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News and Reviews

Alpha 7 nicotinic acetylcholine receptor and its effects on Alzheimer's disease

Kai-Ge Ma[a,b], Yi-Hua Qian[a,c,*]

[a] Department of Human Anatomy, Histology and Embryology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, 76 Yanta West Road, Xi'an 710061, China

[b] Institute of Neurobiology, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi 710061, China

[c] Key Laboratory of Environment and Genes Related to Diseases (Xi'an Jiaotong University), Ministry of Education of China, Xi'an Jiaotong University Health Science Center, 76 Yanta West Road, Xi'an 710061, China

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ABSTRACT

Alzheimer's disease (AD) is one of the major disabling and lethal diseases for aged individuals worldwide. To date, there are more than 10 hypotheses proposed for AD pathology. The beta-amyloid (Aβ) cascade hypothesis is the most widely accepted and proposes that the accumulation of Aβ in the brain is one potential mechanism for AD pathogenesis. Because some Aβ-overloaded patients do not have AD syndrome, this hypothesis is challenged from time to time. More recently, it has been shown that intracellular Aβ plays a key role in AD pathology. Aβ is internalized by receptors distributed on the cell membrane. Among these receptors, the alpha7 nicotinic acetylcholine receptor (α7 nAChR) has been shown to play an important role in AD. The α7 nAChR is a ligand-gated ion channel and is expressed in pivotal brain regions (*e.g.*, the cerebral cortex and hippocampus) responsible for cognitive functions. The α7 nAChR is localized both presynaptically and postsynaptically, where it activates intracellular signaling cascades. Its agonist has been investigated in clinical studies to improve cognitive functions in AD. Although many studies have shown the importance of the α7 nAChR in AD, little is known regarding its role in AD pathology. Therefore, in the current review, we summarized the basic information regarding the structures and functions of the α7 nAChR, the distribution and expression of the α7 nAChR, and the role of the α7 nAChR in mediating Aβ internalization. We subsequently focused on introducing the comprehensive α7 nAChR related signaling pathways and how these signaling pathways are integrated with the α7 nAChR to play a role in AD. Finally, we stressed the AD therapy that targets the α7 nAChR.

1. Introduction

1.1. The β-amyloid hypothesis of Alzheimer's disease

Alzheimer's disease (AD), characterized by cognitive and memory deficits, is one of the main causes of mental disability and death among seniors. AD has a mean duration of approximately 8.5 years from the onset of clinical symptoms to death (Francis et al., 1999). To date, the pathogenesis of AD has remained unclear; however, several hypotheses have been proposed, such as the β-amyloid (Aβ) cascade hypothesis, acetylcholine system abnormalities, pathogenic hyperphosphorylated microtubule-associated protein *tau*, chronic inflammation and oxidative stress. The main cause of AD remains controversial between two of the most convincing hypotheses, the tau hypothesis and the β amyloid hypothesis. It has been more than 10 years since the amyloid hypothesis was first proposed as a potential mechanism for AD. It hypothesizes that the accumulation of Aβ in the brain of AD patients is the primary driver for AD progression. According to the amyloid hypothesis, the remaining disease processes, such as the formation of neurofibrillary tangles that contain tau, are the result of an imbalance between Aβ accumulation and Aβ clearance (Hardy and Selkoe, 2002). Moreover, *tau* was first discovered in 1975 as a microtubule-associated protein, which stimulates tubulin assembly into microtubules in the brain (Gong and Iqbal, 2008). These proteins are abundant in neurons and expressed at very low levels in astrocytes and oligodendrocytes of the central nervous system. The *tau* hypothesis states that an excessive or abnormal phosphorylation of tau disassembles microtubules and sequesters normal *tau*, microtubule associated protein1 (MAP1), MAP2 and ubiquitin into tangles of paired helical filament. These insoluble structures damage cytoplasmic functions and interfere with neuron transportation, which

* Corresponding author at: Department of Human Anatomy, Histology and Embryology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, 76 Yanta West Road, Xi'an 710061, Shaanxi, China.
E-mail address: qianyh38@mail.xjtu.edu.cn (Y.-H. Qian).

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may lead to cell death. However, these major *tau* kinases, including glycogen-synthase kinase-3β (GSK-3β), cyclin-dependent protein kinase 5 (CDK5), cAMP-dependent protein kinase (PKA), and stress-activated protein kinases, are all involved in Aβ-induced AD pathological processes, which suggests that Aβ could eventually cause tau hyperphosphorylation through these signaling pathways.

The Aβ cascade hypothesis is accepted and studied by the majority of researchers. It was first suggested by Hardy and Higgins in 1992'(Hardy and Allsop, 1991; Hardy, 1992) and they proposed that Aβ deposition may due to a certain gene defect, which leads to an overexpression of amyloid precursor protein (APP) or a reduced hydrolytic process. They proposed that the extracellular insoluble amyloid protein plaque is the key factor for AD pathology (Hardy, 1992; Selkoe, 1991; Wertkin et al., 1993). However, recent findings indicate that soluble intracellular Aβ oligomer rather than extracellular insoluble Aβ plaque is the main pathogenic factor of AD (Lacor et al., 2004). Although it was suggested by Grundke-Iqbal 20 years ago, it was not until recently that increasing *in vivo* experiments have shown intracellular Aβ deposition appeared before extracellular Aβ deposition in neurons at the early stage of AD, before extracellular Aβ was detected (Grundke-Iqbal et al., 1989).

1.2. Intracellular Aβ plays an important role in AD

Accumulating evidence suggests that intracellular accumulation of Aβ is an early pathological marker in AD patients and animal models of AD. Morphologically, studies using electron microscopy have suggested that prior to Aβ plaque formation, intracellular Aβ could deposit at axon terminals, dendrites, mitochondria, and lysosomes and affect the synaptic plasticity (LaFerla et al., 2007; Ma et al., 2016; Takahashi et al., 2002; Yang et al., 2015; Yang et al., 2014). Physiologically, intracellular Aβ also causes potential long-term memory deficits. Moreover, intracellular Aβ alone could cause cell death and cognitive deficits in APP/PS1 (transgenetic mice that overexpress the amyloid precursor protein, APP and presenilin-1, PS1 gene)transgenetic mice, and these deficient were significantly reduced after the removal of intracellular Aβ (Billings et al., 2005). Moreover, there is also evidence that extracellular Aβ could cause the previously described pathological changes. Are there relations between these two phenomena? Studies have shown that intracellular Aβ appears before extracellular plaques and intraneuronal Aβ levels decrease as extracellular plaques accumulate (Ma et al., 2018; Mori et al., 2002). Furthermore, extracellular amyloid plaques were seeded from intracellular Aβ (Hu et al., 2009). Collectively, it is possible that the toxicity and pathological affects caused by extracellular plaques may be a long-term effect of the intracellular Aβ accumulation or at least partially caused by intracellular Aβ in the early stage of AD. Intracellular Aβ has been shown to cause AD by inducing axon degeneration and (or) synaptic loss and cell death (Umeda et al., 2011). Intracellular Aβ originates from the hydrolyzation of APP or the internalization of extracellular Aβ through Aβ internalization receptors. It has been reported that many receptors participate in Aβ internalization (Lai and McLaurin, 2010), such as low-density lipoprotein receptor-related proteins (Ma et al., 2016; Yang et al., 2015; Fuentealba et al., 2010), apolipoprotein E receptors (Dafnis et al., 2010), and the alpha 7 nicotinic acetylcholine receptor (α7nAChR) (Yang et al., 2014; Nagele et al., 2002). Here, we reviewed the α7nAChR, which is one of the most relevant receptors mediating Aβ internalization (Yang et al., 2014; Lykhmus et al., 2015; Medeiros et al., 2014). It has been shown to play an important role in the prevention and treatment of AD. Therefore, understanding the Aβ internalization process and its related receptor is important for identifying potential targets for AD therapy.

