

Review

# Research Progress on the Etiology and Pathogenesis of Alzheimer's Disease from the Perspective of Chronic Stress

Yun-sheng Liu<sup>1#</sup>, Hua-fu Zhao<sup>1#</sup>, Qian Li<sup>1</sup>, Han-wei Cui<sup>2, 3\*</sup>, Guo-dong Huang<sup>1\*</sup>

<sup>1</sup>Department of Neurosurgery, Shenzhen Second People's Hospital/the First Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, China. <sup>2</sup>The Central Laboratory, Shenzhen Second People's Hospital/the First Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, China. <sup>3</sup>Central Laboratory, Shenzhen Samii Medical Center, Shenzhen, China.

[Received October 19, 2022; Revised December 9, 2022; Accepted December 12, 2022]

**ABSTRACT:** Due to its extremely complex pathogenesis, no effective drugs to prevent, delay progression, or cure Alzheimer's disease (AD) exist at present. The main pathological features of AD are senile plaques composed of  $\beta$ -amyloid, neurofibrillary tangles formed by hyperphosphorylation of the tau protein, and degeneration or loss of neurons in the brain. Many risk factors associated with the onset of AD, including gene mutations, aging, traumatic brain injury, endocrine and cardiovascular diseases, education level, and obesity. Growing evidence points to chronic stress as one of the major risk factors for AD, as it can promote the onset and development of AD-related pathologies via a mechanism that is not well known. The use of murine stress models, including restraint, social isolation, noise, and unpredictable stress, has contributed to improving our understanding of the relationship between chronic stress and AD. This review summarizes the evidence derived from murine models on the pathological features associated with AD and the related molecular mechanisms induced by chronic stress. These results not only provide a retrospective interpretation for understanding the pathogenesis of AD, but also provide a window of opportunity for more effective preventive and identifying therapeutic strategies for stress-induced AD.

**Key words:** Chronic Stress, Alzheimer's disease, Gut microbiota, Neuroinflammation, Glutamate system, Immune system

## 1. Introduction

Alzheimer's disease (AD), a progressive degenerative disease of the central nervous system (CNS) characterized by learning and memory impairment and progressive decline in cognitive function, was first discovered and described by the German psychiatrist named Alois Alzheimer in 1906 [1]. With the gradual increase in human life expectancy, as well as improvements in the methods of diagnosis, the incidence and total number of AD cases are increasing every year. AD has become one of the most important threats to the quality of life and

health of the elderly, posing a huge challenge to global economic development. The main pathological features of the AD brain are senile plaque depositions formed by the aggregation of  $\beta$ -amyloid ( $A\beta$ ) and neurofibrillary tangles formed by hyperphosphorylation of the microtubule-associated protein tau, and neuronal loss in specific areas of the brain [2].

No drugs are available to cure AD. Current treatments approved by the US Food and Drug Administration are acetylcholinesterase inhibitors and memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist. However, these drugs only improve the

\*Correspondence should be addressed to: Dr. Han-wei Cui (Email: cuihanwei@ssmc-sz.com), and Dr. Guo-dong Huang (Email: huang\_guodong\_sz@126.com), Shenzhen Second People's Hospital/the First Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, China. #These authors contributed equally to this work.

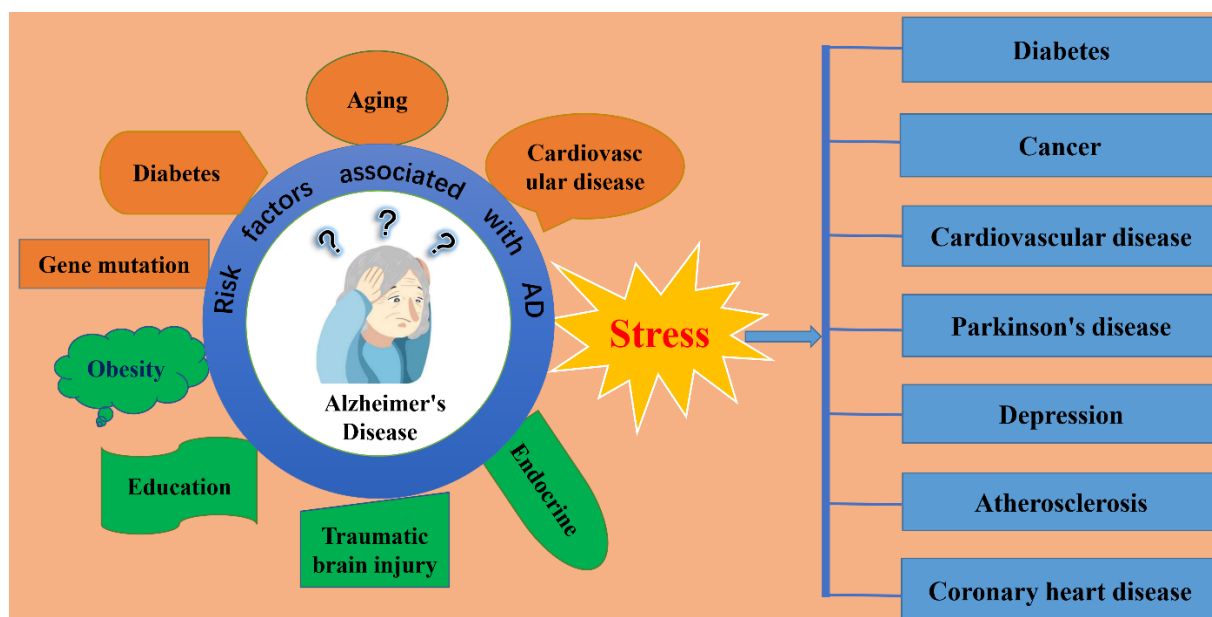
**Copyright:** © 2022 Liu YS. et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

symptoms of AD and cannot reverse the course of the disease. The etiology and pathogenesis of AD are still unclear, and it is therefore difficult to find an accurate and effective treatment. Consequently, there is an urgent need to explore alternative strategies to prevent and treat AD.

In addition to genetic mutations, there are many risk factors related to the onset of AD, including sex, aging, stress, traumatic brain injury, obesity, education level, and endocrine and cardiovascular factors [3, 4] (Fig. 1). Undoubtedly, advanced age is the most important factor. Stress includes both acute and chronic stress. Acute stress is generally believed to be the body's adaptation to unfavorable environments or stimulation, and it always involves a protective response. However, in recent years, chronic stress has become an area of great interest in the study of AD etiology. Relevant studies have shown that environmental factors, especially exposure to chronic stress, can induce the onset of AD-related pathology in wild-type mice and worsen it in AD transgenic models [5-7]. Due to the complexity of the modern living environment and the variety of pressures we face daily, stress has become an inevitable component of everyday

life. In-depth research on the mechanism by which chronic stress promotes the onset and development of AD-related pathologies could provide a theoretical basis for the development of effective clinical interventions.

To study the relationship between stress and AD, researchers have developed a large number of chronic stress animal models, including restraint stress, social isolation stress, noise stress, and unpredictable stress, which have been shown to induce AD-related symptoms. The development of these stress models provides a promising opportunity to study the relationship between stress and AD pathogenesis. However, the AD-like pathological features often differ between models, suggesting that the mechanisms involved may be different. This review summarizes the most common models for chronic stress currently used in research, describes the different AD-like pathological features induced by each of them, and explores the putative underlying mechanisms in order to provide some theoretical bases for the potential prevention and treatment of AD by regulating stress levels.



**Figure 1. Chronic stress is not only a risk factor for Alzheimer's disease, but also for other age-related diseases.** The left side of the illustration depicts common factors known to influence the onset of Alzheimer's disease, including stress, cardiovascular disease, aging, diabetes, gene mutation, obesity, education, traumatic brain injury, and endocrine function. The right-side lists age-related diseases for which stress is a risk factor, including diabetes, cancer, cardiovascular disease, Parkinson's disease, depression, atherosclerosis, and coronary heart disease.

## 2. The history of stress

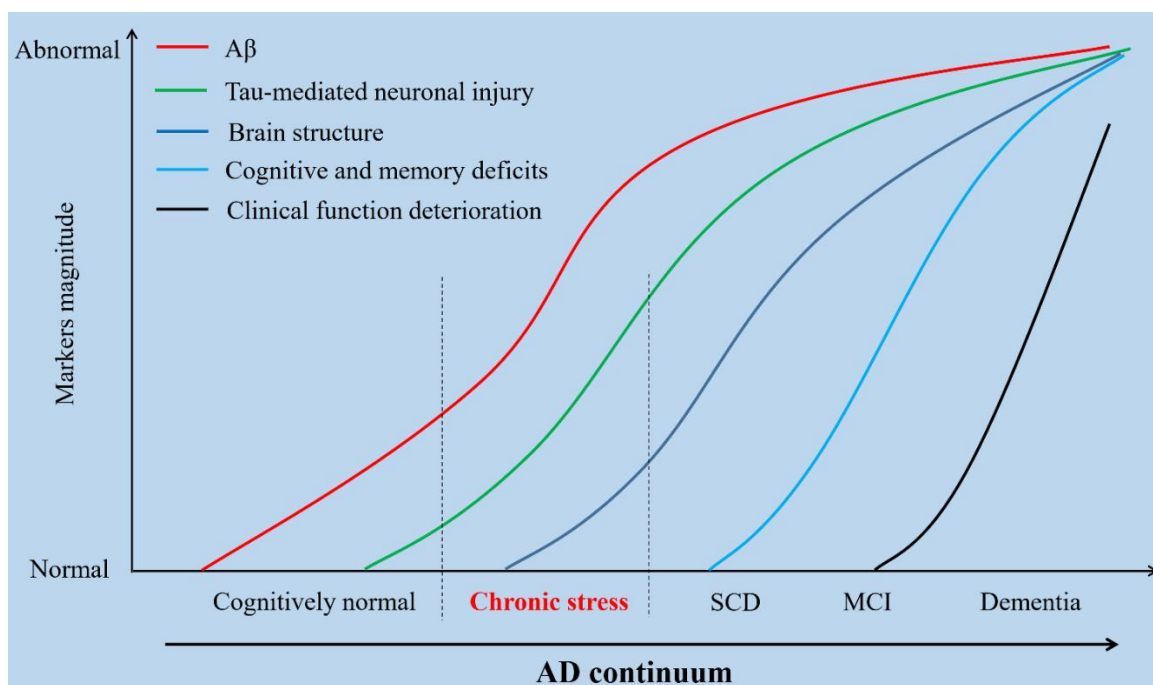
Stress is a syndrome caused by the body's adaptive response to various internal and external environmental stimuli, as proposed by Hans Selye in 1936 [8]. In another words, stress describes the response to an experience that

is emotionally and physiologically challenging [9]. It has been proposed that constant stress could dismantle biochemical protection mechanisms, thus making individuals vulnerable to attack by diseases. It is generally believed that the negative impact of excessive stress on health manifests in two aspects: one is to aggravate

existing diseases by weakening protection mechanisms, and the other is to enhance the vulnerability of certain organs to diseases. Owing to excessive work pressure and a complex living environment, individuals are susceptible to continuous stress. In the 1970s, Mason proposed a theory of psychological stress to explain the mechanism underlying some mental illnesses. Plenty of clinical data shows that stress is closely related to the onset of many age-related diseases, including diabetes, cancer, cardiovascular disease, Parkinson's disease, depression, atherosclerosis, and coronary heart disease, as well as Alzheimer's disease [10-14] (Fig. 1). As life rhythms accelerate and more stressful events need to be faced daily, the prevalence and number of diseases caused by

stress, and their associated economic burden, are also increasing every year.

