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Review

Glutamate receptors in preclinical research on Alzheimer's disease: Update on recent advances

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ABSTRACT

The cognitive and related symptoms of Alzheimer's disease are mainly attributable to synaptic failure. Here we review recent research on how the Alzheimer's disease amyloid ß-protein (Aß) affects glutamate receptors and fast excitatory synaptic transmission and plasticity of that transmission. L-glutamate, the main excitatory neurotransmitter in the brain, has long been implicated in causing NMDA receptor-mediated excitotoxicity leading to neurodegeneration in the late stages of the disease. However there is now extensive evidence that soluble Aß oligomers disrupt synaptic transmission and especially synaptic plasticity via non-excitotoxic glutamatergic mechanisms. New data highlight the relatively selective involvement of certain glutamate receptor subtypes including GluN2B (NR2B) subunit-containing NMDA receptors and mGlu5 receptors. Aß exerts direct and indirect effects on synaptic plasticity-related glutamate receptor signaling and trafficking between different neuronal compartments. For example, Aß-induced ectopic NMDA and mGlu receptor-mediated signaling coupled with caspase-3 activation may cause inhibition of long-term potentiation and facilitation of long-term depression. Intriguingly, some of the disruptive synaptic actions of Aß have been found to be dependent on endogenous tau located in dendrites or spines. Given the role of glutamatergic transmission in regulating Aß production and release, future therapies targeting glutamate offer the opportunity to remedy both mis-processing of Aß and cellular mechanisms of synaptic failure in early AD.

Contents

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; hAPP, human amyloid precursor protein; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; BDNF, brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; EphB2, ephrin type-B receptor 2; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; GSK3, glycogen synthase kinase 3; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mGlu, metabotropic glutamate; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; PKC, protein kinase C; PSD-95, postsynaptic density protein 95; Src, protein-tyrosine kinase; STEP, striatal-enriched phosphatase; TNF-α, tumor necrosis factor-alpha; trkB, tropomyosin-related kinase B.

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1. Introduction

Numerous reviews that address the role of glutamate receptors and related synaptic mechanisms in preclinical research on Alzheimer's disease (AD) and other neurodegenerative disorders have been published recently (Johnson et al., 2009; Lau and Tymianski, 2010; Luscher and Huber, 2010; Ondrejcak et al., 2010; Palop and Mucke, 2010a,b; Randall et al., 2010). The present review provides an update on some of the recent findings in this rapidly advancing area of research.

AD is the main cause of dementia and can now be diagnosed years before clinically severe symptoms arise (Perrin et al., 2009). Several different animal models are currently used to elucidate the mechanisms of AD, especially in its early stages (Jucker, 2010). Because a high proportion of familial forms of AD are caused by misprocessing of amyloid precursor protein (APP) and patients with trisomy 21 (Down syndrome) develop cerebral pathology and dementia characteristic of AD, transgenic over-expression of human APP (hAPP) is commonly studied in mice. Many of these transgenic lines display cognitive impairment but little or no neurodegeneration. In sporadic forms of AD, although there is evidence for increased activity of ß-secretase, the enzyme that cleaves APP prior to amyloid ß-protein (Aß) production, it is likely that reduced clearance of Aß is a critical factor. Genetic or pharmacological disruption of Aß clearance is therefore of great interest, but most commonly the effects of exogenously applied Aß are examined. Many different forms of synthetic and animal/human-derived Aß have been investigated, with particular emphasis on water soluble, non-fibrillar aggregates of Aß. These range from low-n oligomers to large soluble protofibrils (O'Nuallain et al., 2010). Much recent discussion has focused on the prion-like propagation of Aß (Eisele et al., 2010).

Because hyperphosphorylated and aggregated forms of the microtubule-associated tau protein are present in AD brain and cerebrospinal fluid, much recent attention has been devoted to investigating tau in animals. Like Aß, there is a growing realization that pre-fibrillar aggregates of tau may be most culpable in AD (Hoover et al., 2010; Zempel et al., 2010).

A major still unresolved issue is the relative role of "loss" versus "gain" of function in mediating the actions of Aß and tau in AD. Thus tau and Aß may have physiological roles that are usurped when these proteins aggregate or get misprocessed leading to loss of function in addition to the more widely accepted view that abnormally aggregated proteins interact with novel targets to cause a toxic "gain" in function.

In addition to Aß and tau pathology, key factors influencing the onset and progression of AD including aging, cerebrovascular dysfunction, pro-inflammatory, and cellular and behavioral stress mechanisms have been the focus of research. Such factors are likely to promote or trigger Aß and tau pathogenic mechanisms but may also interact as additive, independent causes of dementia (Bishop et al., 2010; Pimplikar et al., 2010).

In structural terms synaptic loss rather than frank neurodegeneration is more relevant to decline of cognitive and other functions in clinical dementia. Thus, understanding the relationship between pathological factors such as Aß and tau and disruption of synapses is of paramount importance. Given the early loss of glutamatergic neurons in AD in vulnerable pathways such as the medial temporal lobe/hippocampal network, the role of irreversible excitotoxic mechanisms has long been hypothesized (Greenamyre and Young, 1989). More recently, synaptic transmission and plasticity of this transmission, before detectible loss of synapses, have been found to be disrupted in several models, increasing the possibility of targeting disease mechanisms at a potentially reversible stage. Interestingly, Aß accumulates relatively selectively at certain synapses (Deshpande et al., 2009) and is released at synapses in a use-dependent manner (Bordji et al., 2010; Hoey et al., 2009).

2. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor-mediated transmission (see also Fig. 1)

Most investigators to date have reported that acute exogenous application of sub-micromolar concentrations of Aß has little or no acute effects on AMPA receptor-mediated transmission. However, a possible physiological role of sub-nanomolar concentrations of endogenous rodent Aß in the facilitation of activity-dependent presynaptic vesicular release of glutamate was reported recently (Abramov et al., 2009). Thus, lowering extracellular concentration of Aß at cultured hippocampal neurons reduced synaptic facilitation whereas inhibition of Aß metabolism caused a rapid increase in the frequency, but not amplitude, of AMPA receptor-mediated miniature EPSCs. The increase in release probability was associated with reduced paired-pulse facilitation such that excitatory synapses behaved like low-pass filters, facilitating low frequency activation of AMPA receptors in hippocampal slices. How this presynaptic facilitatory action relates to the putative negative feedback postsynaptic actions of endogenously-generated human Aß (Hsieh et al., 2006; Wei et al., 2010) is not clear. If confirmed, caution will be needed in the use of anti-Aß therapies that might interfere with such physiological processes.

The loss of AMPA-receptor-mediated transmission in AD is likely to be at least partly caused by the generation of non-physiological assemblies of Aß. Li et al. (2009) reported that cell-derived oligomeric human Aß acutely increased extracellular glutamate concentration in hippocampal slices. Whereas low nanomolar concentrations of these oligomers reduced the amplitude of AMPA receptor-mediated evoked EPSCs there was no change in AMPA receptor-mediated field EPSPs or paired-pulse facilitation. Somewhat similarly, certain oligomer-enriched preparations of synthetic Aß1-42 can potently and rapidly trigger a reduction in evoked AMPA receptor-mediated EPSCs and/or field EPSPs with no significant change in paired pulse facilitation (Cerpa et al., 2010; Kessels et al., 2010; Ronicke et al., 2011). Although there are many possible explanations, Li et al. (2009) found that an agent that blocks AMPA receptor desensitization, cyclothiazide, prevented the oligomer-induced reduction of EPSCs, consistent with Aß acting by inhibiting glutamate uptake. Indeed, micromolar concentrations of synthetic Aß1-42 oligomers, especially in the presence of cyclothiazide, apparently can rapidly trigger AMPA receptor-dependent inward currents and delayed neurodegeneration in cultured cortical neurons (Alberdi et al., 2010). Taken together, these findings indicate that agents designed to directly boost AMPA receptor function in AD may have a relatively narrow therapeutic window.

Evidence for a more direct interaction between AMPA receptors and Aß oligomers was provided in a recent paper that confirmed the ability of high nanomolar concentrations of Aß oligomers to preferentially bind to excitatory dendritic spines in cultured hippocampal neurons (Zhao et al., 2010). Ca^{2+} impermeable AMPA receptors containing the GluA2 (also named GluR2) subunit were particularly implicated in Aß binding and certain AMPA receptor antagonists prevented this binding. Importantly, the binding was associated with the rapid, clathrin-dependent, endocytosis of AMPA receptors via activation of calcineurin (protein phosphatase 2B) and dynamin. Moreover Aß oligomers were also internalized in a calcineurin-dependent manner. Further support for the importance of GluA2-containing AMPA receptors was independently provided by Liu et al. (2010) who reported that micromolar Aß oligomers induced a protein kinase C-dependent phosphorylation and internalization of these receptors (Liu et al., 2010). GluA1-containing receptors are also internalized in response to treatment with micromolar Aß oligomers in cortical slice cultures, consistent with the predominant heteromeric assembly of AMPA receptors (Gu et al., 2009). The removal of AMPA receptors was associated with a selective and delayed (>1 h, <24 h) reduction in AMPA receptor-mediated synaptic currents and

