



Research Progress on Alzheimer's Disease and Resveratrol

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Abstract

Alzheimer's disease (AD), a common irreversible neurodegenerative disease characterized by amyloid- β plaques, neurofibrillary tangles, and changes in tau phosphorylation, is accompanied by memory loss and symptoms of cognitive dysfunction. Increases in disease incidence due to the ageing of the population have placed a great burden on society. To date, the mechanism of AD and the identities of adequate drugs for AD prevention and treatment have eluded the medical community. It has been confirmed that phytochemicals have certain neuroprotective effects against AD. For example, some progress has been made in research on the use of resveratrol, a natural polyphenolic phytochemical, for the prevention and treatment of AD in recent years. Elucidation of the pathogenesis of AD will create a solid foundation for drug treatment. In addition, research on resveratrol, including its mechanism of action, the roles of signalling pathways and its therapeutic targets, will provide new ideas for AD treatment, which is of great significance. In this review, we discuss the possible relationships between AD and the following factors: synapses, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (AMPA), silent information regulator 1 (SIRT1), and estrogens. We also discuss the findings of previous studies regarding these relationships in the context of AD treatment and further summarize research progress related to resveratrol treatment.

Keywords Alzheimer's disease · Resveratrol · AMPAR · SIRT1 · Estrogen · AMPK · PI3K/Akt

Introduction

Alzheimer's disease (AD), the most prevalent neurodegenerative disease related to ageing, affects more than 40 million people worldwide [1, 2] and has become a major public health problem with substantial personal, social, and financial burdens [3]. AD is a central nervous system (CNS) degenerative disease and is characterized by pathological brain hallmarks such as amyloid- β (A β) plaques, neurofibrillary tangles and tau protein phosphorylation changes [4]. AD is mainly accompanied by symptoms including oxidative stress, impaired synaptic function, neurotrophin and neurotransmitter imbalance, mitochondrial dysfunction, and neuropsychiatric symptoms such as progressive cognitive impairment and memory impairment [5, 6]. The current

mainstream view is that ageing is one of the major risk factors for AD progression [7], although the brain changes associated with AD may begin many years before substantial changes in cranial capacity and cognition appear [8]. However, the exact aetiology and pathogenesis of AD are still controversial. Furthermore, there is no available treatment to prevent or cure disease progression [9].

The tremendous increases in knowledge regarding the molecular biology, pathophysiology, and diagnosis of AD hold promise for future prevention and therapies but have also begun to erode assumptions about the main theoretical foundation of AD [10]. Additionally, new treatments typically focus on immunization against A β aggregation into plaques and blockade of A β production, but some researchers are looking into ways to prevent tau from forming tangles and treating brain cell inflammation using nonsteroidal anti-inflammatory drugs [11]. Treatments that can delay AD onset for 5 years are considered to reduce economic costs by nearly half a million dollars per person [12]. Novel targets for identification of the abnormal molecular mechanisms of AD-related pathophysiology will contribute to AD research.

Resveratrol (trans-3,40,5-trihydroxystilbene), a natural polyphenol found in berries, nuts, traditional Asian

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medicines, and red wine, is a well-known biologically active compound synthesized by plants [13, 14]. By virtue of its functions, including anti-inflammatory, anti-carcinogenic, cardio-protective, mitochondrial biogenesis-promoting, mitochondrial respiration-promoting, and gluconeogenesis-promoting functions [15], resveratrol has shown considerable potential as a therapeutic agent [16] for many diseases. Of note, the effects of resveratrol treatment on neurodegenerative disorders have been tested with positive results [17]. For example, resveratrol can reduce the levels of secreted and intracellular A β peptides to protect against ageing and age-associated neuronal degradation [18]. Resveratrol also phosphorylates and inactivates the key target protein GSK3- β , decreases brain levels of phosphorylated tau and further exhibits neuroprotection [19]. Some studies have pointed out that the effects of resveratrol are consistent with activation of AMP-activated protein kinase (AMPK) and silent information regulator 1 (SIRT1) [20], reductions in the levels of secreted and intracellular A β peptides [19], alleviation of neuronal oxidative damage [21] and action on the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway [22].

In this review, we focus on the mechanisms of AD pathogenesis and progression. In addition, we review the existing resveratrol treatment strategies associated with the pathophysiological mechanisms of AD that have been described in the literature.

Resveratrol, Synaptic Transmission and α -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA)-Type Glutamate Receptor (AMPA) Biosynthesis

Synapses and AD

Synapses, which are the functionally connected parts of neurons and are key parts of the rapid transmission of neuronal information, are composed of presynaptic membranes, synaptic clefts and postsynaptic membranes [23, 24]. It has been hypothesized that synaptic mechanisms optimize energy-information rate balance during neuronal transmission [25]. Synaptic dysfunction is involved in the formation of disease characteristics associated with many neurobiological and neurochemical lesions [26]. According to previous in-depth reports on neurotransmitter changes in AD, cholinergic neuron death is one of the first findings in AD pathology [27]. Therefore, maintaining synaptic transmission may be an important strategy for the treatment of developing AD.

Changes in synaptic strength are critical for the storage of information during memory formation, and the experience dependence of changes in synaptic strength is described as synaptic plasticity [28]. The most common manifestations

of synaptic plasticity are long-term potentiation (LTP) and long-term inhibition (LTD), which are thought to be synaptic mechanisms that regulate learning and memory, leading to increases and decreases in signal intensity [29, 30]. Synaptic plasticity, which includes functional plasticity and structural plasticity, varies with the type of nerve cell, the stage of development, and the method of activation. Neuronal information processing requires multiple forms of synaptic plasticity mediated by AMPARs, N-methyl-D-aspartate receptors (NMDARs), and mGluR [31, 32].

As synaptic plasticity is the neural basis of learning and memory, its formation mechanism is complex and diverse [33] and has long been a hot research topic in the fields of molecular and cellular neurobiology. In neurodegenerative diseases, changes in synaptic plasticity caused by cytokines may be adaptive mechanisms to compensate for synaptic or neuronal loss [34]. Of note, reductions in the numbers of neuronal connections caused by synaptic disturbance and synaptic fragmentation are considered to be early events in AD-related neurodegenerative disease [35, 36]. According to in-depth coverage of neurotransmitter changes in AD, death of cholinergic neurons is among the first findings in AD pathology [27].

A number of studies have shown that in the earliest stages of AD, synapse loss and altered connectivity occur. In the APPswe/PS1dE9 mouse model of AD, abnormalities in dendritic calcium transients and synaptic depots are observed, supporting the existence of early synaptic deficits in AD [37]. Assessment of the gene expression profile of AD by microarray has shown that in the process of AD, many synaptic-related genes are downregulated, and synaptic function is affected in many ways: through changes in synaptic vesicle transport and release, neurotransmitter receptors and receptor transport, postsynaptic density scaffolds, cell adhesion, and neuromodulation systems that regulate synaptic stability [38].