2. The structure, function and distribution of α7nAChR

2.1. The structure of α7nAChR

The acetylcholine receptor (AChR) is an integral membrane protein that responds to the binding of acetylcholine, a neurotransmitter. This receptor belongs to the super family of pentameric ligand-gated ion channels (Karlin and Akabas, 1995; Paterson and Nordberg, 2000). Ion-channel linked receptors regulate ionic events by the ACh-opening of nAChR channels.The AChR changes the ion-permeability of the cellular membrane and mediates fast signaling transportation. Therefore, it is also referred to as a ligand-gated ion channel. The AChRs was grouped into two classes, nicotinic and muscarinic AChRs (nAChRs and mAChRs, respectively) (Changeux et al., 1998; Gault et al., 1998).

nAChRs belong to the ligand-gated ion channel family. In humans, this family is composed of 16 subunits, including: α1–7, α9–10, β1–4, γ, δ and ε. These subunits form homologous or heterologous nAChRs with unequable structures and functions. Although there are various complexed forms of nAChRs, only two subtypes are highly expressed in the central nervous system. One subtype has α4β2 subunits, which has high affinities for nicotine and cytosine and a lower affinity for α-BTX (α-bungarotoxin). Another subtype has five α7 subunits, referred to as α7 nAChR, which has a high affinity for α-BTX and lower affinities for nicotine and cytosine. The α7 nAChR is particularly important in AD pathology. It not only participates in the cholinergic anti-inflammatory pathway related to autoimmune disorders but is also involved in learning and memory. Upregulation of the α7nAChR is a therapeutic goal for AD and schizophrenia. To achieve this goal, the fundamental information of the α7 nAChR requires elucidation.

The α7 nAChR is the only homologous receptor in the human brain and has five α7 subunits. Its gene is located at q14 chromosome 15 with a total length of 75,000 bp. It contains a 1509 bp cDNA, 10 exons, and 9 introns (Fig. 1A). Studies have shown that protein structures coded by the 4th, 6th, and 7th exons are the binding sites for α7 nAChR agonists. Each subunit consists of 502 amino acids and 4 transmembrane domains (M1, M2, M3, and M4). There are approximately 100–200 amino acids between the M3 and M4 domains (Fig. 1B). Peptides from the M2 domain to the N-terminal are responsible for positive ion transportation. Thus, the M2 domain is the key part for Ca^{2+} permeability. The α7 nAChR contains one extracellular ligand binding site and three extracellular glycosylation sites. The N-terminal of the extracellular ligand binding site also has a high affinity for α-BTX (Fig. 1C) or α-BTX-like antagonists (Gault et al., 1998; De Jonge and Ulloa, 2007). Interestingly, only well assembled, folded and functional α7 nAChRs could bind to α-BTX. Gu et al. have identified NACHO (nicotinic acetylcholine receptor regulator chaperone) as a novel assemble regulator of the α7 nAChR (Gu et al., 2016). They also found that no ACh-evoked currents were detected in HEK cells transfected with α7nAChR alone, while cotransfection of NACHO with α7nAChR yielded rapidly desensitizing ACh-evoked currents. These findings suggest that brain α7nAChR assembly requires NACHO.

2.2. The functions of α7nAChR

α7 nAChR dysfunction is associated with AD. Studies have shown that the levels of α7 nAChR in the brain change with age. The α7 nAChR level is significantly higher at the early stage of embryonic development and the adult stage than in the late embryonic stage, which indicates that the α7 nAChR could play a crucial role in growth, development and aging. Interestingly, for patients with neurodegenerative lesions, the α7 nAChR level substantially decreased. The α7 nAChR regulates the plasticity of the neural circuit, neuronal differentiation, proliferation, apoptosis and clearance of aged neurons. In addition, the α7nAChR has vital functions in glia cells (Orr-Urtreger et al., 2000). A functional α7nAChR was detected in astrocytes of the hippocampus, and it could upregulate the free Ca^{2+} concentration in

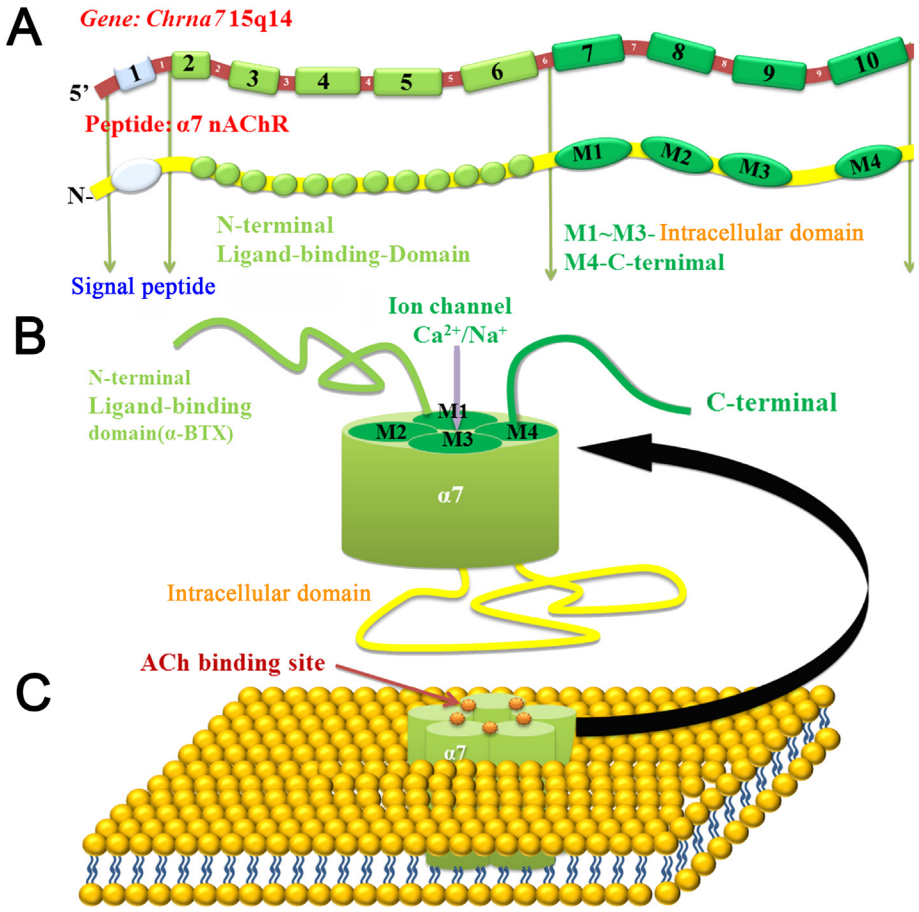

Fig. 1. The structure of α7 nicotinic acetylcholine receptor. (A) Chrna1 gene is located at the 15q14 chromosome. This gene comprises 10 exons (Rectangle numbered from 1 to 10) and 9 introns (Red line numbered from 1 to 9). From which code a 50 kDa α7nAChR protein. Peptides coded by the 2th to 6th exons are the binding sites for α7nAChR ligand like α-BTX and 7th to 10th are transmembrane proteins for (ellipse). (B) The α7nAChR has an N-terminal signal peptide; and ligand binding domain which has high affinity with α-BTX, or α-BTX-like antagonists; 4 transmembrane domains (M1, M2, M3, M4), in which M2 is the key part for Ca^{2+} permeability; and a regulatory intracellular domain between M3 and M4. (C) Nicotinic acetylcholine receptors (nAChR) is a ligand-gated ion channel family. α7nAChR belongs to the nicotinic acetylcholine receptors which mostly distributed in the central nervous system. α7nAChR has high affinity for α-BTX, forms homo-pentameric ion channel receptors and it is the only α-BTX receptor identified in mammalian brain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the cytoplasm (Sharma and Vijayaraghavan, 2001).

