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Review article

The role of AMPKα subunit in Alzheimer's disease: In-depth analysis and future prospects

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ABSTRACT

The AMP-activated protein kinase α (AMPKα) subunit is the catalytic subunit in the AMPK complex, playing a crucial role in AMPK activation. It has two isoforms: AMPKα1 and AMPKα2. Emerging evidence suggests that the AMPKα subunit exhibits subtype-specific effects in Alzheimer's disease (AD). This review discusses the role of the AMPKα subunit in the pathogenesis of AD, including its impact on β-amyloid (Aβ) pathology, Tau pathology, metabolic disorders, inflammation, mitochondrial dysfunction, inflammasome and pyroptosis. Additionally, it reviews the distinct roles of its isoforms, AMPKα1 and AMPKα2, in AD, which may provide more precise targets for future drug development in AD.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia. With the exacerbation of population aging, the incidence, prevalence, and mortality of AD are increasing, imposing a significant economic burden on families and society, making it a crucial public health issue [1,2]. Clinical manifestations of AD include decline in learning and memory abilities, cognitive impairment, behavioral abnormalities, and social dysfunction. Its typical pathological features include the formation of senile plaques (SPs) composed of β-amyloid (Aβ) outside cells, neurofibrillary tangles formed by excessive phosphorylation of tau protein inside cells, and degeneration and loss of neurons and synapses [2]. However, the etiology and pathogenesis of AD are not fully understood, and there are currently no effective interventions to cure or slow down the progression of AD. The brain, as one of the organs with high energy consumption, is vulnerable to disturbances in energy metabolism, with ample evidence indicating that reduced energy metabolism is an early and consistent feature of AD [3]. AMP-activated protein kinase (AMPK), as a cellular energy sensor, plays a significant role in the pathophysiology of AD [4–6] and may be associated with its pathogenesis [7], being considered a potential therapeutic target for AD.

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AMPK is a sensor of cellular energy and nutrient status, activated under low energy conditions to maintain cellular homeostasis [8]. In eukaryotes, it is almost universally expressed as a heterotrimeric complex consisting of catalytic subunits (α), scaffolding subunits (β), and regulatory subunits (γ), in a 1:1:1 ratio [9]. AMPK is mainly activated through two mechanisms: (1) one is the AMP/ADP-dependent energy stress signal: in the absence of AMP, the autoinhibitory domain of AMPKα keeps the kinase in an inactive conformation; when the cellular AMP:ATP ratio increases, AMP binds to the γ subunit, leading to a conformational change in the α subunit or activation of AMPK by preventing phosphatases from dephosphorylating the Thr172 site [10]. Additionally, an increase in AMP levels can activate LKB1 [11], calcium/calmodulin-dependent protein kinase kinase (CaMKKβ) [12], or transforming growth factor β-activated kinase 1 (TAK1) [13], leading to phosphorylation of the α subunit Thr172 site and thereby activating AMPK. (2) Another non-AMP/ADP-dependent pathway involves the sensing of various nutrients: (a) Glucose: Activation of AMPK occurs through the sensing of fructose-1,6-bisphosphate (FBP) by aldolase, in the absence of which AMPK is activated [14]. Since the discovery of this pathway, glucose deprivation has been widely used as an effective method to activate AMPK in cultured cells [15]. The possible mechanism involved is that glucose deprivation leads to a conformational change in the v-ATPase regulatory complex, thereby activating AMPK [16]; (b) Fatty acids: Research on the allosteric drug and metabolite site ligands has shown that long-chain fatty acyl-CoAs (LCFA-CoAs) are natural ligands of AMPK, and their binding can activate AMPK [17]; (c) Glycogen: The AMPKβ subunit contains a glycogen-binding site on the β-carbohydrate binding module (β-CBM), which can stabilize AMPK *in vivo* [18–21]. Additionally, AMPK activation also occurs in response to nuclear DNA and lysosomal damage, as well as ionizing radiation [22–27]. Once activated, AMPK phosphorylates proteins involved in catabolic pathways to increase ATP synthesis, while phosphorylating or inactivating proteins involved in anabolic pathways. The dysregulation of AMPK signaling in AD has complex effects. For example, AMPK can promote the phosphorylation of Tau protein and inhibit Tau phosphorylation or aggregation by inhibiting glycogen synthase kinase 3β (GSK3β) or activating recombinant Sirtuin 1 (SIRT1) mediated Tau deacetylation [28,29]. AMPK activation can increase Aβ through endoplasmic reticulum stress [30] or upregulation of β-secretase (BACE1) [31], as well as enhance autophagy to increase Aβ clearance [32]. Activation of AMPK by metformin alleviates mitochondrial damage and improves pathology and cognitive function in AD models [33,34]; however, AMPK inhibitors correct the toxic effects of Aβ on synaptic function [4,5]. These controversies highlight the complexity of AMPK's role in AD and the complexity of AMPK itself. The α, β, and γ subunits of AMPK have multiple subtypes, and the activation of different subtypes may be the reason for the complexity of AMPK action [35]. Among them, the AMPKα subunit is considered a key factor determining AMPK activity [36] and plays a crucial role in regulating Aβ production [37] and aggregation [38], Tau phosphorylation [39] and aggregation [38], metabolic disorders [40], inflammation [41], mitochondrial dysfunction [42] and apoptosis [43] in AD. Recent studies have discovered subtype-specific roles of the AMPKα subunit in the pathogenesis of AD [44,45]. For instance, inhibiting AMPKα1 effectively rescues synaptic defects and memory loss in AD model mice [46], while AMPKα2 is associated with Aβ load in AD model mice [47]. Therefore, elucidating the role of the AMPKα subunit in AD may provide more precise therapeutic targets for AD treatment. This article will review the research progress on the role of the AMPKα subunit in the pathogenesis of AD.

