



Research Progress on Mechanism of Neuroprotective Roles of Apelin-13 in Prevention and Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common type of dementia. Currently, more than 50 million people live with dementia worldwide, and this number is expected to increase. Some of the typical pathological changes of AD include amyloid plaque, hyperphosphorylation of tau protein, secretion of inflammatory mediators, and neuronal apoptosis. Apelin is a neuroprotective peptide that is widely expressed in the body. Among members of apelin family, apelin-13 is the most abundant with a high neuroprotective function. Apelin-13/angiotensin domain type 1 receptor-associated proteins (APJ) system regulates several physiological and pathophysiological cell activities, such as apoptosis, autophagy, synaptic plasticity, and neuroinflammation. It has also been shown to prevent AD development. This article reviews the research progress on the relationship between apelin-13 and AD to provide new ideas for prevention and treatment of AD.

Keywords Apelin-13 · AD · Amyloid beta · Neuroprotection

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease which is considered the most common cause of dementia [1]. The recent diagnostic criteria and guidelines for AD indicate that brain changes in patients with AD begin before symptoms such as memory loss. Therefore, intervention for early brain changes is critical in preventing and decelerating development of the disease [2]. Most patients in an advanced stage of the disease need nonstop care, which brings great pressure on their family and society

at large. Such problems have especially become more apparent during COVID-19 [3]. Apelin-13 is acknowledged to be the predominant neuropeptide in neuroprotection functioning in preventing the onset of AD and arresting AD's progression [4]. First, apelin-13 exerts its neuroprotective effects by acting directly or indirectly on anti-apoptosis, autophagy regulation, promoting microglial polarization and improving neuronal synaptic plasticity, which help in arresting the progression of AD [5]. Second, it reduces the production of β -amyloid protein ($A\beta$) and phosphorylation of tau protein and then lowers the risk of AD occurrence. In addition, apelin-13 arrests the progression of AD through reducing oxidative stress, anti-neuroinflammation and other mechanisms [6]. This study reviews the research progress on the regulatory role of apelin-13 in cell activity and neuronal microenvironment associated with AD.

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Alzheimer's Disease

Globally, there are over 50 million patients with dementia with most of them having Alzheimer's disease. With the aging trend of the world population, the number of patients with AD in the world is expected to double by the year 2050 [1]. The main pathological hallmarks of AD are amyloid plaques. They consist of aggregated $A\beta$, neurofibrillary

tangles (NFTs) contributed by hyperphosphorylation of tau protein in general neurons [7]. Aggregation of A β causes a decrease in synapse number and a reduction of synaptic plasticity because of persistent neuronal damage in the brain. Neurofibrillary tangles (NFTs) also perturb the transport of nutrients and essential molecules in neurons, leading to neuron death [8]. The brains of patient with late-stage AD manifest inflammation, significant atrophy and widespread fragments of dead neurons [9]. Currently, the amyloid hypothesis is generally adopted [10]. However, recent research shows that A β is proposed to regulate learning and memory, angiogenesis, neurogenesis, repair leaks in the blood–brain barrier (BBB) and act as an antimicrobial peptide and tumor suppressor [11, 12]. It has been reported that many roles of A β contradicts the traditional concept. This provides a novel insight into role of A β in physiological regulation. However, these outcomes are affected by multiple variables and hence statistical research as well as further experimental research are required to account for the heterogeneity and the peculiar phenomena.

Although the effect of anti-A β therapy on blocking AD progression is striking, it's not the only target for AD therapy [13]. Another typical pathological characteristic of AD is the formation of NFTs [14]. In addition, neuroinflammatory reactions driven by microglia and astrocytes also play a prominent role in the pathogenesis of AD [9]. A series of cellular activities including autophagy, apoptosis, lipid metabolism and synaptic plasticity also indicates the pathogenesis of AD [15]. The pathogenesis of AD is orchestrated through plenty of regulation mechanisms [16, 17]. Interactive networks bring difficulties to further research and simultaneously provide more targets and options for AD's treatment.

Overview of Apelin-13

Apelin is a signaling molecule for impulse transmission between neurons [18]. It is widely expressed in many tissues and organs containing central nervous system (CNS), kidney and other peripheral organs [19]. The plasma content of apelin-13 is the highest and it is the main neuroprotective peptide. As the endogenous ligand of angiotensin domain type 1 receptor-associated proteins (APJ), apelin-13 system participates in several physiological and pathological processes such as vasculopathy, energy metabolism and maintenance of humoral homeostasis [20, 21]. Apelin-13/APJ system promotes proliferation of endothelial cells (ECs), which is a pivotal component of BBB [22]. Furthermore, apelin-13 plays a prominent role in repair of myocardial infarction [23]. Expression of apelin-13/APJ is down-regulated with aging. Knockout of apelin-13 and APJ gene accelerates aging in mouse model, while restoration of apelin-13 gene

restore vitality, behavior recovery and circadian rhythm phenotype [24]. It has been reported that the muscle function of mice lacking apelin-13 or its receptors deteriorates significantly with aging [25]. Elsewhere, experimental studies have indicated that apelin-13 leads to neuroprotection. This may be partly related to inhibition of autophagy and regulation of apoptosis in neurodegenerative disease [26]. Apelin-13 acts as an anti-inflammation factor by exerting an inhibitory effect on inflammation [27]. Additionally, the apelin-13/APJ system alleviates acute lung injury or acute respiratory distress syndrome by repressing oxidative reaction induced by mitochondrial reactive oxygen species (ROS), mitochondrial apoptosis and inflammatory response [6]. Furthermore, apelin-13 improves insulin sensitivity, lower blood glucose and blood lipids hence regulates the pathology of tumor [28–31]. It has protective effects in some neurodegenerative situations. A previous study suggests that apelin-13 plays a protective role against pentylentetrazole (PTZ)-induced toxicity by calcium blocking, antioxidant, anti-inflammatory and anti-apoptotic activity [32]. Roles of apelin-13 in anti-aging, anti-inflammation, anti-oxidation and proliferation as well as repair-promotion, are found firmly associated with AD. Therefore apelin-13 has shown to be a neuroprotective factor, which may be a suppressor for pathogenesis and development of AD (Fig. 1).