At the root of AD is A β peptide-mediated neuronal excitability (hyper- vs hypo-excitability of neurons) in the AD environment [39, 40] and duplication of the presenilin-1 mutant and amyloid precursor protein secretomes, whereas in trisomy of chromosome 21 (trisomy 21), neuronal secretomes induce dysfunction through extracellular tau. The above changes collectively contribute to synaptic loss of neurite retraction and synaptic dysfunction [41–43]. On the other hand, mitochondria in presynaptic neurons in AD brains undergo abnormal changes and decrease in number in a region-specific manner, which impairs synaptic stability and leads to synaptic deficits [44]. Similarly, severe stellate cell metabolism dysfunction during AD, as well as impaired glutamate signalling and glutamate–glutamine cycle aberrations, can greatly affect synaptic transmission [45, 46]. Modification of key membrane channels (AMPARs, NMDARs, mGluR, etc.) and corresponding adjustments caused by

oxidative stress change synaptic plasticity and reduce synaptic strength, which are driving forces of synaptic dysfunction and collapse in the AD environment [47–49].

In conclusion, synaptic changes are early and critical molecular pathological events in AD, and therapeutics that can protect against these changes will be beneficial.

AMPArs and AD

The role of synaptic plasticity depends on the states of post-synaptic neurons [33]; however, the research on synaptic plasticity has focused largely on the mechanisms of compositional and quantitative changes in postsynaptic membrane AMPARs. AMPARs, as glutamate receptors, mediate rapid excitatory synaptic transmission and signalling pathways in the CNS [50]. Postsynaptic changes in AMPARs abundance are the main cellular mechanisms of synaptic plasticity and play crucial roles in higher brain function [51]. Additionally, AMPARs participate in the regulation of learning and memory activities, and their dynamic expression in the postsynaptic membrane is associated with induction and maintenance of LTP and LTD [52].

AMPArs are tetrameric isomers assembled from four subunits, GluA1–GluA4 [53, 54]. The functions of ionotropic glutamate receptors are diverse, including subunit assembly, selective gene binding, and editing of pre-transcriptional mRNA. GluA1-containing AMPARs are inserted into synapses upon the induction of LTP in brain slices and play a prominent role in memory formation [55]. GluA2 controls AMPAR synaptic stability [56]. Its expression can increase the lengths, widths, and densities of synaptic dendrites and the numbers of functional synapses as well as change the conductivity of channels, especially calcium channels [57]. GluA3 has been proposed to play a major role in AD pathology, as mice lacking GluA3 are protected against A β -driven synaptic deficits, spine loss, and memory impairment [58]. It is worth noting that modification of the AMPAR subunit composition causes changes in receptor kinetics, further leading to synaptic decay responses [59]; mediates the neurotoxicity of excitatory amino acids, further leading to neuronal damage; and causes cognitive dysfunction in AD patients. Analyses of the subunits of ionotropic glutamate receptors at different sites have shown definite associations between AMPARs and AD.

Cognitive impairment can occur due to combinations of many factors. A β disrupts the intracellular signalling cascades of normal synapses and further leads to synaptic disorders [60]. Synaptic disorders and soluble A β oligomers collectively activate parallel pathways that affect neuronal functions through distinct mechanisms [61, 62]. Excessive endocytosis and cleavage of AMPARs under the action of A β cause loss of AMPARs in the postsynaptic membrane, which can cause synaptic damage and dysfunction; such

pathological changes are closely related to early cognitive impairment in AD [63]. AMPARs are also involved in glutamate-mediated excitatory damage [64], and aberrant CP-AMPA expression causes excessive intracellular Ca²⁺ influx that leads to synaptic dysfunction and neurodegeneration in AD neurons [65]. Moreover, AMPARs activate neuronal activity, leading to the release of tau [66], and participate in the abnormal phosphorylation of tau protein. Abnormally modified tau, a hallmark of AD pathogenesis, leads to the formation of insoluble aggregates [66] and to synaptic impairment [67]. Together, these findings indicate that although the pathogenesis of AD is unclear, abnormal numbers and functions of postsynaptic membrane AMPARs are closely related to the risk factors for AD. Given the association of AMPARs subunits with AD, it is concluded that AMPARs play an important role in the development of AD and are thus potential targets for the treatment of AD.

Aside from AMPARs, NMDARs are also responsible for the majority of fast excitatory transmission in the brain and contribute to synaptic plasticity, which underpins learning and memory [68]. NMDARs, which are glutamate-gated ion channels located in neuronal cell membranes at synaptic and extrasynaptic locations, are believed to mediate distinct physiological as well as pathological processes and are essential for synaptogenesis [47]. NMDARs can increase cellular lipid and calcium levels under the regulation of nitrated A β oligomers and further trigger excitotoxicity, which is a hallmark event of AD [69]. Additionally, internalization of synaptic NMDARs has been suggested to contribute to deficits in LTP and synaptic loss in AD [70]. It should be pointed out that AD drugs that are now on the market target NMDARs [71], and NMDAR research has implications for advancing the treatment of AD.

Given that postsynaptic NMDAR Ca²⁺ influx and the dynamic expression of AMPARs are related to LTP, it is believed that AMPARs and NMDARs have synergistic effects [72] and can mediate excitatory synaptic transmission [73]. Research has revealed that AMPARs and NMDARs share a key transport regulator, striatal-enriched protein tyrosine phosphatase (STEP61), and activity-dependent regulation of STEP61 and its substrates GluN2B and GluA2 may contribute to homeostatic stabilization of excitatory synapses [74]. Stimulation of AMPARs and NMDARs can induce AMPAR trafficking to lysosomal compartments and degradation, and blocking AMPAR lysosomal targeting inhibits hippocampal LTD [75]. Further research on the compensatory mechanism of synaptic input between AMPARs and NMDARs has revealed that elegant combinations of these receptors normalize the ability of distributed synapses to either drive action potential initiation in axons or drive dendritic spikes locally. In the process of common mediation, AMPAR expression in synapses increases with distance from the soma along dendrites, whereas NMDAR

expression decreases [76]. Therefore, it is reasonable to infer that although the expression of AMPARs and NMDARs differs in the context of synaptic transmission, these receptors can jointly regulate synaptic transmission and can be used as potential research targets for the treatment of AD.

