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Review article

Synaptic dysfunction in Alzheimer's disease: Mechanisms and therapeutic strategies

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ABSTRACT

Alzheimer's disease (AD), the most prevalent neurodegenerative disease in the elderly population, is characterized by progressive cognitive decline and pathological hallmarks of amyloid plaques and neurofibrillary tangles. However, its pathophysiological mechanisms are poorly understood, and diagnostic tools and interventions are limited. Here, we review recent research on the amyloid hypothesis and beta-amyloid–induced dysfunction of neuronal synapses through distinct cell surface receptors. We also review how tau protein leads to synaptotoxicity through pathological modification, localization, and propagation. Finally, we discuss experimental therapeutics for AD and propose potential applications of disease-modifying strategies targeting synaptic failure for improved treatment of AD.

Contents

1. Introduction

Alzheimer's disease (AD), which was first described in 1906 by Dr. Alois Alzheimer, has become the most prevalent and burdensome neurodegenerative disease (Querfurth & LaFerla, 2010). Current treatments merely ameliorate symptoms and are unable to stop or reverse disease progression. Despite intensive research efforts towards AD over several decades, researchers have not successfully translated promising disease-modifying strategies identified in laboratories into clinical applications.

The etiology of AD is extremely complex and involves the combinatorial contributions of multiple intrinsic and extrinsic factors. The

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid; APP, amyloid precursor protein; Cdk5, cyclin-dependent kinase 5; GPCRs, G protein-coupled receptors; GSK-3β, glycogen synthase kinase 3 beta; HMW, high-molecular-weight; LMW, low-molecular-weight; LTD, long-term depression; LTP, long-term potentiation; MC4R, melanocortin 4 receptor; mGluRs, metabotropic glutamate receptors; NMDA, *N*-methyl- D-aspartic acid; PKA, protein kinase A; PrP^{c}, cellular prion protein..

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hallmarks of AD are the extracellular deposition of senile plaques formed by beta-amyloid (Aβ) and the intracellular accumulation of neurofibrillary tangles formed by hyperphosphorylated tau protein. However, the mechanistic linkage between these hallmarks and the cognitive deficits observed in AD remain poorly understood. Accumulating evidence suggests that the loss of neuronal synapses occurs in the early stage of AD pathogenesis and is associated with cognitive decline (Querfurth & LaFerla, 2010). Furthermore, recent research suggests that Aβ and tau act at neuronal synapses and exert their pathological roles during disease progression (Forner, Baglietto-Vargas, Martini, Trujillo-Estrada, & LaFerla, 2017). Accordingly, in this review, we focus on the molecular mechanisms underlying the dysfunction of excitatory synapses in AD and discuss potential disease-modifying strategies.

2. Synapses and cognitive functions

Synapses are formed when navigating axons identify their correct target cells. This is followed by the specialization of presynaptic axon terminals, which release vesicles containing neurotransmitters, and the maturation of postsynaptic compartments, which transduce the incoming signals by neurotransmitter receptors such as *N*-methyl-D-aspartic acid receptors (NMDA receptors) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA receptors) (Waites, Craig, & Garner, 2005). The number, structure, and function of synapses change over time, strengthening or weakening their synaptic contacts. This process, termed "synaptic plasticity," optimizes the neuronal connections crucial for cognitive functions such as learning and memory. Synapses are the basic unit that transduces information among neurons and are under tight spatiotemporal regulation. Importantly, their aberrant function might be implicated in various neurological disorders (Fu & Ip, 2017). Specifically, synaptic dysfunction is most closely correlated with cognitive decline in AD patients. Upon postmortem examination, the brains of AD patients have significantly fewer synapses than those of healthy controls (de Wilde, Overk, Sijben, & Masliah, 2016). Synaptic loss or deregulation is also apparent in various AD transgenic animal models, accompanied by deficits in learning and memory (Forner et al., 2017; Sheng, Sabatini, & Sudhof, 2012). Restoring excitatory synaptic transmission in the hippocampus through different approaches including genetic manipulation or administration of small molecules, short peptides, or antibodies can effectively ameliorate the cognitive deficits in AD animal models (Nistico, Pignatelli, Piccinin, Mercuri, & Collingridge, 2012), thus opening new avenues for developing disease-modifying approaches to treat AD progression.

3. Aβ-mediated neurotoxicity and synaptic dysfunction

3.1. Amyloid hypothesis

Aβ peptides are short peptides comprising 39–43 amino acids that are generated from amyloid precursor protein (APP). APP is a ubiquitously expressed type I integral membrane glycoprotein (Sosa et al., 2017) that can undergo two competitive cleavage pathways: the amyloidogenic or non-amyloidogenic pathway. In the amyloidogenic pathway, APP is sequentially cleaved by β-secretase and γ-secretase, generating a soluble extracellular fragment (sAPPβ), Aβ, and an APP intracellular domain (AICD). Meanwhile, in the non-amyloidogenic pathway, α-secretase processes APP at the Aβ domain to generate sAPPα, followed by γ-secretase cleavage, which generates P3 peptide and AICD fragment (Sheng et al., 2012). $Aβ_{42}$ is the most toxic Aβ species generated by amyloidogenic processing. "The amyloid hypothesis," which posits that Aβ plays a causative role in AD pathogenesis was supported by early genetics studies showing that autosomal-dominant mutations or duplication of *APP*, or mutations of *PSEN1* or *PSEN2* (the genes that encode γ-secretase subunits) lead to early-onset familial AD (Hardy & Selkoe, 2002). The senile plaques formed by extracellular Aβ deposition were thought to be the major pathogenic substance in AD. However, clinical investigations of AD patients did not reveal a strong association between extracellular Aβ deposition (i.e., amyloid plaque) burden and the level of cognitive decline (Querfurth & LaFerla, 2010).

Nonetheless, the roles of Aβ in synaptic dysfunction and cognitive decline were re-examined following the identification of soluble Aβ oligomers, also known as Aβ-derived diffusible ligands, which are the major form of Aβ aggregates that induce synaptotoxicity (Sheng et al., 2012). Aβ monomers go through distinct pathways to generate higher-order assemblies (Velasco et al., 2012), indicating the concurrence of a mixture of Aβ species including low-molecular-weight (LMW) oligomers (e.g., dimers, trimers, and tetramers) and high-molecular-weight (HMW) oligomers (50–150 kDa) (Forner et al., 2017). During disease progression, the conformations of Aβ and APP take on pathological phenotypes and Aβ aggregation begins to be enriched at synapses, which occurs before the formation of amyloid plaques or accumulation of phosphorylated tau at synapses (Bilousova et al., 2016; Klementieva et al., 2017). Furthermore, *in vitro* administration of Aβ to neurons or organotypic brain slices reduces the number of dendritic spines, increases synaptic protein loss, and compromises the surface expression of neurotransmitter receptors; this occurs together with a reduction of miniature excitatory postsynaptic currents or impairment of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD). Similar findings have also been reported in various AD transgenic mouse models with increased levels of soluble Aβ species (Tu, Okamoto, Lipton, & Xu, 2014). Nonetheless, oligomeric Aβ might exert its action in a hypothetical, inverted, U-shaped profile (Palop & Mucke, 2010). That is, intermediate levels of Aβ (i.e., much lower than the pathological level of Aβ in AD) might potentiate presynaptic facilitation and enhance cognitive performance in mice (Abramov et al., 2009; Puzzo et al., 2008). However, abnormally low levels of Aβ can result in compromised presynaptic facilitation leading to impaired synaptic plasticity, whereas pathologically high levels of Aβ are the key factor in the induction of synaptotoxicity in AD (Palop & Mucke, 2010). Accordingly, research on the molecular mechanisms underlying Aβ-induced synaptic toxicity has provided invaluable information and targets for AD intervention.