α7 subunits have a high permeability to Ca^{2+}. When Ca^{2+} is activated, it is transported into the cellular membrane and forms an instantaneous inward electric current and unregulated free Ca^{2+} level instantly, which opens the ion gate directly or indirectly and subsequently activates the voltage dependent Ca^{2+} channel (Sharma and Vijayaraghavan, 2001; Perry et al., 1992). A high level of free Ca^{2+} activates protein kinase, which then upregulates gene expression and protein production, leading to alterations in the structures and functions of neurons. After the activation of presynaptic α7 nAChR, Ca^{2+} influx is increased, the presynaptic membrane is depolarized and vesicles with neuron transmitters in the synapse merge with the presynaptic membrane, which increases exocytosis and a massive release of transmitters, such as glutamic acid, norepinephrine (NE), ACh, dopamine (DA) and γ-amino butyric acid (GABA), to the synaptic cleft. Postsynaptic α7nAChR activation could not only depolarize the postsynaptic membrane but also regulate the release of GABA transmitter, resulting in long-term changes in normal functions, such as cognitive function.

2.3. The expression and distribution of α7nAChR in central nervous system

The α7nAChR is widely distributed in the central nervous system, such as in the cerebral cortex, hippocampus, basal nucleus and reticular thalamic nucleus (Gotti et al., 2006a; Hogg et al., 2003a). It is mostly expressed in cognitive related regions, including the CA1, CA3, and dentate gyrus of the hippocampus and layers I and VI of the cortex. It has also been shown to be located in the marginal zone under the cortex and brainstem, such as the ventrolateral tegmentum and substantial nigra (Murakami et al., 2013). More recently, the α7nAChR was found most abundant in the hippocampus and neocortex, where there was progressive atrophy and a high affinity to Aβ in AD. In addition, the α7nAChR was strongly expressed in GABAergic interneurons in layers I-III of the rat retrosplenial granular cortex (RSG) and hippocampal pyramidal cells. This result is consistent with the *in situ* hybridization α7nAChR-mRNA detection experiment, which suggests that ACh likely carries a diffuse signal in the superficial layers of the RSG and modulates the inhibitory neurotransmission among interneurons (Deardorff et al., 2015a).

In the brain, the α7nAChR has been shown to be distributed in neurons, astrocytes, mature dendritic cells, and microglia cells (Clarke et al., 1985). Moreover, it may be detected at both pre/postsynaptic membranes to perform its functional abilities, such as synaptic transportation, neurotransmitter release, and synaptic plasticity. The activation of the α7nAChR in the prefrontal cortex and ventral tegmental could directly regulate the release of excitatory amino acids without cellular membrane depolarization (Tribollet et al., 2004).

The α7nAChR inhibitors methyllycaconitine (MLA) and α-BTX both have a high affinity to the α7nAChR. Thus, they were used to detect the expression of α7nAChR. I^{125}, the radioactive isotope of iodine, has been used to label α-BTX and detect the distribution of α7nAChR in the rat brain. Furthermore, the massive distribution of the α7nAChR in the hippocampus and its high permeability to Ca^{2+} is the foundation for mediating the physical and pathological functions in the hippocampus (Yang et al., 2014; D'Andrea et al., 2002).

3. The α7nAChR and AD

3.1. Role of α7nAChR in amyloid accumulation in AD

Aβ has been shown to be primarily accumulated in vulnerable neurons prior to plaque formation. The overburdened intracellular Aβ

accumulation, particularly $A\beta_{1-42}$, causes neuron, dendrite, and synapse lysis and eventually forms dense core plaques, diffuse plaques and astrocytic plaques. In response to $A\beta_{1-42}$ accumulation, a significant upregulation of the α7nAChR was identified in 4-month-old AD transgenic mice prior to the appearance of Aβ, and the upregulation of α7nAChR remained detectable until 17–19 months old (D'Andrea and Nagele, 2006). Gyure et al. found that intraneuronal accumulation of Aβ was detectable much earlier before significant Aβ extracellular deposition and plaque formation. Therefore, targeting the α7 nAChR to prevent $A\beta_{1-42}$ -induced cytotoxicity and slowing down amyloid plaque deposition should be considered in young adults to prevent the further development of AD. Disordered expression of CHRNA7 (also referred to as 15q13.3 deletion syndrome), the gene encoding for α7 nAChR, is associated with several neuropsychiatric disorders, thus highlighting the important roles of the α7 nAChR in the developing brain and normal processes of attention, behavior, cognition and memory throughout life (Deutsch et al., 2016; Gyure et al., 2001).

Aβ and α7 nAChR have a high affinity and form the α7 nAChR-Aβ complex, which could be resistant to detergent and may be detected in the complexed form by Western blotting. This complex was first formed in dendrites, followed by internalization *via* endocytosis, and it was eventually transported within endocytotic vesicles and retrogradely to neuronal perikaryon in the pyramidal cell layers. This explains why neurons appear to selectively accumulate Aβ (D'Andrea and Nagele, 2006). Moreover, evidence indicates that intracellular Aβ accumulates in α7 nAChR positive neurons, which explains the selective vulnerability of cholinergic neurons in AD brains.

More recently, Deutsch et al. reviewed that the binding of Aβ peptides to the α7nAChR may influence the organization of lipids and proteins on the cell membrane. This binding can be toxic for cells expressing the α7nAChR on their surface. Moreover, the internalization of the α7nAChR-Aβ complex may lead to cell lysis and extracellular deposition of amyloid plaques (Deutsch et al., 2016; Gyure et al., 2001; Deutsch et al., 2014). Therefore, it has been suggested that stimulation of the α7 nAChR protects neurons from Aβ-induced degeneration. It was also understandable that drugs that block the initial interaction of Aβ and the α7nAChR could reduce the levels of Aβ in the blood and cerebrospinal fluids and maintain the Blood-Brain Barrier (BBB) integrity, which may have a positive effect on cognitive function, as well as additional therapeutic benefits by slowing down the progression of AD (D'Andrea and Nagele, 2006).

3.2. The α7nAChR regulates Aβ internalization in neurons

Evidence indicates that neurons containing intracellular Aβ peptide could invariably express relatively high levels of α7 nAChR. Intracellular Aβ could form toxic Aβ oligomers and can be up taken by lysosomes, endoplasmic reticulum, and mitochondria, thereby leading to organelle damage and neuronal cell necrosis or apoptosis (Umeda et al., 2011). It has previously been demonstrated that the α7 nAChR mediated Aβ internalization in neurons. Furthermore, α7nAChR mediated Aβ internalization is sequence-specific. α7 nAChR transfected cells exhibited rapid binding, internalization and accumulation of the exogenous toxic peptide $A\beta_{1-42}$ rather than $A\beta_{1-40}$ (Godyn et al., 2016). After Aβ binds to the α7nAChR, the postsynaptic signaling pathway mediated by the α7nAChR is blocked and normal ligand-binding activity to the α7nAChR is interrupted, which subsequently causes neuron dysfunction and cognitive deficits. Coimmunoprecipitation studies have indicated that $A\beta_{1-42}$ and α7nAChR formed the $A\beta_{1-42}$-α7nAChR complex in SH-SY5Y cells (Yang et al., 2014). As a result, this increased the internalization of $A\beta_{1-42}$ and led to intracellular $A\beta_{1-42}$ aggregation. The intracellular $A\beta_{1-42}$ could aggravate the formation of extracellular amyloid plaques (Langui et al., 2004; Li et al., 2011; Nunomura et al., 2010; Palop and Mucke, 2010; Wang et al., 2000).