2. AMPKα subunit and its isoforms

AMPKα subunit is the catalytic subunit of AMPK, with its N-terminus containing a traditional serine/threonine kinase domain, followed by an auto-inhibitory domain (AID), and then an extended "linker peptide" that connects the AID to the C-terminal domain (α-CTD) [48]. The α-CTD is a crucial structure for the interaction of the α subunit with the β and γ subunits [49]. The AMPKα subunit plays a significant role in AMPK activation, primarily through two general pathways: 1) Binding of AMP to the γ subunit domain causes a conformational change in the α subunit, activating AMPK; 2) Increased AMP levels activate the CaMKKβ [12], LKB1 [11] and TAK1 [13], leading to the phosphorylation of a serine residue in the N-terminal kinase domain activation segment of the α subunit (usually referred to as Thr-172 due to its position in the rat gene sequence) [50], thereby activating AMPK [51–53]. Therefore, the AMPKα subunit is a key factor determining the activity of AMPK [36].

The AMPKα subunit currently known has two subtypes: AMPKα1 and AMPKα2, encoded by the PRKAA1 gene on chromosome 5 and the PRKAA2 gene on chromosome 1, respectively [54]. The α1 and α2 subtypes exhibit tissue specificity. The α1 subtype is strongly expressed in embryos, but its expression decreases during development [55]. In adults, the expression of the α1 subtype in the liver is 250 times that of the α2 subtype [56]. In skeletal muscle and cardiac tissue, the α2 subtype is the main catalytic subtype and plays a major role in glucose uptake in skeletal muscle and energy metabolism in the heart [57,58]. In the central nervous system, both the α1 and α2 subtypes have high levels in the embryonic hippocampus and are present in neurons throughout the adult brain [55]. Specifically, the α1 subtype is mainly expressed in astrocytes, while the α2 subtype is the primary catalytic unit expressed in the adult brain and spinal cord, with the highest expression found in cortical and hippocampal neurons as well as Purkinje cells in the cerebellum [59]. Studies on the subcellular distribution of the α2 subtype at the central cell level suggest that in neurons, it is mainly located in the cell nucleus, while in glial cells, it is primarily found in the cytoplasm [59]. Recent evidence has revealed the potential roles of AMPKα subtypes in both neurophysiology and neuropathophysiology [6]. For instance, downregulation of the AMPKα1 subtype promotes oxidative stress in astrocytes [60]. Knockout of the AMPKα1 subtype in mice results in severe demyelination and inflammatory reactions in the brain and spinal cord [61]. Activation of the AMPKα1 subtype significantly inhibits the nuclear translocation of nuclear factor-k-gene binding (NF-κB) and the expression of pro-inflammatory factors in BV2 microglial cells [62]. These findings indicate a specific role of the AMPKα1 subtype in maintaining central oxidative balance, myelin formation, and anti-inflammatory functions. Similarly, the AMPKα2 subtype also exhibits specific functions in the central nervous system. For example, brain-specific inhibition of the AMPKα2 subtype leads to cognitive impairments, highlighting the importance of the AMPKα2 subtype in maintaining normal cognitive function [63]. Enzyme assays in the hypothalamic region of rodents suggest that appetite-suppressing hormones (such as the

fat-derived hormone leptin) inhibit the AMPKα2 subtype [64], indicating a relationship between the AMPKα2 subtype and appetite control in the hypothalamus. In mice with the AMPKα2 gene knocked out, the expression of catecholamines increases [65], suggesting a link between the AMPKα2 subtype and the regulation of sympathetic nervous system activity. However, the exact role of AMPKα subtypes in the central nervous system remains incompletely understood at present.