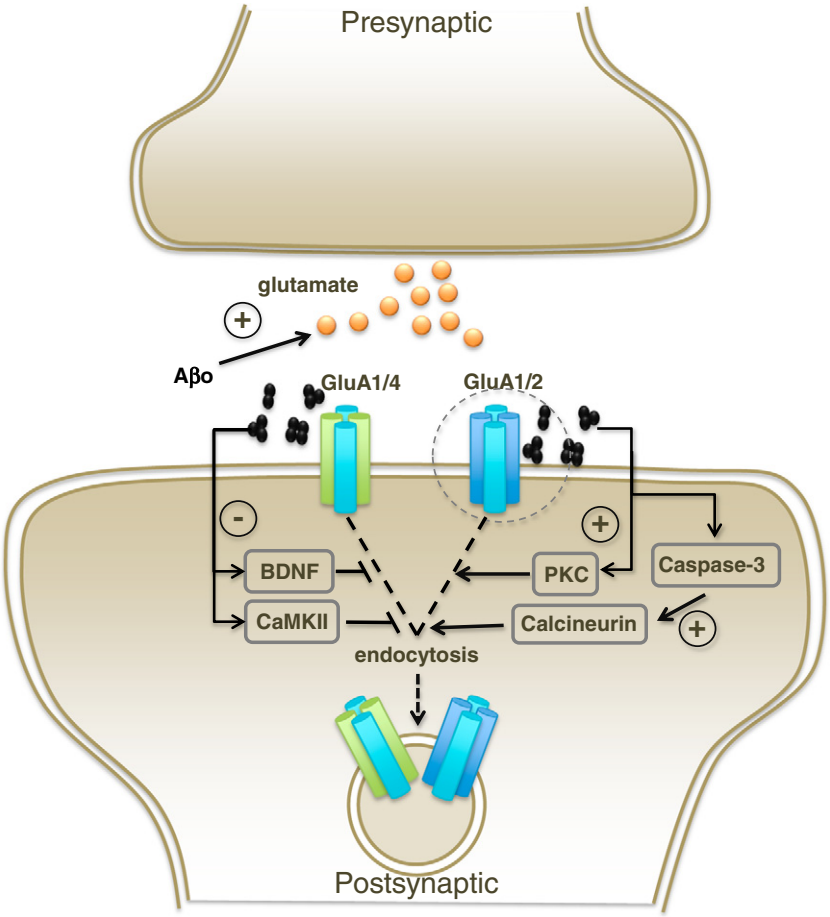

Fig. 1. AMPA receptors and Alzheimer's disease (AD) Aß-mediated synaptic dysfunction. Changes in postsynaptic AMPA receptor function and number (through a process of synaptic trafficking) may play a crucial role in AD pathogenesis. Aβ oligomer (Aßo)-induced synaptic dysfunction has been attributed to AMPA receptor removal and trafficking defects leading to synaptic inhibition. In dendritic spines, oligomeric Aβ binding occurs at the synapses that express mainly GluA2 subunit-containing AMPA receptors, which are calcium-impermeable. An Aß-triggered, caspase-3-dependent and calcineurin-mediated dephosphorylation of GluA1 subunit or a protein kinase C (PKC)-mediated phosphorylation of GluA2 subunit may be responsible for a rapid internalization of surface AMPA receptor subunits. Aβ oligomers were also reported to reduce both protein levels of BDNF and synaptic pool of Ca^{2+}/calmodulin-dependent protein kinase (CaMKII). Since these factors are necessary for maintaining AMPA receptors in the postsynaptic membrane, their reduction by Aß may trigger internalization of GluA1 subunit-containing receptors, presumably including GluA2-lacking receptors. See text for references.

a redistribution of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) away from the synapse. Indeed loss of hippocampal dendritic spines, reduced GluA1-containing AMPA receptors, decreased AMPA receptor-mediated synaptic transmission, and memory impairments were all attributable to Aß oligomer-induced caspase-3 activation in young hAPP transgenic mice (D'Amelio et al., 2011). The authors provided evidence that these morphological, molecular, cellular and behavioral deficits are due to a reversible oxidative stress-induced increase in caspase-3 cleavage of calcineurin (thereby increasing its activity), which in turn promotes dephosphorylation of postsynaptic AMPA receptors, thereby triggering their internalization.

There is growing evidence that tau may mediate synaptic dysfunction in AD. Thus, accumulation of mis-sorted hyperphosphorylated tau in dendritic spines has been implicated in disruption of AMPA (and NMDA) receptor trafficking and anchoring (Hoover et al., 2010). Indeed micromolar Aß oligomers, like glutamate, can cause rapid mis-sorting of several proteins including phosphorylated tau into dendrites and local depletion of mitochondria and subsequent loss of spines in cultured hippocampal neurons (Zempel et al., 2010). Furthermore, prolonged exposure to soluble AD brain extracts that contain nanomolar Aß oligomers cause synaptic loss in a tau-dependent manner (Jin et al., 2011). Interestingly, cortical spine loss associated with soluble Aß was detected in vivo in hAPP-tau transgenic mice with confocal imaging only in spines that accumulated hyperphosphorylated tau (Bittner et al., 2010). Furthermore, abnormal increased hippocampal excitatory synaptic transmission in hAPP transgenic mice is absent when these mice are crossed with tau-deficient mice (Roberson et al., 2011).

An emerging view is that the most pathologically relevant concentrations and assembly states of Aß acutely can indirectly increase extracellular glutamate levels with relatively subtle immediate effects on AMPA receptor-mediated transmission. Prolonged exposure or higher acute concentrations of Aß oligomers cause AMPA receptor endocytosis and may consequently trigger synaptic loss, probably as a result of non-apoptotic activation of certain caspases.

3. NMDA (N-methyl-D-aspartate) receptor-mediated transmission (see also Fig. 2)

An Aß-mediated increase in extracellular glutamate levels would be expected to modulate NMDA receptor- as well as AMPA receptor-mediated transmission. Indeed, Li et al. (2009) reported that in hippocampal slices the peak amplitude of NMDA receptor-mediated EPSCs was rapidly reduced by low nanomolar cell-derived Aß oligomers but the total charge transfer was not significantly affected due to prolongation of the EPSC. Interestingly, the relative contribution of different NMDA receptors to transmission was changed. Thus pharmacological evidence was provided that following Aß oligomer