The heterogeneity of Aβ species coexisting in the AD brain obfuscates their actions at synapses, as synapses can be contacted by a mixture of Aβ species that might induce diverse biological reactions. High-throughput imaging analysis shows that Aβ oligomers of varying size are present in the synaptic regions (Pickett et al., 2016). Compared to LMW aggregates, HMW Aβ oligomers exhibit higher binding affinity to synapses in mature hippocampal neurons; indeed, strong synaptic binding is only observed in a subset of HMW oligomers (Velasco et al., 2012). Although HMW oligomers are dominant in the aqueous extracts of human AD brains, they are less active and toxic to neurons. HMW Aβ oligomers cause a transient decline of cognitive functions without obvious synaptic pathology, whereas LMW Aβ oligomers induce more rapid and persistent cognitive impairment with significant reduction of pre- and postsynaptic proteins (Figueiredo et al., 2013). However, these HMW oligomers can dissociate into the more active LMW populations to impair synaptic plasticity, and the amyloid plaques likely play a role in sequestering HMW oligomers to control the generation of LMW oligomers (T. Yang, Li, Xu, Walsh, & Selkoe, 2017). In contrast, the dissociation of Aβ oligomers into monomers by an Aβ-binding small molecule reduces the synaptotoxicity and Aβ pathology *in vivo* (Kim et al., 2015). Therefore, it is important to identify the distinct synaptic targeting mechanisms of LMW and HMW Aβ oligomers in order to understand the synaptotoxicity of Aβ and design Aβ-based therapeutic strategies.

3.2. Aβ-induced presynaptic dysfunction

Under pathological conditions, Aβ predominantly accumulates at synapses upon aberrant accumulation of β-site APP cleaving enzyme 1

(BACE1), the major neuronal β-secretase for Aβ generation, at the presynaptic terminals (Ye et al., 2017). The elevated synaptic Aβ level subsequently leads to deficits in crucial presynaptic functions including axonal transport, synaptic vesicle cycling, and neurotransmitter release.

Axonal transport is a key process that transfers cellular components to and from the cell soma. Aβ oligomers co-localize with axonal voltage-gated calcium channels to facilitate calcium influx and impair fast axonal transport of cargos such as brain-derived neurotrophic factor (BDNF) (Gan & Silverman, 2015). Aβ can disrupt axonal transport via mechanisms independent of tau or microtubule destabilization but requires the activation of NMDA receptors, calcineurin (a calcium-dependent phosphatase), glycogen synthase kinase 3 beta (GSK-3β), or casein kinase 2 (CK2) (Decker, Lo, Unger, Ferreira, & Silverman, 2010; Gan & Silverman, 2015; Pigino et al., 2009; Ramser et al., 2013). Recent studies have revealed that Aβ oligomers that bind to distal axons sequentially trigger local protein synthesis of transcription factor ATF4 within the axon and retrograde axonal transport to the soma, leading to neuronal degeneration (Baleriola et al., 2014). These findings suggest that presynaptic Aβ induces prominent neurodegeneration not only by disrupting physiological axonal transport, but also by initiating pathological axonal transport to spread AD pathology in a retrograde manner.

Neurotransmitter-containing synaptic vesicles are the key messengers that relay trans-synaptic signals. Aβ affects the key steps of synaptic vesicle cycling, including the trafficking, release, and recycling of synaptic vesicles (Ovsepian, O'Leary, Zaborszky, Ntziachristos, & Dolly, 2018). Oligomeric Aβ-induced presynaptic calcium influx can enhance the release probability of neurotransmitter-containing synaptic vesicles, resulting in an abnormally high level of glutamate in the extracellular space and enhanced spontaneous postsynaptic activity (Brito-Moreira et al., 2011). APP dimers at the presynaptic plasma membrane can serve as Aβ receptors and mediate the presynaptic potentiation via Go-coupled intracellular signaling; in turn, this further enhances Aβ generation, thus constituting a positive feedback mechanism of Aβ-induced synaptic hyperactivity (Fogel et al., 2014). In addition to potentiating the release probability of the readily releasable pool of synaptic vesicles, Aβ impairs vesicle recycling by reducing the recycling pool and increasing the resting pool via the calpain-dependent increase of the activity of cyclin-dependent kinase 5 (Cdk5). Indeed, Cdk5 inhibitor exhibits a beneficial effect on the recovery of the size of the vesicle pool, providing a brake for the Aβ-induced deregulation of synaptic vesicle cycling (Park, Jang, & Chang, 2013).

D-Serine is the dominant co-agonist of NMDA receptor-mediated synaptotoxicity. D-Serine level is elevated in multiple brain regions in AD patients, including the hippocampus, cortex, and cerebrospinal fluid (CSF), although the increase of D-serine in CSF is controversial (Biemans et al., 2016; Madeira et al., 2015). Upon binding to neurons, Aβ triggers the increase of extracellular D-serine, probably through alanine–serine–cysteine transporter 1 (asc-1) at the presynaptic terminal (Ferreira & Klein, 2011; Martineau, Parpura, & Mothet, 2014). Interestingly, loss of APP leads to a reduction of extracellular D-serine, concomitant with an increase of total D-serine and a decrease of dendritic spine dynamics (Zou et al., 2016). Therefore, blocking the pathological APP cleavage that overproduces Aβ and promotes the physiological functions of APP is crucial for maintaining D-serine homeostasis and cognitive functions. It should be noted that glial cells reserve a large pool of D-serine, which might come from the uptake of released neuronal D-serine synthesized from glial-derived L-serine (Martineau et al., 2014). However, the major source of aberrant D-serine release upon AD pathogenesis and the underlying signaling mechanisms remain unclear.

3.3. Aβ-induced postsynaptic dysfunction

Aβ oligomers target the postsynaptic compartment of excitatory synapses with high affinity, altering the structure, composition, and function of synapses (Koffie et al., 2009). The action of Aβ oligomers at postsynaptic membranes can be mediated through their binding to various cell surface molecules, forming putative Aβ receptor complexes to potentiate synaptotoxicity. However, it is unclear which molecules or mechanisms underlie the initial targeting and binding of Aβ to synapses. Furthermore, the specificity of Aβ species (i.e., LMW vs. HMW) targeting different "receptors" or cell-type selectivity is also unclear. Because of space limitations, this review will focus on ionotropic neurotransmitter receptors, G protein-coupled receptors (GPCRs), and receptor tyrosine kinases. Other Aβ receptors or receptor complexes on neuron membranes, such as cellular prion protein (PrP^c), Frizzled receptors, Neuroligin, insulin receptor, paired immunoglobulin-like receptor B (PirB), and Fcγ receptor II-b (FcγRIIb) have been reviewed elsewhere (Ferreira, Lourenco, Oliveira, & De Felice, 2015; Xia, Cheng, Yi, Gao, & Xiong, 2016).