The human brain is susceptible to stressful events, and an increasing number of studies on AD-specific neuropathological changes elicited by stress have recently attracted intense attention. Chronic stress may precede and trigger subjective cognitive decline (SCD), which precedes mild cognitive impairment (MCI), which in turn often occurs before the early clinical symptoms of AD [15] (Fig. 2). Chronic stress can change neuronal properties in the brain and disturb learning, memory and cognitive processes, suggesting that this event may function as a trigger for AD pathology.



**Figure 2. Theoretical dynamics of the AD continuum.** Changes in dynamic biomarkers ( $A\beta$ , tau-mediated neuronal injury, brain structure, cognitive and memory deficits, clinical function deterioration) during the AD pathological cascade are shown. Chronic stress precedes and acts as a trigger for subjective cognitive decline (SCD), which may precede mild cognitive impairment (MCI), which in turn becomes manifests before the early clinical symptoms of dementia.  $A\beta$ , amyloid  $\beta$ .

However, due to the inherent difficulty of performing a large-scale study of the relationship between stress and AD pathogenesis in human subjects, choosing a suitable animal model is crucial. This review describes several models for chronic stress commonly used in current research, and the insight on the mechanisms by which stress promotes the onset and development of AD that has been gained from these models.

### 3. Chronic restraint stress

The chronic restraint stress (CRS) animal model is used as one of the techniques used to monitor physiological and

psychological changes caused by stress. Under this model, the animals are repeatedly placed in conical tubes with holes for ventilation for half an hour to several hours per day during several weeks or months, without physical pressure or pain involved [16]. It has been reported that CRS can promote AD-type pathology in wild type rats and mice, and in transgenic models for AD, including aggregation and deposition of  $A\beta$ , hyper-phosphorylation of tau protein, and degeneration and massive loss of neurons, as well as decline in learning and memory ability (Table 1) [7, 17-20].

**Table 1.** Rodent studies on impact of chronic restraint stress (CRS) on AD-related markers.

Stress paradigm	Procedure	Animal model	Relevance to AD	Ref.
CRS	Mice were placed in 50 ml conical tubes with holes for ventilating, 30 min each day for 18 days.	C57BL/6 mouse	p-tau ↑ Tau insolubility ↑	6
	Mice were restrained in conical tubes for 6 h/d for 6 d/week, and for 4 weeks.	Tg2576 mouse	A $\beta$ <sub>40</sub> , A $\beta$ <sub>42</sub> and p-tau ↑ Neurodegeneration	7
	Rats were placed in flat-bottom acrylic restrainers with ventilation for a daily episode of 30 min of restraint for 14 days.	Wistar rat	p-tau ↑	17
	The stress was performed with a stainless mesh that allowed for a close fit to rats for 6 h/d for 21 days.	Fisher rat	Neuronal loss and cognitive dysfunction	18
	Mouse was subjected to 6 h/d of immobilization stress in a mouse stress box (4.5W×10L×4.5H cm), for 4 days per week, and for 8 months.	APP <sup>V717T</sup> -CT100 transgenic mouse	Learning and memory impairments A $\beta$ and APP-CTFs ↑	19
	Rats were restrained in Plexiglas tubes for 6 h/d for 21 days.	Sprague Dawley rat	Impairment in memory performance and the loss of dendritic spines	20
	Mice were restrained in ventilated 50-mL conical tubes for 30 min/d for 14 days.	C57BL/6 mouse	p-tau ↑ tau filaments and aggregate ↑	25
	Mice were placed into well-ventilated 50-mL conical tubes for 6 h/d for 21 days.	C57BL/6 mouse	Learning and memory deficits	51
	Mice were placed head-first into a well-ventilated 50 ml polypropylene conical tubes for 2 h/d for 14 days.	B6.Cg-TgN transgenic mouse	Dendrite and dendritic spine loss	57
	Mice were placed in modified 50-mL centrifuge tubes for 1 h per day for 14 days.	C57BL/6 mouse	Cognitive Impairments	58

### 3.1 HPA axis

Studies have found that the HPA (hypothalamic-pituitary-adrenal) axis is dysfunctional in AD, and the basal corticosterone level is significantly increased [21]. After stress stimulation, corticotrophin-releasing hormone (CRH) secreted by the hypothalamus acts on the pituitary gland to induce the release of adrenocorticotrophic hormone (ACTH), which further acts on the adrenal gland to promote the release of glucocorticoids (corticosterone (CORT) in mice and rats, cortisol in primates) [22]. The increase in the level of CORT is associated with damage to synaptic function in AD (Fig. 3). Chronic stress or administration of CORT can accelerate the degradation of hippocampal function and cause AD-like lesions, including neuronal loss, increased A $\beta$  deposition, tau phosphorylation, and loss of cognitive and memory function [23]. However, it has been reported that transgenic mice expressing a mutated form of tau (PS19) that were implanted with slow-release subcutaneous CORT pellets failed to show an increase in tau phosphorylation, suggesting that CORT may not be the key hormones mediating tau phosphorylation in response to stress [7].

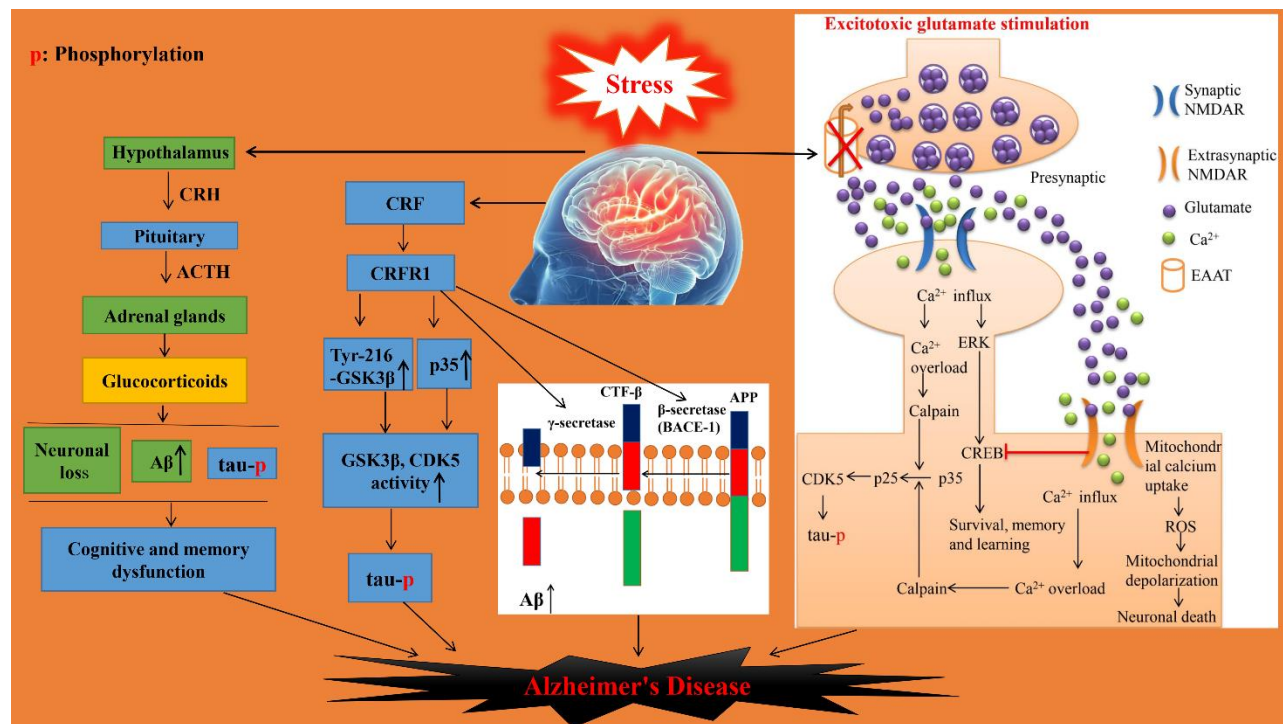
### 3.2 CRF system

The expression of corticotropin-releasing factor (CRF) and its receptor, CRFR, is significantly increased in the brains of AD [24]. Studies have shown that CRF may play a crucial role in stress-induced A $\beta$  increase and tau phosphorylation, which can accelerate the pathogenesis of AD (Fig. 3); These results were not only confirmed in wild type mice, but also in AD transgenic mice, which indicate that CRF plays a propelling role in the progression of AD [7, 25]. The CRF receptor is composed of two subtypes: CRFR1 and CRFR2. Rissman et al. found that CRFR2 can inhibit tau phosphorylation induced by stress [26]. However, most studies concluded that CRFR1 plays a positive regulatory role in the stress response [7, 27]. Tau phosphorylation and learning and memory impairment triggered by stress were reversed in AD transgenic mice receiving CRFR1 antagonist [7], CRFR1 knockout mice, and wild-type C57BL/6 mice treated with CRFR1 antagonist [25]. The mechanism involved was CRFR1 upregulation of the active form (Tyr-216 phosphorylated) of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and alteration of p35 expression levels [26]. It is well known that GSK3 $\beta$  and cell cycle-dependent protein



kinase 5 (CDK5) are the two most important kinases in the brain regulating tau protein phosphorylation, and CDK5 activity requires p35 or p25 regulatory subunits.

Increased tau phosphorylation and A $\beta$  levels lead to synaptic degeneration, which in turn impairs learning and memory behavior in mice [28].



**Figure 3. Chronic restraint stress (CRS) induces AD pathogenesis by disrupting the HPA axis, and the CRF and glutamate signaling pathways.** (1) CRS induces an increase in circulating glucocorticoids through the HPA axis, which in turn promotes an increase in A $\beta$  generation, tau phosphorylation, and neuronal degeneration. (2) CRS promotes tau phosphorylation and A $\beta$  generation through the corticotropin-releasing factor (CRF) pathway. (3) CRS inhibits the expression of glutamate transporter EAAT, leading to persistent excitatory toxicity in neurons. On one hand, excitotoxicity induces tau protein phosphorylation through Ca<sup>2+</sup> overload mediated by synaptic and extrasynaptic NMDA receptors (NMDARs). On the other hand, activated extrasynaptic NMDARs induce neuronal apoptosis by excess ROS production. Moreover, activated extrasynaptic NMDARs can also inhibit the CREB signaling pathway, which mediates the physiological effects of synaptic NMDARs.

A $\beta$  is derived from the cleavage of the amyloid precursor protein (APP) by  $\beta$ - and  $\gamma$ -secretases [29].  $\beta$ -secretase (BACE-1) cleaves APP to generate the C99 fragment (also known as APP CTF- $\beta$ ), which comprises the N-terminus of A $\beta$  [30]. When  $\gamma$ -secretase cleaves CTF- $\beta$ , A $\beta$  is released in several forms of fragments, the most abundant of which is composed of A $\beta$ <sub>38</sub>, A $\beta$ <sub>40</sub>, and A $\beta$ <sub>42</sub>, respectively. A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> peptide monomers are flexible hydrophobic peptides that can rapidly self-aggregate into pro-inflammatory dimers, oligomers, and fibrils to drive AD pathogenesis [31]. The removal and elimination of excessive A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> peptide monomers represents a promising strategy for preventing AD. APP CTF- $\beta$  and A $\beta$  peptides were significantly reduced in the brains of mice treated with CRFR1 antagonists, and in CRFR1 knockout mice [32, 33], indicating that CRFR1 regulates  $\beta$ - or  $\gamma$ -secretase expression, activity, and/or trafficking (Fig. 3).