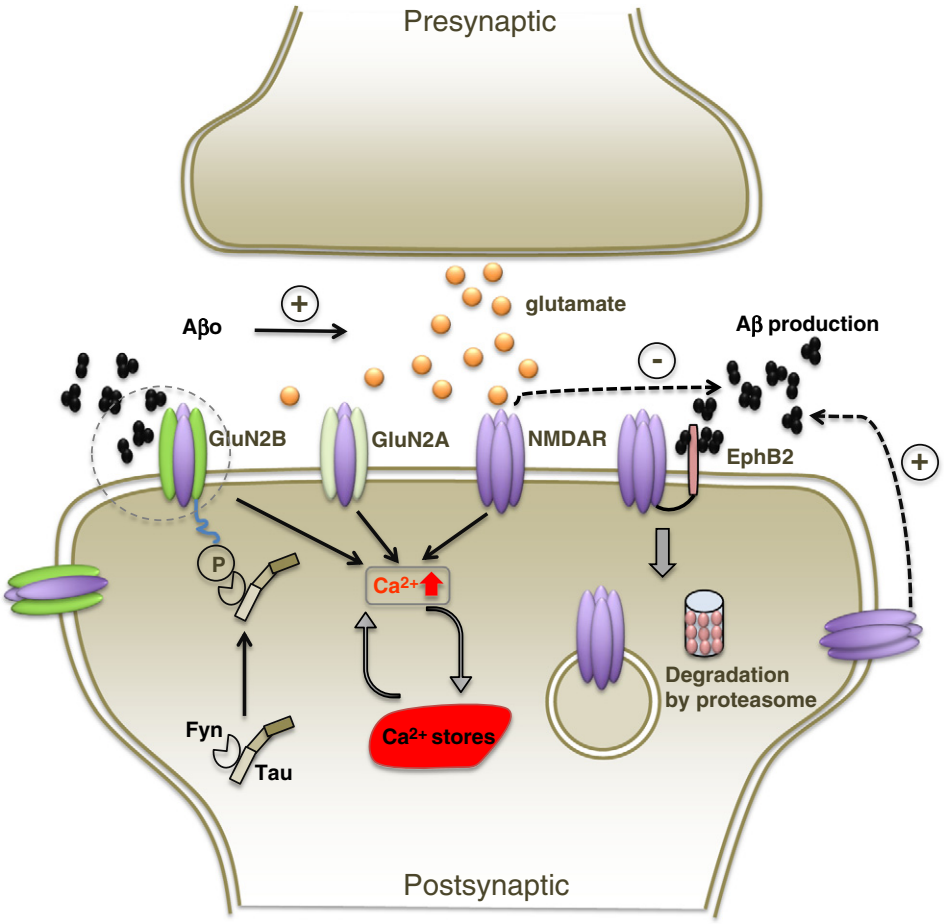

Fig. 2. NMDA receptors and Aß-mediated synaptic dysfunction. Aberrant enhancement of glutamate caused by Aβ initially may activate synaptic NMDA receptors including GluN2A/GluN2B (formerly NR2A/B)-containing receptors and further activate peri- and/or extrasynaptic NMDA receptors which are also GluN2B-containing. The activation of both synaptic and peri/extrasynaptic NMDA receptors leads to a rise of intracellular Ca^{2+} concentration which may trigger an aberrant calcium release from endoplasmic reticulum through ryanodine receptor-regulated stores. Also, Aβ may directly co-localize with GluN2B enriched NMDA receptors. Aβ can also directly bind the extracellular region of EphB2 and this binding leads to degradation of EphB2 in the proteasome. Since EphB2 modulates NMDA receptors by tyrosine phosphorylation and may be involved in NMDA receptor recruitment, the depletion of EphB2 reduces surface NMDA receptor levels by endocytosis. Fyn, a Src kinase, can phosphorylate GluN2B after it trafficks to the spine in a tau-dependent manner. This phosphorylation enhances the interaction between NMDA receptors and the scaffolding protein PSD-95 thereby increasing the linkage between NMDA receptors and downstream pro-convulsant signaling. Activation of synaptic NMDA receptors decreases Aβ production while activation of extrasynaptic NMDA receptors increases Aβ production. See text for references.

treatment the relative contribution of GluN2B (also known as NR2B) subunit-containing NMDA receptors and extrasynaptic NMDA receptors increased markedly. In a separate study (Cerpa et al., 2010), a high nanomolar oligomer-enriched preparation of synthetic Aß1-42 also caused a rapid and relatively large reduction in the amplitude of evoked NMDA receptor-mediated EPSCs in hippocampal slices. However these authors did not report the kinetics of the currents or the total charge transfer. In contrast, in cultured cortical neurons micromolar Aß1-42 oligomers either rapidly triggered inward currents that were NMDA receptor-dependent (Alberdi et al., 2010) or had no significant effect on NMDA-evoked currents (Gu et al., 2009). Furthermore, and unlike AMPA receptor-mediated EPSCs, there was no change in NMDA receptor-mediated EPSCs in cortical (Gu et al., 2009; Goussakov et al., 2010) or hippocampal neurons (D'Amelio et al., 2011) from young hAPP transgenic mice. However electrically evoked NMDA receptor-triggered increases in dendritic Ca^{2+} concentration were greatly enhanced in cortical neuron spines and dendrites of these mice due to aberrant calcium induced calcium release from ryanodine receptor-regulated intracellular stores (Goussakov et al., 2010). A putative mechanism proposed for this synergism is formation of a complex between GluN2B subunits and ryanodine receptors (Seeber et al., 2004).