3.3.1. NMDA receptors and AMPA receptors

NMDA receptors and AMPA receptors are two key types of ionotropic glutamate receptors at excitatory postsynaptic membranes (Scheefhals & MacGillavry, 2018). NMDA receptor is a heterotetramer comprising two GluN1 and two GluN2 subunits and is enriched at the postsynaptic membranes of excitatory neurons. The activation of its channel activity is controlled by glutamate binding, D-serine or glycine binding, and membrane depolarization to release Mg^{2+} block. Upon activation, NMDA receptor facilitates calcium influx to stimulate intracellular signaling cascades such as calcium/calmodulin-dependent protein kinase II (CaMKII) or calcineurin-mediated calcium signaling in postsynaptic neurons (Scheefhals & MacGillavry, 2018). Aβ oligomers bind to NMDA receptor-containing protein complexes at the neuronal surface and elicit distinct downstream pathways to induce synaptotoxic effects (De Felice et al., 2007; Decker et al., 2010). For example, NMDA receptor-dependent LTD is facilitated by Aβ via the inhibition of glutamate uptake and increased extracellular glutamate level (S. Li et al., 2009). Upon Aβ treatment, NMDA receptors recruit PTEN (a lipid phosphatase) to the postsynaptic density and facilitate synaptic depression (Knafo et al., 2016). Interestingly, Aβ-induced synaptotoxicity is dependent on the subunit composition of NMDA receptors. For example, GluN2A but not GluN2B is required for the Aβ-induced loss of dendritic spines (Tackenberg et al., 2013). In contrast, Aβ activates GluN2B-containing NMDA receptors at extrasynaptic regions through α7 nAChR-mediated astrocytic glutamate release, which leads to the aberrant activation of p38 mitogen-activated kinase (MAPK), inhibition of cAMP response element-binding (CREB) signaling, and impairment of LTP (Li et al., 2011; Talantova et al., 2013). The activation of extrasynaptic NMDA receptors also leads to the impairment of synaptic plasticity and cognitive functions by facilitating the proteasome-dependent degradation of the DNA repair factor, BRCA1 (Suberbielle et al., 2015).

On the other hand, AMPA receptors are the key glutamate receptors that mediate fast excitatory synaptic transmission. They have a heterotetrameric subunit composition, with dimerized dimers of GluA1, GluA2, GluA3, or GluA4 subunits (Greger, Ziff, & Penn, 2007). Early studies showed that AD patients exhibit reduced AMPA receptor expression in the entorhinal cortex and hippocampus (Dewar, Chalmers, Graham, & McCulloch, 1991; Yasuda et al., 1995). Furthermore, elevated Aβ level can induce the removal of AMPA receptors from excitatory synapses, which in turn leads to a loss of dendritic spines and synaptic depression (Chang et al., 2006; Guntupalli, Widagdo, & Anggono, 2016; Hsieh et al., 2006; Minano-Molina et al., 2011). While the functions of AMPA receptors can be modulated by post-translational modification (e.g., phosphorylation and ubiquitination) of its subunits (Chater & Goda, 2014), Aβ reduces GluA1 phosphorylation at Ser845 with a concomitant increase of GluA1 ubiquitination. Given that GluA1 phosphorylation at Ser845 is critical for AMPA receptor trafficking, expression of phosphomimetic GluA1 mutant reduces AMPA receptor ubiquitination and perturbs the Aβ-induced removal of AMPA receptors from the synaptic surface,

suggesting that GluA1 phosphorylation at Ser845 is negatively associated with ubiquitination in AD (Guntupalli et al., 2017). In addition, an elevated Ca^{2+} level in the presence of Aβ triggers the protein kinase C (PKC)-dependent phosphorylation of GluA2 at Ser880 and its subsequent removal from synapses (Liu, Gasperini, Foa, & Small, 2010). However, a recent study demonstrated that only GluA3-expressing neurons suffer from Aβ-induced insult, although the underlying mechanism remains elusive (Reinders et al., 2016). Furthermore, the precise composition of AMPA receptors that mediates Aβ-induced synaptic dysfunction awaits further investigation.

3.3.2. GPCRs: Metabotropic glutamate receptors and melanocortin 4 receptor

Metabotropic glutamate receptors (mGluRs) belong to the GPCR superfamily, which couple different G proteins to elicit downstream signaling through phospholipase C or adenylate cyclase and modulate glutamatergic synaptic transmission (Reiner & Levitz, 2018). A member of group I mGluRs, mGluR5, plays a modulatory role in regulating excitatory transmission at glutamatergic synapses and regulating NMDA receptor-dependent synaptic plasticity (Harney, Rowan, & Anwyl, 2006). Recent evidence further suggests that mGluR5 is a key player in Aβ-induced synaptotoxicity and a potential therapeutic target for AD (Kumar, Dhull, & Mishra, 2015). After Aβ oligomers bind to and accumulate at synaptic sites, the lateral diffusion of the oligomers decreases sharply and is accompanied by aberrant clustering of mGluR5, which results in synaptotoxicity (Renner et al., 2010). Moreover, in an AD transgenic mouse model that overproduces Aβ, genetic depletion of mGluR5 alleviates spatial learning deficits and amyloid pathology while reducing the activity of mammalian target of rapamycin (mTOR) and the expression of downstream fragile-X mental retardation protein (FMRP); in turn, this downregulates the translation and processing of APP (Hamilton, Esseltine, DeVries, Cregan, & Ferguson, 2014). Interestingly, mGluR5 physically interacts with PrP^c, a key component of putative Aβ receptor complex, coupling Aβ oligomers to the activation of Fyn kinase and neurotoxicity (Haas et al., 2016; Um et al., 2012; Um et al., 2013). The interaction between mGluR5 and PrP^c increases upon Aβ binding, inducing the deregulation of protein translation in dendrites through the phosphorylation of eukaryotic elongation factor 2 (eEF2), accompanied by a loss of dendritic spines and the facilitation of LTD (Haas, Kostylev, & Strittmatter, 2014; N. W. Hu et al., 2014; Um et al., 2013). Administration of mGluR5 agonist upregulates the association between mGluR5 and PrP^c, whereas administration of its antagonist downregulates this interaction (Haas et al., 2014). Thus, attenuating mGluR5 activation is an alternative approach to ameliorate Aβ-induced synaptic failure.

Meanwhile, melanocortin 4 receptor (MC4R) and its ligand, alpha-melanocyte–stimulating hormone (α-MSH), are well known for their roles in metabolic homeostasis (Krashes, Lowell, & Garfield, 2016). Our laboratory previously identified a microcircuit in the hippocampus: pro-opiomelanocortin (POMC) neurons expressed in the CA3 region generate α-MSH via proteolytic cleavage, which activates MC4R expressed in the CA1 region (Shen et al., 2016). Furthermore, postsynaptic activation of MC4R promotes the maturation of dendritic spines and augments the protein kinase A (PKA)-dependent phosphorylation of AMPA receptor subunit GluA1 at Ser845 to enhance both its surface expression at synapses and LTP (Shen, Fu, Cheng, Fu, & Ip, 2013). Further studies revealed that MC4R activation is deregulated in AD mouse models during disease progression (Shen et al., 2016). Importantly, attenuating MC4R activation by either presynaptic depletion of POMC neurons or postsynaptic antagonization of MC4R with its endogenous inverse agonist, agouti-related protein (AgRP), further impairs LTP in AD model mice (i.e., APP/PS1 mice). Meanwhile, the LTP deficits can be rescued by enhancing MC4R activity through the MC4R agonist, D-Tyr MTII (Shen et al., 2016). Thus, the findings of these studies provide a novel approach to targeting a specific microcircuit within the hippocampus to restore cognitive function in AD.