Advances in Research on the Effects of Resveratrol on Synapses

In recent years, studies have shown that resveratrol affects factors related to changes in synapses. Analyses of the effects of resveratrol on A β have indicated that resveratrol inhibits A β fibril formation and can bind to A β ₄₂ by aromatic packing and hydrophobic forces, resulting in the formation of less-toxic oligomers with modified conformations [17, 77]. Electrophysiological monitoring of the rat cornu ammonis (CA1) region has revealed that resveratrol decreases the neuron voltage threshold and has a large attenuating effect on increases in spontaneous excitatory postsynaptic currents (sEPSCs) in hippocampal pyramidal neurons. These findings prove that resveratrol can inhibit pyramidal neuron signaling by reducing induced neural activity [37]. It is worth noting that further research on the PC12 rat pheochromocytoma cell line, HT22 cells, etc. has shown that resveratrol can induce mitochondrial SOD2 expression through the PI3K/Akt signalling pathway, reduce neuronal apoptosis and protect neurons from oxidative stress and neuronal damage [78]. In addition, studies have shown that resveratrol treatment increases neurogenesis in hippocampal astrocytes through stimulation of sensory neurons in the gastrointestinal tract [79]. Furthermore, by observing the effects of resveratrol on astrocytes in the primary cortex, Lucia et al. showed that resveratrol can increase the antioxidant activity of astrocytes and increase intake of glutamate. Furthermore, glutathione content can affect the redox environments of glutamate transporters. The above findings show that resveratrol affects astrocyte activation, as indicated by *in vitro* increases in glutamate uptake and glutathione content [80]. On the other hand, in a study on the effect of resveratrol on oxygen/glucose deprivation (OGD)-induced pyramidal neuron excitatory damage in hippocampal slices of acute ischaemic rats, resveratrol markedly reduced the frequency and amplitude of AMPA-mediated sEPSCs in pyramidal neurons. Studies have also found that reducing OGD-enhanced AMPAR/NMDAR-mediated neuronal excitatory postsynaptic currents (EPSCs) reduces early neuronal damage in OGD-stimulated ischaemic slice models [81]. Finally, an electrophysiological study on ventral tegmental area (VTA) dopamine neurons in male C57BL/6J mice has shown that resveratrol can enhance the release of dopamine from these neurons and regulate inhibitory effects on neuronal synaptic transmission and plasticity [82].

The research conducted thus far has revealed that resveratrol can maintain the stability and reduce the toxicity of A β peptides in brain diseases, inhibit neuronal excitability, act on synaptic transmission disorders caused by astrocyte changes, and act on synaptic plasticity, exhibiting protective effects against pathogenic changes in key membrane channels (AMPARs, NMDARs). Based on the associations of these factors with AD, it is reasonable to believe that resveratrol has therapeutic potential for neuroprotection against AD mediated by synaptic effects. However, it should be noted that there have not been sufficient studies on the protective effects of resveratrol against the occurrence of synaptic pathogenic changes in AD. There is still more space for future research on the correlations between resveratrol's key targets, including synaptic plasticity, neuronal excitability, and loss of synapses/neurite retraction, and AD. Another promising potential study area regarding AD involves signalling pathways that influence synaptic changes in neurons.

Advances in Research on the Effects of Resveratrol on AMPARs

Wang et al. found that in rat primary neurons, resveratrol stimulates the translation of receptor proteins to rapidly increase AMPAR protein levels. Without affecting receptor mRNA transcription or protein degradation rates, resveratrol increases neuronal AMPAR synaptic accumulation and excitatory synaptic transmission. Additionally, upstream of this signalling cascade, resveratrol can increase intracellular Ca²⁺ levels, activate Ca MKK β , and ultimately lead to the activation of AMPK [83].

Resveratrol, which has been proven to act as an activator of AMPK [83–85], produces neuroprotective effects targeting the CNS [86]. AMPK activation leads to regulation of the downstream PI3K/Akt signalling pathway [87]. Notably, overexpression of dominant-negative PI3K (PI3K DN) in hippocampal neurons significantly reduces the accumulation of synaptic GluA1 [88]. Of more importance is that activation of AMPK causes eukaryotic initiation factor (eIF) 4E/4G-mediated translation of AMPAR proteins. In other words, elevated protein synthesis can cause increases in resveratrol-induced AMPAR expression by regulating the eIF4E/4G complex. Conversely, interruption of the translation initiation complex completely blocks resveratrol-dependent AMPAR upregulation (as illustrated in Fig. 1) [84].

Overall, resveratrol upregulates AMPAR by activating the AMPK and PI3K/Akt pathways [89], which involve AMPAR trafficking and synaptic plasticity, while increasing AMPAR protein synaptic localization, leading to the enhancement of synaptic transmission power. Therefore, it is speculated that resveratrol may regulate brain function by promoting AMPAR biosynthesis and synaptic transmission

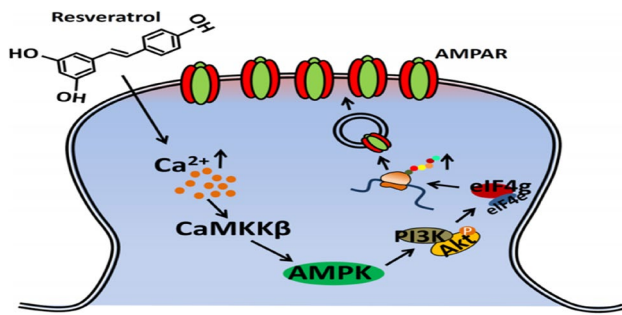


Fig. 1 Schematic diagram of potential signal transduction pathway regulation mediated by resveratrol-induced upregulation of AMPAR. Resveratrol activates CaMKK β by causing Ca²⁺ levels to increase in the cell, which leads to AMPK activation. AMPK activation leads to the regulation of the downstream PI3K/Akt signalling pathway, which causes eIF4E/4G-mediated AMPAR protein translation. Resveratrol activates the PI3K/Akt signalling pathway via activation of AMPK

and thus have the potential to treat AD. However, studies on the AMPAR-related effects of resveratrol on AD are insufficient. In addition, the effects of resveratrol on the AMPAR subunit itself and how resveratrol affects the pathogenesis of AD through changes in AMPAR still need to be further determined.

SIRT1

SIRT1 and AD

SIRT1, a mammalian homologue of the nicotinamide adenine dinucleotide (NAD)-dependent deacetylase sir-tuin family, which has been linked to cellular processes, is responsible for the deacetylation of transcription factors during inflammation [90] and may reduce apoptosis by deacetylating P53 [91]. SIRT1 is mainly expressed in neurons and regulates nerve progenitor cell fate, axon elongation, dendritic branches, synaptic plasticity and endocrine function [92]. Through in vitro culture experiments, Sugino et al. demonstrated that cytoplasmic SIRT1 can promote nerve growth factor (NGF)-induced pheochromocytoma axon growth and play central roles in axonal proliferation and differentiation [93]. SIRT1 interacts with proteins such as the key protein cassette transcription factors P300 and P53 in various signalling pathways [94], while SIRT1 inhibition reduces IGF-1/IRS-2/Ras/ERK1/2 signalling, which protects neurons [92, 95, 96]. Minzhe Li's research [97] showed that SIRT1 can enhance the ability of astrocytes to clear A β during early stages, which essentially delays the formation of amyloid deposits. Subsequent studies have demonstrated that by inhibiting NF- κ B signalling and upregulating A β precursor protein (APP) processing by α -secretase, SIRT1 reduces the production and toxicity of A β [96, 98].

In addition, SIRT1 plays an important role related to tau pathology, which is an additional risk factor for AD progression [99]. Studies have demonstrated that SIRT1 overexpression ameliorates the propagation of tau pathology by reducing neuroinflammation [100]. Furthermore, SIRT1 itself has a specific impact on tau: it can affect the conversion of p-tau and affect the tau protein at the transcriptional level. The above process is beneficial for reducing the phosphorylation and aggregation of tau and leads to deacetylation of tau by preventing the formation of tau protein [101, 102]. Notably, SIRT1 can promote proteasomal degradation of tau via deacetylation, which increases available sites for the ubiquitination of tau and therefore increases targeting of tau to the proteasome [103]. A large number of studies have shown that neurofibrillary tangles, deposition of A β and tau phosphorylation are well-characterized hallmarks of AD [104].

