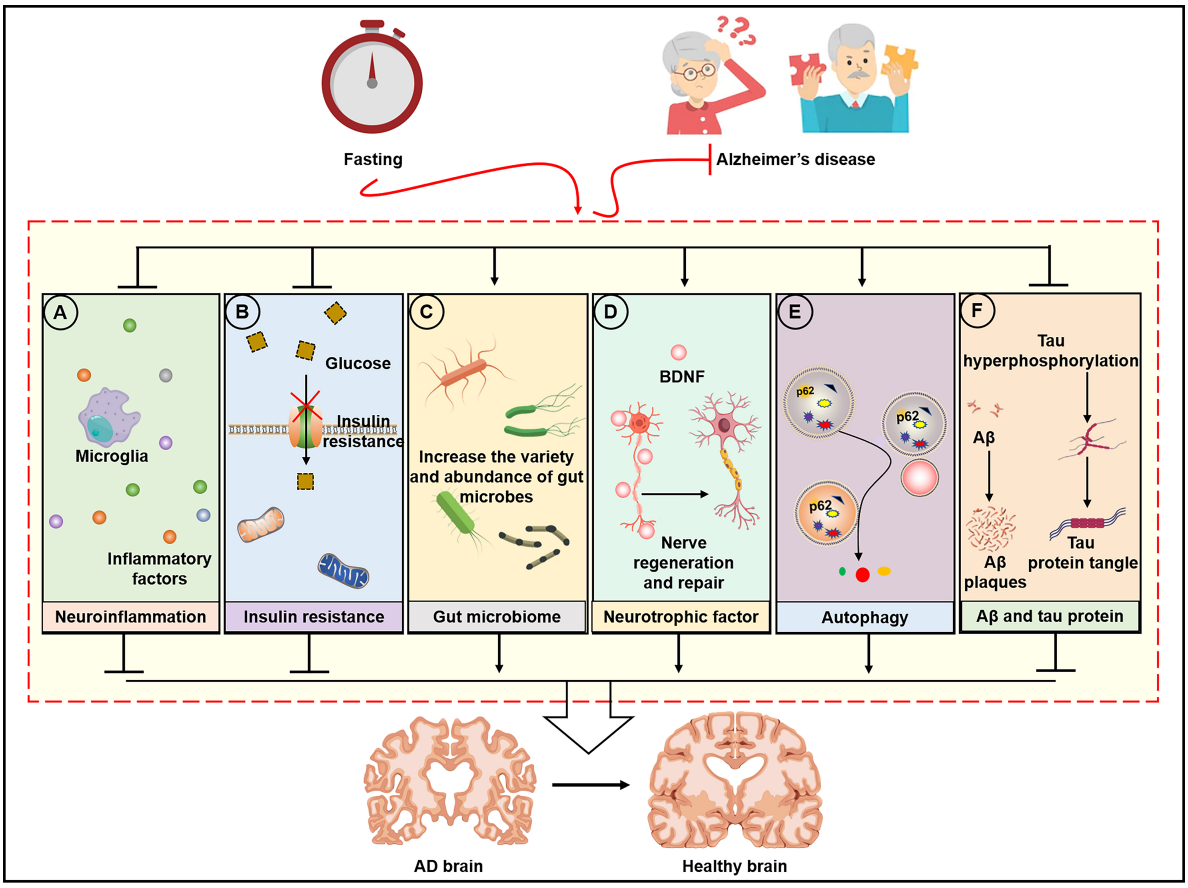

Fig. 2. Molecular mechanism of fasting intervention in AD. (A) Fasting improves neuroinflammation by reducing inflammatory factors, (B) reduces insulin resistance and increases glucose transport in neurons, (C) regulates gut microbes to improve the "gut-brain" axis, (D) improves neurotrophic factors to induce nerve regeneration and repair, (E) activates autophagy, and (F) reduces Aβ deposition and tau protein hyperphosphorylation. These molecular changes collectively improve learning and cognitive ability, as well as attenuate the severity of AD symptoms. BDNF, brain-derived neurotrophic factor; Aβ, amyloid-β; AD, Alzheimer's disease.

had a mitigating effect on cognitive impairment resulting from excessive carbohydrate consumption [46]. Notably, in 17-month-old mouse models of AD, fasting demonstrated improvements in age-related behavioral deficits [47]. In oestrogen-deficient rat models of AD, fasting proved effective in ameliorating memory impairments and mitigating symptoms related to metabolic disorders [14], indicating that the effects of fasting might vary between sexes. Despite counterarguments against the therapeutic use of fasting [48], the aforementioned body of evidence supporting the therapeutic advantages of fasting suggest its considerable potential in preventing and treating AD.