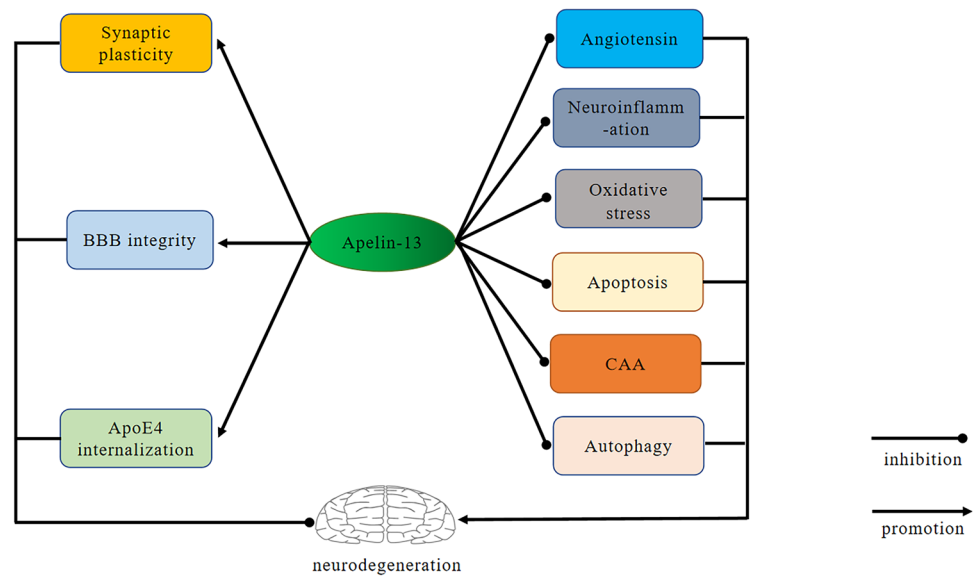
Mechanism in Inhibition Effects of Apelin-13 on AD

Alzheimer's Disease, Apelin-13 and Apoptosis Inhibition

Alzheimer's Disease and Apoptosis

Abnormal apoptosis of non-regenerative neurons in CNS contribute to a structural and functional damage of neural network. This has been demonstrated to be closely correlated with multiple neurodegenerative diseases [33]. It has been reported that neuronal apoptosis induced by A β , amyloid precursor protein (APP), ROS and other injurious factors causes pathogenesis of AD [34]. A β has been shown to induce nuclear translocation by regulating Yes-related proteins (YAP) and then promote expression and activation of Bcl-2-associated X protein (Bax), which eventually cause neuronal apoptosis [35]. Ischemic stroke-conditions that affect the brain and its blood supply is a common risk factor of AD [36]. Research studies have indicated that endoplasmic reticulum stress (ERS) and subsequently triggered unfolded protein response may be a crucial role in ischemia/reperfusion (I/R)-induced neuronal apoptosis in ischemic stroke [37].

Fig. 1 Overview of the main effects of Apelin-13 on Alzheimer’s disease. Apelin-13 exerts a positive effect on neurodegeneration by promoting improvement of synaptic plasticity, blood brain barrier (BBB) integrity, Apolipoprotein E4 (ApoE4) internalization and inhibiting neuroinflammation, apoptosis, autophagy, oxidative stress, angiotensin signaling and cerebrovascular amyloid angiopathy (CAA) formation



Apelin-13 and Apoptosis

Apelin-13 inhibits rotenone and Aβ induced injury and apoptosis in SH-SY5Y cells [38, 39]. It is also known that apelin-13 blocks apoptosis and excitotoxicity in mice with ischemic brain injury [40, 41]. Further, it has been found to increase cell survival under oxidative stress and decreased Bax/Bcl-2 ratio and caspase-3 protein’s expression in antioxidant stress experiment of hair cell-like cells derived from bone marrow mesenchymal stem cells [42]. Moreover, apelin-13 alleviated the motor behavioral defects and inhibited dopaminergic neurodegeneration in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridin (MPTP)-induced mice [43]. Inositol-requiring enzyme α (IRE1α) is necessary and sufficient to trigger ERS. There are clinical trials illustrating that a feedback mechanism exists to attenuate IRE1α ribonuclease activity in the presence of X-box binding protein 1 (XBP1) [44]. C/EBP homologous protein (CHOP) is important in ERS-induced apoptosis. Previous studies shows that apelin-13 also alleviated the activation of IRE1α/XBP1/CHOP signaling pathway in MPTP-induced mice [45]. For instance, it has been shown to activates the Galpha (i)/Galpha (q)-casein kinase 2 (CK2) signaling pathway and attenuates eukaryotic translation initiation factor 2 (eIF2)-activating transcription factor 4 (ATF4)-CHOP mediated apoptosis of neurons in ischemic stroke mice [46].