Indeed high nanomolar Aß oligomer-induced delayed reduction in AMPA receptor-mediated transmission and synaptic pruning in hippocampal neurons is also GluN2B-dependent, being ameliorated by selective antagonists for NMDA receptors containing this subunit (Ronicke et al., 2011). This deleterious effect was related to a GluN2B-dependent translocation to the nucleus of a signaling protein termed Jacob and subsequent activation of the CREB shut-off pathway. Interestingly, low nanomolar concentration of cell-derived Aß oligomers also increase the activity of a tyrosine phosphatase, striatal-enriched phosphatase 61 (STEP) which promotes the endocytosis of GluN2B-containing NMDA receptors in cortical slices via dephosphorylation of the Src kinase Fyn and GluN2B at Y1472 (Kurup et al., 2010). Furthermore, genetic knockout of STEP prevented a reduction in hippocampal synaptic GluN2 content and cognitive impairment in hAPP and hAPP-tau transgenic mice (Zhang et al., 2010).

Remarkably, although tau, the other key player in AD pathology, is normally considered to be principally involved in the stable assembly of microtubules, a key role in regulating the phosphorylation of GluN2B subunits by the Src kinase Fyn has been reported (Ittner et al., 2010). Tau may traffic Fyn into dendritic spines thereby enabling Fyn to phosphorylate Y1472 in the extreme C terminus of GluN2B

subunits. Phosphorylation at this site facilitates the interaction of the GluN2B subunit with the postsynaptic density (PSD) protein PSD95. This interaction somehow couples NMDA receptors to pro-convulsant downstream signaling, but apparently does not directly affect NMDA (or AMPA) receptor-mediated fast excitatory synaptic transmission. Importantly, genetic ablation of tau, or peptide (Tat-NR2B9c)-mediated inhibition of NMDA receptor association with PSD-95, reduced the increased seizure susceptibility, T-maze errors and premature death seen in hAPP transgenic mice. Furthermore, the protective effects of Tat-NR2B9c persisted for 4 months after ceasing intracerebroventricular infusion in these mice.

Also implicating a role for GluN2B subunit-containing NMDA receptors, the activity-dependent synaptic localization and binding of Aß oligomers in the hippocampus has been reported to be ifenprodil-sensitive (Deshpande et al., 2009). Whether or not Aß binds less efficiently to synapses lacking GluN2B subunits or if the accumulation of larger aggregates leads to more profound synaptic dysfunction remains to be elucidated.

Interestingly, Aß1-42 fibrils, but not oligomers, slightly depolarized cortical and hippocampal neurons, similar to membrane depolarization found in hAPP transgenic mice (Minkeviciene et al., 2009). Such depolarization would be expected to partially relieve NMDA receptors from their Mg^{2+} block. Indeed fibrillar Aß1-42 was recently reported to enhance NMDA evoked firing via ß1 integrin and Src kinase in the hippocampus in vivo (Uhasz et al., 2010).

Overall there is a growing consensus that acute and delayed synaptic effects of pathophysiologically relevant concentrations of Aß oligomers are dependent on activation of GluN2B-containing NMDA receptors. This activation may be accompanied by modulation of NMDA receptor-mediated synaptic transmission and neuronal excitability. A putative role of synaptic tau is a matter of ongoing intensive research.

4. MGlu receptor trafficking and related signaling (see also Fig. 3)

Clearly, Aß-induced excessive extracellular glutamate concentration will cause increased activation of metabotropic as well as ionotropic glutamate receptors. However, evidence of a more direct link between mGlu receptors and Aß's synaptic actions was recently reported (Renner et al., 2010). Using antibodies, Renner et al. (2010) discovered that relatively low nanomolar Aß oligomer binding to cultured hippocampal neuron synapses was dependent on mGlu5 but not AMPA receptors and confirmed a dependence on NMDA receptors and cellular prion protein, which were non-additive contributors to binding. They found that Aβ1-42 oligomers rapidly bind to neuronal membrane, diffuse laterally and then gradually accumulate in clusters at excitatory synapses. These clusters altered the distribution and reduced the mobility of associated mGlu5 receptors. The slower lateral mobility of these receptors impaired their exchange between synaptic and extrasynaptic locations, which in turn increased synaptic mGlu5 receptors. Consequently, aberrant activation of mGlu5 receptors in ectopic signaling platforms promoted an increased intracellular Ca^{2+} and the removal of NMDA receptors from synapses (Renner et al., 2010). mGlu5 and NMDA receptors are closely

