Role of amyloid β protein receptors in mediating synaptic plasticity (Review)

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Abstract. There are few diseases in modern biomedicine that have garnered as much scientific interest and public concern as Alzheimer's disease (AD). The amyloid hypothesis has become the dominant model of AD pathogenesis; however, the details of the hypothesis are changing over time. Recently, given the increasing recognition, subtle effects of amyloid β protein (Aβ) on synaptic efficacy may be critical to AD progression. Synaptic plasticity is the important neurochemical foundation of learning and memory. Recent studies have identified that soluble Aβ oligomers combine with certain receptors to impair synaptic plasticity in AD, which advanced the amyloid hypothesis. The aim of the present review was to summarize the role of Aβ-relevant receptors in regulating synaptic plasticity and their downstream signaling cascades, which may provide novel insights into the understanding of the pathogenesis of AD and the development of therapeutic strategies to slow down the progression of AD-associated memory decline in the early stages.

Contents

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1. Introduction

Alzheimer's disease (AD) is a chronic and progressive age-associated neurodegenerative disorder that represents 70% of all dementia, with 36 million cases worldwide. These cases may increase to 115 million by 2050 (1). Extracellular amyloid plaques composed of misfolded amyloid peptides and intracellular neurofibrillary tangles composed of hyperphosphorylated tau are the two characteristic pathologic features of AD (2). Memory loss and cognitive function decline are the early symptoms of AD, which are due to the loss of synapses in the hippocampus and cortex (3). The amyloid hypothesis holds a dominant position in AD pathogenesis, which states that the accumulation of amyloid β protein (Aβ) induces neuronal loss and cognitive impairments (2,4). As scientists attempt to make this hypothesis more precise, neurotoxicity appears to be caused by diffusible oligomeric assemblies of Aβ, rather than mono-Aβ or the amyloid fibril protein. Currently, AD is considered to be a disease of synaptic failure; Aβ interrupts the function of synapses that facilitated with encoding novel declarative memories (5,6). Substantial evidence suggests that AD begins with subtle alterations of hippocampal synaptic efficacy, which is prior to neuronal degeneration, and that synaptic dysfunction is predominantly caused by diffusible oligomeric assemblies of Aβ (7-9). Multiple lines of evidence indicate that there is an early, pre-plaque phase when learning and memory deficits are not detected in AD transgenic mice, although long-term potentiation (LTP) is already impaired (5,6,10,11). Therefore, the change of synaptic plasticity induced by Aβ may be the earliest non-clinical symptom of AD, and may even occur in the high-risk population of AD. The abnormal levels of Aβ mediate the change of synaptic plasticity to trigger the cascade reaction, which causes a gradual transition from an impairment of synaptic function to synaptic loss and subsequently cell apoptosis. Advances in molecular and cellular mechanisms underlying AD-associated synaptic dysfunction and memory deficits have been reported (12). However, to the best of our knowledge, the interaction of Aβ and Aβ-relevant receptors and receptor-mediated synaptic plasticity damage have not been systematically clarified. In addition, synaptic plasticity is closely linked with other neurodegenerative diseases, nerve regeneration barriers, clinical depression, neuropathic pain and drug dependence. The elucidation of

Aβ-relevant receptors in regulating synaptic plasticity will provide novel insights into the understanding of the pathogenesis of AD and novel therapeutic strategies to slow down the progression of AD at early stages, but also advances our understanding of the normal regulation of synaptic plasticity in learning and memory.

2. Association between synaptic plasticity and Aβ

Synaptic plasticity is the ability of synapses to strengthen or weaken over time in response to increases or decreases in their activity. LTP and long-term depression (LTD) are the primary performance models for synaptic plasticity. Synaptic plasticity is considered to be the mechanism of learning and memory. Numerous factors, such as glial cells, calcium ions and the neurotrophic factor family are key in regulating synaptic plasticity (13,14).