One of the established downstream effects of AMPK is the regulation of protein synthesis or mRNA translation. AMPK can regulate protein synthesis through at least two classical mechanisms: eukaryotic elongation factor 2 kinase (eEF2K) and mammalian target of rapamycin complex 1 (mTORC1) signaling cascade targets. In brief, AMPK phosphorylates and activates eEF2K, leading to the phosphorylation of the translation factor eEF2, thereby inhibiting general protein synthesis. Additionally, AMPK inhibits (directly or indirectly) the mTORC1 signaling pathway, whose activation promotes the synthesis of translational machinery and cap-dependent translation initiation [54]. Several studies have shown that the AMPKα subunit can regulate changes in the mTOR-induced autophagy pathway [66–68], lipid metabolism [69,70], and transcriptomics show that knocking down the AMPKα subunit affects gene expression involved in lipid and carbohydrate metabolism as well as insulin/insulin-like growth factor signaling (IIS) [71]. However, it is not fully understood how AMPK subunits or isoforms affect the translation of specific proteins in the brain. Proteomic analysis of the hippocampus of mice with specific knockout of AMPKα1 and α2 isoforms has revealed the identities of proteins sensitive to AMPKα1 or α2 isoforms [72]. In the hippocampus of mice with knockout of AMPKα1 or AMPKα2 isoforms, upregulation of proteins related to binding, catalytic activity, structural molecular activity, and transporter protein activity was detected, with proteins such as protein kinase C in neuronal protein 2 and protein D2 containing an EF-hand domain being upregulated in both hippocampi. Conversely, downregulated proteins showed some differences between the two. In the hippocampus of AMPKα1 knockout mice, the downregulated proteins were classified into three categories: binding, catalytic activity, and translation regulatory activity, while in AMPKα2 knockout mice, they were classified into five categories: binding, catalytic activity, structural molecular activity, translation regulatory activity, and transporter protein activity [72]. It is worth noting that the proteasome subunit alpha type-7 was upregulated in the hippocampus of AMPKα2 knockout mice, and the protein Cullin-3, which was downregulated in the hippocampi of both AMPKα1 and α2 knockout mice, is involved in lysosomal protein hydrolysis and the ubiquitin-proteasome pathway, both of which are dysregulated in AD [72,73]. However, the exact impact of AMPKα subunits on the pathogenesis of AD is not yet fully understood.

3. AMPKα subunit and AD

The AMPKα subunit is correlated with different pathogenic mechanisms in AD (including Aβ pathology, Tau pathology, metabolic disorders, inflammation, mitochondrial dysfunction, and pyroptosis). Similarly, as our understanding of the AMPKα subunit deepens, it becomes increasingly clear that the AMPKα subunit plays a significant role in the onset and progression of AD. Here, we outline the potential roles and mechanisms of the AMPKα subunit in various pathogenic mechanisms of AD.

3.1. AMPKα subunit and Aβ

Aβ is the main component of SPs formed by the cleavage of amyloid precursor protein (APP) by BACE1 and γ-secretase [74]. The formation of Aβ in SPs is considered a key pathological event in AD [75]. Efforts have been made to explore methods to alleviate Aβ pathology to mitigate AD symptoms, including reducing Aβ production [76–78], inhibiting Aβ aggregation [79–81], and enhancing Aβ clearance [78,82,83]. The AMPKα subunit regulates the activation of AMPK, which can modulate cholesterol and sphingolipid metabolism, Cholesterol and sphingolipids are involved in the regulation of APP processing and Aβ production [84]. In neurons with AMPKα2 knockout, increased Aβ production suggests that activation of the AMPKα subunit reduces Aβ production by regulating the generation of APP [4]. Studies have shown that upregulation of AMPKα subunit can inhibit Aβ expression in the mouse brain [37]. Additionally, the phosphorylation of AMPKα has been found to inhibit Aβ aggregation [38]. Autophagy plays a neuroprotective role in AD by mediating the degradation of Aβ. The AMPKα subunit can inhibit mTOR to enhance autophagy, reducing Aβ deposition and exerting a neuroprotective effect [85]. While these studies demonstrate the potential of the AMPKα subunit in regulating Aβ pathology, further research, including clinical trials, is needed to validate its feasibility as a therapeutic target for AD. Nevertheless, experimental data support the promising role of the AMPKα subunit in regulating Aβ pathology and potentially alleviating the progression of AD.