Glucagon-like peptide-1 receptor (GLP-1R) is a member of the G protein coupled receptor superfamily which is widely expressed in neurons [47]. The inhibitory effect of GLP-1R on neuronal apoptosis has been reported in the case of subarachnoid hemorrhage (SAH). In SAH mice, GLP-1R expression dramatically increased and reached its highest peak in 24 h [48]. Further, apelin-13 treatment upregulated the expression of GLP-1R, which inhibited cortical neuronal

apoptosis. However, LY294002 [inhibitor of phosphoinositide 3-kinase (PI3K)/the serine/threonine kinases/Akt signaling pathway] and GLP-1R siRNA partly reversed the neuroprotective effects of apelin-13 [49]. Therefore, apelin-13 plays a critical role in neuroprotection and anti-AD properties by inhibiting the neuronal apoptosis induced by Aβ or others.

Alzheimer’s Disease, Apelin-13 and Autophagy Promotion

AD and Autophagy

To the best of our knowledge, autophagy involves productive and degradative process of Aβ and tau protein. Normally, autophagy promotes the degradation and clearance of Aβ and APP [50, 51]. Autophagy lysosome system not only degrades and clears Aβ, but also produces Aβ under pathological or aging conditions [52]. It has been described that Aβ production is detected in immature autophagic vacuoles and aggregated immature autophagic vacuoles are found in the brain of AD mice [53, 54]. This suggests that aggregated immature autophagic vacuoles may be one source of increased Aβ in AD. Therefore, inhibiting the formation of immature autophagic vacuoles may be an effective way of arresting the progression of AD. In addition, autophagy is responsible for the extracellular release of Aβ [55]. It is postulated that many vacuoles with membranous structure will be manufactured in the course of autophagy. Immature vacuole requires to be modified by autophagy-related molecules to convert into a mature vacuole. The mature vacuoles fuses with lysosome and then initiates the degradation process [56]. However, accumulated immature vacuoles due to excessive production and interruption of transformation

process chooses to fuse with cell membrane and then release the contents [57]. Autophagy is also involved in degradation of tau. Several studies have shown that the dysfunction of autophagy lysosome system leads to the formation of oligomers and insoluble polymers of tau, but the promotion of autophagy reverses this outcome [58]. Furthermore, deletion of crucial autophagy components such as ATG5 or ATG7 in the neurons of mice causes behavior deficits and neurodegeneration [59]. However, research has revealed that role of autophagy in A β plaque and tangles degradation was limited. Autophagy performs its beneficial effects on AD only before the stable plaques and tangles are formed [60, 61]. In conclusion, autophagy plays a dual role in A β regulation and its harmful effects seem to be more predominant because of its weak ability to degrade A β .

Apelin-13 and Autophagy

There are several discrepancies regarding the relationship between autophagy and apelin-13. In H9C2 cells, apelin-13 stimulates autophagic vesicles, autophagy lysosome formation and increased expression of the autophagy markers Beclin-1 and LC3II/I [62]. In NP cells under oxidative stress, apelin-13 promotes autophagic flow, as evidenced by an increase in LC3II/I and a decrease in p62 [63]. In tumor cells A549 cells, apelin-13 has been found to induce autophagy by activating ERK1/2 signaling [64]. Apelin-13 (APJ) reduces the degeneration of dopaminergic neurons in the substantia nigra and striatum of rotenone-treated mice through activation of AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR)/UNC-51-like kinase (ULK) 1 signaling pathway mediated autophagy [39]. It has also been shown that apelin-13 activates cardiomyocyte autophagy by acting on the PI3K/Akt pathway [65]. Further, the effect of apelin-13 on MPTP-induced neurotoxicity was inhibited [45]. Therefore, these studies suggest that apelin-13 contributes to autophagy. However, it has also been shown that apelin-13 has an inhibitory effect on autophagy. Expression levels of Beclin-1 and LC3II In METH-induced PC-12 cells, were significantly increased compared to controls. It was found that apelin-13 pretreatment significantly reduced the expression of these two proteins [66]. In I/R injury model, apelin-13 inhibited autophagy by activating the PI3K/Akt/mTOR signaling pathway. The use of LY294002 attenuated the inhibitory effect of apelin-13 on autophagy [67].

Apelin-13 has both promotive and inhibitory effects on autophagy and studies have hence suggested that apelin-13 has a heterogeneous effect on the regulation of autophagy. Furthermore, this heterogeneity may be related to the cell line selected for the experiment, the animal model, the mode of administration, the type of agent, the dose of the agent and many other confounding factors. A different study has reported that A β significantly increases the escape latency

and reduce traveled distance, swimming speed and time spent in target quadrant in AD model of rat with A β 25-35 injected in the hippocampal CA1 region. The ratio of mTOR/mTOR and LC3II/I ratio increased. However, the use of apelin-13 significantly reversed these results and reduced AD symptoms [26]. In conclusion, apelin-13 exerts an anti-AD effect by inhibiting autophagy. However, studies directly demonstrating the relationship between apelin-13 and autophagy in AD models are still lacking and the circumstances in which apelin-13 promotes autophagy in AD remain to be further elucidated.