3.3. The dual effects of Aβ on α7 nAChR-induced synaptic plasticity and cognitive ability

3.3.1. The α7 nAChR antagonist and agonist, which one rescues Aβ-induced cytotoxicity?

Studies have indicated that the α7 nAChR plays an important role in regulating cognitive, sensory, pain, neuronal transmitter release and neuron protection functions (Deutsch et al., 2016; Deutsch et al., 2014; Klink et al., 2001). More importantly, massive evidence has indicated that $A\beta_{1-42}$-α7 nAChR could mediate synaptic plasticity; however, the mechanisms of the $A\beta_{1-42}$-α7 nAChR complex in the regulation of synaptic plasticity and cognitive ability have not been clear. In most studies, Aβ was regarded as a "garbage" product of APP metabolism. Furthermore, Aβ is considered responsible for synaptic dysfunction, memory loss and the structural damage of the brain in AD patients at the later stages. However, recent research proposes that Aβ is not simply a "garbage" product of APP metabolism that strikingly causes cognitive deficits in a certain stage; it is a peptide that can contribute to neurotransmitter release and the synaptic plasticity of both reference and contextual fear memory (Puzzo and Arancio, 2013a).

A recent study illustrated that the large aggregates of Aβ upregulated the α7 nAChR expression and caused a reduction of the cell viability. These effects were reversed by MLA, an α7nAChR antagonist, which suggests that the α7 nAChR mediates Aβ induced neurotoxicity (Hu et al., 2008). However, it is interesting to note that most potential drug investigations of AD involve α7 nAChR agonists. The concentration of $A\beta_{1-42}$ in the brain white matter of AD patients is 60 pM/L (Collins-Praino et al., 2014; Liu et al., 2007). In Liu's study, Aβ was used at 100 nM for 10 days, which is a "high" and toxic concentration for an *in vitro* experiment. Therefore, it is possible that blocking the Aβ/α7 nAChR interaction by MLA prevents its toxicity. However, during the Aβ induced effect, the α7 nAChR was shown to play an important role. Therefore, the effect of α7 nAChR agonists or antagonists is dependent on the concentration and treatment duration of Aβ.

3.3.2. Aβ induces LTP enhancement through α7nAChR

Long-term potential (LTP) is the dominant model of activity-dependent synaptic plasticity. Aβ only affects LTP when it is added prior to stimulation (Puzzo et al., 2008; Puzzo and Arancio, 2013b; Puzzo et al., 2011). A previous study performed a dose response curve to investigate the effect of Aβ on LTP. Surprisingly, the concentration/response curve showed a significant enhancement of LTP in the CA1 region of hippocampal slides where the Aβ concentration was approximately 200 pM. In contrast, an impairment of LTP at the synapses between the Schaeffer collateral fibers was identified when the Aβ concentration was approximately 200 pM and treated for 20 min (Puzzo et al., 2008; Puzzo and Arancio, 2013b; Puzzo et al., 2011). To date, little is known regarding how Aβ induces this enhancement in LTP and synaptic plasticity, with a significant increase of Ca^{2+}. The glutamate receptors, such as AMPA and NMDA receptor currents, did not exhibit changes during perfusion with Aβ (Puzzo et al., 2008; Puzzo et al., 2015). However, the increase of Ca^{2+} produced by Aβ alone is not sufficient compared to the previously described Ca^{2+} increase. Considering the α7 nAChR is necessary for the Aβ-induced increase of synaptic plasticity and memory and the α7 nAChR is a Ca^{2+} channel and involved in diverse brain functions, such as synaptic plasticity and memory, Aβ binds selectively to the α7 nAChR at picomolar concentrations and could activate the α7 nAChR at presynaptic nerve endings (Puzzo et al., 2015). Therefore, it is promising to propose that the picomolar Aβ-induced enhancement of synaptic plasticity is mediated by α7 nAChR.

3.3.3. Why is there a dual effect of Aβ on α7nAChR induced synaptic plasticity?

According to a series of studies, the effect of Aβ on synaptic plasticity is determined by several factors. Primarily, the concentration of

Aβ is responsible for its dual effects. Second, the duration of Aβ treatment also causes different effects. Finally, the time point that Aβ is applied (Puzzo et al., 2008; Puzzo and Arancio, 2013b; Puzzo et al., 2011).

For picomolar Aβ, the concentration is closely associated with the endogenous Aβ concentration (Puzzo et al., 2008; Puzzo and Arancio, 2013b; Puzzo et al., 2011; Puzzo et al., 2015; Phinney et al., 2003), and it has a positive effect on synaptic plasticity and memory formation. These findings suggest that instead of a "garbage" product, endogenous Aβ is likely a critical player in synaptic plasticity and memory in the normal central nervous system. Furthermore, studies have reported that anti-rodent Aβ antibody could delete endogenous Aβ and reduce LTP, as well as contextual fear memory and reference memory. Not surprisingly, this effect was reversed by the addition of human Aβ. Furthermore, hippocampal Aβ production was found to be enhanced during memory induction, which requires the participation of the α7nAChR. In α7 nAChR KO mice, there is no LTP reduction observed with anti-rodent Aβ antibody treatment (Puzzo et al., 2011), which suggests that the α7nAChR and transmitter release are necessary for the effects of endogenous Aβ on plasticity and memory.

More recently, a model was proposed to interpret AD pathogenesis as an alteration of the negative feedback loop between Aβ and its physiological receptors, focusing on α7 nAChRs (Puzzo et al., 2015; Phinney et al., 2003). According to this model, when Aβ cannot exert its physiological function, a negative feedback mechanism would induce a compensatory increase in its production, thereby leading to an abnormal accumulation of Aβ, which subsequently reduces α7 nAChR function and causes synaptic dysfunction and memory loss. From this perspective, the indiscriminate Aβ removal might worsen neuronal homeostasis, causing a further impairment of learning and memory (Phinney et al., 2003; De Strooper and Karran, 2016). Even if further studies are required to better understand and validate these mechanisms, we believe that a greater understanding of the role of Aβ in physiological conditions might represent a key point to elucidate important aspects of AD pathogenesis.

Due to the different concentrations of Aβ used in various experiments, contradictory results have been reported on Aβ induced effects and its interaction with cholinergic receptors. Elisa Mura and her colleagues reported that Aβ has a dual effect in mediating the α7 nAChR and controlling the release of aspartate, glutamate and GABA transmitters, which are stimulated by the activation of presynaptic cholinergic nicotinic receptors and are typically involved in learning and memory. Nicotine could stimulate an overflow of neurotransmitters, such as aspartate, glutamate and GABA. This transmitter stimulation effect was substantially inhibited by the highest concentrations of Aβ (10 μM *in vivo* and 100 nM *in vitro*) (Olivero et al., 2014).