Aβ is a protein produced by normal metabolism that is derived from amyloid precursor protein (APP) via sequential cleavage by β- and γ-secretases (15-17). Aβ possesses certain physiological functions, and early studies indicate that very low concentrations of soluble Aβ promote neuronal survival and axonal branching, adjust the function of K^+ ion channels and are involved in the normal functioning of neurons. Much evidence suggests that the accumulation of Aβ is a critical component of AD pathogenesis (18-20). Abnormal Aβ and the change of synaptic plasticity appear simultaneously during the early stage of AD. However, the association between synaptic plasticity and Aβ is complicated. Recent studies indicate that synaptic activity regulates Aβ levels in AD, which are primarily associated with the regulation of APP endocytosis and cleavage. Glutamatergic, cholinergic, serotonergic, leptin, adrenergic, orexin, and gamma-amino butyric acid receptors, as well as the activity-regulated cytoskeleton-associated protein are all involved in these processes (21). Aβ exists in numerous accumulation forms, including Aβ monomer, Aβ oligomers and Aβ fibrils. The highest correlation of pathology associated with AD dementia is synapse loss, and the extent of synapse loss is associated with soluble Aβ levels. Diffusible oligomeric assemblies of Aβ cause synaptic dysfunction during the earliest processes of AD (5,22).

The soluble Aβ oligomers, with dimers being the smallest species, are necessary and sufficient to disrupt normal learning and memory function (18,23,24). Previous studies (13,25,26) indicate that dimers and trimers may be the early initiators of synapse failure, and that trimers are more potent in disrupting LTP than dimers (26,27). In addition, previous studies suggest that soluble Aβ oligomers induce the loss of LTP, increase LTD and decrease dendritic spine density in hippocampal slices (18,25,28). N-methyl-D-aspartate receptors (NMDARs), mitochondrial reactive oxygen species, glycogen synthase kinase-3, and the mammalian target of rapamycin signaling pathways are reportedly involved in mediating the toxic effects of Aβ on synaptic function (12). Multiple lines of evidence indicate that the deleterious effects of Aβ prior to neuronal loss are mediated by NMDARs, particularly GluN2B-NMDARs (29). However, the molecular mechanism of Aβ modulating synaptic plasticity via Aβ-relevant receptors has rarely been investigated.

3. Aβ-relevant receptors involved in regulating synaptic plasticity

Aβ oligomers exert effects on synaptic plasticity and memory by binding to associated receptors and thereby activating downstream signaling (30,31). The Aβ-associated receptors include cellular prion protein (PrP^c), ephrin type B receptor 2 (EphB2), paired immunoglobulin (Ig)-like receptor B (PirB), IgG Fcγ receptor II-B (FcγRIIB), p75 neurotrophin receptor (p75NTR), and α7 nicotinic acetylcholine receptors (a7nAChRs). The aim of the present review was to evaluate the Aβ-associated receptors involved in modulating synaptic plasticity and receptor-mediated downstream signal transduction in regulating synaptic plasticity, which may lead to an effective target to prevent the pathologic process of AD during the early stages.

PrP^c. Prion protein (PrP) exists in two forms: the cell form PrP (PrP^c) and the pathogenic form PrP (PrP^{Sc}). The universal recognition of prion doctrine suggests that the normal prion protein, PrP^c is converted into its abnormally-folded isoform, PrP^{Sc} with protease resistance. PrP^{Sc} further aggregates and deposits in the central nervous tissue and leads to certain pathological changes, including neurons loss, fibrous astrocytes hyperplasia and spongy degeneration. The types of degenerative brain disease includes transmissible spongiform encephalopathies and Creutzfeldt Jakob disease (CJD). CJD is caused by PrP^{sc}, which invades the central nervous system of humans, and has a long incubation period and poor prognosis. Although AD and CJD are different types of diseases, they belong to misfolded protein diseases, which are characterized by abnormal protein folding that translates the α-helix into a beta sheet. This conformational change causes normal soluble proteins to change into insoluble protein polymers (32), and induces the pathology of protein aggregates. The former pathology is Aβ deposition and the latter pathology is PrP^{sc} deposition.