Alzheimer's Disease, Apelin-13 and Improvement on Synaptic Plasticity

Alzheimer's Disease and Synaptic Plasticity

Accumulating findings suggests that synaptic loss and dysfunction are important causes of cognitive function impairment in patients with AD [68]. Long term potentiation (LTP), the most common type of synaptic plasticity, is the basis of learning and memory. Dopamine (DA) improves synaptic plasticity, LTP induction and structural learning by acting on dopaminergic receptor (DR) 1 [69, 70]. *N*-methyl *D*-aspartate receptors (NMDARs) play an essential role in neuronal synaptic plasticity through maintenance of neuronal excitability, Ca²⁺ influx and memory formation [71]. NMDARs has high permeability to Ca²⁺ and mediates postsynaptic Ca²⁺ influx [72]. Under normal conditions, NMDARs perform its protective role in synaptic plasticity through LTP and long-term depression (LTD), separately induced by Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and phosphatases [73]. Nonetheless, excessive accumulation of Ca²⁺ induces activation of nitric oxide synthase (NOS) and phospholipase A2 (PLA2). This incurs production of ROS and reactive nitrogen species (RNS) and eventually causing synaptic impairment and cell death [74]. This excitotoxic course triggered by over-secreted glutamate may be the potential mechanism of AD.

Apelin-13 and Synaptic Plasticity

Apelin-13 is a predominant neuropeptide with inhibiting effect on synaptic plasticity and has pivotal effects on cognition memory as well as neuronal protection [75]. Previous studies have shown that apelin-13 reduces 6-hydroxydopamine induced hippocampal early long-term potentiation (E-LTP) damage. It also induces the decrease of hippocampal synaptic proteins such as post synaptic density protein and DR1 [70]. Moreover, apelin-13 activates soluble guanylate cyclase and increases the level of cyclic guanosine monophosphate (cGMP) through endothelial nitric oxide (eNO) signal pathway and then improve synaptic plasticity

[76]. Apelin-13 improves the synaptic plasticity by decreasing the excitotoxicity induced by overactivated NMDARs [77]. To protect neurons from NMDAR-dependent excitotoxicity, apelin-13 activates cell survival signals in neurons through IP3, PKC, MEK1/2, Raf/extracellular signal-regulated kinase 1/2 (ERK1/2) and AKT signaling pathways. On the other hand, it inhibits excitotoxicity by inhibiting the activity of NMDARs [78]. In conclusion, apelin-13 improves synaptic plasticity and protect neurons from excitotoxicity, which may improve the symptoms of AD.

Alzheimer's Disease, Apelin-13 as a Neuroinflammation Inhibitor

Microglia, Neuroinflammation and AD

That the inflammatory markers are elevated in patients with AD, suggesting that neuroinflammation may be an important driver of AD [79]. Microglial M1/M2 polarization, A β deposition and the cytokines network play a determinant role in inflammatory environment regulation associated with neurodegeneration [80, 81]. Microglia play a predominant role in the neuroinflammation regulation by switching into a M1 or M2 phenotype promoting and curbing the inflammation respectively [82]. The stimulation of triggering receptor expressed in myeloid cells 2 (TREM2), a cell surface receptor on microglia, initiates signal transduction pathways that promote microglia chemotaxis, phagocytosis, survival and proliferation [83, 84]. It is thought that the TREM2–APOE axis works in the microglia clearance of A β aggregation and thus may be important for neuronal protection in AD [85]. TREM2 deficiency augment A β and Tau accumulation due to a dysfunctional response of microglia [86, 87]. When toxic A β and Tau accumulates in the stressed or damaged neurons, they induce microglia to enter the M1 proinflammatory state, where they devour synapses, secrete neurotoxic cytokines that damage neurons and contribute to AD [88]. A β stimulates Toll-like receptors (TLRs) and the NLRP3 inflammasome leading to microglia production of tumor necrosis factor-alpha (TNF- α), interleukin (IL)-1 β and other inflammatory cytokines [89]. Apolipoprotein E (APOE) 4's toxic effects in the context of tau pathology are correlational with increased TNF- α production by microglia in vitro [90]. In AD, amyloid protein, a neurotoxic substance, induces the activation of astrocytes and microglia after ischemia. This results in to injury and death of general neurons and glial cells [91]. Further, it has been shown that A β stimulates the microglia transforming into a pro-inflammatory phenotype [92]. Therefore, A β -induced neuro-inflammation may be a crucial mechanism for AD.

Recent genetic studies have provided overwhelming evidence of targeting microglia polarization that may be an effective avenue for neuroprotection and reducing

neurological impairment in AD [93]. Curcumin reduces the imbalance of triggering receptor expressed on myeloid cells 2 and toll-like receptor 4 by transforming M1 microglia into M2. It also attenuates the activation of downstream nuclear factor-kappa B (NF- κ B), which significantly reduces the LPS-induced inflammatory response and plays a neuroprotective role [94]. Several findings suggest that microglia may always, directly or indirectly cause some “collateral damage” to neighboring neurons while performing their clearing function after being activated into M1 phenotype [95]. Upon activation of M1 microglia, the inflammatory cascade is triggered by the release of TNF- α , IL-6 and other pro-inflammatory molecules [96, 97]. Therefore, these changes lead to amyloid aggregation, tau formation, synaptic damage, neuronal loss and progression to AD [98]. A different study has indicated that as AD progresses, pro-inflammatory cytokines are produced in response to A β deposition. The cytokines down-regulate genes in response to A β clearance and decrease expression of the A beta-binding scavenger receptors (scavenger receptor A (SRA), CD36, the A beta-degrading insulysin, neprilysin) therefore contributing to A β accumulation [99, 100]. Therefore, the imbalance between M1/M2-polarized microglia in healthy brain causes neuronal degeneration and hence AD-related pathological changes [101]. In conclusion, the pro- or anti-inflammatory process mediated by different cells (such as microglia and astrocytes) at different stages of AD may be harmful or beneficial to the organism.