Several studies have indicated that fasting helps alleviate symptoms of neurodegenerative diseases, including AD, Parkinson's disease, epilepsy, and multiple sclerosis; possibly by regulating neuroinflammation, insulin resistance, autophagy, and the gut microbiome [49]. Experiments involving individuals with MCI, AD, and healthy individuals have discovered that fasting might improve cognitive function by influencing processes such as the synthesis and degradation of ketone bodies, the gluconeogenesis pathway, and the up-regulation of Homer protein homolog 1 protein expression [4,40]. In the context of AD models, fasting has been found to reduce inflammation, mitigate insulin resistance, regulate intestinal microbes, and lower Tau protein phosphorylation. It can also reduce Aβ deposition by regulating insulin/insulin-like growth factor 1, adenosine monophosphate-activated protein kinase (AMPK), sirtuins, and autophagy. Fasting has also been found to be effective at increasing brain-derived neurotrophic factor (BDNF) in the hippocampus and restorating aquaporin-4 (AQPA4) polarity in AD models [7,13,32,50].

Currently, increasing research conducting clinical trials involving fasting interventions for patients with AD, including in-depth exploration of the effects of fasting through low-protein diets, time-restricted diets, and the use of rosiglitazone XR (which might mimic the effects of fasting). Furthermore, the potential clinical benefits of dietary restrictions have prompted new investigations aimed at scientifically quantifying fasting strategies according to individual physical conditions, thus improving their clinical adaptability.

4. The Molecular Mechanism of Fasting in the Prevention and Treatment of AD

Fasting, as an economical, convenient, and non-invasive intervention, holds the potential for widespread application in clinical settings to delay the onset of AD [51]. The molecular mechanisms underlying the therapeutic benefits of fasting in patients with AD encompass factors such as neuroinflammation, insulin resistance, mitochondrial integrity, gut microbiome composition, nerve regeneration, autophagy, and the regulation of Aβ and tau protein.

4.1 Neuroinflammation

Excessive inflammation within the body is regarded as an indicator of disease. While a certain level of inflammation is typically maintained in a healthy state without causing harm, an increasing body of evidence implicates both peripheral and central acute and chronic inflammation in the onset and progression of AD [52,53]. Fasting has demonstrated its capacity to mitigate inflammation, thereby serving as a preventive and therapeutic approach to disease management [54]. Inflammation has emerged as a primary target for treating neurodegenerative diseases. AD, in particular, results in a significant increase in neuroinflammation, and efforts to alleviate this excessive inflammation are anticipated to yield improvements in disease symptoms [55]. Intermittent fasting has exhibited a significant reduction in phosphorylated (p)-nuclear factor kappa B (NF-κB)/NF-κB and p-c-Jun N-terminal kinases (JNK)/JNK levels in the brains of ageing senescence-accelerated mouse-prone 8 mice, signifying a reduction in inflammation [56]. Similarly, when the triple-transgenic mouse model of AD (3xTg AD) underwent a fasting regimen, the intervention significantly reduced the activation of microglial cells, suppressed the expression of inflammatory factors in the hippocampus and cortex, and ameliorated cognitive deficits (Fig. 2A) [7]. Fasting has also proven effective at attenuating inflammation induced by arthritis in a murine AD model, while simultaneously enhancing performance in learning and memory tests [57]. However, it is worth noting that some studies have reported that alternate-day fasting might exacerbate inflammation in the cerebral cortex, along with the associated AD symptoms [58]. The discrepancy might be attributed to the timing and pattern of fasting, as the provision of appropriate nutrient supplementation during the disease process could accelerate the body's recovery.