PrP is expressed in almost all tissues, although Pr^{Pc} is primarily distributed in the central nervous system. Recent research demonstrates that PrP^c is involved in synaptic plasticity processes in the neonatal hippocampus (33). In addition, PrP^c has been proposed as an additional possible mediator of oligomer action. PrPc binds synthetic Aβ oligomers with high affinity and is involved in the oligomer-mediated inhibition of LTP (34). Laurén *et al* (35) injected Aβ into mice and detected electrophysiological changes in the process of memory recovery. When injecting Aβ into a mouse with loss of PrP^c, no electrophysiological changes were observed. The study indicated that PrP^c mediates synaptic plasticity damage caused by Aβ (35). Experiments *in vivo* demonstrate that PrP^c and Aβ are co-localized, and *in vitro* experiments indicate that PrPc easily binds to Aβ via fragments from 95 to 110. The authors concluded that PrP^c acts as a receptor and trigger a series of chain reactions, eventually leading to neuronal damage (35); however, Balducci *et al* (36) reported that mice injected with Aβ continued to suffer brain memory damage even in the absence of PrPc. In the study by Raeber *et al* (37), Aguzzi observed gene-engineered mice that produce a large number of Aβ, a phenomena similar to that of Balducci *et al* (36). Kessels *et al* (38) attempted to repeat the experiment by

Laurén *et al* (35); and obtained a negative result. However, these studies do not deny the role of PrP^c, as the regulation of synaptic plasticity involves a complex network, and additional Aβ-associated receptor-mediated changes in synaptic plasticity in PrP^c knockout animals remain. Gimbel *et al* (39) reported that the absence of PrP^c eases memory damage of mice with an excessive accumulation of Aβ. This finding supports the results of their previous research (40). Previously, in studies by An *et al* and Hu *et al* (41,42) Rowan used antibodies to block PrPc to reduce the influence of Aβ on electrophysiological changes associated with memory, which supports Strittmatter's conclusions [from the study by Gimbel *et al* (39)] at a conference on European neuroscience. Bitel *et al* (43) reported that PrP^c and Aβ appeared as aggregates and co-localized in a diabetic rabbit model, which suggested that Aβ and PrP^c may interact.

Aβ oligomers bind with PrP^c receptors on the membrane, forming annular amyloid pores and membrane ion channels to induce aberrant spine cytoskeletal changes. However, the mechanism underlying the combination of PrP^c and Aβ requires investigation. Um *et al* (44) predicted the distribution, the specificity and possible activating signaling pathways of the Aβ-PrP^c complex, and whether this complex functions to regulate the NMDAR. Research has found that PrP^c predominantly aggregates in the postsynaptic density area (PSD) and the combination of Aβ-PrP^c may activate Fyn kinase, resulting in the phosphorylation of the NR2B subunits of NMDA, thus, reducing the number of NMDARs (44). Fyn also causes a lack of dendritic spines and the release of lactate dehydrogenase through Aβ interaction with PrP^c. This is consistent with recent reports that Aβ oligomers bind with PrP^c on the membrane and form annular amyloid pores and membrane ion channels to induce aberrant spine cytoskeletal changes (45). The above-mentioned studies support that Aβ oligomers combined with PrP^c activate Fyn kinase to cause the change of synaptic plasticity.

EphB2. Eph is predominantly distributed in the excitatory synapses and is the largest family of receptor tyrosine kinases, which primarily participates in the formation of tissue, and the occurrence of vascular and axon guidance in the growth process. In addition, Eph is important in the mature brain and participates in regulating synaptic plasticity (46). Furthermore, Eph is significant in the pathogenesis of AD.