Apelin-13 and Neuroinflammation Within AD

Apelin-13 has beneficial properties on memory impairment and neuronal injury associated with AD [102]. Treatment with apelin-13 inhibits the increase of myeloperoxidase activity, decreased the expression of inflammatory cytokines such as TNF- α and intercellular adhesion molecule-1 (ICAM-1) and significantly reduced the neurological deficit and infarct volume in I/R rats [103]. It has been reported that non-invasive intranasal administration of apelin-13 in post-stroke mouse model, inhibits the inflammatory activity of ischemic brain [104]. Neuro-inflammation plays an important role in early brain injury after SAH. On the other hand, apelin-13 performs a neuroprotective role by inhibiting the activation of microglia and the neuroinflammation caused by endoplasmic reticulum stress [105]. Apparently, it was found that in the cases of cerebral infarcts, apelin-13 treatment improved the prognosis of nervous system, reduced brain edema and inhibited apoptosis and neuro-inflammation [106]. Furthermore, correlative studies have reported that apelin-13 inhibits the expression of pro-inflammatory M1 microglial marker CD86 and promote the expression of anti-inflammatory M2 microglial marker CD206 [107]. Apelin-13 inhibits the activation of microglia and astrocytes,

decreases the expression of IL-1 β and TNF- α . It reduces the expression defect of brain-derived neurotrophic factor (BDNF)/ tyrosine receptor kinase B (TrkB) in the hippocampus and improves the cognitive deficits in streptozotocin-induced AD phenotype rats. Elsewhere, it was found that apelin-13 mediated effect blocked by TrkB receptor antagonist K252A [108]. Overall, various research studies have shown that apelin-13 promotes the M2 microglia polarization but prevents the M1 microglia polarization, which is expected to become a new target of anti-AD therapy.

Alzheimer's Disease, Apelin-13 and Oxidative Stress

Alzheimer's Disease and Oxidative Stress

Previous studies have shown that at least two events, including decreased energy metabolism and increased oxidative stress in the brain caused by mitochondrial dysfunction, are characteristics of AD [109]. Oxidative stress is associated with protein oligomerization and mitochondrial dynamics leading to a vicious cycle of mitochondria and endoplasmic reticulum (ER) impairment as well as neurodegeneration [110]. The disorder of cell ion homeostasis and substance metabolism caused by A β oxidative stress makes neurons prone to apoptosis. A β aggregation interacts with Fe²⁺ or Cu²⁺ to produce H₂O₂ [10]. When A β aggregates on the cell membrane, membrane-related oxidative stress leads to lipid peroxidation and ER dysfunction [111]. Copper ions in A β are electrochemically active and promoting the production of ROS. These ROS leads to lipid peroxidation of neuronal cell membranes and malfunction of glucose transporters and ion channel ATPase, terminally contributing to cell injury or death [112]. Glycogen synthase kinase 3(GSK-3) is a serine/threonine protein kinase, which participates in a variety of cellular activities, including apoptosis and the regulation of oxidative stress, and the pathophysiology of AD [113, 114]. Oxidative stress activates glycogen synthase kinase 3(GSK-3) and c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinases (MAPK) and hence increases NFTs and A β by, respectively. This causes tau phosphorylation and β -site APP-cleaving enzyme 1/ β -secretase (BACE1) expression [5, 115].

Apelin-13 and Oxidative Stress Within AD

Apelin-13 is a novel adipocytokine and is also known to be a powerful antioxidant. The distribution of apelin and APJ suggests that apelin-13 may be a key mediator in the development of stress-related behavior [116]. Transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the gene expression of anti-oxidation and anti-inflammation cytoprotective protein and plays an important role in oxidative stress [117]. It has been found that long-term exposure

to methamphetamine (METH) triggers mental disorders. However, apelin-13 reduces METH-induced neurotoxicity by reducing oxidative stress, apoptosis and autophagy [66]. AMPK is a cellular energy receptor that plays a protective role in global cerebral ischemia [118]. Further, apelin-13 has been reported to induce the expression of antioxidant protein through AMPK/P-GSK-3/Nrf2 pathway, which also protects PC12 cells from I/R induced oxidative stress [106]. It plays an anti-depressant role and improves recognition and memory by activating PI3K and ERK1/2 signaling pathways in stress depressed and memory impaired rats [119]. Oxidative stress plays a crucial role in early brain injury after SAH. Apelin-13 reduces oxidative stress after SAH and early brain injury through AMPK/thioredoxin interacting protein/NLRP3 signal pathway [105]. Additionally, reports about the role of apelin-13 in SH-SY5Y cells treated with A β have demonstrated that apelin-13 evidently reduced the generation of intracellular ROS and Ca²⁺ at the dose of 2.5/5.0 μ g/ml [38]. Therefore, apelin-13-mediated antioxidant stress is a critical mechanism of anti-AD.