3.3.3. Receptor tyrosine kinases: EphA4 and EphB2

Eph receptors are by far the largest family of receptor tyrosine kinases. The 16 identified members can be divided into the EphA and EphB families, which preferentially bind to ephrinA and ephrinB ligands, respectively. The membrane-tethered nature of these receptors and ligands enables bidirectional signal transduction in both receptor- and ligand-expressing cells (Chen, Fu, & Ip, 2012; Kania & Klein, 2016). We and others have demonstrated that activation of EphA4 signaling via neuron–glia communication induces the retraction of dendritic spines in hippocampal neurons and that chronic elevation of neuronal activity facilitates the removal of AMPA receptor subunit GluA1 via a ubiquitin-proteasome pathway mediated by EphA4 (Bourgin, Murai, Richter, & Pasquale, 2007; Filosa et al., 2009; Fu et al., 2007; Fu et al., 2011; Murai, Nguyen, Irie, Yamaguchi, & Pasquale, 2003; Zhou et al., 2007). On the other hand, EphB receptors (EphB1–EphB3) play important roles in the development and maturation of dendritic spines (Henkemeyer, Itkis, Ngo, Hickmott, & Ethell, 2003; Kayser, Nolt, & Dalva, 2008; Murata & Constantine-Paton, 2013). EphA4 and EphB2 expression is reduced in the brains of early AD patients (Braak stage II/III), and altered EphA4 localization in the hippocampus with a notable concentration in neuritic plaque areas can be detected as early as Braak stage II (Rosenberger et al., 2014; Simon et al., 2009). These findings suggest that Eph family receptors are involved in AD pathogenesis.

Soluble Aβ exhibits high affinity for the extracellular domain of EphB2, which leads to the proteasome-mediated degradation of EphB2. Restoring EphB2 expression in the hippocampus in AD transgenic model mice reverses their cognitive impairment (Cisse et al., 2011; Hu et al., 2017). The beneficial effect of EphB2 depends on its ability to transduce signaling via its intracellular domain. Meanwhile, the γ-secretase–dependent cleavage of EphB2, which generates a C-terminal fragment, is important for NMDA receptor phosphorylation and surface expression; this can be inhibited by AD-associated familial presenilin 1 mutant (Litterst et al., 2007; Xu, Litterst, Georgakopoulos, Zaganas, & Robakis, 2009). The C-terminal PDZ-binding motif of EphB2 is the critical motif for ameliorating Aβ-induced deficits through regulating the association between EphB2 and intracellular PDZ proteins (Miyamoto, Kim, Knox, Johnson, & Mucke, 2016). EphB2 activation might also suppress GSK-3β activity and in turn alleviate tau hyperphosphorylation in AD (Jiang et al., 2015). Nevertheless, it remains unclear whether EphB1 and EphB3, which have overlapping functions with EphB2 at synapses (Henkemeyer et al., 2003), are also involved in Aβ-induced synaptic deficits and cognitive decline.

EphA4 is a substrate of γ-secretase, which cleaves EphA4 to generate EphA4 intracellular domain (EICD) upon elevated synaptic activity (Inoue et al., 2009). In the human AD brain, EICD level is reduced in the frontal lobes accompanied by reduced expression of its downstream effector, Rac1, which might be associated with the reduced dendritic spines and synaptic scaffold proteins observed in AD (Inoue et al., 2009; Matsui et al., 2012). EphA4 phosphorylation and activation are elevated in young AD model mice—much earlier than the appearance of obvious cognitive decline (Fu et al., 2014). Furthermore, the level of active EphA4 is significantly elevated in the human AD brain (Huang et al., 2017). Knockdown of EphA4 by shRNA or blockade of EphA4 activation by EphA4 inhibitory peptide, which targets its ligand-binding region, rescues the deficits of hippocampal LTP through the inhibition of the aberrant activation of downstream Cdk5 and c-Abl kinase (Fu et al., 2014; Vargas et al., 2014). The AD genetic risk factor, sortilin-related receptor with LDLR class A repeats (SORLA) might cause the deregulation of EphA4 in AD. Specifically, the activation and clustering of EphA4 are attenuated upon the interaction with SORLA. Moreover, enhancing SORLA–EphA4 interaction in SORLA transgenic mice ameliorates Aβ-induced synaptic deficits, neurodegeneration, and cognitive impairment (Huang et al., 2017). Nevertheless, further studies are needed to confirm whether blocking EphA4 activation and clustering in

postsynaptic neurons regulates astrocyte function through reverse signaling and in turn modulates synaptic functions in AD.

4. Tau pathology and synaptic dysfunction in Alzheimer's disease

4.1. Post-translational modification of tau

Tau is a major microtubule-associated protein that binds and stabilizes microtubules in neurons. Tau can undergo several post-translational modifications including phosphorylation, acetylation, glycosylation, glycation, nitration, sumoylation, ubiquitination, etc. Aberrant post-translational modifications, in particular, phosphorylation, induce conformational changes and aggregation of tau; this results in the formation of neurofibrillary tangles, one of the key hallmarks of neurodegeneration (Morris, Maeda, Vossel, & Mucke, 2011).

Phosphorylation is the most important post-translational modification of tau and can occur at serine/threonine sites, tyrosine sites, or both. Furthermore, the status of tau phosphorylation is an indicator of aberrant kinase and phosphatase activity during AD progression (Hanger, Anderton, & Noble, 2009). Accumulating evidence suggests that increased tau phosphorylation in CSF is a potential biomarker of AD that might help differentiate AD from other types of dementia (Blennow, Hampel, Weiner, & Zetterberg, 2010; Kandimalla et al., 2013).

Multiple sites of tau protein can be phosphorylated by proline-directed protein kinases (PDPKs) or non-proline-directed protein kinases (non-PDPKs) (Wang & Mandelkow, 2016). Key PDPKs that act on tau protein include Cdk5, GSK-3, and extracellular signal-related protein kinase (Erk). Aberrant Cdk5 activity in AD induces the loss of dendritic spines and impairment of synaptic plasticity as well as tau hyperphosphorylation (Kimura, Ishiguro, & Hisanaga, 2014). GSK-3 is believed to be the major kinase associated with the aberrant phosphorylation of tau. Interestingly, before GSK-3 acts on its target sites, it requires pre-phosphorylation of its substrate by priming kinases at the adjacent sites. Non-PDPKs such as PKA, CK1, and CK2 often play a regulatory or priming role in GSK-3–mediated phosphorylation. Cdk5 might also act as a priming kinase for GSK-3 (Hanger & Noble, 2011). These lines of evidence provide additional potential targets for antagonizing aberrant GSK-3 kinase activity in AD.

Recent evidence suggests that tau is acetylated in the brains of early-stage AD patients. Acetylation at multiple sites leads to decreased tau turnover, increased tau aggregation and phosphorylation, and increased cognitive impairment (Gorsky et al., 2017; Gorsky, Burnouf, Dols, Mandelkow, & Partridge, 2016; Min et al., 2015; Trzeciakiewicz et al., 2017). Acetylated tau protein exhibits increased somatodendritic localization and disrupts the postsynaptic localization of the memory-associated protein KIdney/BRAin (KIBRA), activity-dependent cytoskeletal dynamics, and AMPA receptor trafficking, consequently impairing synaptic plasticity and memory functions (Sohn et al., 2016; Tracy et al., 2016). Furthermore, investigation of the enhanced nitric oxide signaling through glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in AD brains revealed that nitric oxide shifts the balance between acetyltransferase p300 and deacetylase sirtuin towards tau acetylation; moreover, attenuating GAPDH-mediated nitric oxide signaling rescues the Aβ-induced memory impairment (Sen, Saha, & Sen, 2018). However, further study is needed to understand the biological relevance of different post-translational modifications of tau as well as the factors that initiate the changes in pathological conditions.

4.2. Pathological tau disrupts synaptic functions

Pathological modifications of tau alter its binding affinity for distinct partners, accompanied by aberrant aggregation, missorting to subcellular compartments, and enhanced propagation to different brain regions, which result in widespread tauopathy in AD (Spillantini & Goedert, 2013).