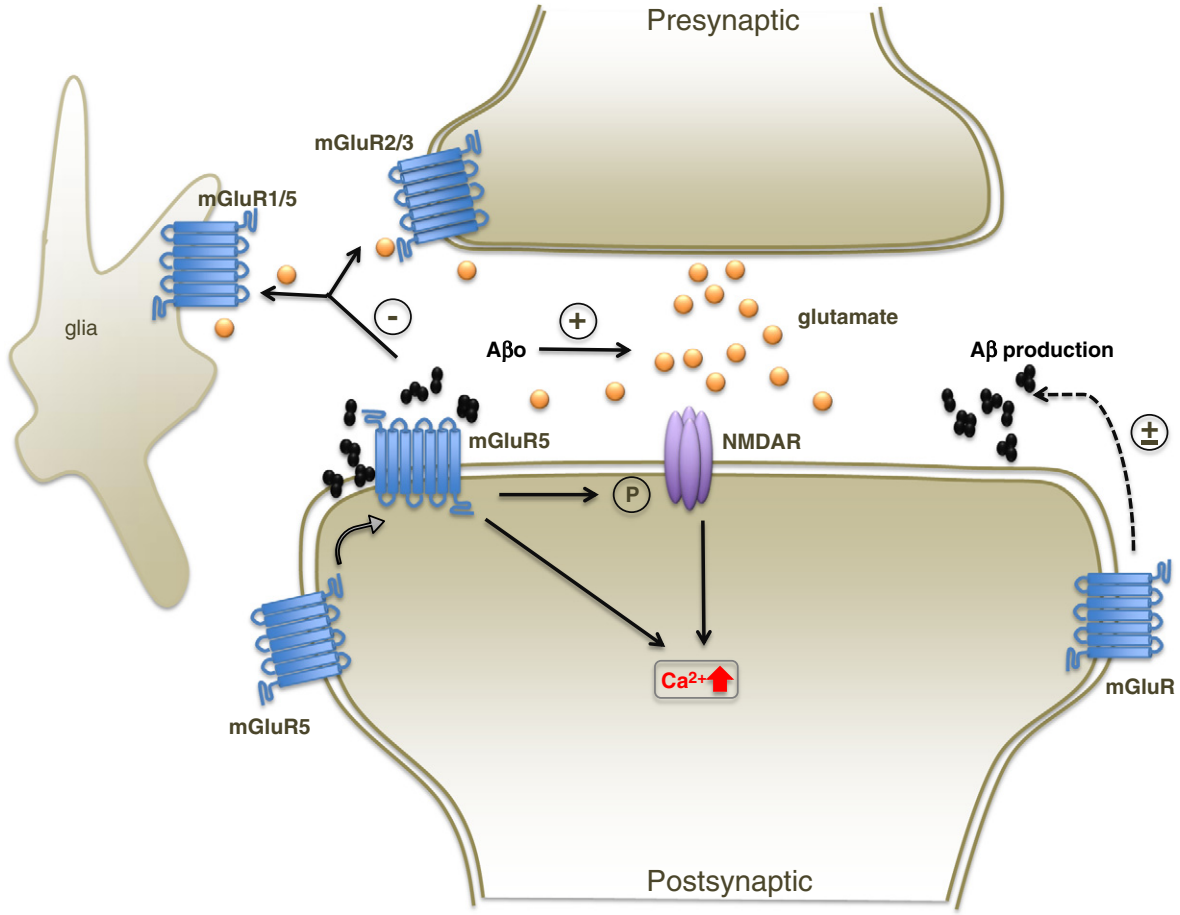

Fig. 3. mGlu receptors and synaptic dysfunction induced by Aß. Apart from increasing extracellular glutamate concentration Aβ forms clusters at excitatory synaptic plasma membranes, which may trigger the redistribution of mGlu5 receptor and cause an increase of synaptic mGlu5 receptors. Aberrant activation of ectopic clusters of mGlu5 receptor may increase intracellular Ca^{2+} directly or indirectly via NMDA receptors. Activation of both group I and group II mGlu receptors may increase Aβ production but the mechanisms are not fully understood. See text for references.

associated signaling partners, e.g. activation of mGlu5 receptors potentiates NMDA receptor function (Niswender and Conn, 2010) and the authors concluded that NMDA receptor-dependent synaptic effects are downstream of mGlu5 receptors.

Interestingly, by using astrocyte-rich cultures, Casley et al. (2009) found that Aβ can also enhance the magnitude of the intracellular calcium mobilization induced by the mGlu5 receptor activation. Whether or not similar mechanisms to those described for receptor clustering in neurons applies to glia requires further study.

5. Plasticity of AMPA receptor-mediated synaptic transmission (see also Fig. 4)

Synaptic plasticity mechanisms underlie cognitive functions including memory, and are exquisitely sensitive to Aß oligomers, which potently enhance long-term depression (LTD) and inhibit long-term potentiation (LTP) (Li et al., 2009). Since the expression of LTP often requires increased insertion and enhanced function of AMPA receptors in the postsynaptic membrane whereas conversely, the expression of LTD requires increased removal and decreased function of these receptors, AD-related reductions in postsynaptic AMPA receptor function and number may be caused by disruption of synaptic plasticity mechanisms.

In support of this view, some studies on the mechanisms of Aß-triggered reduction of baseline AMPA receptor-mediated synaptic transmission have confirmed parallels with the mechanisms underlying electrically or chemically induced long-term depression (LTD), reviewed by Collingridge et al. (2010). Both NMDA and mGlu receptor-dependent forms of LTD are facilitated by Aß (Kim et al., 2001; Li et al., 2009). In the case of Aß-facilitated NMDA receptor-dependent LTD these authors reported a requirement for activation of glycogen synthase kinase 3 (GSK3) and calcineurin but not p38 MAP kinase or intracellular Ca^{2+} stores. As noted in Section 2 above, baseline reductions in AMPA receptors induced by Aß oligomers are calcineurin-dependent (D'Amelio et al., 2011; Liu et al., 2010; Zhao et al., 2010). Moreover, a role for GSK3 was implicated in Aß-mediated inhibition of baseline and chemically-induced rapid membrane insertion of AMPA receptors in cultured hippocampal neuron spines using a selective inhibitor (Rui et al., 2010). Interestingly, spines associated with mitochondria, and showing surface accumulation of AMPA receptors, tended to be more resistant to Aβ-mediated inhibition of AMPA receptor trafficking.