3.2. AMPKα subunit and Tau

Tau is a microtubule-associated protein that stabilizes neuronal structures. However, in AD, Tau undergoes abnormal modifications, such as hyperphosphorylation, leading to the formation of neurofibrillary tangles within neurons [86]. Previous studies have shown that at 8 months of age, APP/PS1 transgenic mice exhibit hyperphosphorylated Tau-positive neuroinflammatory structures near amyloid plaques in the brain [87]. Pedro et al. also found a twofold increase in phosphorylated Tau protein levels in the hippocampus and frontal cortex of APP/PS1 mice compared to wild-type controls [88]. Recent clinical research indicates that abnormal phosphorylation of Tau protein in the brain occurs before Aβ deposition [89]. Excessive phosphorylation of Tau can induce endoplasmic reticulum stress, synaptic dysfunction, and neurodegeneration, exacerbating the progression of AD [90]. The evidence suggests that the role of abnormally hyperphosphorylated Tau protein is significant in the advancement of AD. Therefore, reducing the levels of hyperphosphorylated Tau protein could effectively alleviate AD progression [91,92]. In recent years, the AMPKα subunit has been found to have a role in reducing Tau aggregation. Researchers such as Kai conducted *in vivo* and *in vitro* experiments using diabetic and aging mice, as well as SH-SY5Y cells, to investigate the neuroprotective effects of FGF21 and found that FGF21 can promote AMPKα phosphorylation to inhibit Tau aggregation [38]. Additionally, Dorlors and colleagues discovered that increased expression of AMPKα

can reduce phosphorylated Tau aggregation by enhancing autophagy [93]. Apart from contributing to the inhibition of phosphorylated Tau aggregation, the AMPKα subunit also plays a role in inhibiting Tau phosphorylation. Studies have shown that AMPKα deactivates phosphorylation at the Thr172 site of protein phosphatase 2A (PP2A), thereby reducing phosphorylation at the Tau-Ser262 site [39]. In summary, the AMPKα subunit plays a role in regulating Tau protein aggregation and phosphorylation processes. However, the underlying mechanisms are not yet clear, which limits a deeper exploration of the relationship between AMPKα and Tau pathology. Therefore, further exploration of AMPKα-related pathways or target effects on Tau pathology is necessary to gain a clearer understanding of the relationship between the AMPKα subunit and Tau pathology.

3.3. AMPKα subunit and metabolic disorders

It is known that abnormalities in energy metabolism and dysfunction in the hypothalamus are associated with AD [94]. Specifically, hypothalamic dysfunction can impact the progression of AD and contribute to its onset [95]. Mitochondrial dysfunction and endoplasmic reticulum stress induced by AD, in turn, exacerbate the burden on the hypothalamus, further damaging metabolism [90]. Metabolic disturbances link AD with diseases such as diabetes, revealing connections between these conditions. Notably, 80 % of AD patients exhibit impaired glucose tolerance or have type 2 diabetes [96]. Impaired glucose tolerance and insulin resistance have been observed in AD mouse models [97,98]. The risk of dementia in individuals with type 2 diabetes is increased by 1.5–2 times compared to the general population [99]. Insulin resistance in type 2 diabetes also contributes to the deposition of Aβ plaques [100]. The AMPKα subunit regulates energy metabolism in the body, but its role in regulating energy metabolism in AD is not yet fully understood. In recent years, researchers such as Camila have discovered that icariin can restore metabolic disturbances in APP/PS1 mice by restoring AMPKα subunit activity [40], elucidating the role of the AMPKα subunit in metabolic disruptions in AD. Furthermore, other studies have explored the correlation between the AMPKα subunit and insulin resistance. As mentioned earlier, insulin resistance is also present in AD and is associated with the deposition of Aβ plaques. Therefore, targeting insulin resistance for treatment or even prevention of AD may be effective. It is noteworthy that the AMPKα subunit has been shown to be associated with insulin resistance, and its activation in the body can improve insulin resistance and the expression levels of the Glucose Transporter 4 (GLUT4) gene [101]. Additionally, inhibition of the AMPKα-related pathway SIRT1/AMPKα/Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC1-α) can lead to insulin resistance and affect energy metabolism [102,103]. The regulation of the AMPKα/Mechanistic Target of Rapamycin (mTOR) pathway is also related to insulin resistance [104,105]. In conclusion, metabolic disturbances are a key aspect of the pathogenesis of AD, serving as a bridge between AD and metabolic diseases such as diabetes. The AMPKα subunit can regulate metabolic disruptions in AD and may hinder the progression of AD pathogenesis by modulating insulin resistance in AD.

3.4. AMPKα subunit and inflammation

Inflammation is one of the characteristics of AD and can lead to neuronal degeneration and loss, fundamentally impacting disease progression [106,107]. AD mouse models exhibit high levels of inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interferon-gamma (INF-γ) [86]. The activation of inflammatory signals can promote the expression of APP, increase the activity of γ-secretase, and result in the release of a large amount of Aβ peptides [108]. The excessive activation of inflammatory responses in AD is intricately linked to the activation of neuroglial cells. Both AD patients and AD mouse models show activation of astrocytes and microglia in the brain regions with Aβ plaques [109]. Caveolin-1 is expressed in various neural cells, including astrocytes, and is involved in the pathogenesis of AD [110]. Researchers such as Gang have found an interaction between AMPKα subunit and Caveolin-1, which induces neuroinflammation. Metformin can modulate this interaction and alleviate the inflammatory response [41], and it is also believed to play a role in alleviating AD-related inflammation [111]. Therefore, the AMPKα subunit may be a key regulatory factor in the neuroinflammatory response associated with astrocytes in the Aβ plaque regions. Furthermore, the AMPKα subunit is associated with the activation of microglia in AD. Inhibiting the release of pro-inflammatory factors in microglia can have anti-inflammatory effects, a process regulated by the AMPKα subunit [112]. In summary, the AMPKα subunit has the ability to regulate the activation of neuroglial cells and inflammatory responses in AD, and it may be a key regulatory factor in the neuroinflammatory response associated with astrocytes in the Aβ plaque regions.