EphB2, a member of the B subtype of Eph receptor tyrosine kinases, is a transmembrane protein, which has extracellular and intracellular structures that are highly conserved. Recent studies (47) indicate that the extracellular region of EphB2 comprises a ligand-binding (LB) domain, a cysteine-rich (CR) domain, and a fibronectin type III repeats (FN) domain. Aβ oligomers mainly bind to the FN domain of EphB2 and activate the degradation of the protease of EphB2 to deplete neuronal EphB2 by enhancing its proteasomal degradation. In addition, Aβ oligomers reduce EphB2 mRNA levels; however, the reduction is subtle and is unlikely to account for the severe EphB2 protein depletion. The Aβ-induced EphB2 depletion impairs synaptic plasticity. The proximal membrane region of the intracellular structure, composed of several conserved tyrosine residues, modulates the activity of the kinase domain. The tyrosine kinase domain (KD) is the predominant active region, the activation of which may occur by self-phosphorylation and phosphorylation of tyrosine residues of downstream substrate proteins, which then activate downstream signal transduction pathways, as sterile α-motif mediates interactions among proteins, C-terminal PSD95, *Drosophila* disc large tumor suppressor, and zonula occludens-1 protein (PDZ) binding domain mediates the combination between kinase and proteins that contain the PDZ domain (48,49).

Activity-dependent synaptic plasticity and memory formation require NMDA-type glutamate receptors expressed on the postsynaptic membrane of excitatory synapses (50). Ca^{2+} permeation of the NMDA receptor is crucial for synapse formation and the regulation of synaptic strength in adults (44). EphB2 was recently shown to interact with NMDARs at excitatory synapses (51,52). Numerous experiments show that EphB2 receptors are required for the formation of forebrain commissures (53), retinal axon path finding (54), normal vestibular function (55), and the development of the vasculature (56). Further studies indicate that EphB2 receptors associate with NMDARs at synaptic sites and are involved in synaptogenesis. Grunwald *et al* (57) concluded that the EphB2 receptor is a kinase-independent receptor required in hippocampal synaptic plasticity by modulating signaling pathways implicated in synaptic plasticity and crosstalk with NMDAR-activated signaling pathways. The reduced expression level of EphB2 is associated with the impairment of synaptic plasticity. Grunwald *et al* (57) demonstrated that mice lacking EphB2 possessed normal hippocampal synapse morphology, but displayed defects in synaptic plasticity. Other studies reported that EphB2-deficient mice exhibited LTP deficits (57,58). In the brain of AD transgenic mice, Tg2575, the expression level of EphB2 demonstrated an age-dependent regional decrease and a lower expression level of EphB2 was observed in the hippocampus. EphB2 plasmid overexpression in the dentate gyrus reversed the lower NMDAR-dependent LTP, and cure learning and memory impairment in hAPP transgenic mice.

EphB2 regulates glutamatergic neurotransmitter transmission via NMDAR (51); however, knowledge of the underlying mechanism of crosstalk of the EphB2/NMDAR signaling pathways remains limited. Studies show that EphB2 regulates NMDAR-dependent Ca^{2+} influx and downstream transcription factors involved in LTP formation (59). EphB2 is critical in mediating synaptic plasticity. The activation of EphB induces the phosphorylation of three Src kinase-dependent tyrosine residues of NR2B, which is critical for regulating expression levels of NMDAR in the synapses. The number of excitatory synapses decreases in mice with EphB1-3 three-gene knockout, while synaptic NMDAR currents are reduced in mice with only EphB2 gene knockout, and the LTP of the hippocampus is also inhibited (58). All of these results indicate that EphB2 has an important regulatory effect on synaptic NMDAR expression.

Soluble Aβ oligomers influence synaptic plasticity by inhibiting NMDAR-dependent LTP, thus contributing to learning and memory deficits in AD (18,60,61). Thus, Aβ oligomers combine with the FN domain of EphB2 to cause EphB2 depletion and contribute to the impairment of synaptic plasticity, which is associated with the NMDAR. Cisse *et al* (47) found that an increased expression level of EphB2 improves the LTP of the dentate gyrus region, and promotes learning and

memory capabilities. If this effect can be confirmed, drug treatment strategies will include improving the expression levels and activity of EphB2. The study by Cisse *et al* (47) also suggested that small molecules block Aβ oligomers combined with the fibronectin type II repeat region of EphB2 or prevent the degradation of EphB2 protease, which may reduce the interaction between Aβ and NMDAR.