4.2 Insulin Resistance

AD is sometimes referred to as "type 3 diabetes" because of its frequent co-occurrence with diabetes. This strong association is partly attributed to insulin resistance in the brain [59,60]. AD often coincides with a decrease in the body's insulin resistance and a subsequent increase in blood sugar, which contribute to the onset and development of AD [61]. Fasting interventions have demonstrated their ability to ameliorate insulin resistance [62]. In an AD model involving the injection of Aβ protein into the hippocampus of ovariectomized female rats, a study discovered that subjecting these rats to a one-meal-a-day diet significantly improved their cognitive performance by activating insulin signaling pathways [14]. This finding aligns with the observation that insulin deficiency impairs insulin signaling, exacerbates the formation of Aβ42 conformers, and leads to tau hyperphosphorylation, thus accelerating AD progression [48] (Fig. 2B). Providing further support for the role of insulin in AD, a Mendelian randomization analysis of single nucleotide polymorphisms associated with insulin resistance and fasting insulin levels revealed that genomes predicting higher insulin resistance were associated with a higher risk of developing AD [63]. While one study involving patients with AD observed that administering insulin injections to older individuals with insulin resistance did not improve AD-related symptoms [64], another investigation found that intranasal insulin administration improved cognition in individuals with early-stage AD [65]. In contrast, attempts at early intervention through Aβ regulation have yielded poor results. Collectively, these studies contribute to the growing body of evidence supporting the positive impact of fasting on insulin resistance and its potential benefits in addressing AD.

4.3 Gut Microbiome

The microorganisms that parasitize the intestinal tract form the gut flora, a vital contributor to human health. The medical and healthcare fields increasingly acknowledge the significance of regulating the diversity and abundance of the gut microbiome as an effective means to prevent and control diseases. A 13-month longitudinal study investigating the effects of time-restricted feeding and dietary macronutrient regulation on the cognitive abilities of 8-month-old mice revealed that differences in gut microbiome diversity and composition were consistent with variations in dietary intervention, with time-restricted feeding demonstrating the most substantial improvement in cognitive function [66]. These results highlight the influence of the gut microbiome on brain function, indicating that the gut microbiome's health plays a crucial role in the progression of neurodegenerative diseases. This association is supported by evidence showing that fasting-mediated regulation of the gut microbiome can mitigate cognitive impairment in a murine model of AD [67]. Moreover, administering 200 mL probiotic supplements containing *Lactobacillus acidophilus*, *Lactobacillus* casei, *Bifidobacterium*, and *Lactobacillus fermentum* to older adults with AD for 12 weeks was found to elevate plasma malondialdehyde and high-sensitivity C-reactive protein levels while enhancing β-cell function, reducing insulin resistance, and improving cognitive performance [68]. In AD mouse model, fasting remodeled the gut microbiome and promoted the enrichment of probiotic species [10] (Fig. 2C). A fasting inter-

vention lasting up to 16 weeks was observed to enhance learning and memory abilities in a APP/presenilin 1 (PS1) mouse model of AD. This effect was attributed to the regulation of the "gut-brain" axis, which improved the integrity of the intestinal barrier, increased the abundance of lactic acid bacteria, regulated metabolite levels, and consequently reduced Aβ plaque deposition associated with neuroinflammation [69]. In summary, fasting demonstrates the potential to actively improve pathogenic factors in AD patients by modulating the gut microbiome to relieve symptoms.

4.4 BDNF

AD is associated with structural and functional abnormalities in neuronal synapses [70], along with reduced neurotrophic signaling that exacerbates AD progression [71]. Elevating BDNF has been shown to mitigate neuronal loss and promote nerve regeneration and repair [72,73]. While strategies like sleep and exposure to hypoxia can upregulate BDNF, they come with inherent risks when applied to older patients [74,75]. Exercise is another approach that elevates BDNF, presenting significant potential for patients with AD [76,77]. However, the symptoms and age of onset associated with AD might render exercise impractical and possibly dangerous. Fasting positively affects BDNF levels, offering a more viable alternative without the limitations of the a forementioned interventions [78–80]. In the 3xTg AD mouse model, intermittent fasting promoted the differentiation and maturation of hippocampal neurons by activating glycogen synthase kinase 3β, AMPK, protein kinase A, and BDNF-related pathways, thereby improving learning and memory [81] (Fig. 2D). Additionally, fasting significantly increased the density of hippocampal neurons in mice with experimentally induced cognitive impairment [82]. Fasting mimetics such as 2-deoxyglucose can bolster resilience to AD by increasing BDNF transcription [83]. Therefore, fasting might exert a positive influence on AD by regulating BDNFs.