Alzheimer's Disease, Apelin-13 and Blood Brain Barrier Protection

Dysfunction blood brain barrier protection directly leads to decreased clearance of A β and reduced cerebral plasma albumin and glucose uptake, leading to continued deterioration of AD [120]. Several studies have shown that apelin-13 plays a role in anti-ECs dysfunction by promoting vascular ECs proliferation and reducing vascular endothelial apoptosis [121]. Apelin-13/APJ system promotes vascular EC proliferation endothelium repair by activating eNOS, AMPK, ERK1/2/PI3K/P70S6K, PI3K/AKT, MAPK [22]. Hypoxia-induced ROS production causes Endoplasmic Reticulum (ER) stress, which leads to apoptosis of ECs, endothelial dysfunction and release of neurotoxic substances [122]. Apelin-13 reduces the apoptosis of ECs and help neurons in avoiding neurotoxic injury by up-regulating the level of AMPK and inhibiting ER stress [123]. Astrocyte is a key composition of BBB which may have an effect on the clearance of A β [59]. A previous study has shown that apelin-13 reduces the apoptosis of astrocytes, promotes angiogenesis and thus protecting the BBB [124]. Another study showed that apelin-13 also significantly increased aquaporin-4 (AQP4) expression, decreased BBB permeability, increased vascular endothelial growth factor, upregulated eNO synthase, down-regulated inducible NOS, decreased neurological function score and reduced infarct volume [125]. Cerebrovascular ECs is part of BBB and hence the apelin/APJ system maintains the integrity of BBB. In addition, reduced ECs stress reduces the release of neurotoxic substances [104, 126]. Therefore, it has been described that apelin-13 may be a promising therapeutic target for AD by maintaining

the structural and functional integrity of BBB and vascular endothelium.

Alzheimer's Disease, Apelin-13 and Cerebral Amyloid Angiopathy Inhibition

About 80% of patients with AD experience cerebrovascular amyloid angiopathy (CAA) [127]. Previous studies have shown that CAA is associated with cognitive decline in AD patients [128]. During the pathological process of CAA, uncleared A β from the brain accumulates on arterial and arteriole walls, causing decreased capillary stretch, vascular degeneration, vascular stenosis as well as occlusion. Further development of CAA leads to BBB damage, microischemia and cerebral infarction [129, 130]. The activities of β - and γ -secreting enzymes are increased under hypoxia and ischemia, resulting to an increase in the production of APP [131]. At the same time, the damage of BBB blocked the clearance of neurotoxic substances such as APP and A β , which further led to the formation of amyloid plaques, massive loss of neurons as well as brain atrophy, and hence exacerbate the performance of AD [132]. This suggests that the abnormal deposition of A β in patients with AD leads to local CAA lesions, which further aggravates the pathological progress of AD. Cerebrovascular amyloid angiopathy (CAA) pathogenesis is depressed by eNO which plays a promoting role in vascular elasticity, expression of A β transporter and A β clearance [133]. Apelin-13 increases the expression of eNO, thus promoting A β clearance [5]. Therefore, apelin-13 is considered as a therapeutic target for CAA and related disorders and may promote A β clearance while reversing endothelial dysfunction.

Alzheimer's Disease, Apelin-13 and Apolipoprotein E

Apolipoprotein Es (APOEs) in the brain is mainly synthesized and secreted by astrocytes as well as microglia and participates in the lipid metabolism of neurons [134]. They are divided into APOE2, APOE3, APOE4 and other phenotypes. After lipidation with cholesterol transported across cell membrane by ATP-binding cassette transporter (ABC) A1 or ABCG1, APOEs acquire the ability to internalize into cells expressing corresponding receptors [135]. Many reports have shown that APOE is involved in the regulation of AD pathogenesis. Apolipoprotein E gene abnormalities are commonly seen in late-onset AD. The e4 allele of APOE is related to the pathogenesis and severity of AD [136]. Apolipoprotein Es directly interacts on soluble A β and A β fibrils [137]. Among them, APOE2 is considered to be beneficial for AD [138]. It promotes A β aggregation in interstitial fluid and prevents A β clearance as compared with APOE2 and APOE3 [139]. ATP-binding cassette transporter A1 (ABCA1) and ABCG1 agonists enhances the lipidation

of APOE4 by promoting the cholesterol efflux and promotes the internalization of APOE4 and thus reduces the level of A β in interstitial fluid [140]. So far, a few studies have reported that there may be a signal pathway of apelin-13 acting on APOE. Apelin-13 increases the level of ABCA1 protein by activating protein kinase C α (PKC α) and inhibiting calmodulin-induced ABCA1 degradation in THP-1 macrophage-derived foam cells [141]. This suggests that apelin-13 can promotes the internalization of APOE4, thus promotes A β clearance and inhibits the formation of pathological A β plaques and finally depresses the progression of AD. Further experimental studies should be carried out to clarify whether apelin-13 acts on APOE2 and APOE3. Further studies should also be carried out to ascertain whether apelin-13 can act on other regulatory signals like ABCG1 to promote the lipidation of APOE4.

Alzheimer's Disease, Apelin-13 and Angiotensin

Studies show that upregulation of angiotensin II (Ang II) aggravates AD progression through its effects on cerebral blood flow [142]. Ang II promotes expression of GSK3 β , APP and increases BACE1 activity, thus upregulating p-tau and A β [143, 144]. Evidence from previous studies has shown that apelin-13 inhibits Ang II signaling pathway, promotes the conversion of Ang II to angiotensin 1–7 with memory and cognitive enhancing function, and reduces production of APP [5]. It has been reported that apelin-13/APJ combines with Ang II type-1 receptor (AT1) to form an APJ-AT1 heterodimer, which prevents the Ang II from binding to AT1 [145]. Apelin-13 also inhibits BACE1 in PC-12 cell line and reduces the formation of A β [5]. Inhibition of IRE1 α /XBP1/CHOP signaling pathway has been shown to mediate the neuroprotective effects of Telmisartan, one unique Ang II type 1 receptor blocker. This indicates that Ang II induces neuronal apoptosis in an IRE1 α /XBP1/CHOP-dependent manner [146]. Uric acid can induce oxidative stress by activating renin-angiotensin system (RAS) in 3T3-L1 adipocytes. A study showed that intraperitoneal injection of apelin-13 for 12 weeks in rats with hyperuricemia decreased oxidative stress, down-regulated RAS levels, and up-regulated APJ expression in adipose tissue [147]. Angiotensin also mediates the inhibitory effects of apelin-13 on A β production.