3.5. AMPKα subunit and mitochondrial dysfunction

Mitochondria are important double-membrane organelles in the cytoplasm of eukaryotic cells [113,114], crucial for the production of Adenosine Triphosphate (ATP) and the maintenance of calcium homeostasis [115,116]. The brain is one of the most metabolically active organs in the human body, primarily using glucose as its main energy source. As a high-energy-consuming organ, approximately 93 % of its energy requirements are provided by ATP generated by mitochondria [117]. Oxidative phosphorylation on the inner mitochondrial membrane is the main process for ATP production [118]. Previous studies have found that ATP levels in the brains of AD mice are lower than in wild-type mice, indicating that mitochondrial dysfunction is an important pathogenic mechanism in AD [119]. This viewpoint is receiving increasing attention and prompting exploration of new therapeutic strategies aimed at improving mitochondrial function to enhance AD treatment [120–122]. As mentioned earlier, the AMPKα subunit is the main catalytic subunit of the AMPK complex and plays a crucial role in the activation of the AMPK complex. Recent studies have found a close association between the AMPKα subunit and mitochondrial dysfunction in AD. Mitochondrial proteomic analysis of brain tissues from 5 × FAD mice revealed that changes in the phosphorylation level of AMPKα can increase mitochondrial biogenesis by modulating the AMPK/PGC-1α

pathway [42]. Knocking down the AMPKα subunit can block the protective effect of drugs on mitochondrial damage in neurons of APP/PS1 mice, indicating the important role of the AMPKα subunit in AD-related mitochondrial dysfunction [123]. However, research on the association between the AMPKα subunit and mitochondrial dysfunction in AD lacks investigation in other AD models related to Tau, leading to a partial and limited understanding. Overall, current research suggests that the AMPKα subunit is associated with mitochondrial dysfunction in AD and regulates mitochondrial biogenesis through the AMPK/PGC-1α pathway.

3.6. AMPKα subunit and inflammasome

In the central nervous system, the main inflammasomes are nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain-containing protein 1 (NLRP1), nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain-containing protein 3 (NLRP3), and absent in melanoma 2 (AIM2) [124], with NLRP1 and NLRP3 showing high expression in the brain tissues of AD patients [125]. These inflammasomes are regulated by Aβ: on one hand, Aβ can induce neuronal pyroptosis through the NLRP3-caspase-1 signaling pathway by cleaving gasdermin D (GSDMD) [126]; on the other hand, Aβ can increase the levels of primary NLRP1 in cortical neurons, thereby activating caspase-1 signaling [127], indicating that NLRP1 and NLRP3 are key factors in Aβ-mediated neurotoxic effects and play crucial roles in the pathogenesis of AD. Research has shown that knocking down the AMPKα subunit using siRNA can enhance the expression of NLRP3, Apoptosis-associated speck-like protein containing a CARD (ASC), and caspase-1 in SH-SY5Y cells, indicating the role of the AMPKα subunit in inhibiting cell inflammasomes [43]. However, it is currently unknown whether the dysregulation of the AMPKα subunit affects NLRP1 inflammasomes. Furthermore, activation of NLRP3 inflammasomes in microglial cells is associated with AD [128]. Studies have found that activation of AMPKα subunit can suppress activation of spinal cord microglia [129,130] and improve the production of pro-inflammatory mediators by microglia [131–133]. However, whether the effect of AMPKα subunit on microglia is mediated in whole or in part through NLRP3 inflammasomes remains unclear. Overall, there is limited research on the association between the AMPKα subunit and pyroptosis in AD. Given the increasing attention to pyroptosis in the pathogenesis of AD, further research will clarify the relationship between the AMPKα subunit and pyroptosis, potentially identifying meaningful therapeutic targets.