3.4. The α7nAChR as a therapeutic target in AD

Aβ is crucially involved in AD and capable of inhibiting endogenous ACh from activating α7 nAChRs. The interaction of Aβ and the α7 nAChR influences neurotransmission, synaptic plasticity, learning and memory. In the 1990s, several acetylcholinesterase inhibitors, which are all nonselective enhancers of nAChR function, were approved for the treatment of mild to moderate AD, including tacrine (approved in 1993), donepezil (1996), rivastigmine (2000) and Galantamine (2001). Surprisingly, no acetylcholinesterase inhibitor has been approved since then. Eptastigmine and phenserine were discontinued in clinical trials due to their adverse effects or insignificant benefits (Yang et al., 2017).

3.4.1. Nicotine

Nicotine, a well-known α7nAChR agonist, is a potential therapeutic agent for AD. In 1988, Newhouse's team administered nicotine to 6 CE patients and identified an improvement of learning and memory ability (Newhouse et al., 1988). White et al. found that nicotine improved the attention of AD patients. Moreover, animal studies have shown that nicotine improved working memory, short-term memory and long-term memory (Levin and Simon, 1998; White and Levin, 1999). However, the mechanisms remain elusive.

Liu et al. found that the α7 nAChR mediated the effect of nicotine on AD treatment (Liu et al., 2007). Nicotine attenuates the aggregation of Aβ in the cortex and hippocampus of APP transgenic mice. It inhibits the ERK and p38 MAPK signaling pathways and prevents NF-κB and c-Myc activation. Moreover, it induces the interaction of NOS with NF-κB and down regulates the NO level. In addition, the results from an RNA interference experiment also suggest that the α7 nAChR is essential in nicotine related memory improvement. Nicotine activates the α7 nAChR through the MAPK-NF-κB-c-Myc cascade and attenuates Aβ aggregation and cell apoptosis in the brain. Consequently, Liu et al. suggested that nicotine attenuates the Aβ toxic effect through a new anti-inflammatory mechanism (Liu et al., 2007; Akiyama et al., 2000; Sheta et al., 2006; Zhu et al., 2008).

Recent research published by Inestrosa et al. indicated that nicotine prevents the synapse damage of primary neurons from Aβ-induced toxicity through the α7 nAChR/PI_3K signaling cascade. Furthermore, the learning and memory abilities of APP/PS1 transgenic mice are both improved. It is proposed that the interaction between α7 nAChR/PI_3K and the *Wnt* signaling pathway may be another potential drug target for AD (Inestrosa et al., 2013; Inestrosa and Varela-Nallar, 2014).

3.4.2. ABT-107

ABT-107, a full agonist of the α7 nAChR, in contrast to nicotine, which induces psychomotor excitement, has a stable effect. A series of experiments carried out by Bitner's research team discovered that ABT-107 improved learning and memory functions in mice, rats, and monkeys. Acute administration of ABT-107 increased the phosphorylation levels of ERK and CREB. Subcutaneous injection of ABT-107 in AD transgenic mice for 10 days inhibited the GSK-3β activation at the Ser-9 site and decreased the *tau* hyperphosphorylation level (Bitner et al., 2010; Bitner et al., 2009).

3.4.3. ABT-126

ABT-126 was developed by AbbVie (formerly Abbott) as an α7 nAChR agonist. ABT-126 treatment significantly improved memory in a phase II clinical trial in patients with mild-to-moderate AD compared with placebo. Furthermore, ABT-126 showed a significant improvement of negative symptoms; however, it did not ameliorate cognitive deficits. Due to this reason, it was terminated in 2014 (Florian et al., 2016).

3.4.4. AZD0328

AZD0328 is an optimized molecule that acts as a partial α7 nAChR agonist. It is very stable, which suggests that this compound could be suitable for clinical trials. AZD0328 enhances cortical dopamine release in rat models and improves cognitive decline in mice through the activation of α7nAChRs. It is also reported to improve working memory in a spatial delayed response test in Rhesus macaques (ClinicalTrials.gov 2018) However, AstraZeneca terminated AZD0328 for a phase II clinical trial due to its failure to meet the target product profile in 2008 (ClinicalTrials.gov 2018).

3.4.5. MEM3454

MEM3454 was developed by Memory Pharmaceuticals and has been shown to have pro-cognitive effects in normal and aged rodents. Similarly, MEM3454 enhanced nAChR stimulation and ACh efflux for its antagonistic property for the 5-HT_3 receptor. However, in a phase II clinical trial, MEM3454 failed to improve cognitive deficits in patients with schizophrenia; nevertheless, moderate negative symptoms in patients were significantly improved (Rezvani et al., 2009).

3.4.6. GST-21(DMXB)

GST-21(DMXB), a partial agonist for the α7nAChR, is another potential medication for AD. An *in vitro* experiment of this drug was

initiated two decades ago, and the results showed that it improved learning and memory functions in mice, rats, monkeys, and rabbits (Arendash et al., 1995; Kem, 2000; Meyer et al., 1997; Woodruff-Pak et al., 1994). In 2003, Phase I clinical studies showed that DMXB has no obvious toxic effect on healthy men and it has a better effect on cognitive behavior (Freedman et al., 2008) The result from another experiment indicated that DMXB improved AD patient's anesthesia and cognitive deficits. More importantly, it has fewer side effects than nicotine. Studies of DMXB on AD have entered the Phase II clinical trial stage; however, the mechanism of its effects is still needed for further exploration (Bitner et al., 2010; Freedman et al., 2008; Zawieja et al., 2012).

3.4.7. Encenicline, a novel and partial selective agonist of the α7nAChR

Studies have shown that agonists of the α7nAChR improved the performance of learning and memory tasks (Godyn et al., 2016) Encenicline (EVP-6124, MT-4666) is a novel and partial selective agonist of the α7nAChR, and it has been assessed for the treatment of AD and cognitive deficits in schizophrenia (Prickaerts et al., 2012) Encenicline was evaluated *in vitro* and *in vivo* with Sprague-Dawley rats by Prickaerts et al. Encenicline activates the α7nAChR at low nanomolar brain concentrations in rats, which suggests that encenicline improves memory performance by potentiating the acetylcholine response of α7nAChRs. This co-agonist mechanism of encenicline is expected to increase the drug safety margin and minimize undesired interactions with other receptors (such as other nAChR subunits or muscarinic acetylcholine receptors) (Prickaerts et al., 2012).

Barbier et al. reported 2 single-dose studies that evaluated the relative bioavailability, pharmacokinetic profile, tolerability and cognitive effects of encenicline in healthy volunteers. The results showed that encenicline appeared to be well tolerated at single doses up to 180 mg. Doses as low as 1 mg had dose- and time-dependent pharmacodynamic effects on the central nervous system. The oral capsule and solution were bioequivalent. No effect of food on the pharmacokinetic profile of encenicline was identified (Barbier et al., 2015). In the same year, encenicline was assessed in clinical Phase I and Phase II trials with AD patients. Treatment with encenicline in Phase I and II trials involving patients with mild-to-moderate AD was well tolerated and appeared to significantly improve the cognitive and functional measures compared to the placebo group. Furthermore, two Phase III trials under the title COGNITIV AD evaluated the efficacy and tolerability of encenicline in patients with mild-to-moderate AD (Deardorff et al., 2015b). In view of the completed clinical trials and proposed mechanism of action, encenicline may represent a good candidate for therapy in combination with cholinesterase inhibitors.