### 3.3 Glutamate system

Glutamate is the most important excitatory neurotransmitter with the highest content in the CNS. As a neurotransmitter, glutamate must be eliminated immediately after it is released into the synaptic cleft to prevent excitatory toxicity. Glutamate is eliminated mainly through reuptake, relying on the high-affinity excitatory amino acid transporters (EAAT) 1-5 expressed on the presynaptic and glial cell membranes [34]. Among them, EAAT1 is mainly present in the cerebellum, hippocampus, cortex, and striatum, whereas EAAT2 is mainly distributed to the cerebral cortex, hippocampus, and striatum. They both belong to the glial glutamate transporter family and bind glutamate with high affinity. Therefore, any reduction in EAAT1 and EAAT2 protein levels directly affects extracellular glutamate concentration. EAAT2 accounts for 95% of the uptake and transport of glutamate, and EAAT2 deficiency shows overlap with human aging and AD at the transcriptomic level [35]. Shan et al. found that after CRS, the expression

of EAAT1 and EAAT2 in the brains of wild type mice decreased in both total protein and membrane-bound forms, and the decrease in the membrane components of the brains of aged mice was more remarkable than that in younger subjects [6].

NMDARs are glutamate-gated ion channels that are critical for neuronal communication and play a vital role in the dysfunction of glutamatergic transmission [36]. Our previous study found that CRS increased the expression levels of the glutamate NMDAR subunits GluN2A and GluN2B in the hippocampus and prefrontal cortex of wild type mice [37]. GluN2A and GluN2B can be detected in both synaptic and extrasynaptic NMDARs in the adult brain, with GluN2A mainly located in synaptic NMDARs and GluN2B mainly in extrasynaptic NMDARs [38]. In addition, increased expression of extrasynaptic GluN2B was found in the brain of APP/PS1 transgenic mice, and xanthoceraside significantly improved the learning and memory behavior in APP/PS1 transgenic mice by inhibiting the overexpression of extrasynaptic GluN2B [39]. Stimulation of NMDARs at synaptic sites with physiological concentrations of glutamate promotes cell survival, learning, and memory via the  $\text{Ca}^{2+}$ -ERK-CREB pathway. However, prolonged activation of extrasynaptic NMDARs with excitotoxic glutamate stimulation causes calcium overload and neuronal apoptosis. The initial calcium influx following excitotoxic glutamate stimulation triggers a secondary intracellular calcium overload, and this secondary response strongly correlates with neuronal injury and death. The main reason is the involvement of mitochondria in the maintenance of cellular calcium homeostasis. Mitochondria can restore intracellular calcium concentrations by absorbing large amounts of calcium. In response to excitotoxic glutamate stimulation, the mitochondrial uptake of calcium results in the generation of an excessive amount of reactive oxygen species (ROS), leading to mitochondrial depolarization and excitotoxic neuronal death [40]. In addition, the activation of extrasynaptic NMDARs can also inhibit the ERK signaling pathway, which mediates the physiological function of synaptic NMDARs [38, 41].

Memantine is a voltage-dependent noncompetitive antagonist of NMDAR channels that preferentially binds to extrasynaptic NMDARs and blocks their hyperactivation without affecting the synaptic NMDAR signaling underlying various physiological functions [42, 43]. Compared with other ionotropic glutamate receptors, NMDARs have stronger permeability to  $\text{Ca}^{2+}$ . Under normal circumstances,  $\text{Ca}^{2+}$  influx regulates physiological processes such as synaptic plasticity [44]. However, excessive intracellular  $\text{Ca}^{2+}$  levels can also cause excitotoxicity. Chronic stress induces the influx of large amounts of  $\text{Ca}^{2+}$  into neurons through synaptic and extrasynaptic NMDARs, and persistent  $\text{Ca}^{2+}$  overload in

neurons leads to progressive dysregulation of synaptic function, and ultimately to neuronal cell death. This involves the activation of the  $\text{Ca}^{2+}$ /calpain pathway by  $\text{Ca}^{2+}$  overload in neuronal cells, which in turn activates CDK5 through the Calpain/p25/CDK5 pathway to promote the phosphorylation of tau protein. This provides theoretical support for the clinical use of memantine in the prevention and treatment of stress-induced AD. The above results also suggest that abnormal glutamate signaling system is involved in the AD-related pathology induced by CRS (Fig. 3).

### 3.4 Neuroinflammation

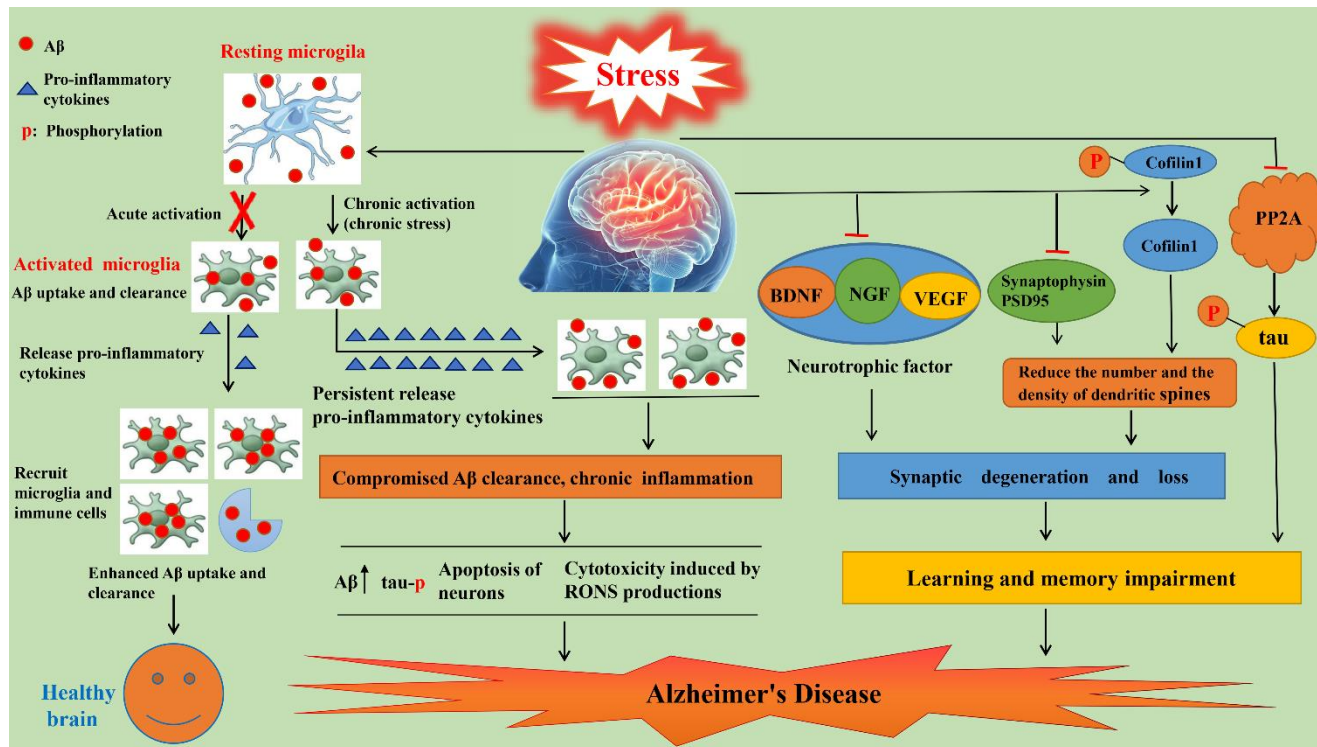
Neuroinflammation is a common pathological feature of AD. To reduce the damage caused by stress to the body, microglia and astrocytes secrete inflammatory factors that promote immune cells recruitment, thereby clearing infected or damaged tissues and cells. Microglia are the main immune cells in the brain and play a crucial role in the maintenance of brain homeostasis and immune surveillance [45]. When A $\beta$  is abnormally deposited, microglia can engulf the aggregated proteins and secrete pro-inflammatory cytokines to recruit additional microglia and immune cells, enhancing A $\beta$  uptake and clearance [46, 47]. However, although this initial immune response has a beneficial effect by removing accumulated A $\beta$ , the persistent inflammatory response caused by CRS is harmful to neuronal survival and synaptic function, and eventually also damages the phagocytosis of A $\beta$  by microglia [48]. Furthermore, the excessive release of inflammatory factors may even promote A $\beta$  generation and tau hyperphosphorylation [49, 50]. Therefore, neuroinflammation plays a dual role in AD pathogenesis, under physiological conditions, it contributes to the clearance excess of A $\beta$  secreted by nerve cells, while a continuous and excessive inflammatory response directly promotes AD-related pathology (Fig. 4). Increased inflammation is a common event in brains affected by chronic stress and may represent one mechanism by which stress promotes AD pathology.

### 3.5 Synaptic dysfunction

Synaptic dysfunction is closely related to learning and memory impairment. Studies have found that CRS can not only reduce the number and density of hippocampal dendritic spines but also reduce the expression levels of the presynaptic membrane marker synaptophysin, the postsynaptic membrane marker post-synaptic density-95 (PSD-95), and the neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF) [51-53] (Fig. 4). BDNF plays an important role in

synaptogenesis and cognition by promoting synaptic plasticity, and synaptogenesis [54]. VEGF can improve cognition by reducing A $\beta$  production [55]. In addition, studies have shown that a decline in serum VEGF levels

is directly associated with the onset of AD [56]. Finally, NGF is essential for neuronal survival.



**Figure 4. The mechanism of CRS-induced AD pathogenesis.** (1) Under physiological conditions, neuroinflammation contributes to A $\beta$  clearance, whereas a continuous and excessive inflammatory response induced by CRS compromises A $\beta$  uptake by microglia. This promotes AD-related pathology, namely, an increase in A $\beta$  production and tau phosphorylation. Ultimately, synaptic function is damaged and neuronal apoptosis is induced. (2) CRS inhibits the expression of neurotrophic factors (BDNF, VEGF, NGF) and synapse-associated proteins (PSD-95, synaptophysin), reduces the expression of PP2A, and promotes the dephosphorylation of cofilin1 at the Ser3 site, leading to degeneration and loss of synapses, which contribute to the onset of AD.

### 3.6 Cofilin1 and PP2A

Cofilin1 is essential for the growth and remodeling of dendrites and dendritic spines. Downregulation of cofilin activity can increase dendritic spine density. Cofilin1 is activated by dephosphorylation at Ser3, and CRS can promote the dephosphorylation at this particular site, increasing cofilin activity. This leads to the reduction in the number of dendritic spines and has an impact on learning and memory in mice [57] (Fig. 4). Zhang et al. showed that CRS inhibits the expression of the protease PP2A, which is a crucial enzyme for the dephosphorylation of tau. Approximately 70% of the phosphorylated tau is dephosphorylated by PP2A, and a reduction in PP2A expression leads to the aggregation of hyperphosphorylated tau and to a disruption in memory function in mice [58] (Fig. 4).