3.7. AMPKα subunit and pyroptosis

Pyroptosis is one of the programmed cell death pathways and a crucial innate immune response *in vivo*. Typically, its occurrence activates the immune system to eliminate pathogens; however, excessive activation can exacerbate inflammatory reactions [134]. Research has found that gasdermin family member GSDMD, a direct substrate of caspases, executes pyroptosis by inducing membrane permeabilization after caspase cleavage. Moreover, almost all members of the GSDM family have the ability to form pores in membranes, thereby redefining pyroptosis as a form of programmed cell death mediated by GSDMs [135]. Currently, pyroptosis has been implicated in the pathological mechanisms of AD; the inflammasomes and pro-inflammatory cytokines in the pyroptosis activation pathway are linked to AD pathogenesis. Additionally, AD hallmarks such as Aβ and tau proteins have been shown to participate in pyroptosis, although the mechanisms remain unclear [125]. Studies have identified a role for AMPKα subunit in inhibiting neuronal pyroptosis in the context of AD, potentially through inhibiting the activation of NLRP3 inflammasomes [43]. However, research on the association between AMPKα subunit and pyroptosis in AD is limited. Given the increasing attention to pyroptosis in AD pathogenesis, further research will elucidate the relationship between AMPKα subunit and pyroptosis, potentially identifying meaningful therapeutic targets.

4. The subtype-specific role of AMPKα subunit in AD

The AMPKα1 and AMPKα2 subtypes are widely expressed in neurons [55], although AMPK plays an important role in AD, and the AMPKα subunit is the main catalytic subunit, it has not been elucidated which AMPKα subtype is associated with the disease. Therefore, we separately elucidate the subtype-specific actions of AMPKα1 and AMPKα2 in AD.

4.1. AMPKα1 and AD

Recently, The study found that the AMPKα1 subtype has specific actions in AD. Zimmermann and colleagues [46] found that the expression of the AMPKα1 subtype is continuously elevated in the hippocampus of sporadic and familial AD patients, as well as in the Tg19959 APP transgenic mouse model, whereas AMPKα2 expression is decreased in the hippocampus of sporadic AD patients. This change in AMPKα subtype expression appears to be AD-specific, as no changes in AMPKα subtype were found in Lewy body dementia and frontotemporal dementia. Importantly, reducing the expression of AMPKα1 subtype, but not AMPKα2, in hippocampal and cortical neurons effectively rescued synaptic defects and memory decline in an AD mouse model [46]. Zhou and colleagues found that the specific inhibition of mouse AMPKα1 subtype improved age-related memory impairment by reducing the expression of eukaryotic initiation factor 2α (eIF2α) [44], suggesting that the mechanism by which inhibiting the AMPKα1 subtype improves AD symptoms may be related to the decreased expression of eIF2α. However, Lv [136] and colleagues found that the direct activator of AMPKα1 subtype, DW14006, improved learning and memory impairments in APP/PS1 mice. The mechanism involved stimulating the M2 phenotype transformation of microglia and enhancing autophagy to reduce inflammation through the activation of the AMPKα1/Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)/Cluster of Differentiation 36 (CD36) and AMPKα1/Inhibitor of nuclear factor kappa-B (IκB)/NFκB pathways. The dysregulation and complexity of AMPKα1 subtype in AD suggest that AMPKα1 subtype may,

similar to the AMPK complex [137], provide neuronal protection when appropriately activated, while long-term and intense stimulation may be detrimental to neurons. In addition to the central nervous system, Wang and colleagues examined changes in AMPKα subtypes in the plasma of patients diagnosed with mild cognitive impairment (MCI) and AD. They found a decrease in AMPKα1 subtype levels in the plasma of MCI and AD patients, while AMPKα2 levels remained unchanged. Furthermore, the levels of AMPKα1 were correlated with characteristic changes in AD cerebrospinal fluid biomarkers (including decreased $A\beta_{42}$, increased total Tau protein, and phosphorylated Tau protein) [138]. Whether in the central or peripheral system, the evidence above indicates a close association between the AMPKα1 subtype and the pathogenesis and pathology of AD. Its role in the pathogenesis of AD may be similar to the inflammatory response in the body, where appropriate activation through the AMPKα1/PPARγ/CD36 and AMPKα1/IκB/NFκB pathways enhances autophagic responses for protection. However, excessive activation may increase eIF2α levels, leading to learning and memory impairments. Nonetheless, the relevance of the AMPKα2 subtype to AD cannot be ruled out.

4.2. AMPKα2 and AD

Current research indicates a close association between the AMPKα2 subtype and AD. Studies have found that the AMPKα2 subtype is associated with aging [139] and plays a key role in cognition and long-term synaptic plasticity [63]. Conditional knockout mice lacking the AMPKα2 subtype show impaired learning and memory, reduced hippocampal postsynaptic density formation, abnormal dendritic spine morphology, and related synaptic plasticity defects, while knockout of the AMPKα1 subtype has no effect [63]. The role