Summary and Future Prospects

Recent epidemiological studies have shown that AD occurs in patients with dementia. Although the currently used drugs slows down the progression of AD, they are not effective in preventing neuronal damage. Therefore, there is a need to develop new drugs for AD. Studies have shown that abnormal

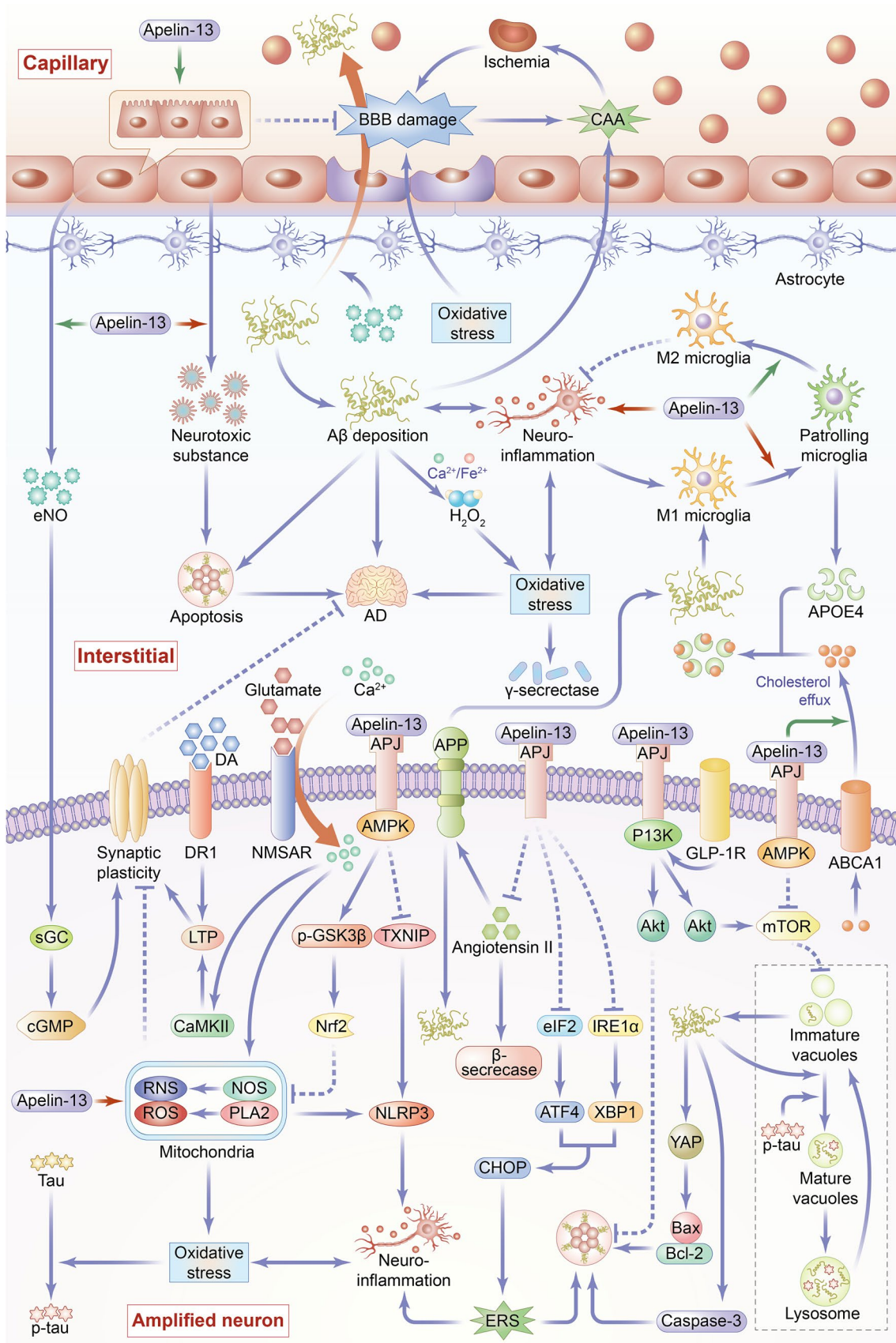


Fig. 2 Overview of the main mechanisms and signaling pathways of Apelin-13 in regulating Alzheimer's disease. The pathogenesis of AD is complex and diverse, and its occurrence and development are closely related to many factors, such as increased apoptosis, enhanced autophagy, synaptic plasticity disorder, elevated level of neuroinflammation, increased oxidative stress, destruction of blood brain barrier (BBB), formation of cerebrovascular amyloid angiopathy (CAA), and unesterified apolipoprotein E (APOE4). Apelin-13 plays an anti-AD role through the following mechanisms. 1. *Apoptosis* (1) Apelin-13 inhibits the production and aggregation of β -amyloid protein ($A\beta$), whereas $A\beta$ induces apoptosis by regulating the Yes-related proteins-related protein (YAP) to increase the Bax/Bcl-2 ratio and promote caspase-3 protein expression. (2) Apelin-13 inhibits the cell apoptosis by promoting Glucagon-like peptide-1 receptor (GLP-1R) expression. (3) Apelin-13 enhances phosphoinositide 3-kinase (PI3K)/Akt signaling pathway to inhibit neuronal apoptosis. (4) Apelin-13 reduces endoplasmic reticulum stress (ERS) by inhibiting inositol-requiring enzyme α (IRE-1 α)/X-box binding protein 1 (XBP1)/C/EBP homologous protein (CHOP) and eukaryotic translation initiation factor 2 (eIF2)/activating transcription factor 4 (ATF4)/CHOP signaling pathways, thereby inhibiting cell apoptosis. 2. *Autophagy* Apelin-13 plays a both promoting and inhibiting roles in autophagy through activation of (AMP-activated protein kinase) AMPK/(mammalian target of rapamycin) mTOR/(UNC-51-like kinase 1) ULK1 signaling pathway and of PI3K/Akt/mTOR signaling pathway. Apelin-13 exerts its anti-AD effects mainly through the inhibition of cellular autophagy, which inhibits the formation of immature autophagy follicles and produce of $A\beta$. 3. *Synaptic plasticity* (1) Apelin-13 activates soluble guanylate cyclase (sGC) and increases the level of cyclic guanosine monophosphate (cGMP) through endothelial nitric oxide (eNO) signal pathway then improves synaptic plasticity. (2) Normally, *N*-methyl *D*-aspartate receptors (NMDAR) induce long term potentiation to improve synaptic plasticity. Apelin-13 inhibits oxidative stress induced by overactivated NMDAR, thereby reducing synaptic damage and improving synaptic plasticity. (3) Apelin-13 increases dopaminergic receptor 1 (DR1) levels and promotes DA-induced LTP, thereby promoting synaptic plasticity. 4. *Neuroinflammation* (1) Apelin-13 exerts an anti-inflammatory role by promoting microglia polarization to M2 phenotype and inhibiting microglia polarization to M1 phenotype. (2) Apelin-13 reduces reactive oxygen species (ROS)-induced oxidative damage in mitochondria and inflammatory response induced by nucleotide-binding and oligomerization domain-like receptor (NLR) family pyrin domain-containing 3 inflammasome activation. (3) Apelin-13 reduces ERS, thus inhibiting neuroinflammation. 