SIRT1 is the downstream regulator of AMPK [105]. AMPK phosphorylates transcription factors and coactivators that regulate gene expression, including FoxO3, PGC1- α , p300, and HNF4. Interestingly, transcription factors are further regulated by SIRT1 [106]. Of those, FoxO3, PGC1- α , and p300 are thought to be involved in the pathogenesis of neurodegenerative diseases and are specifically involved in AD neuropathology. FoxO3 is a major transcriptional regulator that plays a key role in maintaining brain balance [107]. AD research has revealed that increasing the production of toxic A β species via a ROCK1-dependent mechanism promotes A β -induced neurotoxicity, and its upward adjustment causes neuronal death [108]. SIRT1 is able to deacetylate FoxO3 in vitro and in vivo; this deacetylation leads to failure of FoxO3 transcription and suppresses inflammatory proteins [109]. PGC1- α is involved in mitochondrial biogenesis, and its activation can compensate for neuronal mitochondrial loss, increase the levels of synaptic proteins, and participate in the formation and maintenance of dendritic spines [110, 111]. SIRT1 has been shown to interact with PGC-1 α , consequently increasing PGC-1 α activity levels and leading to the promotion of mitochondrial biogenesis [112]. The histone acetyltransferase p300 also contributes to miR-132/212-mediated neuronal death and induces tau acetylation directly or indirectly through unknown mechanisms [101, 108], which may have an impact on neurodegeneration. However, SIRT1 induces p300 downregulation via the ubiquitin–proteasome pathway by deacetylating lysine residues and targeting them for ubiquitination. This negative regulation of P300 by SIRT1 enhances sirt1-induced protein deacetylation [113]. Notably, HNF4 is an important regulator of liver and intestinal epithelial cell function and has been shown to play a role in liver inflammation. Recent studies have shown that HNF4 can indirectly control intestinal flora and prevent the development of inflammatory bowel diseases. Thus far, there have been no studies on HNF4 and neuroinflammation [114]. Considering that

neuroinflammation and inflammatory bowel disease may be connected through the gut-brain axis, related research has increased in recent years. Therefore, research on SIRT1 has been emphasized given the importance of treating AD.

Resveratrol and SIRT1

Resveratrol stimulates SIRT1 activity by stabilizing protein-substrate interactions [115]. A study involving 7- μ s explicit-water molecular dynamics (MD) simulations as well as fragment-centric topographical mapping analysis has revealed that resveratrol treatment changes the N-terminal domain (NTD) conformation of SIRT1, promoting tighter binding between SIRT1 and the substrate [116]. Resveratrol increases SIRT1 mRNA expression levels in addition to enhancing SIRT1 protein expression levels and SIRT1 activity [117, 118]. However, it can also counteract detrimental effects on SIRT1 functions [119, 120]. These findings suggest that resveratrol could be a potent agonist of SIRT1.

It is generally believed that SIRT1 is a key protein associated with multiple effects of resveratrol, and its activation has been deemed to be the basis of resveratrol-mediated protection. Resveratrol can reduce apoptosis, inhibit the inflammatory response, reduce oxidative stress and promote normalization of autophagic flux through the SIRT1 signalling pathway in human-derived neuroblastoma cell lines [99, 121]. Of note, compelling research has supported that the pivotal role of autophagy in the clearance of aggregate-prone proteins is closely associated with several neurodegenerative disorders, including AD [122]. In addition, studies have identified that resveratrol mediates neuroprotection of PC12 A β ₂₅₋₃₅ cells by upregulating SIRT1 and can protect against microglia-dependent A β toxicity by inhibiting NF- κ B signalling [120, 123]. Taken together, these findings demonstrate that resveratrol can confer neuronal protection against AD by increasing SIRT1.

In previous studies, we found that resveratrol can rapidly increase AMPAR protein levels, synaptic accumulation, and excitatory synaptic transmission intensity in rat primary neurons. However, it is worth noting that the effects of resveratrol on AMPAR protein expression are not dependent on SIRT1 but rather are mediated by the subsequent downstream PI3K/Akt signalling pathway [83, 124] and AMPK [125, 126]. Does resveratrol have a cascade reaction with SIRT1, AMPK and the PI3K/Akt signalling pathway? NAD⁺, provided by AMPK, is the fundamental cofactor for sirtuins. A study on the effects of resveratrol on cortical neurons has revealed that AMPK may indirectly sustain sirtuin 1 activation by resveratrol [127]. In addition, ablation of SIRT1 by siRNA knockdown or genetic deletion reduces the activation of AMPK [128]. It follows from the above that resveratrol treatment induces coordinate regulation of AMPK and SIRT1 to form a feed-forward cycle in the

context of disease. In an earlier study, the AMPK/SIRT1 signalling cascade was found to mimic calorie-restricted metabolism [129], confirming the possibility of a feed-forward cycle between AMPK and SIRT1. On the other hand, some advances in resveratrol research have been made regarding the coexistence of transcription factor/coactivator-mediated regulation of AMPK and SIRT1 gene expression. In 18-month-old C57BL/6 mice, resveratrol activates SIRT1/AMPK signalling, allows the concurrent deacetylation and phosphorylation of their target proteins PGC-1 α and FoXo, and decreases susceptibility to ageing [114]. Moreover, a study on the effects of resveratrol on articular cartilage defects has revealed that resveratrol activates and upregulates the expression of the SIRT1 protein, further modifying the levels of factors downstream of the PI3K/Akt signalling pathway. This process reduces the degeneration of articular cartilage in osteoarthritis [4]. Resveratrol can play a protective role through SIRT1/PI3K/Akt and may be an upstream factor in the cascade reaction. In summary, these findings together show that resveratrol may have protective effects on signalling molecules in the SIRT1/AMPK and PI3K/Akt/SIRT1 signalling pathways, but there are still limitations to the existing research on neuroprotective mechanisms.

Successful treatments not only fight the pathogenic factors of disease but also promote cellular neuroprotective pathways [130]. The above studies suggest that resveratrol exerts a neuroprotective effect by acting on SIRT1. In this mechanism of action, the AMPK signalling pathway and the PI3K/Akt signalling pathway play roles in a cascade with SIRT1. Therefore, the AMPK-PI3K/Akt pathway has potential value in the effects of resveratrol treatment on AD. However, there have been no accurate and reliable studies showing whether a resveratrol-AMPK pathway and a resveratrol-PI3K/Akt signalling pathway exist in neurons. In the future, more research should be carried out on the neuroprotective effects of resveratrol mediated by SIRT1 and the SIRT1-based cascade.