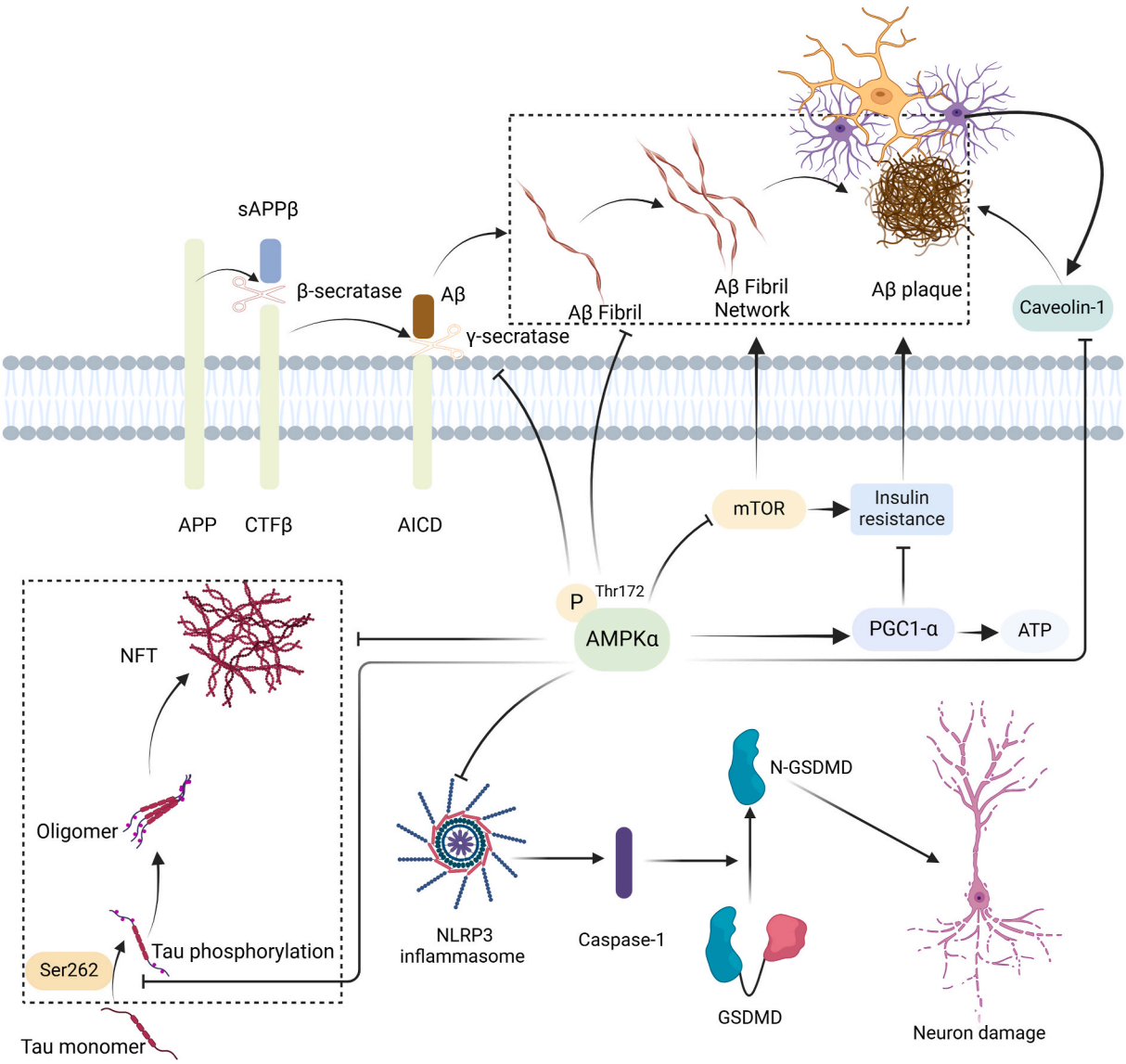

Fig. 1. Simplified mechanistic representation of the role of AMPKα subunit in the pathogenesis of Alzheimer's disease.

of the AMPKα2 subtype in aging and cognition suggests that it may also have a specific role in AD. Previously, Won and colleagues first discovered that AMPK can negatively regulate the generation of Aβ, and this effect is related to the AMPKα2 subtype. Increased Aβ production was observed after knocking out the AMPKα2 subtype [140]. However, Wang and colleagues found that the expression of the AMPKα2 subtype is positively correlated with Aβ pathology. The AMPKα2 subtype is overactivated in the hippocampus of non-human primate models of AD, and its dysregulation is associated with increased brain Aβ plaque load, elevated soluble Aβ oligomers, and decreased cerebrospinal fluid $A\beta_{42}$ levels [47]. Given the limited research on the role of the AMPKα2 subtype in regulating Aβ pathology, more research results are needed to evaluate whether the AMPKα2 subtype positively or negatively regulates Aβ pathology. Future studies should further elucidate the specific mechanisms by which the AMPKα2 subtype regulates Aβ production. In addition to Aβ pathology, several studies suggest that AMPK can regulate AD-related Tau protein pathology [141,142]. However, there is currently no research indicating the relationship between the AMPKα2 subtype and AD-related Tau pathology, which could be a potential focus for future research. Furthermore, it is known that diabetes is often associated with cognitive impairment, and severe cognitive impairment can progress to AD [143]. AMPK is considered a bridge between AD and diabetes [144]. Recent research by Li and colleagues found that the activity of the AMPKα2 subtype is inhibited in the hippocampus of mice with diabetes-related brain damage, indicating the involvement of the AMPKα2 subtype in the pathogenesis of diabetes-related brain damage [145]. Therefore, it can be reasonably speculated that the AMPKα2 subtype may be a key factor linking AD and diabetes, but further experiments are needed to verify the accuracy of this speculation. In summary, as the main catalytic subunit of AMPKα in the brain, AMPKα2 plays a crucial role in cognition, learning and memory, and synaptic plasticity. Its ability to regulate Aβ production may make it a potential therapeutic target for AD-related treatments (Fig. 1).