4.2.1. Tau-induced dysfunction of axonal transport and synaptic transmission

Tau is a microtubule-associated protein predominantly enriched in axons under physiological conditions. Interestingly, the physiological binding of tau to microtubules competes with its pathological misfolding, because the two processes require the same set of evolutionarily conserved residues (Kadavath et al., 2015). Moreover, tau competes with dyneins and kinesins (retrograde and anterograde molecular motors, respectively) through binding to microtubules, limiting the speed of axonal transport in both directions (Dixit, Ross, Goldman, & Holzbaur, 2008). In a recent study, disease-associated tau mutants exhibited a decreased association rate with microtubules with an unchanged dissociation rate, resulting in a net decrease of microtubule binding (Niewidok et al., 2016). In AD, the pathological hyperphosphorylation of tau leads to its detachment from microtubules, which is accompanied by decreased cytoskeletal stability and impaired axonal transport. The phosphatase-activating domain at the N-terminus of tau, which is present in pathological aggregates but not in soluble monomers, stimulates the activity of protein phosphatase 1 (PP1), which in turn dephosphorylates and activates GSK-3β to phosphorylate kinesin light chain; this causes cargo detachment and consequently disrupts anterograde transport (Kanaan et al., 2011; Kanaan et al., 2012; Stern, Lessard, Hoeprich, Morfini, & Berger, 2017). In addition, the extracellularly localized oligomeric forms of tau can be taken up by neurons, trigger abnormal tau accumulation in axons, and deregulate the axonal transport of membranous organelles (Swanson et al., 2017; Wu et al., 2013). On the other hand, pathological tau, with its N-terminal sequence, binds to synaptic vesicles through synaptogyrin-3 (a transmembrane vesicle protein) and disrupts presynaptic functions (McInnes et al., 2018; Zhou et al., 2017). Presynaptic accumulation of tau induces a transient increase of spontaneous neurotransmitter release mediated by intracellular calcium release from the endoplasmic reticulum; this is followed by persistent synaptic depression due to the resultant deficits in exocytosis (Moreno et al., 2011; Moreno et al., 2016). In addition, the presence of a pro-aggregation tau mutant at presynaptic boutons leads to the enlargement of boutons and depletion of the synaptic vesicle pool, concomitant with impaired synaptic transmission and plasticity (Decker et al., 2015; Fa et al., 2016). Thus, the maintenance of microtubule stability, transport along axons, and synaptic vesicle cycling require an optimal level of presynaptic tau.

4.2.2. Missorting of pathological tau

A tau diffusion barrier at the axon initial segment controls the homeostatic balance of axonal and somatodendritic tau (Li et al., 2011). The physiological translocation of tau to synapses is dependent on neuronal activity, which is disrupted in the presence of oligomeric Aβ (Frandemiche et al., 2014). The Aβ-induced inhibition of microtubule dynamics in the axon initial segment might also impair the normal sorting of tau (Tsushima et al., 2015; Zempel et al., 2017). Consistent with this finding, a substantial portion of tau protein in AD patients is translocated to the postsynaptic compartments, shifting the balance between axonal and somatodendritic localization (Tai et al., 2014). Tau proteins invading neuronal dendrites destabilize microtubules by recruiting spastin, a microtubule-severing enzyme (Zempel et al., 2013). More importantly, the infiltration of tau into dendritic spines results in reduced synaptic clustering of both NMDA and AMPA receptors, compromised excitatory synaptic transmission, and memory deficits (Hoover et al., 2010; Kim et al., 2016; Xia, Li, & Gotz, 2015; Yin et al., 2016; Zhao et al., 2016). Missorting of truncated tau with lower Fyn-binding affinity to cell soma or knockout of tau disrupts Fyn enrichment at the postsynaptic density as well as the subsequent phosphorylation of NMDA receptor subunit GluN2B and recruitment of PSD-95, consequently alleviating Aβ-induced excitotoxicity (Ittner et al., 2010; Roberson et al., 2011). In addition, abolishing the specific phosphorylation of tau at KxGS motifs by kinases such as AMP-activated kinase (AMPK) counteracts the Aβ-induced loss of dendritic spines and

restores synaptic functions (Mairet-Coello et al., 2013; Zempel et al., 2013). However, postsynaptic p38γ-mediated tau phosphorylation mitigates Aβ-induced excitotoxicity, suggesting the existence of protective tau phosphorylation in the postsynaptic compartment (Ittner et al., 2016). Therefore, targeting the somatodendritic missorting of tau and its specific phosphorylation at the postsynaptic compartment are alternative approaches for ameliorating synaptotoxicity in AD.

4.2.3. Tau propagation in AD

AD Braak staging is a tauopathy-based method for describing the gradual progression of neurofibrillary tangles from the transentorhinal region, to the limbic regions such as the hippocampus, and finally to the extensive neocortical regions (Braak & Braak, 1995). Seed-competent tau in the synaptic fraction is enriched before obvious tau pathology manifests in the human brain (DeVos et al., 2018). A low-abundance HMW tau species has been identified as an endogenously propagated form of tau (Takeda et al., 2015). The spread of tau aggregation from one brain region to another is not dependent on the proximity of two regions, but rather occurs between interconnected regions, suggesting that a trans-synaptic propagation mechanism is responsible (Goedert, Eisenberg, & Crowther, 2017). For example, tau has been observed spreading in a circuit-based manner from the entorhinal cortex to the dentate gyrus and cornu ammonis regions in the hippocampus (C. Li & Götz, 2017). Furthermore, the presence of synaptic contacts and elevated neuronal activity can enhance the spread of tau (Calafate et al., 2015; de Calignon et al., 2012; Wu et al., 2016). The identification of microglia-mediated tau internalization and seeding via exosomes indicates the existence of an alternative tau propagation mechanism independent of synaptic connections (Asai et al., 2015). Tau is also suggested to propagate in a prion-like manner (Clavaguera et al., 2013; Kaufman et al., 2016; Sanders et al., 2014). However, the finding that the propagation of misfolded tau does not require endogenous tau is unconducive with the prion-like propagation model, which posits that the templated misfolding of endogenous tau in recipient cells is necessary to maintain the prion-like tau conformation (Wegmann et al., 2015). Multiple approaches to block tau propagation, such as reduction of acetylation, inhibition of endocytosis, depletion of microglia, or administration of specific antibodies, can efficiently alleviate tau pathology, thereby opening new avenues to target tauopathy in AD (Asai et al., 2015; Calafate, Flavin, Verstreken, & Moechars, 2016; Min et al., 2018; Yanamandra et al., 2013). However, the specific tau species required for spreading, differential mechanisms for the release and uptake of tau of different molecular weights and conformations, and the cellular machinery that determines the circuit specificity of the spread of tau remain unclear.

5. Current experimental therapeutics for Alzheimer's disease

The currently available treatments for AD target cholinergic neurotransmission (i.e., donepezil, rivastigmine, and galantamine), glutamatergic synapses (i.e., memantine), or both (i.e., Namzaric, a combination of donepezil and memantine), providing limited relief of AD symptoms (Knight, Khondoker, Magill, Stewart, & Landau, 2018). While more than 100 clinical trials have failed, there are 112 ongoing trials of drugs with anti-amyloid, anti-tau, anti-inflammation, neurotransmitter-modulating, or other effects. Among these trials, amyloid- and tau-related strategies remain predominant (Cummings, Lee, Ritter, & Zhong, 2018).

5.1. Amyloid-related clinical development

Several anti-amyloid immunotherapies and small molecules have been designed to decrease the amyloid load in the brain either by reducing the generation and aggregation of Aβ or by enhancing its clearance.