Estrogen

Estrogen and AD

The incidence of AD is much higher in women than in men, and AD biomarker abnormalities are most pronounced in postmenopausal women [131]. Gender and age are associated with different degrees of susceptibility to disease, suggesting that AD is largely related to ovarian sex hormone levels [132, 133]. Estrogen has been shown to protect and regulate mitochondrial function in the brain as well as to play major roles in regulating neural plasticity and forming synapses [134]. It participates in numerous modes of signal transduction and has been demonstrated to

impact a number of distinct cell types, neuronal signalling cascades, and nervous system substrates associated with cognitive ageing, injury, and disease [135]. Furthermore, studies have found that changes in estrogen affect cognitive function, network function, pathogenic protein levels and neurolipid raft structure [136, 137].

Estrogen and agonism of estrogen receptors (ERs) play important roles in protecting the CNS from the noxious consequences of neuroinflammation and neurodegeneration [138]. Neurodegeneration in AD is associated with increased apoptosis as well as parallel increases in A β levels and mitochondrial dysfunction caused by abnormal calcium homeostasis [139]. Estrogen itself, the most potent estrogenic compound produced in the human body, prevents A β -induced apoptosis of rat hippocampal neuronal cultures. Oestradiol treatment prior to A β exposure can significantly reduce the numbers of apoptotic neurons and increase intracellular glutamate-mediated Ca²⁺ levels to limit mitochondrial dysfunction [139]. In addition, by inhibiting microglial and astrocyte activation and preventing caspase-3 and calpain-mediated tau cleavage, estrogens can attenuate neurodegeneration mediated by the A β peptide [140]. Binding of estrogen to ERs can initiate different cellular signalling cascades to inhibit the production of superoxide in the hippocampus and regulate the stress kinase signalling pathway to exert protective effects against neurodegeneration [141]. In AD mice, estrogen can rapidly and continuously activate membrane receptors through the MARK/ERK and PI3K/Akt cell signalling pathways, thereby protecting neurons [142]. It is worth mentioning that in its interaction with the PI3K/Akt signalling pathway, estrogen activates the synthesis of arginase 1 (ARG1) mRNA, which directs the resolution of inflammation towards the acquired deactivation stage and generates repair of damaged tissues in the AD phenotype [143]. In addition, estrogen may maintain the metabolic balance of A2 neurons and protect against bio-energy-related damage by upregulating the expression of energy pathway enzymes and inhibiting upstream AMPK kinase expression [144]. Taken together, these findings demonstrate that estrogen can play a neuroprotective role by regulating the expression of kinases in signalling pathways, including the PI3K/Akt and AMPK pathways. Notably, estrogen can decrease tau hyperphosphorylation levels and protect against memory impairment by stimulating the degradation of A β and downregulating neurogenic inflammation and amyloidogenesis [145, 146].

Recent studies have shown the value of estrogen and its receptors in neuroprotection, providing additional ideas for the treatment of AD. However, it should be noted that estrogen may not be able to reverse disease that has already started to develop. Therefore, further development

of estrogen therapies for AD at different stages may be pursued as a new research focus.

Resveratrol and Estrogen

As a phytestrogen with estrogenic properties, resveratrol plays a dual role as an ER agonist and antagonist [147, 148]. Its chemical structure resembles that of mammalian 17 β -oestradiol; hence, resveratrol is expected to interfere with the functions of E2 [149]. Resveratrol, which regulates mitochondrial function and SIRT1/AMPK signalling pathways, is therefore a potential alternative to estrogen therapy [150].

The distributions of ERs differ in different regions of the brain. In regions associated with learning and memory, such as the cerebral cortex, hippocampus and basal forebrain, estrogen receptor β (ER β) is the main receptor type. In resveratrol-treated pregnant mouse experiments, comparisons of the effects of oral resveratrol treatment before or after birth on the expression of ER β have revealed that resveratrol activates ER β through the ER β promoter, mediating the demethylation of DNA and histones and minimizing oxidative stress and mitochondrial dysfunction in the brain [151]. Our previous research results are consistent with this finding. Experiments on AD model (SAMP8) mice have revealed that resveratrol increased the levels of ER β and ChAT, suggesting that resveratrol has estrogen-like effects and can improve the pathogenesis of AD by regulating the expression of ERs [152]. Notably, in our previous study on the effects of high-fat diet feeding of male C57BL/6J mice on vascular ageing, the expression of ER β was found to be regulated by SIRT1, and the promoter region of ER β was found to bind to PPRE via a SIRT1-PPAR γ /RXR-p300 complex. The results indicated that SIRT1 negatively regulates ER β , minimizes reactive oxygen species generation and DNA damage and increases mitochondrial function [153]. Therefore, SIRT1 is suspected to be involved in the neuroprotective effects of estrogen. However, research on the estrogen-related effects of resveratrol on the nervous system is generally uncommon. Existing studies have often implicated the estrogenic effects of resveratrol in cancer [154, 155]. For example, resveratrol can significantly increase the mRNA levels of ER β and inhibit the expression of ER α in breast cancer cell lines. In addition, resveratrol removes reactive oxygen species produced by estrogen metabolism in cancer cells and inhibits cancer cell proliferation. It is speculated that the differential expression of ER α and ER β under resveratrol plays an anticancer role [156]. Given the described mechanism of estrogen in neuroprotection, it is suggested that resveratrol may be an ER agonist with potential value for the treatment of AD. However, research on the mechanisms by which resveratrol ameliorates AD through estrogenic effects remains insufficient. In the future,

researchers may elucidate the ameliorative effects of resveratrol on AD by studying the effects of SIRT1 and cascading AMPK/PI3K/Akt signalling pathways and learning from the mechanisms of cancer treatments.

AMPK and PI3K/Akt

Based on the effects of resveratrol on AMPARs, synapses, the SIRT1 signalling pathway and estrogen, the AMPK and PI3K/Akt signalling pathways are involved in three ways. To determine whether these two pathways are related to AD and to elucidate how resveratrol affects these two pathways, we searched for key words, including AMPK-PI3K/Akt and AD-resveratrol, individually and in combination.

AMPK

AMPK and AD

As the primary energy sensor and regulator of energy homeostasis in eukaryotes, AMPK plays a major role in the regulation of bioenergy metabolism [157]. AMPK expression in a variety of metabolically related organs can be triggered by low-energy states in various types of cells, and AMPK is sensitive to and regulated by a wide range of intracellular and extracellular signals [158]. AMPK coordinates cell growth and metabolism and regulates autophagy under various physiological and pathological conditions [159, 160]. Additionally, AMPK functions in regulating mitochondria; its activation leads to inhibition of ATP-consuming anabolic processes and activation of ATP-producing catabolic processes that maintain cellular energy storage [106, 161]. As an upstream target for SIRT1 and PI3K/Akt, AMPK is also engaged in the biosynthesis of many other downstream targets. Phosphorylated AMPK activates downstream Nrf2 to promote the expression of antioxidant proteins, reduce glial cell-mediated neuroinflammation, and prevent oxidative damage caused by inflammation [162, 163]. Via participation in redox-related mechanisms, AMPK controls neuronal maintenance in the brain [162, 164–166].

Whether AMPK's effects on neurons can be further extended to show a close relationship with AD was examined. A search for the terms AMPK and AD revealed that a series of studies have shown associations between AMPK and AD-related factors, including APP processing, protein synthesis, synaptic dysfunction, neuronal death, and tau phosphorylation.