4.5 Autophagy

Autophagy is the cellular process through which ageing and damaged organelles, as well as misfolded proteins, can be eliminated. This process involves encapsulating these components in a phospholipid bilayer and then binding the vesicle to lysosomes, where they are broken down into reusable amino acids, glucose, and other essential substances [84]. Given the implication of abnormal autophagy levels in the pathophysiology of AD, the regulation of autophagy has emerged as a potential target in AD treatment [85]. Both exercise and fasting, even when implemented in the short term, have been shown to induce the regulation of autophagy in neurons [34]. In PDAPP-J20 transgenic mice, a 6-week fasting regimen yielded a neuroprotective effect by significantly increasing the number of LC3-positive glial cells and reducing intracellular Aβ levels (Fig. 2E) [86]. This fasting-induced neuroprotection, characterized by reduced intracellular Aβ, was further demonstrated *in vitro* [87]. Compounds that mimic reduced energy conditions, such as metformin, resveratrol, and rapamycin, have also been found to promote autophagy [88]. However, injecting enhanced green fluorescent protein-light chain 3 (EGFP-LC3) lentivirus into the brains of murine AD models increased autophagy levels and did not resolve the Aβ deposits within the neural tissue [12]. It is worth noting that the significant increase in autophagy levels observed via two-photon microscopy after injecting EGFP-LC3 lentivirus did not eliminate the Aβ deposits in the AD mouse brain [89], and the result suggests that brief periods of autophagy activation might be insufficient to resolve AD-induced degeneration. Therefore, the effectiveness of shorter fasting periods and the subsequently limited periods of autophagy promotion should be explored further.

4.6 Aβ and Tau Protein

Basic experiments and the development of pharmacotherapies for AD have strongly implicated Aβ deposition in the brain and the subsequent hyperphosphorylation of tau protein in the pathogenesis of AD [90], creating a self-reinforcing cycle. The formation of neurofibrillary tangles further accelerates disease progression, a phenomenon supported by drug development and basic experiments based on Aβ and tau. Studies investigating AD have also linked fasting to Aβ deposition and tau protein hyperphosphorylation. Among these studies, fasting interventions have shown the ability to improve the cognitive function of AD mice by reducing the Aquaporin-4 Polarity M1/M23 (AQP4-M1/M23) ratio in the brain, restoring AQP4 polarity, and reducing Aβ deposition [50]. Calorie-restricted dietary interventions, which increased α-secretase activity subsequently led to reduced Aβ-like amyloid production and a decrease in neural plaques in brain tissue [91]. Additionally, research examining tau hyperphosphorylation revealed that a simulated fasting diet can diminish tau phosphorylation in the brains of AD mouse models (Table 1, Ref. [7,10,14,45,50,56,58,59,67,68,81,87–89,91–95]). This finding aligns with another study that injected Aβ into the rat hippocampus and subjected the animals to an indirect dietary intervention (Fig. 2F) [14], resulting in protection against memory decline. While these findings suggest that fasting might mitigate the damage induced by Aβ deposition and increased tau phosphorylation, the precise molecular mechanisms underlying this relationship remain unclear.

5. Precautions for Fasting in AD Interventions

While an increasing body of evidence supports the positive role of fasting in promoting overall health, disease prevention, and recovery, the literature is not entirely in agreement. Long-term and intermittent fasting might have adverse consequences, including reduced reproductive ca-

Table 1. The Molecular Mechanism of Fasting in Alzheimer's Disease (AD).