Inhibitors of GSK3 also can prevent the inhibition of high frequency stimulation-induced LTP in hAPP transgenic mice (Ma et al., 2010). Furthermore, genetic deletion of FK506-binding protein 12 prevented disruption of LTP by Aß1-42 oligomers. The protective effect of these interventions was attributed by these authors to reversing Aß-mediated inhibition of activity of the Ser/Thr protein kinase mammalian target of rapamycin (mTOR) signaling pathway. Consistent with this, the neurotrophin BDNF, which acts through trkB receptors partly via the mTOR signaling pathway, is critical for synaptic AMPA receptor expression and delivery (Li and Keifer, 2008) and has been found to prevent Aβ1-42-mediated reduction of LTP in hippocampal slices, and LTP-associated CaMKII activation and AMPA

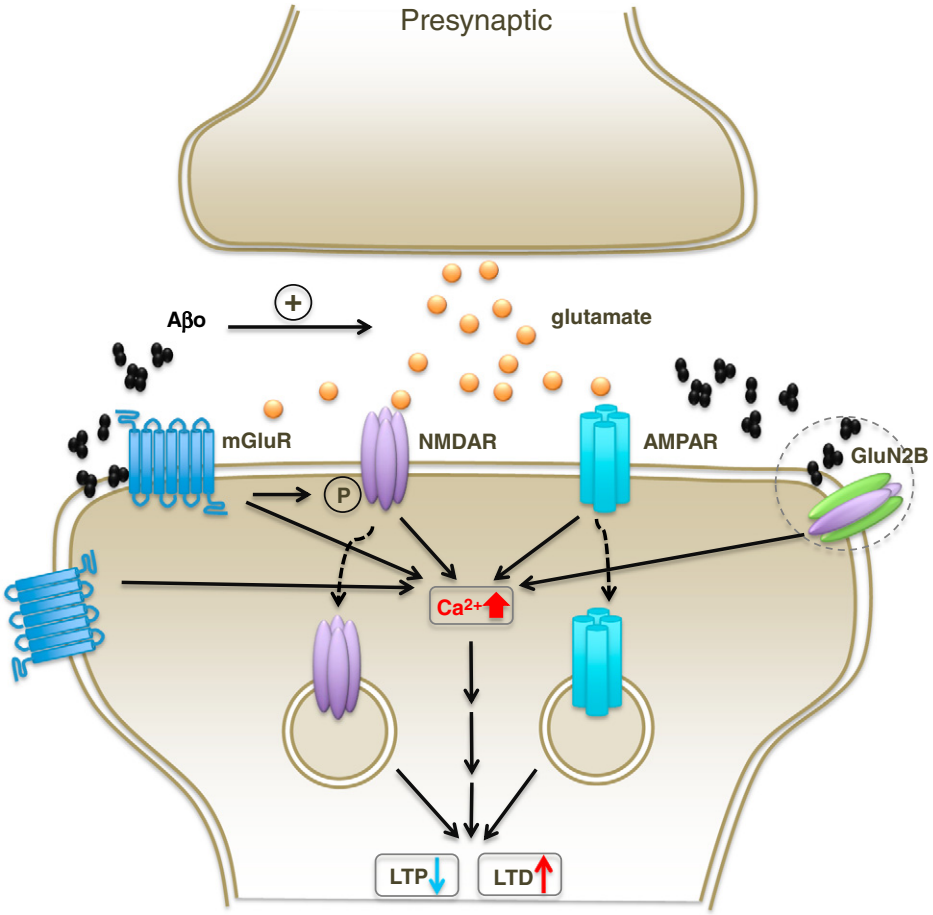

Fig. 4. Overall roles of glutamate receptors in synaptic plasticity disruption. Pathologically elevated Aβ increases extracellular glutamate concentration which activates synaptic and peri-/extrasynaptic glutamate receptors. This aberrant activation of receptors causes an abnormal increase in intracellular Ca^{2+} and internalization of both AMPA and NMDA receptors. As a result, these changes may modify synaptic function by inhibiting LTP and facilitating LTD. Prolonged pathological synaptic actions of Aß and tau would eventually cause synaptic silencing and pruning. See text for references.

receptor phosphorylation at a CaMKII-dependent site (Zeng et al., 2010).

Further support for a key role of GSK3 in mediating Aß-induced disruption of synaptic plasticity in hippocampal slices was recently reported by Shipton et al. (2011). These authors implicated downstream GSK3-mediated phosphorylation of tau since the deficit in LTP was not triggered in slices from tau deficient mice. Remarkably, the acute inhibition of LTP by Aß in hippocampal slices can be reversed by treatment with a selective GSK3 inhibitor even after the application of Aß (Jo et al., 2011). In a very elegant set of experiments strong evidence was provided that the disruption of LTP by Aß was caused by relatively specific activation of caspase 3, which in turn cleaved Akt, a key negative regulator of GSK3 kinase activity (Jo et al., 2011).