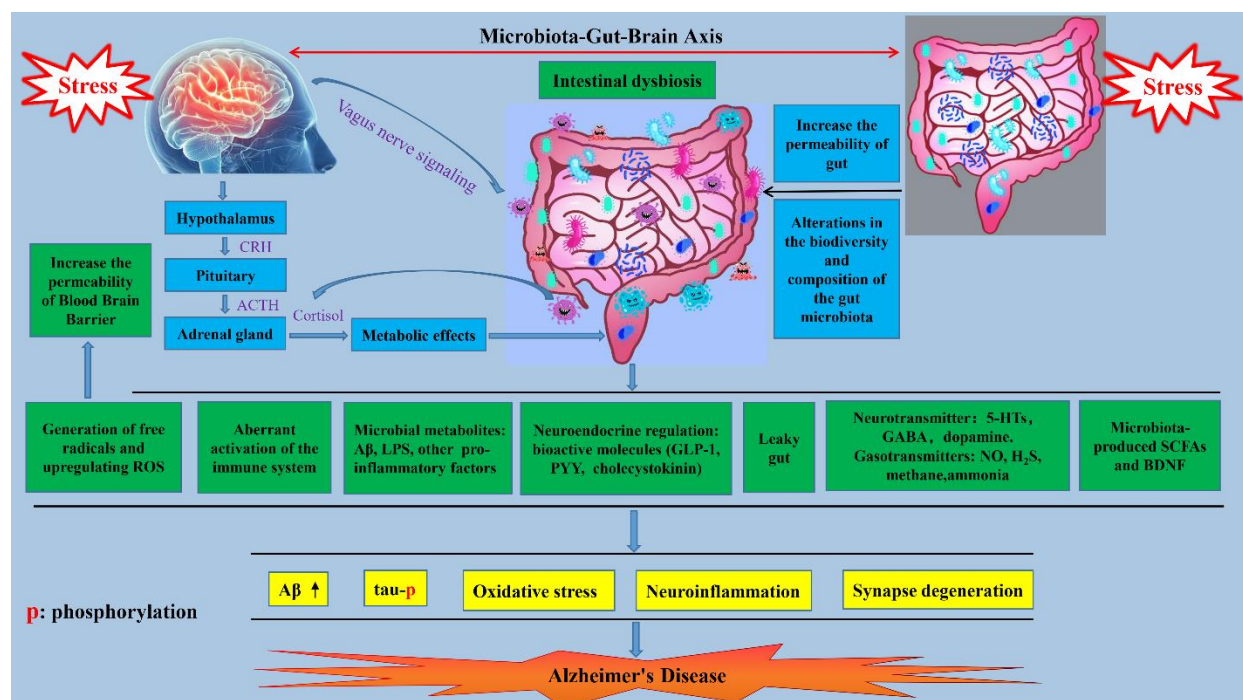
### 3.7 Microbiota–gut–brain axis

“All disease begins in the gut” was purportedly said more than 2,000 years ago by Hippocrates, a Greek physician known as the father of modern medicine [59]. The gut microbiota in humans contains approximately  $10^{14}$  microbes that outnumber the host’s cells by approximately ten-to-one [60, 61]. The function of the gut microbiota was previously thought to be limited to maintaining normal gastrointestinal function, but they also regulate several additional processes, including vitamin and glucose metabolism, immune and inflammatory responses, central and peripheral neurotransmission [62, 63]. Growing evidence has indicated that the gut microbiota plays an active role in obesity, addiction, type 2 diabetes mellitus, cancer, aging, pain, stroke, and even neurodegenerative diseases [59]. In 2018, Lu et al. observed significant memory deficits in germ-free mice, suggesting an essential role of the gut microbiota in memory maintenance [64]. Indeed, numerous studies have provided evidence that *Lactobacillus* and *Bifidobacterium* probiotic supplements



have a positive effect on mouse memory, assessed by object recognition and fear conditioning tests [65, 66]. Moreover, alterations in the biodiversity and composition of the intestinal microbiota have been observed in AD patients as well as in mouse models for AD [67, 68]. Liu et al. studied 97 participants from Hangzhou (China), including 32 healthy controls, 32 patients with amnesic mild cognitive impairment, and 33 patients with AD, and found marked differences in microbiota composition between the groups. Moreover, these alterations were tightly correlated with AD severity [69]. Kim found that transplantation of fecal microbiota from wild type mice mitigated amyloid and tau pathology, memory deficits, and reactive gliosis in an AD mouse model [70].

Probiotics (*Lactobacillus* and *Bifidobacterium*) ingestion by AD patients and murine AD models reduced various pathological markers, such as brain atrophy, A $\beta$  accumulation, learning and memory deficits, and oxidative stress [71, 72]. More recently, mounting evidence has suggested that gut microbiota dysbiosis induced by CRS affects brain structure and function, and individual behavior through the microbiota–gut–brain axis, leading to the onset and development of AD [73, 74]. The microbiota–gut–brain axis is a bidirectional communication system comprising several routes, including the neural and immune systems, microbial metabolites, and endocrine signals (Fig. 5).



**Figure 5. Chronic restraint stress (CRS) induces AD pathogenesis by disrupting the gut microbiota.** Dysbiosis in the gut microbiota induced by CRS is linked to AD pathology in various ways, which include increased permeability of the gut, vasculature, and blood-brain barrier; increased amyloid burden; abnormal secretion of LPS; misregulation of the HPA axis and vagus nerve signaling; neuroinflammation; oxidative stress; aberrant immune activity; alterations in the biodiversity and composition of the gut microbiota; downregulation of BDNF and SCFAs; decreased secretion of related neurotransmitters; and abnormal release of gasotransmitters of microbial origin.

Here, we discuss the mechanisms underlying dysbiosis of the gut microbiota may participate in AD onset. It is known that CRS can accelerate aging, and Lee et al. found that transfer of gut microbiota from aged mice to younger mice was sufficient to reproduce the cognitive decline associated with aging [75]. Multiple reports have confirmed that the gut microbiota naturally secrete massive amounts of A $\beta$ , lipopolysaccharide (LPS), and related microbial secretory products. Considering the huge number of microbes that comprise the human gut microbiota, it is apparent that we need to have an in-built

tolerance to life-long exposure to LPS, A $\beta$  and other related pro-inflammatory pathogenic signals. This exposure is nevertheless likely to increase the burden of amyloid protein and LPS in the CNS and activate the microglial-mediated innate immune and inflammatory responses. In individuals suffering from chronic stress, this may further contribute to AD development.

As mentioned for neuroinflammation, CRS can attenuate amyloid plaque sensing, phagocytosis, and clearance by microglia. Moreover, CRS is known to induce gut microbiota dysbiosis characterized by



increased intestinal permeability and changes in gastrointestinal motility leading to “leaky gut”. As a result, bacteria, pathogens, amyloid protein and LPS can freely cross the epithelial barrier [66]. Extracellular A $\beta$  deposition can cause secondary pathological changes such as tau hyperphosphorylation, oxidative stress, neuroinflammation, synaptic degeneration, and neuronal death, eventually leading to AD [76].

Gram-negative bacteria are predominant in the gut microbiota, and LPS is the major component of their cell wall. The secretory products of the gut microbiota are seriously powerful immune activators and pro-inflammatory factors that affect the host, accelerating the free radical's production and upregulating ROS and/or reactive nitrogen species. This subsequently increases vascular and blood-brain barrier (BBB) permeability, immunogenicity, and aberrant activation of the immune system [77]. The increased permeability of the gut, vasculature, and BBB results in large amounts of A $\beta$  protein and LPS leaking into the CNS and the peripheral circulation, which contributes to the accumulation of amyloids and the production of pro-inflammatory cytokines [interleukin-6 (IL-6), CXCL2, NLRP3, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin 1-beta (IL-1 $\beta$ )]. Gut microbes can also regulate cortisol release by affecting the activation state of the HPA. This in turn has an effect on microglia activation, cytokine release, and monocytes recruitment.

Bostanciklioğlu et al. found that gut metabolites can affect learning and memory through vagal afferent fibers that control the secretion of bioactive molecules (peptide YY, cholecystokinin, glucagon-like peptide-1) by enteroendocrine cells [78]. Therefore, AD pathology may result from a misregulated HPA axis and vagus nerve signaling induced by gut dysbiosis. In addition, dysbiosis of the gut microbiota can inhibit the expression of BDNF, a gene associated to neurogenesis and neuronal growth [72]. Dysbiosis induced by CRS translates into a decrease in the proportion of beneficial microorganisms (*Lactobacillus* and *Bifidobacterium*) and an increase in that of the more harmful ones (*Escherichia*, *Shigella*, *Proteus*, *Klebsiella*), leading to a decrease in the production of short chain fatty acids (SCFAs) [72, 79, 80]. SCFAs have a beneficial effect on the CNS and peripheral circulation and have been shown to play a key role in microbiota-gut-brain communication. SCFAs can interfere with various forms of A $\beta$  peptides, effectively inhibiting aggregation of A $\beta$  fibrils and reducing the accumulation of neurotoxic oligomers in the brain [81]. Dysbiosis of the gut microbiota therefore further decreases intestinal barrier integrity due to this reduction in SCFAs synthesis [73, 82]. SCFAs can also influence neuroinflammation by affecting microglial cell morphology and function as well as immune cells and

immune modulators. Therefore, downregulation of SCFAs may potentially induce impairments in cognition, memory, and emotional response [83].

Recent investigations of microbial endocrinology also demonstrated that neuroactive molecules, such as neurotransmitters produced by gut microbes, can directly contribute to the crosstalk between the gut and the brain [84]. Acetylcholine,  $\gamma$ -aminobutyric acid (GABA), dopamine, and 5-hydroxytryptophan (5-HT), produced by gut microbes from the *Bifidobacterium* and *Lactobacillus* genera, among others, can influence nerve physiology. During CRS-induced dysbiosis, the secretion of these neurotransmitters is decreased, which is a predisposing factor to AD. In addition, gasotransmitters of microbial origin, including nitric oxide (NO), hydrogen sulfide (H<sub>2</sub>S), ammonia, and methane, also play crucial functions in neurophysiology, and may be participated in AD pathogenesis [85, 86]. For example, the elevation of NO increases BBB permeability. Furthermore, NO reacts with superoxide to form peroxynitrite, a potent oxidizing agent that can cause neurotoxicity. Oxidative stress and mitochondrial dysfunction, two well-characterized pathological features in AD, can also be induced by elevation of NO levels, leading to neuronal apoptosis. Moreover, oxidative stress can enhance A $\beta$  production and deposition. Overproduction of H<sub>2</sub>S leads to decreased oxygen consumption of mitochondria and increased expression of pro-inflammatory factors such as IL-6 [87].

Based on the pieces of evidence discussed above, we may conclude that dysbiosis induced by CRS influences AD pathology in several ways. These include increased gut, vasculature, and BBB permeability; accelerated aging; increased amyloid burden; abnormal LPS secretion; misregulation of the HPA axis and vagus nerve signaling; neuroinflammation; oxidative stress; aberrant immune activity; alterations in the biodiversity and composition of the gut microbiota; downregulation of BDNF and SCFAs; decreased neurotransmitters secretion; and abnormal release of gasotransmitters (Fig. 5).

#### 4. Social isolation stress

Social isolation stress (SIS) is a form of chronic stress that refers to a complete or almost complete lack of contact with conspecifics [88, 89]. Since humans are highly social, SIS can affect people of all ages and is known to be a trigger for emotional problems and cognitive dysfunction in adolescents [90]. SIS is also associated with an increased risk of death in the elderly. Robert et al. found that the incidence of AD in individuals affected by SIS was more than double that of the control group [91]. The recent Lancet Commission on Dementia Prevention, Intervention, and Care estimated that if the risk of SIS in

later life was eliminated, the prevalence of dementia would be reduced by 4%. The impact would be greater than that estimated for reducing physical inactivity in later life (2%) or hypertension in midlife (2%).

Positron emission tomography (PET) imaging has shown that A $\beta$  protein load is significantly correlated with increased loneliness [92]. Changes in some pathological markers of AD, such as increased amyloid beta plaques and neurofibrillary tangles, are not always equivalent to the degree of cognitive decline or clinical dementia. The closest neurobiological association with cognitive decline in AD is synaptic degeneration and/or loss. Therefore, many technologies that can directly measure biomarkers of synapse loss or damage have already been adopted in clinical settings. These include PET ligands that label synapses in vivo and biomarkers that detect synaptic degeneration in the cerebrospinal fluid [93-95]. The emergence of these technologies provided new evidence indicating that SIS affects the onset of AD by inducing increased synaptic degeneration and/or loss [96].