Strategies to alleviate Aβ toxicity, such as immunotherapies sequestering specific Aβ species and chemicals blocking amyloid aggregation, have been extensively investigated. Six immunotherapies are currently undergoing phase III development (Cummings et al., 2018). One such immunotherapy, aducanumab (NCT01677572), is a human IgG1 monoclonal antibody derived from a cognitively normal donor that preferentially binds to Aβ aggregates in the parenchymal tissue, and exhibits a dose- and time-dependent effect on the removal of amyloid from the patient's brain while slowing the rate of cognitive decline (Sevigny et al., 2016). In contrast, solanezumab (NCT01900665) is a humanized monoclonal IgG1 antibody that targets Aβ monomers and aims to reduce synaptotoxic Aβ species by enhancing the clearance of soluble Aβ. However, in a recent double-blind, placebo-controlled phase III trial, its effect on preventing cognitive decline in mild AD was not significant (Honig et al., 2018). Despite many ongoing clinical trials, no strategy has proven successful. In particular, the specific Aβ species that is toxic in the brain or at synapses and the precise action mechanisms of Aβ species with different oligomeric forms or conformations remain unclear. Further investigation into these questions would aid the development of Aβ-targeting therapies with higher efficacy and specificity.

Another key target in this category is β-secretase 1, also known BACE1, which controls the rate-limiting step in the cleavage of APP at the β-site to generate Aβ (Das & Yan, 2017). In AD animal models, compromising BACE1 function by inhibiting its activity, reducing its expression, or introducing a protective mutant (A673T in APP) to the sequences near the β-site leads to the reduction of Aβ and alleviates memory impairment (Koelsch, 2017; Vassar, 2014). Among the 14 anti-amyloid therapies at the phase III stage, 5 are BACE1 inhibitors: verubecestat (NCT01953601), lanabecestat (NCT02245737, NCT02783573, NCT02972658), elenbecestat (NCT03036280, NCT02956486), JNJ-54861911 (NCT02569398), and CNP520 (NCT03131453) (Cummings et al., 2018). However, the side effects of inhibiting BACE1 must be considered. In addition to APP, BACE1 acts on other putative substrates in the nervous system (Vassar, 2014). Thus, BACE1 inhibition might abolish the processing of various physiological substrates that affect neuronal functions. On the other hand, attenuating BACE1 function shifts the balance towards the non-amyloidogenic pathway to generate more sAPPα and P3 peptide, which might also disturb neuronal function.

5.2. Tau-related clinical development

Most of the tau-related approaches at the phase II or III stage utilize disease-modifying strategies either by blocking tau aggregation or neutralizing/removing tau to hinder its transneuronal propagation. Other indirect approaches targeting intracellular pathology include stabilizing microtubules or manipulating tau kinases or phosphatases (Cummings et al., 2018).

The only anti-tau agent in the phase III stage is TRx0237 (NCT01689246), which is a reduced form of methylthioninium chloride designed to prevent or dissolve tau aggregation to alleviate tauopathy (Seripa et al., 2016). However, phase III trials of different doses of TRx0237 showed no beneficial effects on the cognitive performance of mild-to-moderate AD patients (Gauthier et al., 2016). Small molecules targeting the post-translational modification of tau, such as GSK-3β-mediated or Fyn-mediated phosphorylation, are under development and aim to block abnormal tau phosphorylation during AD pathogenesis (C. Li & Götz, 2017).

On the other hand, several immunotherapies that extracellularly target tau propagation are in phase II trials. For example, ABBV-8E12 (NCT02880956) blocks tau seeding by recognizing the aggregated form of tau, while RO7105705 (NCT03289143) binds both monomeric and oligomeric tau species (Doody, 2017; West et al., 2017). Meanwhile, LY3303560 (NCT02754830, NCT03019536) is an agent entering phase II trials (Alam et al., 2017) that selectively binds to tau aggregates over monomers; however, it remains unclear if its primary effect is indeed due to neutralizing extracellularly propagating tau. The key benefits of this strategy are easy access to the targets and that antibody uptake by neurons is not required.

Similar to the development of Aβ-related interventions, researchers are still investigating the precise roles of different tau species. The extent to which the extracellular tau pool contributes to AD is also unclear. Therefore, developing tau-related agents that specifically target pathological epitopes might be a path for future exploration.

6. Synapse-modifying strategies for Alzheimer's disease therapeutics

Synaptic failure is an early sign of AD pathogenesis and is closely associated with the observed cognitive decline in AD. Oligomeric Aβ (Fig. 1) or misfolded tau (Fig. 2) interacts with cell surface receptors, scaffold proteins, or intracellular signaling molecules, consequently deteriorating synaptic structure and function. Therefore, targeting the synaptotoxic Aβ or tau species, or the deregulated synaptic components at the early stage of AD might stop or reverse the disease progression.

6.1. Approaches to alleviate Aβ load

Approaches to alleviate Aβ load by enhancing its clearance or sequestration, reducing generation, or shifting the balance between the amyloidogenic and non-amyloidogenic pathways have been studied extensively and reviewed recently (Sala Frigerio & De Strooper, 2016). However, no effective intervention based on this paradigm has been developed. From a synaptic perspective, although oligomeric Aβ plays a key role in the synaptotoxicity in AD, the precise Aβ species that target specific types of synapses remain unknown. Interestingly, memantine, an FDA-approved drug for AD that acts on NMDA receptors, blocks HMW oligomer-induced cognitive impairment in mice but does not exhibit a beneficial effect on LMW oligomer-induced cognitive impairment (Figueiredo et al., 2013). This example highlights the importance of searching for Aβ species-specific interventions. A 56-kDa oligomer, $Aβ^*_{56}$, was recently identified in the brains and CSF of cognitively normal subjects before they developed signs of AD (Amar et al., 2017). Compared to other oligomeric forms of Aβ, $Aβ^*_{56}$ triggers a specific intracellular response to augment tau hyperphosphorylation through CaMKIIα but not GSK-3β or Cdk5; this makes $Aβ^*_{56}$ or its downstream signaling cascades promising targets for early-stage AD interventions (Amar et al., 2017). In addition, because APP processing is regulated by neuronal activity, the manipulation of synaptic transmission is a potential intervention approach to reduce Aβ load (Cheng, Wu, Geng, & Xiong, 2014). Although the activation of extrasynaptic NMDA receptors mediates excitotoxicity, pharmacological activation of synaptic NMDA receptors enhances α-secretase–mediated APP processing, which in turn shifts the balance towards the non-amyloidogenic pathway (Hoey, Williams, & Perkinton, 2009). This suggests that potentiating synaptic function could have a dual beneficial effect on reversing AD pathogenesis by antagonizing synaptic depression and reducing Aβ generation.