Additional, more indirect, mechanisms have been hypothesized to mediate the inhibition of NMDA receptor-dependent LTP by Aß. For example, a reduction in synaptic NMDA receptor function has been proposed to underlie this impairment of plasticity (Cisse et al., 2011). Aß oligomers were found to potently bind to the postsynaptic protein tyrosine kinase EphB2, which in turn was internalized and cleaved. Loss of EphB2, which regulates NMDA receptor trafficking, triggered the removal of synaptic NMDA receptors. Consistent with the hypothesis, the impairment of LTP by Aß and similar LTP deficits and learning impairments in hAPP transgenic mice were ameliorated by genetic overexpression of EphB2. Given the potential redundancy of synaptic NMDA receptors it will be important to determine if the observed reduction in NMDA receptors was sufficient on its own to disrupt synaptic plasticity. Another related putative mechanism for the inhibition of LTP by Aß involves increased activation of STEP with consequent endocytosis of GluN2B subunits (Kurup et al., 2010). Genetic knockout of STEP enhanced LTP in hAPP-tau transgenic mice (Zhang et al., 2010). However, removal of STEP in controls also enhanced LTP and it was unclear if there was an LTP deficit in the transgenic mice.

Given the ability of the clinically used NMDA receptor antagonist memantine to partially prevent the inhibition of LTP in vivo (Klyubin et al., 2011), we (Hu et al., 2009) recently compared the activity of subtype selective antagonists. Doses of GluN2B selective antagonists that did not significantly affect control LTP, completely prevented the disruptive effect of Aß. Similar treatment of animals with relatively low doses of the antagonists with greater preference for GluN2A, C, and D subunits had no significant effect on the inhibition of LTP. Although, as discussed above, Aß oligomer-mediated inhibition of glutamate uptake can lead to inappropriate activation of extrasynaptic NMDA receptors incorporating GluN2B subunits (Li et al., 2009), we found evidence for a role of the cytokine TNFα in mediating the action of Aß. Indeed, a GluN2B antagonist also abrogated a similar plasticity disrupting action of TNFα. It is possible that pro-inflammatory actions of Aß triggers the release of TNFα which in turn may promote increased spillover of glutamate.

6. Conclusions

Collectively, the above reports support a model of early disease pathogenesis in which low concentrations of Aβ oligomers initially preferentially and inappropriately boost activation of certain glutamate receptors, including mGlu5 and GluN2B subunit-containing NMDA receptors. Such activation disrupts synaptic plasticity, promoting LTD and inhibiting LTP of AMPA receptor-mediated synaptic transmission. The associated persistent reduction in the number of functional synaptic AMPA receptors reduces fast excitatory transmission and eventually triggers spine retraction and synaptic loss.

Future studies are likely to probe more deeply into the relationship between rapid and delayed effects of Aß at pre- and post-synaptic sites on glutamatergic synapses. Already it is known that Aß can be released in an activity-dependent manner from both axons and dendrites to disrupt chemically-induced structural plasticity and initiate spine loss in hippocampal slice culture within 1–3 days (Wei et al., 2010). Similarly, the relative importance of synaptic versus extrasynaptic glutamate receptors and their trafficking between different compartments in mediating Aß action needs to be integrated with our growing knowledge of their roles in cognitive decline in other neurodegenerative diseases such as Huntington's disease (Hardingham and Bading, 2010). How, and at what stage, the many different neuronal and non-neuronal (e.g. glial and vascular) binding sites for Aß oligomers contribute to synaptic and non-synaptic mechanisms mediating cognitive impairment is only beginning to be understood.

Of particular interest is how behavioral factors affect Aß-induced changes in glutamate receptor function and distribution. Intriguingly, the profile of changes in synaptic plasticity observed in hAPP transgenic mice are determined by prior training in a learning task (Middei et al., 2010). Thus, an impairment in LTP persistence was only detected in transgenic animals that had undergone water maze training.

As noted in the Introduction, glutamate receptors are not only involved in the process of Aβ-mediated synaptic dysfunction but also play important roles in Aβ production (see also Figs. 2 and 3). Recently it was reported that whereas synaptic NMDA receptor activation promotes non-amyloidogenic α-secretase processing of APP and thereby decreases Aβ production, extrasynaptic receptor activation increases Aβ production (Bordji et al., 2010; Hoey et al., 2009). Furthermore, activation of NMDA receptors by endogenously released glutamate in the presence of glycine can reduce intraneuronal Aβ levels (Tampellini et al., 2009). Similarly group I and group II mGlu receptor subtype selective agents exert differential actions on Aß production and release (Kim et al., 2010). These findings raise many questions such as how endogenous glutamate receptor stimulation affects neuronal Aβ production from healthy and diseased tissue. Given the role of glutamatergic transmission in regulating Aß production and release future therapies targeting glutamate offer the opportunity to remedy both mis-processing of Aß and cellular mechanisms of synaptic failure in early AD. More research is needed to answer these questions and to clarify the potential therapeutic value of selectively targeting specific glutamate receptor subtypes and associated signaling mechanisms.

Acknowledgments

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