Model	Fasting method	Tissue, sample, or evaluation	Molecular mechanism	Refs
AD model (express human APOE4 [E4FAD] and triple-transgenic [3xTg] mice)	The fasting-mimicking diet (FMD); 4 days of FMD and 10 days of refeeding/time, 5 times in total	Hippocampus	phosphorylated (p)-tau/tau, microglia level and activation, $AT8^{+}$, and ionised calcium binding adaptor molecule $1^{+}\downarrow$; neurogenesis, and memory$\uparrow$	[7]
AD model (injection of amyloid-β $[A\beta]_{25-35}$ into the hippocampus of Sprague–Dawley [SD] rats with osteoarthritis)	3 h feeding and 16 h fasting/day, 7 weeks in total	Serum and joint histology	Tumour necrosis factor (TNF)-α and interleukin (IL)-1$\beta\downarrow$; memory$\uparrow$	[58]
AD model (5xFAD mice)	every other day, 4 months in total	Cortex	glutamic acid decarboxylase 67$\downarrow$; TNF-α, p38 mitogen-activated protein kinase, excitatory amino acid transporter 2, glial fibrillary acidic protein$\uparrow$	[59]
AD model (injection of $A\beta_{25-35}$ into the hippocampus of ovariectomised Sprague Dawley [SD] rats)	3 h feeding and 16 h fasting/day, 4 weeks in total	Hippocampus	Aβ, p-tau/tau$\downarrow$; Insulin sensitivity, memory$\uparrow$	[14]
AD model (injection of $A\beta_{25-35}$ into the cornu ammonis region 1 of the hippocampus of ageing SD rats)	Intermittent fasting diet, 8 weeks	Faecal	p-tau/tau, TNF-α, IL-1β, *Clostridales*$\downarrow$; insulin sensitivity, memory, *Lactobacillales*$\uparrow$	[68]
Ageing mice (senescence-accelerated mouse-prone 8)	Alternate day fasting, 8 weeks	Brain	sirtuin 1, brain-derived neurotrophic factor (BDNF), heat shock protein 70$\uparrow$; p-glycogen synthase kinase 3β (GSK3β)/GSK3β, p-tau/tau, p-c-Jun N-terminal kinases (JNK)/JNK, p-nuclear factor kappa B (NF-κB)/NF-κB, acetyl-forkhead box protein O1$\downarrow$	[56]
Ageing mice (Fisher 344x Brown Norway F1, 22 months)	51 kCal standard or ketogenic diet once daily for 8 to 21 months	Faecal	*Allubaculum, [Eubacterium] ventriosum group*$\downarrow$; *Intestinimonas, [Ruminococcus] gauvreauii group*, memory$\uparrow$	[67]
Ageing rats (24 months Wistar rat)	Alternate day fasting, 3 months	Cortex, hippocampus, and hypothalamus; Morris water maze test	Learning and memory function, synaptic and cell adhesion molecule expressions$\uparrow$; Calcineurin expression, protein carbonyl content $\downarrow$	[92]
Ageing human (age over 50 years)	Eating time window less than 10 h, 6 months	Questionnaire evaluation	Cognitive status$\uparrow$	[45]
Patients with AD	Modified ketogenic diet or their usual diet supplemented with low-fat healthy-eating guidelines and optional recipes, 12 weeks	Questionnaire evaluation	Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale, Quality of Life–AD$\uparrow$	[93]
AD model (Amyloid-beta precursor protein $[APP]^{NL\text{-}GF}$ knockin)	Alternate day fasting, 1, 4, or 12 months	Elevated plus maze testing	Spatial learning and memory$\uparrow$	[94]
AD model (APP/presenilin 1 [PS1])	Alternate day fasting, 5 months	Cortex	lipoprotein lipase messenger ribonucleic acid and protein$\uparrow$	[95]

Table 1. Continued.