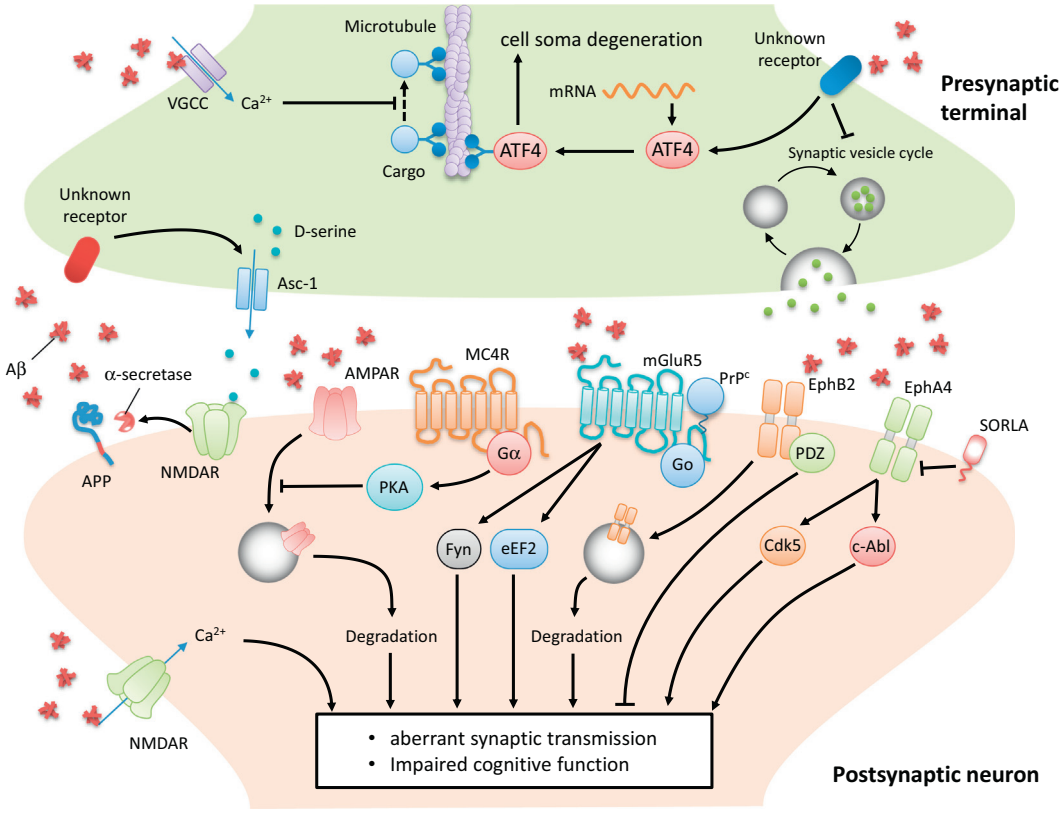

Fig. 1. Aβ-induced synaptic failure and excitotoxicity. Presynaptically, Aβ oligomers enhance calcium influx through VDCC and in turn disrupt the retrograde transport of BDNF. On the other hand, Aβ facilitates the axonal translation of ATF4 and its transport to cell soma, leading to neurodegeneration. Aβ also impairs the key processes in synaptic vesicle cycling, including trafficking, release, and recycling. In addition, Aβ triggers the presynaptic release of D-serine, which acts as the co-agonist of postsynaptic NMDA receptors to mediate synaptotoxicity. Postsynaptically, Aβ binds extrasynaptic NMDA receptors and induces excitotoxicity, while activation of synaptic NMDA receptors shifts APP processing to the non-amyloidogenic pathways mediated by α-secretase. Furthermore, Aβ facilitates the removal of AMPA receptors from the synaptic membrane, leading to synaptic depression; this can be prevented by the activation of MC4R and downstream PKA-mediated AMPA receptor phosphorylation. Another GPCR, mGluR5 physically interacts with PrP^C and induces loss of dendritic spines and impaired synaptic functions through Fyn kinase and eEF2. Moreover, Aβ interacts with cell surface EphB2 receptor and triggers its internalization and degradation. The PDZ-binding motif in the C-terminal of EphB2 is important for antagonizing Aβ toxicity. In addition, aberrant activation of synaptic EphA4 receptor results in synaptic dysfunction through mechanisms dependent on Cdk5 and c-Abl kinases, which can be attenuated by enhanced interaction with SORLA, an AD genetic risk factor.

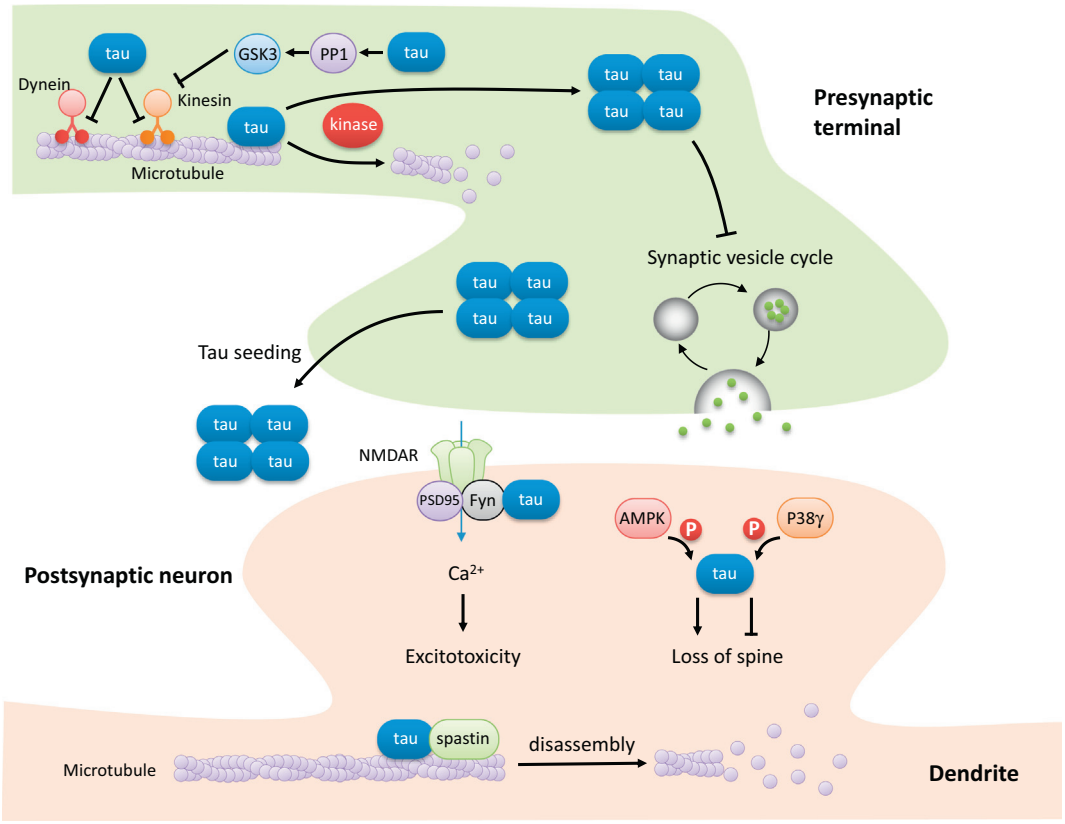

Fig. 2. Pathological tau-mediated synaptic dysfunction. At the presynaptic nerve terminal, hyperphosphorylation of tau mediated by kinases such as GSK-3β and Cdk5 leads to its dissociation from microtubules, concomitant with decreased microtubule stability. In addition, tau competes with the molecular motors dynein and kinesin for microtubule binding, limiting the speed of axonal transport. N-terminal domain of tau activates PP1, which impairs kinesin-mediated axon transport by enhancing GSK-3β–mediated kinesin phosphorylation. Tau also interacts with synaptic vesicles through Syanptogyrin-3 and impairs presynaptic vesicle cycling. Moreover, missorting of tau to neuronal dendrites causes the disassembly of microtubules through the recruitment of the microtubule-severing enzyme, spastin. Tau infiltration into dendritic spines facilitates Aβ-induced excitotoxicity through the recruitment of Fyn to the postsynaptic density and phosphorylation of NMDA receptor subunit. In addition, tau phosphorylation by different kinases (e.g., AMPK and p38) can have opposite effects on dendritic spines and synaptic functions. As part of a key process by which tauopathy is spread, trans-synaptic tau propagation is enhanced by synaptic contacts and activity as well as propagation mechanisms independent of synaptic connections.