AMPK can modulate neuronal cholesterol and sphingolipid levels and regulate the dynamic balance of lipid rafts by regulating gene expression and related enzyme activities. Such changes affect the metabolism of APP and lead to the production of A β in neurons [167]. Next, the

AMPK pathway can regulate cell homeostasis at multiple levels. Activation of AMPK leads to isolation of mRNA and phosphorylation of initiation factors. Mistranslation of the mRNA will reduce the synthesis of new proteins. By regulating protein synthesis, AMPK further regulates brain metabolism and neuronal health [168, 169]. Furthermore, long-term activation of AMPK inhibits the activity of eukaryotic elongation factor 2, a key factor that regulates mRNA translation, resulting in irreversible translational impairment. This hinders the formation of long-term synaptic plasticity and causes synaptic dysfunction [170]. In addition, in response to AMPK activation, neurons may reallocate resources away from vital anabolic processes, such as axonal transport, as well as protein and lipid synthesis. The long-term occurrence of this process can also lead to neurological dysfunction [171]. The existence of neural dysfunction eventually leads to the death of neurons [172]. Finally, in AD, activated AMPK co-localizes with phosphorylated tau in pre-tangle- and tangle-bearing neurons. As a tau kinase in primary neurons, AMPK participates in tau phosphorylation at Ser^{262/356} and Thr²³¹, thereby transiently regulating tau affinity for microtubules [173].

Additionally, disruption of AMPK equilibrium energy homeostasis leads to the amplification of harmful effects and damage to cells [174]. It has been observed that in AD, excessive activation of AMPK leads to loss of synapses. Decreases in synaptic markers have been linked to synaptic loss and are accompanied by decreases in neuronal network functionality [172, 175]. However, abnormal energy metabolism in the human AD brain and in neurons with tau phosphorylation also dysregulates the AMPK signalling pathway, which is over-represented in tangle- and pre-tangle-bearing neurons [166, 176, 177]. Altogether, these observations demonstrate that there is a strong correlation between AMPK and AD. AMPK may be an upstream driver of the progression of AD. In addition, the effects of AMPK on AD are not absolutely static; AMPK inhibition and activation have different effects on AD. Furthermore, AMPK activity is adjusted on account of pathological changes that occur in AD.

Based on the above ideas, we further explored the potential role of AMPK in the treatment of AD. Studies have shown that AMPK activation can promote the expression of genes involved in antioxidant defence mechanisms and activate downstream SIRT1, while activation of AMPK may inhibit neuroinflammation [178]. In addition, since AMPK corresponds to A β 42 oligomers in hippocampal neurons [172], AMPK targeting may be of therapeutic value in alleviating the symptomatic effects of A β 42 oligomers [172]. However, some conflicting perspectives on whether drug-mediated inhibition of AMPK can prevent synaptic plasticity damage exist in the literature [174]. This contradiction indicates that the role of the AMPK pathway in neuroprotection

is complex and that more experiments are necessary to determine the mechanism of action of this pathway. Overall, AMPK could represent a novel and efficacious target for the treatment of AD.

AMPK and Resveratrol

Studies have shown that resveratrol specifically activates AMPK, and research on the mechanisms has made some progress in recent years. Resveratrol-mediated activation depends on cell type and is achieved through the cooperation of two mechanisms: an energy-dependent mechanism (ATP synthase inhibition) and an energy-independent mechanism (SIRT1-Ikb1 activation) [126]. In the initial stage, resveratrol can activate AMPK by enhancing AMPK α 1 phosphorylation and inducing the production of low levels of mitochondrial ROS [172, 179, 180]. This activation can also decrease the production of ATP and cause changes in intracellular Ca^{2+} levels [172, 181]. Furthering understanding of the mechanisms, it has been found that this resveratrol-mediated AMPK activation is a beneficial upstream signalling event [95, 126, 181]. In other words, resveratrol can exert physiological effects through targeted activation of AMPK, including improving mitochondrial function and glucose tolerance [182]. In addition, this process can organize cell-mediated increases in damage and activate the homeostasis maintenance mediated by autophagy under stress [183].

In recent years, tremendous progress has been achieved in disease treatment with resveratrol through mediation of the AMPK signalling pathway. Yang et al. found that resveratrol inhibited the phosphorylation of NMDAR NR1 and the activation of PKC γ in the subthalamic nucleus (STN) in male rats with chronic constriction injury (CCI). This finding led these investigators to obtain evidence, for the first time, that resveratrol administration in peripheral nerves may inhibit glial activation and relieve glia-mediated neuroinflammation via AMPK activation [163]. A later study on nematodes (*C. elegans*) with neuronal expression of human exon-1 huntingtin showed that resveratrol can promote neuronal compensation through a neural network composed of AMPK and other pathways, further enhancing the brain's resistance to neurodegenerative diseases [184]. Consistent with this finding, recent in vivo data from studies on 16-week-old male WKY rats have revealed that resveratrol abolishes the generation of ROS and induces SOD2 activity by lowering the activity of Rac1-induced NADPH oxidase, which can cross the blood–brain barrier and induce protection of the CNS, through the AMPK pathway [185]. These observations suggest that resveratrol can promote neuronal compensation and induce neuroprotective enzymes to exert neuroprotective effects through the AMPK signalling pathway.

Similarly, AMPK signalling pathway-mediated therapeutic mechanisms of resveratrol in other diseases have been

recently discovered. For example, resveratrol treatment reduces AMPK phosphorylation, which further decreases the phosphorylated p38/NF κ B/I κ B cascade, in a mouse model of type 2 diabetes mellitus (T2DM) [186]. Similarly, resveratrol has been shown to regulate apoptosis, oxidative stress and inflammatory responses via the AMPK signalling pathway during the treatment of the T2DM complication nephrotic syndrome [187]. A cancer treatment study on the HL-60 human promyelocytic leukaemia cell line revealed that resveratrol may reduce ROS levels through the AMPK signalling pathway, trigger caspase-3 activation to induce apoptosis and achieve beneficial effects [188, 189]. Collectively, these findings demonstrate that resveratrol exerts favourable effects after administration by activating AMPK. However, the current research on the AMPK signalling pathway-mediated therapeutic effects of resveratrol have concentrated mostly on cardiovascular disease, diabetes, obesity and cancer treatment; research on nervous system disorder treatment is less common [160, 179, 188, 190]. In the future, further research on the use of resveratrol to treat AD by regulating the AMPK signalling pathway needs to be conducted.

Additionally, some studies have examined the effects of different concentrations of resveratrol on different diseases at the cellular level. At low concentrations, resveratrol (< 50 μM) displays preferential cytoprotective effects via AMPK/SIRT1-linked pathways. Treatment with low resveratrol concentrations may activate cytoprotective mechanisms, such as antioxidant defence mechanisms against ageing-related cardiovascular damage and neurodegenerative diseases. At higher concentrations, resveratrol (> 50 μM) causes cancer cell death through changes in (sub-)cellular Ca^{2+} homeostasis, disruption of mitochondrial membrane potential and activation of apoptosis-related caspases [191]. The contradictory effects may result from resveratrol concentration dependency. Overall, we conclude that further research should be conducted on the use of resveratrol to exert neuroprotection and prevent specific mechanisms of AD via activation of AMPK, with a focus on low resveratrol concentrations.