Model	Fasting method	Tissue, sample, or evaluation	Molecular mechanism	Refs
AD model (5xFAD mice)	Intermittent fasting diet (every other day), 10–12 weeks	Hippocampus, and faecal	*Bacteroidetes, Bacteroidia,* A$\beta\downarrow$; *p_firmicutes*, *p_firmicutes*, *g_lactobacillus*, *o_lactobacillales*, *s_lactobacillus_reutei*, memory$\uparrow$	[10]
AD model (3xTg mice)	Intermittent fasting	Hippocampus	Insulin, adenosine monophosphate-activated protein kinase, and protein kinase A signalling, BDNF, memory$\uparrow$	[81]
AD model (PDAPP-J20 transgenic mice), and C6 and BV2 cells	Dietary restriction (40% dietary restriction in dietary restriction (DR), 5 days DR followed 9 days feeding, each cycle lasting 2 weeks, 3 cycles in total)	Hippocampus	Aβ, microglial soma area$\downarrow$; neurogenesis, autophagy, memory$\uparrow$	[87]
Green fluorescent protein-LC3 mice, and N2a cells (Human APP Swedish mutation [N2aSwe], treated with butyric acid [5 µmol/L])	Intermittent fasting for 48 h followed 24 h feeding, 3 weeks; 12, 24, 36, and 48 h	Hippocampus, or N2a cells	Oxidative damage and apoptosis, amyloid precursor protein [APP]$\downarrow$; LC-3II, lysosome-associated membrane protein 2A, autophagy$\uparrow$	[88]
AD model (5xFAD mice)	Fasting 48 h	Hippocampus	Macroautophagy$\uparrow$	[89]
AD model (APP/PS1 mice), and U251 cells	Intermittent fasting diet (every other day), 5 months	Cortex	AQP4-M1/M23, A$\beta\downarrow$; memory, and AQP4 polarity$\uparrow$	[50]
AD model (Tg2576 mice)	Dietary restriction (30% dietary restriction)	Hippocampus	A$\beta\downarrow$	[91]

pacity and a significant decline in short-term memory and verbal expression [96]. Long-term fasting can also disrupt the body's energy levels, metabolism, hormonal balance, immunity, and body weight, resulting in deleterious effects such as muscle atrophy and low immunity [97]. For instance, a single night of fasting was observed to impair handgrip strength and reduce muscle mass in hospitalized adult males [98]. Furthermore, the safety of fasting for critically ill patients remains uncertain and requires additional clinical data [99]. Migraineurs might experience more severe symptoms and disruptions to their daily lives during fasting [100], and fasting can reportedly trigger hypoglycemia-induced coma and other adverse symptoms [101]. Although fasting may have positive effects on health maintenance, it may also have adverse consequences.

However, it is essential to recognize that fasting regimens should not come at the expense of compromising one's health, as they may pose risks for specific groups of individuals. It is important to exercise caution and consider the following groups when contemplating fasting: (1) severely ill patients; (2) individuals with low blood sugar levels; (3) individuals with compromised digestion and absorption; (4) rapidly growing adolescents; (5) pregnant women. These groups exhibit unique physiological conditions, and it remains uncertain whether reduced energy and nutrient intake resulting from fasting could lead to greater damage. Furthermore, it is important to note that fasting methods have only been tested in a limited number of individuals. The suitability of fasting for the elderly population, who are at a higher risk of chronic diseases, might require confirmation through larger-scale studies. Patients in these groups should engage in a systematic assessment of their health status, involving nutritionists, physicians, and rehabilitation specialists. A carefully planned approach, including establishing fasting tolerance limits, monitoring nutritional status, assessing adverse reactions, and having emergency self-rescue measures in place, should be implemented step by step to ensure their well-being.

6. Conclusion

Fasting, a dietary intervention approach characterized by severe regulation and restriction of food intake, has demonstrated therapeutic potential in preventing and treating AD. The primary underlying mechanism for these clinical benefits might involve neuroinflammation, insulin resistance, the gut microbiome, neuronal nutrient factors, autophagy, Aβ deposition, and tau protein hyperphosphorylation. However, it is important to note that the effect of fasting on other molecular processes associated with AD, such as mitochondrial mass, endoplasmic reticulum stress, and metal ion abnormalities, remain unexplored. While the limited research conducted on the use of fasting to prevent and treat AD has yielded predominantly positive results, it is essential to approach its application with caution. AD primarily affects older adults, who might be at a higher risk of developing chronic comorbidities. Whether fasting interventions are generally suitable for preventing and delaying AD in this population requires more systematic evaluation.

Author Contributions

JS, DC and ZZ designed and constructed this article, ZZ conceptualized the study, ZZ and HZ wrote the manuscript, HZ and XW contributed the design and drawing of the figures, and JS and DC completed final editing and revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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