It is well established that various SIS models can induce AD-type pathological features (Table 2). APP/PS1 mice showed normal hippocampal long-term potentiation (LTP) and situational fear conditioning at the age of 3 months, indicating that they had no defects in learning and memory [97]. However, when APP/PS1 mice were raised in social isolation, cognitive impairment was already evident at 3 months of age and was accompanied by a massive increase in A $\beta$ . This latter effect was due to a significant increase in the activity of  $\beta$ - and  $\gamma$ -secretase, resulting in excessive production of A $\beta_{40}$  and A $\beta_{42}$  in the hippocampus [98]. In addition, the researchers also found that SIS increased calpain activity and the p25/p35 ratio, while reducing membrane-associated p35. The main reason for this was that the large amount of A $\beta$  promoted calcium influx and calpain activation. Calpain-mediated proteolysis releases p25 from the N-terminus of p35, and an increased p25/p35 ratio promotes tau phosphorylation and induces neuronal death [99]. Furthermore, membrane-associated p35 interacts with the AMPA receptor subunit GluR1 and  $\alpha$ -CamKII to form the p35-GluR1-CamKII complex. SIS reduces the interaction of p35-GluR1-CamKII. Since the p35-GluR1-CamKII complex is important for synaptic plasticity, learning, and memory, this decrease in the formation of the complex resulting from SIS leads to memory and cognitive impairment in APP/PS1 mice [100, 101]. Cao et al. raised APP/PS1 transgenic AD mice singly for 8 weeks at the age of 1 month. They found SIS increased hippocampal cell apoptosis, synaptic protein loss, glial activation, and triggered inflammatory responses by increasing the expression of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [102].

Huang and colleagues housed seventeen-month-old APP/PS1 mice in isolation for 3 months and found that

this exacerbated hippocampal atrophy, increased the accumulation of hippocampal A $\beta$  plaques, and induced cognitive dysfunction. Expression of  $\gamma$ -secretase was increased, and that of neprilysin (NEP) was decreased. Synapse and myelin loss, as well as glial neuroinflammatory reactions, were exacerbated [88]. NEP and insulin-degrading enzymes (IDE) are two major A $\beta$ -degrading enzymes that play a vital role in maintaining A $\beta$  homeostasis in the brain via A $\beta$  degradation. NEP expression is negatively correlated with A $\beta$  accumulation and cognitive impairment severity, while the expression levels of IDE do not seem to be correlated with these two events. In addition, similarly to what has been noticed for CRS, the large amount of A $\beta$  induced by SIS can promote intracellular calcium ion overload and tau protein hyperphosphorylation, disrupt mitochondrial energy metabolism, aggravate oxidative stress, and activate neuronal apoptosis and other pathways that affect the normal structure and function of the hippocampus negatively [103].

In another APP transgenic mouse model (Tg2576), the subjects developed normally until 9 months of age, and almost no  $\beta$ -amyloid deposits are detectable in the brain [104]. After these mice were individually housed in special cages one-third the size of a standard mouse cage from weaning to 6 months, a large number of senile plaques formed by the deposition of A $\beta_{42}$  were observed in the brain, resulting in impaired the ability to generate new cells in the dentate gyrus of the hippocampus [105]. Neurogenesis of the hippocampal dentate gyrus is thought to be related to learning and memory [106]. Increased A $\beta$  deposition can damage neurons by disrupting intracellular calcium ion homeostasis, inducing oxidative stress, and causing massive release of glutamate [107]. Studies in rats have found that SIS during 6 consecutive weeks can induce tau hyperphosphorylation and deficits in learning and spatial memory in middle-aged rats [89]. Research into the underlying mechanism showed that SIS inhibited the phosphorylation of GSK3 $\beta$  at Ser9, resulting in an increase in GSK3 $\beta$  activity. Since GSK3 kinase plays an essential role in regulating tau phosphorylation, this in turn led to tau hyperphosphorylation and deficits in spatial memory. In addition, the BDNF/PI3K/Akt/GSK3 $\beta$  signaling pathway plays important roles in synapse formation, neuronal differentiation and survival, and regulation of synaptic structure and function [108]. Gong et al. found that SIS reduced the expression of BDNF, serine 473-phosphorylated Akt, and serine 9-GSK3 $\beta$  [109]. Ali et al. found that SIS increased  $\beta$ -secretase, A $\beta$  protein, Tyr-216-GSK3 $\beta$ , phosphorylated tau, malondialdehyde, IL-1 $\beta$ , and TNF- $\alpha$  gene expression levels [110].

**Table 2.** Rodent studies on impact of social isolation stress (SIS) and chronic noise exposure (CNE) on AD-related markers.

Stress paradigm	Procedure	Animal model	Relevance to AD	Ref.
SIS	Mice were singly housed for 3 months.	APP/PS1 transgenic mouse	Cognitive dysfunction and A $\beta$ plaque accumulation $\uparrow$ Exacerbated hippocampal atrophy	88
	Isolated rats were housed in cages measuring 38 $\times$ 22 $\times$ 20 cm, while group rats were maintained in cages measuring 48 $\times$ 30 $\times$ 20 cm, for 6 weeks.	Sprague–Dawley rat	p-tau $\uparrow$ Spatial memory deficit	89
	Mice were individually housed (one mice per cage) for a period of about 7 weeks.	APP/PS1 transgenic mouse	A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> $\uparrow$ Memory impairment	98
	Mice were individually housed (one mice per cage) for a period of about 8 weeks.	APP/PS1 transgenic mouse	p-tau, A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> $\uparrow$ Accelerated cognitive and memory deficits	100
	Mice were individually housed in cages one third the size of a standard cage and placed in a separate room from weaning until 6 months of age.	Tg2576 transgenic mouse	A $\beta$ <sub>42</sub> and $\beta$ -amyloid plaque deposition $\uparrow$ Contextual memory $\downarrow$	105
	Isolated rats were housed individually in cages, while the same size of the cages housed 4 control animals, for 5 weeks.	Wistar rat	A $\beta$ and p-tau $\uparrow$ Spatial learning and memory $\downarrow$	110
CNE	Exposed to 75 dB noise 8 h/d either for the light-cycle group or the dark-cycle group, for 30 days.	C57BL/6NJ mouse	Impairments in learning and memory Hippocampal volume $\downarrow$	114
	Emitted an intermittent 3000Hz frequency sound of 90 dB for 1 sec in the intervals of 15 sec during 24 h.	C57BL/6 mouse	Learning and memory performance $\downarrow$	115
	80 dB, frequency was from 10 to 10,000 Hz, 2h/d, for 6 weeks.	Kunming mouse	p-tau $\uparrow$ Impaired the learning and memory ability	117
	100 dB white noise, 4 h/d, for 14 days.	Wistar rat	p-tau $\uparrow$ Formation of pathological neurofibrillary tangle	120
	Exposed to noise for 4 h every day up to 14 days at 110 dB of noise level.	C57BL/6 mouse	Spatial memory deficits	126

## 5. Chronic noise stress

Noise stress is harmful, particularly to the CNS. According to previous reports, chronic noise exposure (CNE) can induce cognitive impairment and is also a predisposing factor for AD pathogenesis [111–113]. There is a compelling body of research on the effect of CNE on pathological features and mechanisms associated with AD (Table 2) which will be discussed below.

CNE can promote the secretion of CRF and glucocorticoids by activating the HPA axis and the CRF pathway, thereby promoting tau phosphorylation and other AD-related pathologies [114–116]. Hyperphosphorylation of tau reminiscent of what is observed in AD has been found in the brains of rats exposed to long-

term noise. In this rat model, the increase in tau phosphorylation differs between chronic and acute stress, but both can cause cognitive impairment [117, 118]. In the chronic stress model, the phosphorylation of tau is permanently increased, whereas in the acute stress model, tau begins to dephosphorylate 24 h after the stressor is removed [119]. The expression of PP2A in the rat model of CNE is increased, which is the opposite of what has been observed in the AD brain. It has been postulated that when the level of PP2A increases, the increase in GSK3 $\beta$  activity is responsible for the tau phosphorylation, thereby counteracting the dephosphorylation effect of PP2A [120]. Other studies have found A $\beta$  production and abnormal phosphorylation of tau were evident in the

brains of Kunming mice and SAMP8 after CNE [117, 121].

CNE can induce neuronal damage, particularly in the hippocampus, ultimately causing neuronal loss and memory impairments [114]. The hyperphosphorylation and aggregation of tau caused by CNE results in neurofibrillary tangles, and the massive production and deposition of A $\beta$  can cause disorders of synaptic function and apoptosis of nerve cells, ultimately also inducing learning and memory impairments. The hyperphosphorylation of the tau is mediated by the GluN2B subunit of NMDARs. Once this signaling pathway is overactivated, the kinases GSK3 $\beta$  and CDK5 associated with tau phosphorylation are activated through the GluN2B-Fyn signaling pathway. GluN2B can also directly inhibit the activity of PP2A [122]. Other studies have reached similar conclusions, namely, CNE-induced disruption of the NMDAR signaling pathway ultimately leads to high phosphorylation of tau. Use of the NMDAR antagonist MK-801 can reverse the activation of GSK3 $\beta$  and the increase in tau protein phosphorylation induced by noise stress [123]. In addition, CNE can increase the level of glutamate in the brain and thus promotes the influx of Ca<sup>2+</sup>, which triggers ROS production and inhibits LTP [124].

Other researchers have determined that oxidative stress can promote the generation and deposition of A $\beta$  as well as tau phosphorylation. Oxidative stress is increased in response to noise stress and could therefore mediate the occurrence of AD-type pathological features [125, 126]. The main effects of oxidative stress are increased APP expression, decreased  $\alpha$ -secretase activity, and increased expression and activation of  $\beta$ - and  $\gamma$ -secretase [127].

## 6. Chronic unpredictable mild stress

Chronic unpredictable mild stress (CUMS), also called chronic variable stress, refers to an inconsistency in the exposure to stress or to the use of multiple different forms of stress in a single stress model to achieve unpredictable effects. As the stress-inducing procedure varies among different studies, it is difficult to compare the results and draw any general conclusion (Table 3). For example, in a study by Han et al., the results of their CUMS procedure did not show any increase in A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> in the mouse hippocampus. In another study involving APP/PS1 mice, CUMS was introduced under the same conditions, and in this instance, it not only promoted the expression of A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub>, but also induced neuronal injury and cognitive impairment [128]. Consistent with Han's report, Bing et al. found that CUMS induced A $\beta$  deposition and severe impairment of cognitive behavior in APP/PS1 mice for 4 weeks, but they observed no significant effect on wild type C57 mice. The authors believe that the main reason

behind these contradictory results is that six-month-old C57 mice have better tolerance to CUMS because they are at the peak of brain function development. In addition, these results are clearly dependent on the physical conditions of the mice and the skills of the experimenters [129]. Hossein et al. used another model of CUMS and found that it significantly increased A $\beta$  levels in the hippocampus of adult male rats [130], but the effect on tau phosphorylation was not reported. We previously exposed ten-week-old C57 mice to CRS for 4 weeks and detected tau hyperphosphorylation in the hippocampus and prefrontal cortex [37]. In addition, Carroll et al. found that exposure to CRS rather than CUMS for one month exacerbated A $\beta$  levels in Tg2576 transgenic mice [7].

The results obtained in studies that adopted the unpredictable stress model are diverse. It has been reported in the literature that after 4 consecutive weeks of CUMS in wild type rats, tau is abnormally phosphorylated in the hippocampus and prefrontal cortex, and behavioral tests shown a decline in learning and memory ability [131]. Another study reported that CUMS can induce the production of A $\beta$ <sub>42</sub> in the hippocampal CA1 region of rats [132]. Research by Peay et al. found that CUMS only damaged the spatial memory of male rats but had no significant effect on female rats [133]. Studies have confirmed that abnormal expression or activation of Fyn is closely related to tau phosphorylation, amyloid accumulation, and cognitive decline in patients with AD [134-136] and blocking the abnormal activation of Fyn can protect neurons from A $\beta$  toxicity [137]. Lopes et al. utilized another model of CUMS that could induce tau phosphorylation, neuronal atrophy, dendritic spine shortening, and learning and memory disorders in 4- to 6-month-old wild-type mice and found that CUMS upregulated Fyn expression in the hippocampus [138]. Upregulated Fyn interacts with PSD-95 and GluN2B to form a GluN2B/PSD-95/Fyn complex, which regulates the activation of glutamate NMDARs. The activation of NMDARs in turn activates two key tau protein kinases, GSK3 $\beta$  and CDK5. Furthermore, Fyn also plays an important role in mediating tau-induced neuropathology [139].