PI3K/Akt

PI3K/Akt and AD

The classic PI3K/Akt signalling pathway [192] regulates a variety of biological processes and is closely linked to cell survival, cell metabolism and apoptosis [193, 194]. Since this pathway is a downstream target of AMPK activity and since its downstream proteins control key regulators of autophagy, metabolic and oxidative stress [195], the pathway could be a treatment target under certain conditions [156]. Abnormalities in the PI3K–Akt signalling pathway

can cause cancer, neurodegenerative diseases, diabetes, etc. [181, 196].

Previous studies have shown that the PI3K/Akt pathway plays a major role in the CNS [197]. Signalling pathways regulate the proliferation, migration and plasticity of neurons; inhibit the apoptosis of neurons; and restore the vitality of brain cells [198]. With regard to mechanisms of action, PI3K is an intracellular phosphatidylinositol kinase with serine/threonine (Ser/Thr) kinase and phosphatidylinositol kinase activity [199]. PI3K induces the production of a second messenger, PIP3, on the plasma membrane, which binds to the PH protein-containing signalling proteins Akt and PDK1, which in turn promote phosphorylation of PDK1. Mainly expressed in the brain, Akt is the main target for regulating cell growth and migration downstream of PI3K [6, 200]. These initiating mechanisms can be further elaborated as follows: PI3K can be initiated by G-protein coupled receptors or receptor tyrosine kinases, and activated PI3K can subsequently phosphorylate PIP2 to form PIP3. PIP3 can recruit Akt to localize on the membrane, and Akt can then be activated by phosphorylation of PDK1 and mTORC2 to ultimately phosphorylate target proteins through various downstream pathways to exert anti-apoptotic effects. Studies have further documented that high expression of Akt can effectively counter A β -induced cytotoxicity and reduce apoptosis and that overexpression can significantly reverse A β -induced tau protein phosphorylation [201]. With regard to mechanisms of action, a certain mechanistic correlation of PI3K/Akt with the pathogenesis of AD has been increasingly corroborated in recent years.

Research has shown that the PI3K/Akt pathway can regulate GSK-3 β activity and that it is correlated with AD pathological mechanisms. As a tau kinase, GSK-3 β can phosphorylate tau at multiple AD-associated sites and is related to A β overproduction. In addition, GSK-3 β inhibits LTP and impairs synaptic function [202]. These factors are positively correlated with AD-associated neurodegeneration. Activation of PI3K can induce the phosphorylation and activation of downstream Akt, which can negatively regulate GSK-3 β and reduce its activity [203]; this effect in turn reduces tau phosphorylation and improves memory deficits. Furthermore, studies have shown that the PI3K/Akt signalling pathway is involved in A β 25-35-induced autophagy and is highly related to autophagy-mediated A β clearance. PI3K/Akt activation can counteract A β -induced effects on neurons by affecting A β production/clearance and cell death [197, 204, 205], which is considered an important strategy for anti-AD research. In addition, PI3K/Akt can regulate microglial activity. Abnormal activation of microglia induces a number of major cellular responses during the pathogenesis of inflammatory responses, leading to cell death or apoptosis of neural cells. Observations of PI3K/Akt in lipopolysaccharide (LPS)-stimulated PC12 neurons

and an SCH-treated BVC microglia neuroinflammation model have revealed that the PI3K/Akt pathway is involved in microglial inflammatory signalling and microglia-mediated neuronal cell death. Additionally, activation of PI3K/Akt can counteract neurotoxic effects caused by excessive inflammatory activation in nerve cells through certain mechanisms [206]. Finally, activation of the PI3K/Akt signalling pathway can further inhibit apoptosis induced by oxidative stress by enhancing the expression of SOD, which contributes to neuroprotection [207, 208]. Notably, upregulation of antioxidant enzymes is thought to be beneficial in early AD brains [209]. However, the specific mechanism of action still needs to be determined.

Analysis of the mechanism of the PI3K/Akt signalling pathway during the pathogenesis of AD may reveal that this pathway is an important target for the treatment of AD. Further mechanistic study on the related changes in A β and tau protein will be worthwhile.

PI3K/Akt and Resveratrol

Based on the above findings, we have confirmed the effects of AD on PI3K/Akt signalling pathways. Various studies have demonstrated that resveratrol activates the PI3K/Akt signalling pathway and promotes Akt phosphorylation [210, 211]. In recent years, such studies have been conducted on different diseases, but the overall numbers have been small. Hou et al. examined the effects of resveratrol on cerebral ischaemia in adult male Sprague–Dawley rats and visually showed that by upregulating PI3K/Akt, resveratrol can significantly reduce neuronal damage and neuronal apoptosis [212]. Wen et al. found that the neuroprotective effects of resveratrol are reflected by inhibition of A β -induced neurotoxicity mediated by efficient decreases in intracellular ROS via the PI3K/Akt signalling pathway in rat primary cortex neurons [213]. Importantly, A β neurotoxicity is considered to be a key factor in the pathogenesis of AD [214], and inactivation of PI3K/Akt is one of the mechanisms by which A β and ROS exert their neurotoxicity [210]. Furthermore, the results of an integrative study on male Sprague–Dawley rats show that by activating the PI3K/Akt signalling pathway, resveratrol can protect mitochondrial function, reverse mitochondrial damage and protect neuronal cells from oxidative cytotoxicity [121]. Moreover, this action prevents damage to the glutamate uptake system and protects astrocytes in male Wistar rats [215]. Notably, mitochondrial protection in astrocytes is the basis for brain energy balance maintenance and antioxidant defence [214–216]. Although existing studies on the mechanisms that link resveratrol to the regulation of PI3K/Akt and AD are insufficient, such studies have suggested that resveratrol can reduce neurotoxicity through the PI3K/Akt signalling pathway, protect neurons

and astrocytes, and protect mitochondrial function. More experiments on AD model mice will be meaningful in the future.

At present, the overall neuroprotective performance of resveratrol mediated by the PI3K/Akt signalling pathway is thought to be relatively uniform, whereas the mechanisms of action in other diseases have certain complexity. An experiment by Wenping Wang on rat nucleus pulposus (NP) cells indicated that resveratrol can activate autophagy by activating the PI3K/Akt signalling pathway and can partly alleviate high glucose (0.2 M)-induced apoptosis and senescence [216, 217]. In contrast, resveratrol can exert an inhibitory effect on PI3K/Akt to achieve therapeutic purposes in diseases including hepatocellular carcinoma (HCC) [218], hypoxic pulmonary hypertension [216] and osteoporosis. In a study by Chai et al. on hepatocellular carcinoma (HCC) cell lines, inhibition of SIRT1 enzymatic activity by EX527 resulted in increased phosphorylation levels of PI3K and AKT. This research indicates that PI3K/Akt inhibition may be linked to resveratrol-mediated upregulation of SIRT1 [219]. In a study on the treatment of glioblastoma multiforme in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice, resveratrol reduced activation of the PI3K/Akt signalling pathway, thereby affecting glioma-initiating cell (GIC) invasive behaviour [220]. Additionally, in the treatment of osteoporosis in female Sprague–Dawley (SD) rats, resveratrol inhibits oxidative damage and osteoclastogenesis by inhibiting the transcriptional activity of FoxO1 via inhibition of the PI3K/Akt signalling pathway [221]. Taken together, these results suggest that resveratrol exerts opposing effects on the PI3K/Akt signalling pathway in the contexts of different diseases. Overall, results regarding the precise roles of resveratrol in the treatment of AD related to PI3K/Akt activation should be interpreted with caution and should be regarded as preliminary.