5. *Oxidative stress* (1) Apelin-13 inhibits NMDAR activity, sequentially inhibiting the production of ROS and reactive nitrogen species caused by excessive calcium ion influx. (2) Apelin-13 inhibits $A\beta$ aggregation, which interacts with Fe²⁺ or Cu²⁺ to produce H₂O₂ which induces oxidative stress. (3) Apelin-13 induces the expression of antioxidant protein through AMPK/P-GSK-3 β /nuclear factor erythroid 2-related factor 2 (Nrf2) pathway or AMPK/thioredoxin interacting protein (TXNIP)/NLRP3 signal pathway, which relieves oxidative stress-related cell damage. 6. *BBB* (1) Apelin-13 promotes vascular endothelial cell proliferation. (2) Apelin-13 inhibits oxidative stress-mediated BBB damage. 7. *CAA* (1) Apelin-13 promotes endothelial nitric oxide (eNO) secretion by vascular endothelium, and thus enhances the ability of vascular transmembrane transport to $A\beta$, thereby promoting the clearance of $A\beta$ and inhibiting CAA. (2) Apelin-13 has an inhibitory effect on CAA by inhibiting the increase of β and γ secretase activity mediated by oxidative stress. (3) Apelin-13 inhibits the angiotensin II signaling pathway, thereby decreasing the activity of β -site APP-cleaving enzyme 1/ β -secretase and inhibiting the generation of amyloid precursor protein (APP), playing an inhibitory effect on CAA. (4) Apelin-13 promotes the internalization of APOE4 that reduces the level of $A\beta$ in interstitial fluid, thus inhibiting CAA. 8. *APOE4* Apelin-13 promotes the expression of ATP-binding cassette transporter A1 (ABCA1) protein, which facilitates cholesterol outflow to promote the lipidation of APOE, and thus enhances APOE4 internalization

levels of CAA and APOE, deposition of $A\beta$ and tau, neuroinflammatory responses by microglia and astrocytes, ischemia, hypoxia, and NFTs contributes to the development of AD.

The data reviewed here demonstrate that apelin-13 can be a therapeutic target for AD management. Apelin-13 participates in the regulation of autophagy, apoptosis, synaptic plasticity of neurons and polarization of microglia thereby slowing AD progression. Apelin-13 protects neurons by decreasing oxidative stress, neuroinflammation, and blocking Ang II-related signaling pathways. In addition, it inhibits CAA and promotes APOE4 internalization, both of which reduce $A\beta$ deposition in the stroma, neurodegeneration and AD progression (Fig. 2).

Although apelin-13 seems to confer therapeutic benefits in AD, it may cause unexpected side effects given its widespread expression on blood vessels and diverse cellular activities. Moreover, the mechanisms regulating apelin-13 expression in brain tissue are not fully understood. Similarly, the mechanism by which apelin-13 influences polarization of microglia are unclear. Whether, apelin-13 play similar roles in Parkinson's disease, Huntington's disease and AD remain to be clarified. Further research is advocated to resolve these questions and provide new ideas for the prevention and treatment of AD and similar diseases.

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Data Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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