PirB. PirB, also termed p91, is an immuno-inhibitory receptor first discovered by Kubagawa *et al* (62) from murine immune cells in 1997 and is similar to the Fc receptor for human IgA. PirB protein is a type I transmembrane glycoprotein, which has six Ig-like extracellular hydrophobic domains and four intracellular immunoreceptor tyrosine-based motif-like polypeptides. PirB recruits Src homology 1-containing protein tyrosine phosphatase or Src homology 2-containing protein tyrosine phosphatase, and improves immunosuppression. PirB is distributed in different hematopoietic cell lines, including B cells, mast cells, macrophages, granulocytes, dendritic cells, and is widely distributed at the surfaces of different neurons in the damaged central nervous system. Atwal *et al* (63) found that PirB is the second functional receptor for myelin inhibitors of axonal regeneration after the Nogo-66 receptor was first identified. Although PirB is the receptor for axon regeneration inhibitors, including Nogo, monoacylglycerol lipase and oligodendrocyte-myelin glycoprotein, the PirB-regulated molecular mechanism of axonal regeneration inhibition remains unclear. The human homolog of murine PirB is leukocyte Ig-like receptor B (LilrB2), which comprises five family members (63,64). A recent study (65) found that $A\beta_{42}$ oligomers are robustly bound to LilrB2-expressing heterologous cells, and LilrB2/PirB2 and Aβ have an affinity at the nanomole level. Relative to monomeric $A\beta_{42}$, oligomerized $A\beta_{42}$ peptides are bound to PirB-expressing cells approximately six times as much. Kim *et al* (65) found that in AD mice, Aβ oligomer damages the LTP of the hippocampus, which needs to combine with PirB. These studies suggest that PirB/LilrB2, as a receptor for Aβ oligomers, are crucial for modulating synaptic plasticity. This effect may be via enhancing cofilin signaling to facilitate actin depolymerization, resulting in synaptic loss and ultimately leading to altered synaptic plasticity and cognitive deficits.

Increasing research shows that the downstream signaling associated with the effect of Aβ to synaptic plasticity includes altering NMDAR function in response to Aβ (35,44,47). The signaling pathways of the actin-severing protein, cofilin and protein phosphatases, PP2A and PP2B/calcineurin (25,66) that signal upstream of these signaling pathways, including the interaction between Aβ and PirB2/LilrB2, are not well understood. In addition, PirB mediates the dysfunction of learning and memory of adult mice in the transgenic mice AD model, and mediates the lack of synaptic plasticity in the visual cortex of young mice (65) . Given the important role of Aβ and PirB/LilrB2 in modulating synaptic plasticity, blocking the interaction of Aβ and LilrB may be a promising target for treatment of AD even in the prodromal stage.

Fc4 IIB. FcγR belongs to the Ig superfamily and is a type of membrane glycoprotein that is predominantly expressed in the immune cell membranes of the hematopoietic system. Certain FcγR are expressed in the cell surface of histocytes, such as glomerular mesangial cells, follicular dendritic cells, microglial cells and osteoclasts organizations. FcγRIIB, as a member of FcγR, is a type of IgG receptor. FcγRIIB initially combines with IgG to form immune complex-associated antigens and is expressed primarily in B cells, macrophages and neutrophils (67). FcγRIIB is involved in inhibiting the B cell receptor-mediated immunoreactions and is also involved in autoimmune processes (68). A previous study demonstrated that FcγRIIB gene knockout mice easily succumbed to autoimmune disease (69).