AMPK and PI3K/Akt

Given the respective mechanisms of AMPK and PI3K/Akt, we hypothesized that there may be a relationship between the above pathways. To test this hypothesis, we further explored the AMPK and the PI3K/Akt pathways. First, we found that the two signalling pathways can be jointly controlled by external substances. In McGuire's study, an increase in V-ATPase-dependent lysosome acidification upon glucose starvation was found to involve both the AMPK and PI3K/Akt signalling pathways. Notably, the role of V-ATPase as an energy sensor and regulatory assembly in energy homeostasis may offer new directions for the treatment of neurodegenerative diseases [222]. In addition, AMPK can be seen as the upstream factor that controls the expression of PI3K/Akt. Mi et al. found that AMPK may be a direct activator or a positive regulator of PI3K/Akt and that inhibition of

AMPK by reactive oxygen species inhibits phosphorylation of the downstream substrate PI3K/Akt [223]. However, conflicting evidence is available in the literature; some evidence suggests that there may be mutual suppression between the two signalling pathways. For example, studies have demonstrated that the activation of AMPK is downregulated by the PI3K/Akt signalling pathway [224]. Conversely, some drugs can inhibit AMPK phosphorylation via the PI3K/Akt pathway. The above information demonstrates the existence of a cascade reaction between the two AMPK-PI3K/Akt signalling pathways. In recent years, this cascade reaction has also enabled some progress in the treatment of diseases.

A series of studies have demonstrated that the AMPK-PI3K/Akt signalling cascade can jointly affect cell survival and cell cycle progression, regulate cell membrane dysfunction and participate in drug-mediated mitochondrial function protection along with ATP production [225–227]. In a study on nervous system-related diseases, Chao et al. demonstrated that low-dose panaxatriol saponins (PTSs) induced hormetic effects and thereby increased the resistance of neurons to intracellular and extracellular stress by activating the PI3K/Akt/mTOR cell proliferation pathway and the AMPK/SIRT1/FOXO3 cell survival pathway, consequently improving the behavioural phenotypes of neurological diseases in animal models. Stimulation of hormetic adaptive responses in neuronal cells could not only be a general mechanism for the neuroprotective activity of numerous phytochemicals without specific targets but also a new approach for the prevention and treatment of neurodegenerative diseases [228]. This cascade reaction can also provide therapeutic targets for lung cancer-related diseases. Nayeong et al. indicated that docosahexaenoic acid (DHA)-induced autophagy and apoptosis are controlled by repression of mTOR through AMPK activation and PI3K/Akt inhibition [229]. Some natural products have also been demonstrated to improve energy metabolism and mitochondrial respiration by modulating the AMPK-PI3K/Akt signalling pathway, further demonstrating strong potential for improvement of insulin signalling pathways [230, 231]. On the whole, disease-related research on the AMPK-PI3K/Akt signalling cascade has focused mostly on cancer and diabetes/insulin resistance; research on the nervous system is rare. Although the capacity of AMPK-PI3K/Akt signalling cascades to prevent diseases has been studied in recent years, the underlying mechanisms remain to be fully elucidated.

AMPK-PI3K/Akt and Resveratrol

The mechanism of action of the AMPK-PI3K/Akt signalling pathway itself and its role in drug therapy raise the question as to whether resveratrol can ameliorate AD through the AMPK-PI3K/Akt cascade signalling pathway. In a study by Fan et al. on the human promyelocytic leukaemia cell

line HL-60, mitochondrial membrane potential and the levels of apoptosis-related markers and cleaved forms of caspase-8 and caspase-3 were found to rise following resveratrol addition. Additionally, resveratrol increased both the levels of microtubule-associated protein 1 light chain 3-II and the numbers of autophagosomes, further demonstrating that resveratrol-induced autophagy depends on the LKB1-AMPK-mTOR pathway. It can be suggested that resveratrol can inhibit mTOR through the AMPK-PI3K/Akt signalling pathway, thereby inducing cancer cells to undergo autophagy and inhibiting cancer cell proliferation [195]. A publication by Guan et al. on E18 rat foetal primary neurons only briefly mentioned that resveratrol activates the PI3K/Akt signalling pathway via activation of AMPK and plays a neuroprotective role by affecting AMPARs [88]. However, a limitation is that the current research has generally been preliminary; the specific changes that resveratrol produces by regulating the AMPK-PI3K/Akt signalling pathway remain unknown. On the basis of the literature, it can be concluded that resveratrol may exert therapeutic effects in specific diseases through AMPK-PI3K/Akt. Notably, there have been limited studies on the effects of resveratrol on this signalling cascade. Therefore, the related mechanism has not yet been fully established, and there is no research to support whether it can be targeted to ameliorate AD.

Conclusion

In conclusion, the pathogenesis and treatment mechanisms of AD have not been fully established. However, recent studies have expanded the possibilities for the aetiology and treatment of AD. In general, synaptic transmission, AMPARs in the postsynaptic membrane, SIRT1 and estrogen occupy certain positions in the pathogenesis and treatment of AD. Some research progress has been made regarding the use of resveratrol for the treatment of diseases, and the findings are closely linked to AD. Resveratrol, as an estrogenic compound, promotes AMPAR biosynthesis, enhances synaptic transmission, and activates SIRT1, and it plays an important role in protecting the CNS. Among CNS pathways, the AMPK and PI3K/Akt signalling pathways are associated with the therapeutic effects of resveratrol through the above factors. Resveratrol can achieve neuroprotection through the AMPK and PI3K/Akt signalling pathways and has great potential for use in the treatment of AD. In addition, there is a cascade reaction between the two pathways, and the restorative effects of resveratrol at different concentrations achieved through these signalling pathways are disparate. Overall, resveratrol has some potential for the treatment of AD.

However, at present, some resveratrol mechanisms remain relatively superficially understood in the context of AD or

have been more fully elucidated in the contexts of other diseases. Most experiments have been conducted at the cellular or animal level, introducing potential limitations. The mechanisms of AD and the mechanisms of resveratrol therapy complement each other. Future research on the mechanism of resveratrol in AD treatment can be closely combined with research on the pathogenesis of AD. In addition, future research should examine the beneficial effects of resveratrol mediated by regulation of key elements of the identified signalling pathways and the cascade reactions between signalling pathways.

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