3.4.8. Tropisetron, and its effects in Alzheimer's disease

Tropisetron, exhibits high affinity, partial agonist activity at α7 nicotinic acetylcholine receptors, also bound to APP. It promoted greater improvements in memory than memantine and donepezil, the current AD therapeutic drugs. It was known that Aβ deposition and inflammation in the brains causes mild cognitive impairment before the onset of AD. Given the role of α7 nAChR in Aβ deposition and inflammation, tropisetron represents an attractive potential therapeutic drug to delay or prevent mild cognitive impairment and AD. Additionally as this drug is used internationally to treat chemotherapy-induced vomiting, its safety record is already known (Hashimoto, 2014). Electrophysiological studies on human nAChRs expressed in Xenopus oocytes proved the partial agonist activity of tropisetron at α7 nAChR. Moreover, currents evoked by irregular pulses of acetylcholine (40 mM) at α7 and α4β2 nAChRs were enhanced by the exposure of low concentrations of tropisetron (10, 30 nM), showed its co-agonist effect. Furthermore, tropisetron (0.1–10 mg/kg) improved novel object recognition performance in both young and aged rats. In aged male and female rhesus monkeys, tropisetron (0.03–1 mg/kg) produced a 17% increase from baseline levels in delayed match to sample long delay accuracy while combination of donepezil (0.1 mg/kg) and tropisetron (0.03 and 0.1 mg/kg) produced a 24% change in accuracy, which indicates that tropisetron has the ability to improve the effective dose range of current AD therapy (Callahan et al., 2017).

3.4.9. Other potential drugs for AD

In addition to the previously described α7nAChR agonists, ABT-418, RG3487, clozapine, and AQW051 (Pohanka, 2012; Potter et al., 1999) are all considered potential drugs for AD. For example, an *in vitro* study of AQW051 showed significant pro-cognitive effects in rodents, and it has been advanced in phase II clinical trials for schizophrenia and AD (Trenkwalder et al., 2016). TC-5619 is an α7 nAChR full agonist and exhibits excellent activity and selectivity to the α7 nAChR. *In vivo* studies have shown a rapid central nervous system permeability and pro-cognitive effect in rodents. After two phase II clinical trials, it was confirmed that TC-5619 did not improve cognitive deficits and negative symptoms in schizophrenia; however, its role in AD remains to be explored (Walling et al., 2016). SSR-180711, a partial agonist of the α7 nAChR, is expected to exhibit breakthrough progress on the effective prevention and treatment of AD irrespective of the termination of its Phase II trials in schizophrenia patients (in 2008).

3.5. Signaling pathways associated with α7nAChR

Cholinergic dysfunction is regarded as the main problem in the pathophysiology of AD and contributes to the cognitive deficits in AD. The α7 and α4β2 subunits are the most prevalent subtypes in the brain and both play an important role in cognition. They have been shown to be highly expressed in the hippocampus, cortex, thalamus, ventral tegmentum and striatum (Gotti et al., 2006b). Postmortem studies in AD patients have identified a reduction of the α4β2 subunits in the brain. However, the results of the α7nAChR levels are conflicting (Hogg et al., 2003b). These findings suggest a more complicated mechanism of the α7 nAChR in AD. Although the levels of the α7 nAChR in postmortem AD patients' brains are controversial, the rescue experiments through up regulating the α7nAChR expression showed an improvement in cognitive deficits to some level. It has been widely acknowledged that α7nAChR manipulation could be a therapeutic possibility for AD. However, the underline mechanisms and signaling pathways related to the α7 nAChR remain unclear. Glycogen synthase kinase-3β (GSK-3β), phosphoinositide 3-kinase (PI_3K)-Akt (also referred to as protein kinase B, PKB, which is a serine/threonine-specific protein kinase), *Wnt* and the mitogen-activated protein kinase signaling pathway (MAPK) have been shown play a role in the α7 nAChR mediated $Aβ_{1–42}$ internalization in AD.

3.5.1. $Aβ_{1–42}$-α7nAChR activates GSK-3β leading to tau hyperphosphorylation

GSK-3β is an enzyme encoded by the *GSK3B* gene in humans. It is involved in energy metabolism, neuronal development and body pattern formation. The abnormal regulation and expression of GSK-3β have been suggested to be related to bipolar disorder (Luykx et al., 2010). The α7nAChR has an important role in the activation of GSK-3β by $Aβ_{1–42}$. $Aβ_{1–42}$-α7nAChR activates GSK-3β through the α7nAChR and subsequently leads to *tau* hyperphosphorylation. However, strikingly, using both agonists (rescue study, PNU282987, Nicotine) and antagonists (MLA, α-BTX) of the α7nAChR, the phosphorylation level of GSK-3β caused by $Aβ_{1–42}$ was attenuated, which led to a reduction of *tau* phosphorylation (Hu et al., 2008). These findings lead to unknown and complicated questions regarding therapeutic studies using α7nAChR for AD treatment. Whether α7nAChR antagonists or agonists have therapeutic potential or the exposure time is crucial in the manipulation of the α7nAChR for AD require further investigation.

3.5.2. Activation of PI_3K/Akt signaling cascade attenuates GSK-3β

The deactivation of GSK-3β could decrease *tau* phosphorylation

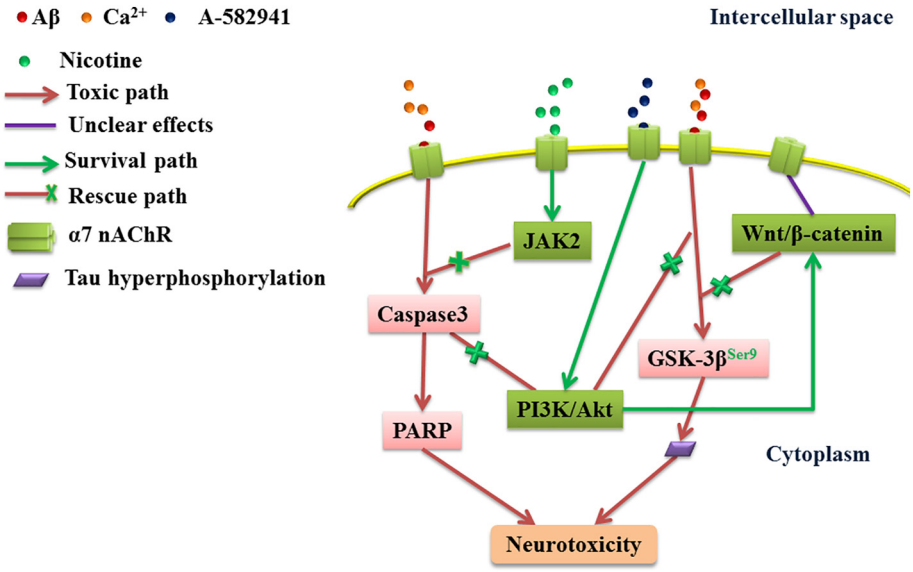

Fig. 2. Aβ induced neurotoxicity and the rescue role of α7nAChR agonist. α7nAChR agonist, A-582941, activate PI3K/Akt signaling cascade and then attenuates GSK-3β activation through Ser 9 phosphorylation. As a result, *tau* hyperphosphorylation is inhibited (Bitner et al., 2009). Aβ activates PI_3K *via* α7nAChR. The activated α7nAChR/PI_3K signaling pathway interacts with *Wnt/β-catenin* signaling pathway (Inestrosa et al., 2013), *Wnt* was also found could inhibit GSK-3β, therefore, *Wnt* may play a role in the α7nAChR induced neuroprotective pathway in AD. Purple line shows that α7nAChR is also a target for *Wnt* signaling pathway (Inoki et al., 2006). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