Recent studies (70) demonstrated that FcγRIIB is important in the process of memory impairment and neurotoxicity caused by Aβ. Exogenously importing Aβ to cortical neurons increases the expression of FcγRIIB significantly. Kam *et al* (70) found the FcγRIIB gene knockout neurons decreased LTD and the deficiency of synaptic function caused by Aβ, and improved the memory ability of the AD model rats. Further research found that FcγRIIB specifically combined with soluble Aβ oligomers, causing the paralysis of synaptic function and the death of neurons, resulting in the abnormal behavior of rats (70). FcγRIIB accelerated the process of memory ability impairments by activating neural immunity in the non-neurons from the AD rat model (71). Therefore, the passive immunization antagonism of Aβ has become a more desirable treatment strategy in the development of AD treatment therapeutic agents. However, the traditional passive immunity will often cause the immune response mediated by FcγRIIB, activating the microglia, causing strong inflammatory reaction, and resulting in angioedema and cerebral hemorrhage. A previous study (72) identified that MABT5102A (MABT), a novel substance that combines with Aβ with high affinity and lowers the immune activity of FcγRIIB, prevents the neurotoxicity induced by Aβ. In addition, Adolfsson *et al* (72) found that MABT reduced the formation of amyloid plaque in hAPP (V7171)/PS1 transgenic mice. Therefore, the in-depth analysis of FcγRIIB identifies a novel strategy for the treatment of AD with a minimum level of immune response.

p75NTR. p75NTR, a member of the tumor necrosis factor receptor superfamily, is a low affinity neurotrophic factor receptor that interacts with a variety of ligands and causes different effects on the nervous system, including pro-survival or induction of apoptosis (73). Basal forebrain ganglia neurons express p75NTR, tropomyosin receptor kinase A (TrkA) and nerve growth factor (NGF); NGF as a neurotrophic factor, contributes to the growth and development of neural survival in the presence of TrkA. NGF combines with p75NTR to cause the phosphorylation of TrkA and activates the phosphoinositide 3-kinase/AKT signaling pathway (74). Endogenous NGF, brain-derived neurotrophic factor and other neurotrophins are involved in neuronal survival, synaptic regeneration, and improvement of cognitive impairment though the p75NTR signaling pathway.

In the pathological process of neurodegenerative disease, p75NTR combined with extracellular receptors, such as Aβ and myelin-associated inhibitory factors, contributes to axonal regeneration inhibition and synaptic dysfunction by activating the downstream signaling pathway. Recent studies demonstrate that in the absence of APP, NGF treatment may preferentially

direct p75-neurotrophin-dependent c-Jun N-terminal kinase activation toward regeneration and plasticity in functionally relevant brain circuits (75).

As a result of the above-mentioned findings, the present study hypothesizes that p75NTR exerts a double-sided regulating function in synaptic plasticity. Under physiological conditions, p75NTR maintains the synaptic plasticity together with TrkA and NGF. Furthermore, as a receptor of Aβ, p75NTR is crucial in impairing synaptic plasticity by binding with Aβ in pathological conditions.

Yaar *et al* (76) found that the annular antagonist peptide of p75NTR competitively combines with p75NTR by competing with Aβ, thus inhibiting neurotoxicity caused by Aβ *in vitro*. Stereotaxic injection of p75NTR annular antagonism peptides into the rat cortex specifically combine with Aβ, thus abating the inflammation and neurotoxicity caused by Aβ (77). Certain non-protein small molecule compounds combine with p75NTR and inhibit the Aβ-induced impairments in synaptic plasticity. Studies found that Aβ stimulates the expression of p75NTR in cell culture systems and in the brain of AD transgenic mouse (particularly in the hippocampus) (78,79), which indicates that Aβ unregulated P75NTR expression in the brain. A previous study indicated that p75NTR expression levels may serve as markers of normal aging and AD (80); p75NTR expression is upregulated and the expression level of TrkA is reduced with increasing age. Furthermore, activation of the p75NTR signaling pathway increases the expression level of β-secretase 1 and accelerates Aβ accumulation (77). In APPswe/PS1 transgenic rats, gene knockout of p75NTR contributed to the decrease of Aβ in the cerebral cortex, indicating that the p75NTR signaling pathways promote the generation of Aβ (81). Thus, Aβ and p75NTR form a positive feedback and further accelerate the damage of synaptic plasticity. However, the extracellular fragment of soluble p75NTR, released by a neuron, inhibits Aβ aggregation and promotes Aβ clearance, resulting in opposite regulation of Aβ deposition (80,82). Previous studies reported that in the AD brain, p75NTR mediated neuronal degeneration and neuronal death (83,84), and participated in the neuronal cell cycle and consumption of neural stem cells (80,85). Thus, p75NTR has an important and complicated role in regulating synaptic plasticity, generation of Aβ and neuronal survival of AD.