Four-month-old Tg2576 transgenic mice were subjected to CUMS for 7 weeks. Almost no AD-type pathological features were detected in the brains of the control group, and their behaviors were normal, whereas the CUMS-exposed group showed A $\beta$  deposition and tau phosphorylation in the brain. Cognitive impairment was also demonstrated in this study using the water maze test. The proposed mechanism was an increase in the activity of  $\beta$ -secretase and an inhibition in the expression of Ser9-GSK3 $\beta$  [140], which is similar to the mechanism underlying the pathological changes in response to noise stress.



**Table 3.** Rodent studies on impact of chronic unpredictable mild stress (CUMS) on AD-related markers.

Stress paradigm	Procedure	Animal model	Relevance to AD	Ref.
CUMS	The stressors included: (1) long swim for 20 min in a 30 °C water bath, (2) cold swim for 2.5 min in a 15 °C water bath, (3) restraint for 15 min in a 50 ml conical tube, (4) housed in isolation for 24 h, (5) housed with soiled bedding for 24 h, and (6) housed under lights-on conditions for 24 h. One stressor per day for 6 d/week, and for 4 weeks.	Tg2576 transgenic mouse	No changes on A $\beta$ <sub>40</sub> , A $\beta$ <sub>42</sub> and p-tau Displayed no spatial memory impairment Displayed impairment on both context and cued fear conditioning	7
	The stressors included: (1) food deprivation for 24 h, (2) water deprivation for 24 h, (3) overnight illumination, (4) removal sawdust for 24 h, (5) soiled cage for 24 h, (6) forced swimming at 8 °C for 6 min, (7) tail nipping, and (8) physically restraint for 2 h. Stressors 2-3 times a day for 4 weeks.	C57BL/6 mouse	No changes on A $\beta$ <sub>40</sub> , A $\beta$ <sub>42</sub> and senile plaque deposition Cognitive deficiency	128
		APP/PS1 transgenic mouse	A $\beta$ <sub>40</sub> , A $\beta$ <sub>42</sub> and senile plaque deposition ↑ Significantly cognitive deficiency	
	The stressors included: (1) bending the cage at 45° for 24 h, (2) 24 h contact with wet bedding, (3) swimming in 4 °C water for 5 min, (4) swimming in 45 °C water for 5 min, (5) overnight illumination, (6) 12 h of food deprivation, and (7) 12 h of water deprivation. One stressor per day for 4 weeks.	Wistar rat	A $\beta$ ↑  Impairment of learning and memory	130
	Application of one of the following stressors, daily: hypertonic saline, overcrowding for 1 h, placement in a confined environment (30 min), or placement on a vibrating/rocking platform (1 h); for 1 month.	Wistar rat	p-tau ↑  Deficits in learning and memory	131
	Application of one of the following stressors, daily: 24-h food deprivation, 24-h water deprivation, 5-min cold swimming (6 °C), 1-min tail pinch, physically restraint for 2 h, exposure to rat odor for 1 h and overnight illumination; for 4 weeks.	Wistar rat	Soluble and insoluble A $\beta$ <sub>42</sub> ↑  Deficits in learning and memory	132
	Animals were exposed to one of the following stressors once a day for 1 hour: restraint, vibrating platform, overcrowding, or a hot air stream on consecutive days; for 6 weeks.	C57BL/6J mouse	p-tau ↑  Impairments in spatial learning and memory	138
	Application of 2-3 following stressors in any 24 h period: Low intensity stroboscopic illumination (8 h), intermittent bell ringing (10 db, 1/10 s), or white noise (4 h), 45° cage tilt (8 h), damp bedding (6 h), rat odor (8 h), darkness during the day (3 h), transfer of cages to another room (4 h), placement of a novel object in the cage (3 h), overnight water and food deprivation, illumination and removal of nesting material (12 h), and swimming in cold water (18 °C, 5 min); for 6 weeks.	Tg2576 transgenic mice	A $\beta$ <sub>40</sub> , A $\beta$ <sub>42</sub> and senile plaque deposition ↑  p-tau ↑  Impairment of learning and memory	140

## 7. Conclusion

We are inevitably affected by stressful events. It is of great significance to investigate the pathological features and mechanisms responsible for AD in response to chronic stress. A reliable animal stress model is essential for this purpose. Although not all stress animal models can fully replicate the AD-type pathological features, tau hyperphosphorylation, A $\beta$  overproduction and deposition, and learning, memory, and cognitive dysfunction can be induced in most of them (Table1, Table2, Table3). HPA axis dysfunction, abnormalities in the CRF system and glutamate systems, neuro-

inflammation, aberrant immune activity, dysbiosis of the gut microbiota, downregulation of neurotrophic factors, synaptic degeneration, and changes in the activity and expression of GSK3 $\beta$ , CDK5, and PP2A in response to chronic stress are all of great significance in the pathogenesis of AD. This line of research provides a basis for the development of more effective prevention and treatments strategies aimed at improving the quality of life of affected individuals.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant number:81471285), Natural Science Foundation of Guangdong Province (grant number:2021A1515012143), China Postdoctoral Science Foundation (grant number: 2019M663104), and Shenzhen Science and Technology Innovation Commission (grant number: JCYJ20220530150616038, JCYJ20220530151209021, JCYJ20190806165001761).

## Conflict of interest

The authors declare no conflicts of interest.

## References

- [1] Taheri-Targhi S, Gjedde A, Araj-Khodaei M, Rikhtegar R, Parsian Z, Zarrintan S, et al. (2019). Avicenna (980-1037 CE) and his Early Description and Classification of Dementia. *J Alzheimers Dis*, 71:1093-1098.
- [2] Rudy CC, Hunsberger HC, Weitzner DS, Reed MN (2015). The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. *Aging Dis*, 6:131-148.
- [3] Barnes DE, Yaffe K (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*, 10:819-828.
- [4] R AA (2019). Risk factors for Alzheimer's disease. *Folia Neuropathol*, 57:87-105.
- [5] Wilson RS, Barnes LL, Bennett DA, Li Y, Bienias JL, Mendes de Leon CF, et al. (2005). Proneness to psychological distress and risk of Alzheimer disease in a biracial community. *Neurology*, 64:380-382.
- [6] Shan Y, Wang DD, Xu YX, Wang C, Cao L, Liu YS, et al. (2016). Aging as a Precipitating Factor in Chronic Restraint Stress-Induced Tau Aggregation Pathology, and the Protective Effects of Rosmarinic Acid. *J Alzheimers Dis*, 49:829-844.
- [7] Carroll JC, Iba M, Bangasser DA, Valentino RJ, James MJ, Brunden KR, et al. (2011). Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *J Neurosci*, 31:14436-14449.
- [8] Szabo S, Yoshida M, Filakovszky J, Juhasz G (2017). "Stress" is 80 Years Old: From Hans Selye Original Paper in 1936 to Recent Advances in GI Ulceration. *Curr Pharm Des*, 23:4029-4041.
- [9] McEwen BS (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*, 87:873-904.
- [10] Dai S, Mo Y, Wang Y, Xiang B, Liao Q, Zhou M, et al. (2020). Chronic Stress Promotes Cancer Development. *Front Oncol*, 10:1492.
- [11] Esler M (2017). Mental stress and human cardiovascular disease. *Neurosci Biobehav Rev*, 74:269-276.
- [12] Antoniuk S, Bijata M, Ponimaskin E, Wlodarczyk J (2019). Chronic unpredictable mild stress for modeling depression in rodents: Meta-analysis of model reliability. *Neurosci Biobehav Rev*, 99:101-116.
- [13] Wirtz PH, von Känel R (2017). Psychological stress, inflammation, and coronary heart disease. *Curr Cardiol Rep*, 19:111.
- [14] Lyons CE, Bartolomucci A (2020). Stress and Alzheimer's disease: A senescence link? *Neurosci Biobehav Rev*, 115:285-298.
- [15] Ávila-Villanueva M, Gómez-Ramírez J, Maestú F, Venero C, Ávila J, Fernández-Blázquez MA (2020). The Role of Chronic Stress as a Trigger for the Alzheimer Disease Continuum. *Front Aging Neurosci*, 12:561504.
- [16] Brivio P, Sbrini G, Corsini G, Paladini MS, Racagni G, Molteni R, et al. (2020). Chronic Restraint Stress Inhibits the Response to a Second Hit in Adult Male Rats: A Role for BDNF Signaling. *Int J Mol Sci*, 21.
- [17] Muñoz-Mayorga D, Rissman RA, Morales T (2020). Reproductive status impacts on tau phosphorylation induced by chronic stress. *Neurobiol Stress*, 13:100241.
- [18] Takuma K, Matsuo A, Himeno Y, Hoshina Y, Ohno Y, Funatsu Y, et al. (2007). 17beta-estradiol attenuates hippocampal neuronal loss and cognitive dysfunction induced by chronic restraint stress in ovariectomized rats. *Neuroscience*, 146:60-68.
- [19] Jeong YH, Park CH, Yoo J, Shin KY, Ahn SM, Kim HS, et al. (2006). Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model. *FASEB J*, 20:729-731.
- [20] Hains AB, Yabe Y, Arnsten AF (2015). Chronic Stimulation of Alpha-2A-Adrenoceptors With Guanfacine Protects Rodent Prefrontal Cortex Dendritic Spines and Cognition From the Effects of Chronic Stress. *Neurobiol Stress*, 2:1-9.
- [21] Masugi F, Ogiwara T, Sakaguchi K, Otsuka A, Tsuchiya Y, Morimoto S, et al. (1989). High plasma levels of cortisol in patients with senile dementia of the Alzheimer's type. *Methods Find Exp Clin Pharmacol*, 11:707-710.
- [22] Saeedi M, Rashidy-Pour A (2021). Association between chronic stress and Alzheimer's disease: Therapeutic effects of Saffron. *Biomed Pharmacother*, 133:110995.
- [23] Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM (2006). Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci*, 26:9047-9056.
- [24] De Souza EB, Whitehouse PJ, Kuhar MJ, Price DL, Vale WW (1986). Reciprocal changes in corticotropin-releasing factor (CRF)-like immunoreactivity and CRF receptors in cerebral cortex of Alzheimer's disease. *Nature*, 319:593-595.
- [25] Rissman RA, Staup MA, Lee AR, Justice NJ, Rice KC, Vale W, et al. (2012). Corticotropin-releasing factor

- receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation. *Proc Natl Acad Sci U S A*, 109:6277-6282.
- [26] Rissman RA, Lee KF, Vale W, Sawchenko PE (2007). Corticotropin-releasing factor receptors differentially regulate stress-induced tau phosphorylation. *J Neurosci*, 27:6552-6562.
- [27] Bale TL, Vale WW (2004). CRF and CRF receptors: role in stress responsivity and other behaviors. *Annu Rev Pharmacol Toxicol*, 44:525-557.
- [28] Zhao D, Zhou Y, Huo Y, Meng J, Xiao X, Han L, et al. (2021). RPS23RG1 modulates tau phosphorylation and axon outgrowth through regulating p35 proteasomal degradation. *Cell Death Differ*, 28:337-348.
- [29] Szaruga M, Munteanu B, Lismont S, Veugelen S, Horré K, Mercken M, et al. (2017). Alzheimer's-Causing Mutations Shift A $\beta$  Length by Destabilizing  $\gamma$ -Secretase-A $\beta$ n Interactions. *Cell*, 170:443-456 e414.
- [30] Willem M, Tahirovic S, Busche MA, Ovsepian SV, Chafai M, Kootar S, et al. (2015).  $\eta$ -Secretase processing of APP inhibits neuronal activity in the hippocampus. *Nature*, 526:443-447.
- [31] Morel B, Carrasco-Jiménez MP, Jurado S, Conejero-Lara F (2021). Rapid Conversion of Amyloid-Beta 1-40 Oligomers to Mature Fibrils through a Self-Catalytic Bimolecular Process. *Int J Mol Sci*, 22.
- [32] Campbell SN, Zhang C, Roe AD, Lee N, Lao KU, Monte L, et al. (2015). Impact of CRFR1 Ablation on Amyloid- $\beta$  Production and Accumulation in a Mouse Model of Alzheimer's Disease. *J Alzheimers Dis*, 45:1175-1184.
- [33] Zhang C, Kuo CC, Moghadam SH, Monte L, Campbell SN, Rice KC, et al. (2016). Corticotropin-releasing factor receptor-1 antagonism mitigates beta amyloid pathology and cognitive and synaptic deficits in a mouse model of Alzheimer's disease. *Alzheimers Dement*, 12:527-537.
- [34] Ageta-Ishihara N, Yamazaki M, Konno K, Nakayama H, Abe M, Hashimoto K, et al. (2015). A CDC42EP4/septin-based perisynaptic glial scaffold facilitates glutamate clearance. *Nat Commun*, 6:10090.
- [35] Sharma A, Kazim SF, Larson CS, Ramakrishnan A, Gray JD, McEwen BS, et al. (2019). Divergent roles of astrocytic versus neuronal EAAT2 deficiency on cognition and overlap with aging and Alzheimer's molecular signatures. *Proc Natl Acad Sci U S A*, 116:21800-21811.
- [36] Paoletti P, Bellone C, Zhou Q (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci*, 14:383-400.
- [37] Liu Y, Cao L, Zhang X, Liang Y, Xu Y, Zhu C (2019). Memantine Differentially Regulates Tau Phosphorylation Induced by Chronic Restraint Stress of Varying Duration in Mice. *Neural Plast*, 2019:4168472.
- [38] Hardingham GE, Bading H (2010). Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci*, 11:682-696.
- [39] Zhu L, Yang L, Zhao X, Liu D, Guo X, Liu P, et al. (2018). Xanthoceraside modulates NR2B-containing NMDA receptors at synapses and rescues learning-memory deficits in APP/PS1 transgenic mice. *Psychopharmacology (Berl)*, 235:337-349.
- [40] Lai TW, Zhang S, Wang YT (2014). Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog Neurobiol*, 115:157-188.
- [41] Babaei P (2021). NMDA and AMPA receptors dysregulation in Alzheimer's disease. *Eur J Pharmacol*, 908:174310.
- [42] Xia P, Chen HS, Zhang D, Lipton SA (2010). Memantine preferentially blocks extrasynaptic over synaptic NMDA receptor currents in hippocampal autapses. *J Neurosci*, 30:11246-11250.
- [43] Hardingham GE (2020). Targeting Synaptic NMDA Receptor Co-agonism as a Therapy for Alzheimer's Disease? *Cell Metab*, 31:439-440.
- [44] Li V, Wang YT (2016). Molecular mechanisms of NMDA receptor-mediated excitotoxicity: implications for neuroprotective therapeutics for stroke. *Neural Regen Res*, 11:1752-1753.
- [45] Borst K, Dumas AA, Prinz M (2021). Microglia: Immune and non-immune functions. *Immunity*, 54:2194-2208.
- [46] Bhaskar K, Maphis N, Xu G, Varvel NH, Kokiko-Cochran ON, Weick JP, et al. (2014). Microglial derived tumor necrosis factor- $\alpha$  drives Alzheimer's disease-related neuronal cell cycle events. *Neurobiol Dis*, 62:273-285.
- [47] Smith JA, Das A, Ray SK, Banik NL (2012). Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. *Brain Res Bull*, 87:10-20.
- [48] Hickman SE, Allison EK, El Khoury J (2008). Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci*, 28:8354-8360.
- [49] Liao YF, Wang BJ, Cheng HT, Kuo LH, Wolfe MS (2004). Tumor necrosis factor-alpha, interleukin-1beta, and interferon-gamma stimulate gamma-secretase-mediated cleavage of amyloid precursor protein through a JNK-dependent MAPK pathway. *J Biol Chem*, 279:49523-49532.
- [50] Quintanilla RA, Orellana DI, González-Billault C, Maccioni RB (2004). Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res*, 295:245-257.
- [51] Kim DM, Leem YH (2016). Chronic stress-induced memory deficits are reversed by regular exercise via AMPK-mediated BDNF induction. *Neuroscience*, 324:271-285.
- [52] Hashikawa-Hobara N, Otsuka A, Ishikawa R, Hashikawa N (2019). Roman chamomile inhalation combined with clomipramine treatment improves treatment-resistant depression-like behavior in mice. *Biomed Pharmacother*, 118:109263.
- [53] Heine VM, Zareno J, Maslam S, Joëls M, Lucassen PJ (2005). Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and

- Flk-1 protein expression. *Eur J Neurosci*, 21:1304-1314.
- [54] Lu B, Nagappan G, Guan X, Nathan PJ, Wren P (2013). BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nat Rev Neurosci*, 14:401-416.
- [55] Guo H, Xia D, Liao S, Niu B, Tang J, Hu H, et al. (2019). Vascular endothelial growth factor improves the cognitive decline of Alzheimer's disease via concurrently inducing the expression of ADAM10 and reducing the expression of  $\beta$ -site APP cleaving enzyme 1 in Tg2576 mice. *Neurosci Res*, 142:49-57.
- [56] Mateo I, Llorca J, Infante J, Rodríguez-Rodríguez E, Fernández-Viadero C, Peña N, et al. (2007). Low serum VEGF levels are associated with Alzheimer's disease. *Acta Neurol Scand*, 116:56-58.
- [57] Xu H, Yu ZH, Ge MJ, Shen JX, Han F, Pan C, et al. (2021). Estradiol attenuates chronic restraint stress-induced dendrite and dendritic spine loss and cofilin1 activation in ovariectomized mice. *Horm Behav*, 135:105040.
- [58] Zhang W, Ou H, Zhang B, Zheng M, Yan L, Chen Y, et al. (2021). Treadmill Exercise Relieves Chronic Restraint Stress-induced Cognitive Impairments in Mice Via Activating Protein Phosphatase 2A. *Neurosci Bull*, 37:1487-1492.
- [59] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaansen TFS, Boehme M, et al. (2019). The Microbiota-Gut-Brain Axis. *Physiol Rev*, 99:1877-2013.
- [60] Alkasir R, Li J, Li X, Jin M, Zhu B (2017). Human gut microbiota: the links with dementia development. *Protein Cell*, 8:90-102.
- [61] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI (2007). The human microbiome project. *Nature*, 449:804-810.
- [62] Larroya-García A, Navas-Carrillo D, Orenes-Piñero E (2019). Impact of gut microbiota on neurological diseases: Diet composition and novel treatments. *Crit Rev Food Sci Nutr*, 59:3102-3116.
- [63] Fung TC, Olson CA, Hsiao EY (2017). Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci*, 20:145-155.
- [64] Lu J, Synowiec S, Lu L, Yu Y, Bretherick T, Takada S, et al. (2018). Microbiota influence the development of the brain and behaviors in C57BL/6J mice. *PLoS One*, 13:e0201829.
- [65] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. (2011). Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A*, 108:16050-16055.
- [66] Kraimi N, Lormant F, Calandreau L, Kempf F, Zemb O, Lemarchand J, et al. (2022). Microbiota and stress: a loop that impacts memory. *Psychoneuroendocrinology*, 136:105594.
- [67] Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. (2017). Gut microbiome alterations in Alzheimer's disease. *Sci Rep*, 7:13537.
- [68] Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. (2017). Reduction of Abeta amyloid pathology in APPS1 transgenic mice in the absence of gut microbiota. *Sci Rep*, 7:41802.
- [69] Liu P, Wu L, Peng G, Han Y, Tang R, Ge J, et al. (2019). Altered microbiomes distinguish Alzheimer's disease from amnesic mild cognitive impairment and health in a Chinese cohort. *Brain Behav Immun*, 80:633-643.
- [70] Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, et al. (2020). Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*, 69:283-294.
- [71] Athari Nik Azm S, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, et al. (2018). *Lactobacilli* and *bifidobacteria* ameliorate memory and learning deficits and oxidative stress in  $\beta$ -amyloid (1-42) injected rats. *Appl Physiol Nutr Metab*, 43:718-726.
- [72] Sharma VK, Singh TG, Garg N, Dhiman S, Gupta S, Rahman MH, et al. (2021). Dysbiosis and Alzheimer's Disease: A Role for Chronic Stress? *Biomolecules*, 11.
- [73] Deng Y, Zhou M, Wang J, Yao J, Yu J, Liu W, et al. (2021). Involvement of the microbiota-gut-brain axis in chronic restraint stress: disturbances of the kynurenine metabolic pathway in both the gut and brain. *Gut Microbes*, 13:1-16.
- [74] Leblhuber F, Ehrlich D, Steiner K, Geisler S, Fuchs D, Lanser L, et al. (2021). The Immunopathogenesis of Alzheimer's Disease Is Related to the Composition of Gut Microbiota. *Nutrients*, 13.
- [75] Lee J, Venna VR, Durgan DJ, Shi H, Hudobenko J, Putluri N, et al. (2020). Young versus aged microbiota transplants to germ-free mice: increased short-chain fatty acids and improved cognitive performance. *Gut Microbes*, 12:1-14.
- [76] Hardy J, Selkoe DJ (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*, 297:353-356.
- [77] Zhao Y, Lukiw WJ (2015). Microbiome-generated amyloid and potential impact on amyloidogenesis in Alzheimer's disease (AD). *J Nat Sci*, 1.
- [78] Bostanciklioğlu M (2019). The role of gut microbiota in pathogenesis of Alzheimer's disease. *J Appl Microbiol*, 127:954-967.
- [79] Xiao Q, Shu R, Wu C, Tong Y, Xiong Z, Zhou J, et al. (2020). Crocin-I alleviates the depression-like behaviors probably via modulating "microbiota-gut-brain" axis in mice exposed to chronic restraint stress. *J Affect Disord*, 276:476-486.
- [80] Cheng Y, Liu J, Ling Z (2021). Short-chain fatty acids-producing probiotics: A novel source of psychobiotics. *Crit Rev Food Sci Nutr*:1-31.
- [81] Ho L, Ono K, Tsuji M, Mazzola P, Singh R, Pasinetti GM (2018). Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. *Expert Rev Neurother*, 18:83-90.