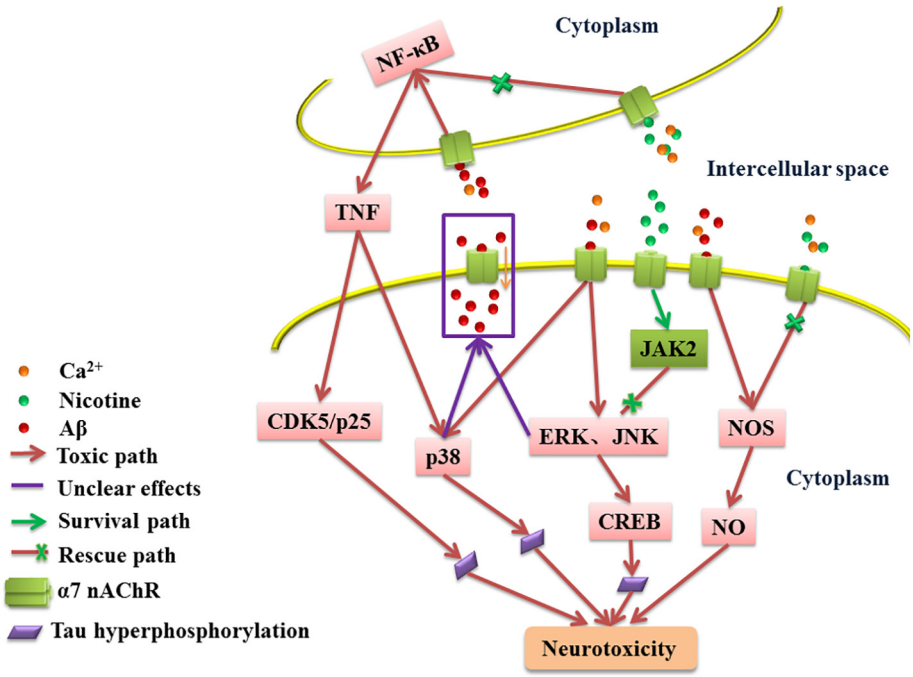

Fig. 3. The signaling pathways related to Aβ induced neurotoxicity and the rescue role of nicotine. Nicotine could activate the α7nAChR and then inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. This leads to the inhibition of tumor necrosis factor (TNF) production. And then activated the p38 MAPK signaling pathway. NF-κB pathway was also detected to induce *tau* phosphorylation (Ser 202, 235) through CDK5/p25 (Conejero-Goldberg et al., 2008). Nicotine prevents activation of NF-κB (left). MAPK is take part in the regulation and activation of α7nAChR, but the mechanism under this is still unclear (purple arrow). The interaction of Aβ and α7nAChR could induce Ca^{2+} influx, which then attenuate the p38 and ERK signaling pathway. The reduction of p38 may prevent *tau* phosphorylation at sites: Ser 202, 296, 422, and Thr 181. The interaction of Aβ and α7nAChR could also lead to the activation of ERK and JNK MAPK signaling pathway, and then down-regulates the phosphorylation of a transcription related protein, cAMP response element binding protein (CREB), and cause memory deficits (Dienetly et al., 2001). Nicotine could down regulate the NOS level, and nicotine could reverse this effect. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 2). In the case of GSK-3β deactivation, downstream Akt of PI_3K could inhibit GSK-3β activity through Ser-9 phosphorylation. An *in vitro* study has proven that the neuroprotective properties of nicotine may be related to α7nAChR stimulation and its subsequent activation of the PI_3K/Akt signaling cascade (Bitner et al., 2009). Therefore, A-582941, an α7nAChR agonist, activated the PI_3K/Akt signaling cascade and subsequently attenuated GSK-3β activation (Fig. 2), resulting in an inhibition of *tau* hyperphosphorylation. Therefore, in this case, activating the α7nAChR could enhance cognitive function. In contrast with the previous study (Hu et al., 2008), in which they found that treatment with MLA, an α7nAChR antagonist, reversed the reduction of the cell viability caused by Aβ, this evidence suggests that an agonist of the α7nAChR is a promising treatment for AD (Bitner et al., 2010; Bitner et al., 2009).

3.5.3. *Wnt signaling pathway may be related to α7nAChR/PI_3K in AD*

Wnt has been shown to be related to several diseases, including cancer, dementia, Parkinson's disease and AD (Logan and Nusse, 2004). While Aβ oligomer activates PI_3K *via* the α7nAChR, the activated α7nAChR/PI_3K signaling pathway interacts with the *Wnt/β-catenin* signaling pathway (Bitner et al., 2010). The α7nAChR-gene analyses have suggested that the α7nAChR is a target of the *Wnt* signaling pathway. Moreover, *Wnt* has been shown to inhibit GSK-3β (Inoki et al., 2006). Thus, it is possible that *Wnt* may play a role in the α7nAChR-induced neuroprotective pathway in AD (Fig. 2). The *Wnt* signaling pathway is critical in several cellular processes, including intracellular Ca^{2+} regulation, gene transcription, cell migration and synaptic activity, as shown by a recent study (Komiya and Habas, 2008).

3.5.4. *α7nAChR/ERK/CREB cascade in AD*

The α7nAChR interacts with Aβ in the hippocampus in brain slice cultures (Bell et al., 2004; Dineley et al., 2001). Their interaction induces Ca^{2+} influx, which triggers the α7nAChR/PI_3K cascade and subsequently activates the ERK signaling pathways. This lead to the

phosphorylation of a transcription related protein, cAMP response element binding protein (CREB). Experiments have indicated an increased accumulation of Aβ in transgenic mice with advancing age, which leads to the long-term increase of α7nAChR expression. These findings suggest that the short time and low concentrations of Aβ treatment do not result in a constant upregulation and activation of the α7nAChR and ERK signaling pathway. However, long-term and high concentrations of Aβ treatment induced abnormal activity of the α7nAChR/ERK/CREB cascade and interrupted the learning and memory function. Thus, it is suggested that the concentration and exposure time of Aβ are two delicate factors in the α7nAChR/ERK/CREB cascade (Fig. 3). Therefore, these two aspects should be considered during drug investigation studies in relation to the α7nAChR/ERK/CREB cascade for AD.

3.5.5. α7nAChR/p38-ERK/TNF/NF-κB

The α7nAChR has also been considered a link between inflammation and neurodegeneration pathways. Nicotine activates the α7nAChR and inhibits tumor necrosis factor (TNFα) production through the inhibition of the NF-κB pathway (Fig. 3). Its inhibition of TNF production is associated with a decrease of activated ERK and p38 MAPK signaling pathways, in which p38 phosphorylates *tau* in neurons and glia cells. It has been shown that the reduction of p38 could prevent *tau* phosphorylation at several sites, including S202, S296, S422 and T181. The NF-κB pathway has also been shown to induce CDK5-mediated *tau* phosphorylation, and nicotine could attenuate this process by blocking NF-κB through α7nAChR activation (Young et al., 2009) (Fig. 3).