5. Summary and outlook

Despite the fact that AMPK typically has a positive impact on the health of organisms, there is evidence suggesting that it may also be involved in the development of diseases. As emphasized in the introduction, some studies have indicated that AMPK activation has a beneficial effect on AD [28,32–34]. However, several other studies have also reported that AMPK activation exacerbates the progression of AD [4,5,30,31]. Despite the controversy, AMPK is still considered to have potential as a drug target for AD development, possibly due to its significant role in the pathophysiology of AD [4–6] and its potential relevance to the pathogenesis [7]. Multifactorial analysis networks also indicate that AMPK plays a central role in the dysregulation of various metabolic factors and energy homeostasis in AD [146], with dysregulation of its expression leading to downstream changes including amyloid-beta plaque formation, neurofibrillary tangle formation, alterations in metabolic signaling, and memory impairment [146]. Given the existence of different subunits and isoforms of AMPK, comprising a total of 12 AMPK complexes [28], one possible reason for the controversial role of AMPK in AD could be differences in activation among its various subunits or isoforms. Therefore, research is increasingly focusing on exploring the roles of subunits or isoforms within AMPK complexes in AD, as previously mentioned. The AMPKα subunit, as discussed earlier, plays a primary role in AMPK activation [48] and is involved in AD pathology such as Aβ pathology [4,37,38,84,85], Tau pathology [38,39,93], metabolic disturbances [40,101–105], inflammation [41,111,112], mitochondrial dysfunction [42,123], inflammasomes, and pyroptosis [43]. Hence, the AMPKα subunit may represent a potential therapeutic target for AD.

Drug research and development can be viewed as a multi-objective optimization problem [147]. In fact, there have been reports of clinical trials related to AMPKα subunit, such as in type 2 diabetes, where metformin activates AMPKα subunit to upregulate mitochondrial autophagy to prevent further deterioration of blood glucose [148,149]; sorafenib synergistically acts with metformin to activate AMPKα subunit and inhibit non-small cell lung cancer proliferation [150]; Huangqin Qingre Chubi Capsules improve oxidative stress in ankylosing spondylitis patients through the AMPKα/FOXO3a pathway [151]. Additionally, activation of AMPKα subunit is beneficial for the human body; for example, increased exercise activates AMPKα subunit to induce skeletal muscle glucose uptake and protein synthesis [152], and exercise training during fasting activates AMPKα subunit, facilitating rapid activation of muscle protein translation after endurance exercise [153]. However, activation of AMPKα subunit also has certain side effects; for instance, Laura et al. found that chronic activation of AMPK can lead to kidney hypertrophy [154], Dominique et al. discovered increased activation of AMPKα subunit in skeletal muscles of multiple sclerosis patients [155], and Zimmermann et al. found that specific inhibition of AMPKα1 in mouse brains can improve its pathophysiology [46]. The differences in AMPKα subunit observed in different clinical trials may be attributed to variations in disease spectrum or insufficient drug targeting. After all, AMPKα subunit has been found to have subtype-specific effects in AD [45].

It is worth noting that although some studies have noted the subtype-specific effects of the AMPKα subunit in AD, research on the role of AMPKα subtypes in the pathogenesis of AD remains limited. To provide more precise therapeutic targets for AD treatment, further clarification of the role of AMPKα subtypes in AD, including their impact on AD-related pathology and the underlying mechanisms, is needed. Additionally, current research findings are primarily based on animal experiments, which show variability possibly due to differences in the types of AD model mice used and experimental methods employed by researchers. Lastly, the β subunit, serving as a scaffold subunit in AMPK, has previously been suggested to have an alternative role in regulating AMPK activity [36]. However, there is currently a lack of research on the relationship between the β subunit or its subtypes and the pathogenesis of AD, leaving room for future studies to address this gap.

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CRediT authorship contribution statement

Lingqiong Xia: Writing – original draft. **Jianhua Chen:** Writing – review & editing. **Juan Huang:** Writing – review & editing. **Xianmei Lin:** Writing – original draft. **Jingyu Jiang:** Writing – review & editing. **Tingting Liu:** Writing – review & editing. **Nanqu Huang:** Writing – review & editing. **Yong Luo:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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