- [82] Gao X, Cao Q, Cheng Y, Zhao D, Wang Z, Yang H, et al. (2018). Chronic stress promotes colitis by disturbing the gut microbiota and triggering immune system response. *Proc Natl Acad Sci U S A*, 115:E2960-E2969.
- [83] Dalile B, Van Oudenhove L, Vervliet B, Verbeke K (2019). The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol*, 16:461-478.
- [84] Wu S, Liu X, Jiang R, Yan X, Ling Z (2021). Roles and Mechanisms of Gut Microbiota in Patients With Alzheimer's Disease. *Front Aging Neurosci*, 13:650047.
- [85] Szabo C (2010). Gaseotransmitters: new frontiers for translational science. *Sci Transl Med*, 2:59ps54.
- [86] Oleskin AV, Shenderov BA (2016). Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. *Microb Ecol Health Dis*, 27:30971.
- [87] Beaumont M, Andriamihaja M, Lan A, Khodorova N, Audebert M, Blouin JM, et al. (2016). Detrimental effects for colonocytes of an increased exposure to luminal hydrogen sulfide: The adaptive response. *Free Radic Biol Med*, 93:155-164.
- [88] Huang H, Wang L, Cao M, Marshall C, Gao J, Xiao N, et al. (2015). Isolation Housing Exacerbates Alzheimer's Disease-Like Pathophysiology in Aged APP/PS1 Mice. *Int J Neuropsychopharmacol*, 18:pyu116.
- [89] Ren QG, Gong WG, Wang YJ, Zhou QD, Zhang ZJ (2015). Citalopram attenuates tau hyperphosphorylation and spatial memory deficit induced by social isolation rearing in middle-aged rats. *J Mol Neurosci*, 56:145-153.
- [90] Fone KC, Porkess MV (2008). Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. *Neurosci Biobehav Rev*, 32:1087-1102.
- [91] Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, et al. (2007). Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry*, 64:234-240.
- [92] Donovan NJ, Okereke OI, Vannini P, Amariglio RE, Rentz DM, Marshall GA, et al. (2016). Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults. *JAMA Psychiatry*, 73:1230-1237.
- [93] Chen MK, Mecca AP, Naganawa M, Finnema SJ, Toyonaga T, Lin SF, et al. (2018). Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging. *JAMA Neurol*, 75:1215-1224.
- [94] Finnema SJ, Nabulsi NB, Eid T, Detyniecki K, Lin SF, Chen MK, et al. (2016). Imaging synaptic density in the living human brain. *Sci Transl Med*, 8:348ra396.
- [95] Galasko D, Xiao M, Xu D, Smirnov D, Salmon DP, Dewit N, et al. (2019). Synaptic biomarkers in CSF aid in diagnosis, correlate with cognition and predict progression in MCI and Alzheimer's disease. *Alzheimers Dement (N Y)*, 5:871-882.
- [96] Matthews GA, Nieh EH, Vander Weele CM, Halbert SA, Pradhan RV, Yosafat AS, et al. (2016). Dorsal Raphe Dopamine Neurons Represent the Experience of Social Isolation. *Cell*, 164:617-631.
- [97] Trinchese F, Liu S, Battaglia F, Walter S, Mathews PM, Arancio O (2004). Progressive age-related development of Alzheimer-like pathology in APP/PS1 mice. *Ann Neurol*, 55:801-814.
- [98] Hsiao YH, Kuo JR, Chen SH, Gean PW (2012). Amelioration of social isolation-triggered onset of early Alzheimer's disease-related cognitive deficit by N-acetylcysteine in a transgenic mouse model. *Neurobiol Dis*, 45:1111-1120.
- [99] Lee MS, Kwon YT, Li M, Peng J, Friedlander RM, Tsai LH (2000). Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature*, 405:360-364.
- [100] Hsiao YH, Chen PS, Chen SH, Gean PW (2011). The involvement of Cdk5 activator p35 in social isolation-triggered onset of early Alzheimer's disease-related cognitive deficit in the transgenic mice. *Neuropsychopharmacology*, 36:1848-1858.
- [101] Barria A, Muller D, Derkach V, Griffith LC, Soderling TR (1997). Regulatory phosphorylation of AMPA-type glutamate receptors by CaM-KII during long-term potentiation. *Science*, 276:2042-2045.
- [102] Cao M, Hu PP, Zhang YL, Yan YX, Shields CB, Zhang YP, et al. (2018). Enriched physical environment reverses spatial cognitive impairment of socially isolated APPswe/PS1dE9 transgenic mice before amyloidosis onset. *CNS Neurosci Ther*, 24:202-211.
- [103] Dhikav V, Anand K (2011). Potential predictors of hippocampal atrophy in Alzheimer's disease. *Drugs Aging*, 28:1-11.
- [104] Hsiao KK, Borchelt DR, Olson K, Johannsdottir R, Kitt C, Yunis W, et al. (1995). Age-related CNS disorder and early death in transgenic FVB/N mice overexpressing Alzheimer amyloid precursor proteins. *Neuron*, 15:1203-1218.
- [105] Dong H, Goico B, Martin M, Csernansky CA, Bertchume A, Csernansky JG (2004). Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience*, 127:601-609.
- [106] Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature*, 410:372-376.
- [107] Selkoe DJ (2001). Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev*, 81:741-766.
- [108] Park H, Poo MM (2013). Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci*, 14:7-23.
- [109] Gong WG, Wang YJ, Zhou H, Li XL, Bai F, Ren QG, et al. (2017). Citalopram Ameliorates Synaptic Plasticity Deficits in Different Cognition-Associated Brain Regions Induced by Social Isolation in Middle-Aged Rats. *Mol Neurobiol*, 54:1927-1938.
- [110] Ali AA, Ahmed HI, Khaleel SA, Abu-Elfotuh K (2019). Vinpocetine mitigates aluminum-induced cognitive

- impairment in socially isolated rats. *Physiol Behav*, 208:112571.
- [111] Jafari Z, Kolb BE, Mohajerani MH (2020). Noise exposure accelerates the risk of cognitive impairment and Alzheimer's disease: Adulthood, gestational, and prenatal mechanistic evidence from animal studies. *Neurosci Biobehav Rev*, 117:110-128.
- [112] Calderón-Garcidueñas L, Villarreal-Ríos R (2017). Living close to heavy traffic roads, air pollution, and dementia. *Lancet*, 389:675-677.
- [113] Paul KC, Haan M, Mayeda ER, Ritz BR (2019). Ambient Air Pollution, Noise, and Late-Life Cognitive Decline and Dementia Risk. *Annu Rev Public Health*, 40:203-220.
- [114] Jafari Z, Kolb BE, Mohajerani MH (2018). Chronic traffic noise stress accelerates brain impairment and cognitive decline in mice. *Exp Neurol*, 308:1-12.
- [115] Jafari Z, Mehla J, Kolb BE, Mohajerani MH (2017). Prenatal noise stress impairs HPA axis and cognitive performance in mice. *Sci Rep*, 7:10560.
- [116] Gai Z, Li K, Sun H, She X, Cui B, Wang R (2016). Effects of chronic noise on mRNA and protein expression of CRF family molecules and its relationship with p-tau in the rat prefrontal cortex. *J Neurol Sci*, 368:307-313.
- [117] Cheng L, Wang SH, Chen QC, Liao XM (2011). Moderate noise induced cognition impairment of mice and its underlying mechanisms. *Physiol Behav*, 104:981-988.
- [118] Manikandan S, Padma MK, Srikumar R, Jeya Parthasarathy N, Muthuvel A, Sheela Devi R (2006). Effects of chronic noise stress on spatial memory of rats in relation to neuronal dendritic alteration and free radical-imbalance in hippocampus and medial prefrontal cortex. *Neurosci Lett*, 399:17-22.
- [119] Cui B, Wu M, She X, Liu H (2012). Impulse noise exposure in rats causes cognitive deficits and changes in hippocampal neurotransmitter signaling and tau phosphorylation. *Brain Res*, 1427:35-43.
- [120] Cui B, Zhu L, She X, Wu M, Ma Q, Wang T, et al. (2012). Chronic noise exposure causes persistence of tau hyperphosphorylation and formation of NFT tau in the rat hippocampus and prefrontal cortex. *Exp Neurol*, 238:122-129.
- [121] Su D, Li W, She X, Chen X, Zhai Q, Cui B, et al. (2018). Chronic noise exposure exacerbates AD-like neuropathology in SAMP8 mice in relation to Wnt signaling in the PFC and hippocampus. *Sci Rep*, 8:14622.
- [122] Chohan MO, Iqbal K (2006). From tau to toxicity: emerging roles of NMDA receptor in Alzheimer's disease. *J Alzheimers Dis*, 10:81-87.
- [123] Cui B, Wu MQ, Zhu LX, She XJ, Ma Q, Liu HT (2013). Effect of chronic noise exposure on expression of N-methyl-D-aspartic acid receptor 2B and Tau phosphorylation in hippocampus of rats. *Biomed Environ Sci*, 26:163-168.
- [124] Arjunan A, Rajan R (2020). Noise and brain. *Physiol Behav*, 227:113136.
- [125] Hahad O, Prochaska JH, Daiber A, Muenzel T (2019). Environmental Noise-Induced Effects on Stress Hormones, Oxidative Stress, and Vascular Dysfunction: Key Factors in the Relationship between Cerebrocardiovascular and Psychological Disorders. *Oxid Med Cell Longev*, 2019:4623109.
- [126] Sikander HE, Park SY, Kim MJ, Park SN, Yang DW (2017). Neuroprotective effects of sildenafil against oxidative stress and memory dysfunction in mice exposed to noise stress. *Behav Brain Res*, 319:37-47.
- [127] Chen Z, Zhong C (2014). Oxidative stress in Alzheimer's disease. *Neurosci Bull*, 30:271-281.
- [128] Han B, Yu L, Geng Y, Shen L, Wang H, Wang Y, et al. (2016). Chronic Stress Aggravates Cognitive Impairment and Suppresses Insulin Associated Signaling Pathway in APP/PS1 Mice. *J Alzheimers Dis*, 53:1539-1552.
- [129] Han B, Wang JH, Geng Y, Shen L, Wang HL, Wang YY, et al. (2017). Chronic Stress Contributes to Cognitive Dysfunction and Hippocampal Metabolic Abnormalities in APP/PS1 Mice. *Cell Physiol Biochem*, 41:1766-1776.
- [130] Bakhtiari-Dovvombaygi H, Izadi S, Zare M, Asgari Hassanoloui E, Dinpanah H, Ahmadi-Soleimani SM, et al. (2021). Vitamin D3 administration prevents memory deficit and alteration of biochemical parameters induced by unpredictable chronic mild stress in rats. *Sci Rep*, 11:16271.
- [131] Sotiropoulos I, Catania C, Pinto LG, Silva R, Pollerberg GE, Takashima A, et al. (2011). Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. *J Neurosci*, 31:7840-7847.
- [132] Gu HF, Nie YX, Tong QZ, Tang YL, Zeng Y, Jing KQ, et al. (2014). Epigallocatechin-3-gallate attenuates impairment of learning and memory in chronic unpredictable mild stress-treated rats by restoring hippocampal autophagic flux. *PLoS One*, 9:e112683.
- [133] Peay DN, Saribekyan HM, Parada PA, Hanson EM, Badaruddin BS, Judd JM, et al. (2020). Chronic unpredictable intermittent restraint stress disrupts spatial memory in male, but not female rats. *Behav Brain Res*, 383:112519.
- [134] Kaufman AC, Salazar SV, Haas LT, Yang J, Kostylev MA, Jeng AT, et al. (2015). Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. *Ann Neurol*, 77:953-971.
- [135] Low CYB, Lee JH, Lim FTW, Lee C, Ballard C, Francis PT, et al. (2021). Isoform-specific upregulation of FynT kinase expression is associated with tauopathy and glial activation in Alzheimer's disease and Lewy body dementias. *Brain Pathol*, 31:253-266.
- [136] Li C, Götz J (2017). Somatodendritic accumulation of Tau in Alzheimer's disease is promoted by Fyn-mediated local protein translation. *EMBO J*, 36:3120-3138.
- [137] Briner A, Götz J, Polanco JC (2020). Fyn Kinase Controls Tau Aggregation In Vivo. *Cell Rep*, 32:108045.

- [138] Lopes S, Vaz-Silva J, Pinto V, Dalla C, Kokras N, Bedenk B, et al. (2016). Tau protein is essential for stress-induced brain pathology. *Proc Natl Acad Sci U S A*, 113:E3755-3763.
- [139] Liu G, Fiock KL, Levites Y, Golde TE, Hefti MM, Lee G (2020). Fyn depletion ameliorates tau(P301L)-induced neuropathology. *Acta Neuropathol Commun*, 8:108.
- [140] Cuadrado-Tejedor M, Ricobaraza A, Frechilla D, Franco R, Pérez-Mediavilla A, Garcia-Osta A (2012). Chronic mild stress accelerates the onset and progression of the Alzheimer's disease phenotype in Tg2576 mice. *J Alzheimers Dis*, 28:567-578.