3.5.6. Other related pathways

Nicotine could prevent the activation of NF-κB and c-Myc by inhibiting the MAPKs, leading to a downregulation of nitric oxide synthase (NOS) and NO (Fig. 3). This signaling pathway provides another mechanistic basis for the potential drug targets for AD treatment (Liu et al., 2007). Jun Kawamata and his colleague (Young et al., 2009) have clarified three survival transductions, including the upregulation of the B cell lymphoma/lewkmia-2 (Bcl2) and Bcl-x (a bcl-2-related gene, which functions as a bcl-2-independent regulator of apoptosis) family by the α7nAChR/Src (Proto-oncogene tyrosine-protein kinase)/PI_3K/Akt pathway, JAK2 (janus kinase 2)/Signal transducer and activator of transcription 3 (STAT3) and MEK (Mitogen-activated protein kinase kinase (also referred to as MAP2K, MEK, MAPKK))/ERK (Extracellular signal-regulated kinases) pathways (Fig. 4). These findings suggest that α7nAChR-mediated neuroprotection is achieved through common signal cascades. Moreover, pretreatment for α7nAChR stimulation may be an effective therapy to delay the progression of neurodegeneration diseases, such as AD. Aβ- induced caspase3/PARP (Poly ADP-ribose polymerase) (Fig. 2) and the ERK/JNK (c-Jun N-terminal kinases) neurotoxicity pathway (Fig. 3) could also be blocked by nicotine through JAK2, a downstream signal of the α7nAChR, and this neuroprotection signal pathway continued as JAK2/PI3K/Akt/FKHRL1 (forkhead transcription factor such as 1) (Fig. 4).

Aβ and α7nAChR related signaling pathways are rather complicated systems, which require substantial attention. Evidence has illustrated that the aggregation status and incubation time of Aβ determines the activation of signaling pathways. The incubation of hippocampal slice cultures with Aβ oligomer for a short time activated the ERK signaling pathway but not JNK. These results confirmed Dineley's results (Bell et al., 2004; Dineley et al., 2001). However, interestingly, another study showed that incubating hippocampal slice cultures with Aβ oligomer/polymer for a long time activated JNK and attenuated ERK (Bell et al., 2004). Moreover, not all activated signaling pathways turned out to regulate the Aβ- induced toxicity, and their role requires further study. For example, the MAPK signaling pathways, p38, JNK and ERK were all activated by $Aβ_{1–42}$ in SH-SY5Y cells. Only the p38 and ERK signaling pathway could regulate the α7nAChR mediated $Aβ_{1–42}$ internalization, and the level of the α7nAChR mRNA was regulated by these two pathways (Yang et al., 2014).

It is well established that $Aβ_{1–42}$ induces the release of pro-inflammatory cytokines in AD. The pro-inflammatory cytokines could be suppressed through the binding of the ACh-α7nAChR. This provides a new range of potential therapeutic approaches for controlling inflammatory responses caused by $Aβ_{1–42}$. Galantamine is a widely used medicine for AD. It has been reported that Galantamine reduced inflammatory mediators (NF-κB, TNF-α, HMGB1 and RAGE) and increased the anti-apoptotic pathway (p-Akt/Bcl-2). A mechanistic study also indicated that Galantamine increased the anti-inflammatory cytokine IL-10 and phosphorylated JAK2, while it reduced the inflammation controller SOCS3. However, combining MLA with Galantamine abrogated the beneficial anti-inflammatory/anti-apoptotic signals, indicating that the α7nAChR/JAK2/SOCS3 signaling pathway is involved

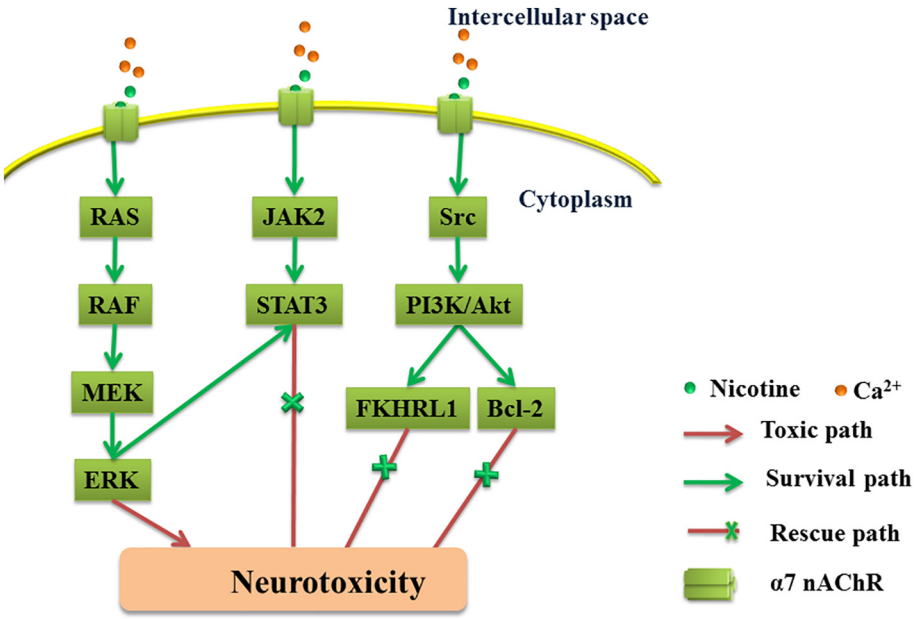

Fig. 4. Three survival transductions activated through nicotine-α7nAChR interaction. Nicotine could activate RAS/RAF/MEK/ERK, JAK2/STAT3, and Src/PI3K/Akt/FKHRL1 to prevent neurons form the toxic effect of Aβ (Kawamata et al., 2011).

in the anti-inflammatory/−apoptotic effects of Galantamine (Kawamata et al., 2011; Wazea et al., 2018).

The apolipoprotein E ε4 gene is a prominent risk factor for AD. ApoE4 disrupts memory function in rodents. An *in vitro* study using rodent synaptosomes showed that $apoE_{141–148}$ promotes $Aβ_{1–42}$-α7nAChR association and $Aβ_{1–42}$-induced α7nAChR-dependent tau phosphorylation. Furthermore, APOE is closely related to heightened $Aβ_{1–42}$-α7nAChR complex levels. The progression of cognitive decline in APOE ε4 carriers is correlated with higher levels of $Aβ_{1–42}$-α7nAChR complexes in lymphocytes and a greater enhancement by their plasma of the $Aβ_{1–42}$-induced $Aβ_{1–42}$-α7nAChR association in rat cortical synaptosomes. Therefore, the increased lymphocyte $Aβ_{1–42}$-α7nAChR complexes may indicate the presence of AD pathology, particularly in APOE ε4 carriers. ApoE4 promotes $Aβ_{1–42}$-α7nAChR interaction and $Aβ_{1–42}$-induced α7nAChR-dependent tau phosphorylation *via* the $apoE_{141–148}$ domain (Wazea et al., 2018).

4. Conclusions

Research on the α7nAChR in normal physiological and pathological functions, particularly related to the improvement of cognitive function, has resulted in new progress in the last decade. Thus, due to the important role of the α7nAChR in the pathogenesis of AD, α7nAChR agonists have become a hot topic in the development of new drugs for the treatment of AD as effective drugs in the world. Recent studies have provided evidence for the importance of intracellular Aβ in AD pathology and highlight the essential role of Aβ receptors, such as the α7nAChR. In existing discoveries, most studies have focused on one single signaling cascade and its role in α7nAChR-mediated Aβ pathology in AD. We reviewed that several signaling pathways participate in this process and their relations are complicated. Therefore, an understanding of the net of the signal pathways is urgent for AD therapy investigations in the future.

Conflict of interest

There are no conflicts of interest to disclose.

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Authors' contributions

Yi-Hua Qian contributed to the importance of alpha 7 nicotinic acetylcholine receptor and its effects on Alzheimer's disease, and the main parts of the manuscript, and Kai-Ge Ma contributes to the preparation, update and the revision of the manuscript and figures. All authors approved the final article.

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