α7nAChRs. nAChRs are included in the large family of ligand-gated ionotropic receptors. They are activated by exogenous nicotine and endogenous acetylcholine (ACh) and define a cation-selective permeability across the plasma membrane of neurons and non-neural cells (86). Their functional properties result from the specific structure of subunit composition. In vertebrates, there are nine α (α2-α10) and three β (β2-β4) subunits that are genetically distinct and combine to form heteromeric or homomeric pentamers in the cell membrane (87). Nicotinic receptors expressed on neurons are represented by homomeric pentamers consisting of α7, α8 and α10 subunits, and heteromeric receptors consisting of α7, α8 and/or α10 subunits, α2-α6 and β2-β4 subunits, in different combinations. In situ hybridization studies demonstrated that homomeric α7, containing α7nAChRs, are highly expressed in the cortex, hippocampus and subcortical areas, such as the basal ganglia, thalamus and limbic regions (88,89).

The functional location of α7nAChRs in the hippocampus indicates the involvement of these receptors in memory formation, and LTP and LTD are proposed to be regulated by cholinergic transmission (90-92). Currently, α7nAChR is proven to be an $A\beta_{42}$ receptor. $A\beta_{42}$ activates the extracellular signal-regulated kinase (ERK2) isoform of the ERK mitogen-activated protein kinase (MAPK) cascade via α7nAChRs, activation of this kinase in the hippocampus is required for contextual and spatial memory formation in mammals (93-96). The cAMP-regulatory element binding protein is the downstream target of ERK/MAPK and is also a necessary component for hippocampus-dependent memory formation in mammals (97). The ERK2/MAPK cascade is known to be critical in hippocampus synaptic plasticity and learning. Furthermore, the ERK/MAPK cascade has been implicated in regulating Aβ production in neurons (98). One of the effects of downregulated ERK2/MAPK activity may be the creation of a positive feedback loop for Aβ accumulation. α7nAChR couple $A\beta_{42}$ to the ERK/MAPK cascade, resulting in the impairment of synaptic plasticity in the hippocampus. Previously, α7nAChRs have been demonstrated to be specifically involved in visual cortex synaptic plasticity (99). Overall, these findings highlight a potential therapeutic target of α7nAChR for reversing the impairment of synaptic plasticity.

4. Conclusion

In conclusion, Aβ-induced impairment of synaptic plasticity is hypothesized to be the initial and prominent motivator in the pathological process of AD and contributes to a novel version of the amyloid hypothesis. The interaction between Aβ and Aβ-binding receptors and the associated mechanisms regulating synaptic plasticity are not fully understood. In addition to binding to Aβ, these receptors bind to other vital ligand proteins to exert vital physiological effects, such as tissue patterning, angiogenesis, axon guidance and anti-apoptosis. The majority of these receptors appear to have certain common features, which cause a preference to bind with Aβ oligomers. As Aβ oligomers are diverse and complex, it remains unclear which types of Aβ oligomers (dimer, trimer or tetramer) prefer to combine with receptors. The details of the interaction between Aβ oligomers and these receptors remain unknown. Furthermore, whether the effect of these receptors in modulating synaptic plasticity is equal or whether one or two receptors are particularly key in synaptic plasticity of AD remains unclear. Further in-depth research is required to clarify the separate signaling pathways and complex crosstalk, which would contribute to a profound understanding of the function of Aβ in synaptic plasticity. This may lead to a novel target in blocking or even reversing the pathological process of AD during the early or even prodromal stage.

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