6.2. Approaches targeting post-translational modifications of tau

Efforts to develop tau-focused therapeutic interventions increased after the finding that in the AD brain, tau load is more closely associated with cognitive decline than Aβ load (Li & Götz, 2017). Accordingly, approaches aiming to remove pathological tau, prevent tau aggregation, or inhibit pathological post-translational modifications of tau have been developed. Moreover, targeting tau modifications to reduce toxicity, inhibit aggregation, or restore normal subcellular localization is also of particular interest. For example, GSK-3β transgenic mice exhibit prominent tau hyperphosphorylation and neurodegeneration, while inhibiting GSK-3β activity by lithium chloride alleviates tauopathy and restores memory functions in AD mouse models (Llorens-Martin, Jurado, Hernandez, & Avila, 2014). Accordingly, clinical trials examining the treatment of AD patients with GSK-3β inhibitors are underway (del Ser et al., 2013). In addition, EphB2, the receptor tyrosine kinase that mediates synapse maturation, attenuates GSK-3β–mediated tau phosphorylation by activating the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, providing an easily accessible extracellular target site for inhibiting GSK-3β activity and tau phosphorylation (Jiang et al., 2015). Thus, multiple mechanisms of tau modification interact with one another and cause tau hyperphosphorylation, providing more avenues to target a specific pathological modification. However, these findings also highlight the difficulties of accurately and specifically targeting tau modification.

6.3. Approaches targeting synaptic receptors

The synaptotoxicity of Aβ is mediated by a plethora of putative receptor complexes, and multiple approaches have been developed to target these cell surface proteins and their downstream signaling pathways. In particular, in patients with mild cognitive impairment, cognitive performance as assessed by the Mini-Mental State Examination is strongly negatively associated with both GluA3 and GluN2B gene expression; similar negative associations have also been observed for EphA4 and ephrinB2, suggesting that these putative receptor complexes play key roles in mediating disease progression (Berchtold et al., 2014). Furthermore, the activity of these receptors could be modulated extracellularly, making them more accessible targets for AD treatment.

6.3.1. Ionotropic glutamate receptors

Memantine is a noncompetitive NMDA receptor antagonist that preferentially inhibits prolonged extrasynaptic Ca^{2+} influx. It also potently inhibits neuronal excitotoxicity, resulting in symptomatic improvement in moderate-to-severe AD patients (Alam, Lingenfelter, Bender, & Lindsley, 2017). Nitromemantine is an improved derivative that can selectively block aberrant extrasynaptic NMDA receptor activity and protect neuronal synapses both *in vitro* and *in vivo* (Talantova et al., 2013). As mentioned above, memantine preferentially targets HMW Aβ-induced synaptotoxicity (Figueiredo et al., 2013). However,

other than its symptom-modifying activity, it remains unclear if memantine can reverse or modify the pathological progression of AD, although it has shown efficacy in mouse models in preclinical studies (Folch et al., 2018). Of note, Chinese medicinal herbs have shown promising results regarding their ability to target glutamate receptor dysfunction in AD at the molecular and cellular levels. Rhynchophylline, a key oxindole alkaloid in the Chinese medicinal herb *Uncaria rhynchophylla*, suppresses the Aβ-induced activation of extrasynaptic NMDA receptors and restores the impaired LTP and spatial memory in AD model mice (Yang et al., 2018). In addition, anemodise A3 is a compound isolated from the Chinese medicinal herb *Pulsatilla chinensis*. It potentiates hippocampal LTP and spatial memory as a noncompetitive NMDA receptor modulator and facilitates GluA1 phosphorylation and trafficking to synapses (Ip et al., 2015). However, its role in alleviating the neurodegeneration in AD awaits further investigation. Moreover, the target specificity of herb-derived compounds requires careful consideration.

6.3.2. GPCRs

GPCRs are currently the largest group of drug targets. Our group's pharmacogenetics studies demonstrate that POMC/MC4R counteracts Aβ-induced synaptic failure by coupling Gs signaling to activate downstream cAMP-dependent mechanisms (Shen et al., 2016). Therefore, manipulating POMC/MC4R activity represents a circuit-specific, disease-modifying approach to alleviating the synaptic deficits in AD. On the other hand, pharmacological inhibition of mGluR5 by its negative or silent allosteric modulator significantly reduces Aβ load, including plaque deposition and oligomeric Aβ level, thus preventing synaptic and cognitive impairment in AD. However, the physiological role of mGluR5 in the regulation of glutamatergic transmission remains unaltered, indicating the presence of distinct physiological and pathological pathways (Haas et al., 2017; Hamilton et al., 2016). In addition to the action of mGluR5 at neuronal synapses, mGluR5 is expressed in non-neuronal cells such as microglia and astrocytes where it regulates the release of inflammatory factors and ATP; however, it is uncertain how extracellular Aβ can activate glial mGluR5 (Biber et al., 1999; Huang et al., 2018; Shrivastava et al., 2013). Nonetheless, mGluR5 likely modulates the process of neurodegeneration in AD by utilizing alternative pathways via glial–neuronal communication (Kumar et al., 2015). Accordingly, developing a disease-modifying strategy based on mGluR5 necessitates an in-depth understanding of its roles in neurons and glia.

6.3.3. Eph receptors

Aberrant hyper- or hypofunction of Eph receptors is prominently associated with synaptic failure or cognitive decline in AD. Screening of approved clinical drug libraries has identified compounds that can specifically inhibit soluble Aβ binding to EphB2 without affecting Aβ binding to other receptors or ephrin-B–EphB2 binding (Suzuki, Aimi, Ishihara, & Mizushima, 2016). A synthetic peptide that blocks the EphB2–Aβ interaction compromises the Aβ-induced depletion of the surface expression of EphB2 and GluN2B-containing NMDA receptors, with a concomitant improvement in memory performance in AD transgenic mice (Shi et al., 2016).

Peptides and small molecules that antagonize EphA4 receptor activation have also been developed. *In silico* screenings of a Chinese medicinal herb-derived compound library as well as FDA-approved drugs have identified several molecules that inhibit EphA4 activation (Fu et al., 2014; Gu et al., 2018). One of these candidates, rhynchophylline, effectively restores impaired synaptic function in an AD mouse model. Thus, these studies raise the intriguing possibility that specific Eph receptors represent therapeutic targets for AD. However, the receptors and ligands in the Eph/ephrin family share high homology. Therefore, a receptor could respond to multiple ligands or vice versa, making effective and specific drug targeting more challenging.

7. Concluding remarks

Synaptic failure occurs early in AD pathogenesis and is closely associated with cognitive decline, which is the primary symptom of AD. Studies in past decades using AD mouse models and human brain samples have revealed numerous signaling cascades that lead to pathological changes in synapse number, structure, and function. In turn, these efforts have yielded distinct therapeutic approaches to restore the synaptic function in AD animal models. However, none of these approaches have been translated into disease-modifying strategies with clinical applications.

Researchers are only beginning to unravel the pathological mechanisms of synaptic dysfunction in AD. The exact synaptotoxic species of Aβ and tau as well as the mechanisms underlying their prion-like spreading, the signaling complexes that mediate their initial contact with synapses, and the subsequent deterioration of synapses all remain unknown. Moreover, the specificities of neuronal cell types, synapses, and circuits affected by AD at specific stages also remain unclear. More importantly, most of our understanding of synaptic failure in AD comes from studies of AD mouse models that overexpress specific familial AD risk genes (i.e., *APP*, *PS1*, or *PS2*) or *tau*. Therefore, it is critical to better understand the dysregulation of synaptic signaling and synaptic failure in sporadic AD, which accounts for 95% of AD cases. In-depth investigations of the molecular and cellular mechanisms of synaptotoxicity are still needed to develop synapse-centered, disease-modifying treatments for AD as well as precision medicine aiming to systematically categorize the causes of synaptic failure in AD.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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