Amyloid-β Receptors: The Good, the Bad, and the Prion Protein*

Several different receptor proteins have been identified that bind monomeric, oligomeric, or fibrillar forms of amyloid-β (Aβ). “Good” receptors internalize Aβ or promote its transcytosis out of the brain, whereas “bad” receptors bind oligomeric forms of Aβ that are largely responsible for the synaptic loss, memory impairments, and neurotoxicity that underlie Alzheimer disease. The prion protein both removes Aβ from the brain and transduces the toxic actions of Aβ. The clustering of distinct receptors in cell surface signaling platforms likely underlies the actions of distinct oligomeric species of Aβ. These Aβ receptor-signaling platforms provide opportunities for therapeutic intervention in Alzheimer disease.

Alzheimer disease (AD) is characterized pathologically by the deposition in the brain of the 40–42-amino acid amyloid-β (Aβ) peptide in extracellular plaques and of the microtubule-binding protein tau in intracellular neurofibrillary tangles. The amyloid cascade hypothesis, formulated over 20 years ago, posits that Aβ, derived from the proteolytic processing of the amyloid precursor protein, is the causative agent in AD pathology and that neurofibrillary tangles, cell loss, vascular damage, and dementia follow (1). A recent and critical interpretation of the existing data concluded that aggregated Aβ acts primarily as a trigger of other downstream processes, particularly tau aggregation, which mediate neurodegeneration (2). Understanding the nature of the interaction of Aβ with neurons and other cell types in the brain is key to a complete understanding of the pathogenesis of AD. Furthermore, identifying the proteins involved in the binding of aggregated forms of Aβ and the downstream cytotoxic signaling pathways that are subsequently activated may reveal sites for therapeutic intervention. In this minireview, we provide an overview of the “bad” receptors involved in the binding and cytotoxic action of Aβ, as well as the “good” receptors involved in Aβ metabolism and clearance from the brain (Fig. 1, Table 1). More detailed information on the Aβ receptors and carriers, including the type of Aβ they bind, the cell type they are expressed on, binding partners, and downstream targets, is provided in supplemental Table 1.

The Ligand: Multiple Forms of Aβ

Any discussion of receptors has to take into account the properties of the ligand(s) that binds to that receptor. In the case of the ligand Aβ, this is complicated by the fact that it exists in multiple forms from monomers, through dimers, trimers, and oligomers to proteofibrils and fibrils that range in size from 4 kDa to assemblies of >100 kDa, and vary in morphology and conformation (3). Aβ oligomers (AβO) appear to be the most neurotoxic species, triggering various processes that underlie AD, including synaptic dysfunction, impairment of long-term potentiation (LTP), Ca2+ dysregulation, mitochondrial dysfunction, endoplasmic reticulum stress, and the activation of pro-apoptotic pathways leading to cell death (4, 5). Various oligomeric forms of Aβ have been isolated from human AD brain and from the brains of AD model mice, as well as from cell culture medium, in addition to being produced from preparations of recombinant or synthetic Aβ peptides (6–10). Almost certainly, preparations of AβO, whether isolated from natural sources or produced in vitro, are composed of a number of oligomeric species with diverse biophysical and biological properties existing in dynamic equilibrium (6, 11). This dynamic equilibrium complicates studies when attempting to isolate a particular population of oligomers, e.g. by size exclusion chromatography, as the resultant “purified” oligomer preparation will remold to other species as the preparation resets its equilibrium. Therefore, it is not surprising that there is controversy over which is the toxic form of AβO, and indeed whether there is a single toxic entity (6).

The conformation of AβO aggregates has emerged as a useful classification method that is more biologically relevant than size, given that the structural motifs present on the surface of a protein will determine its binding partners and biological activities. Various conformation-specific antibodies that react with AβO have been produced and characterized (reviewed in Ref. 6). Two of the more widely used conformation-specific antibodies are the A11 and OC antibodies (12, 13), which recognize mutually exclusive structural epitopes on a range of amyloid-forming proteins, not just Aβ, independent of primary amino acid sequence. A11 antibodies recognize out-of-register anti-parallel β sheet structures, whereas OC antibodies detect in-register parallel β sheets (14–16).

A recent study (16) classified brain-derived AβO into two types based in part on their reactivity to these conformation-specific antibodies. Type 1 AβO were A11-immunoreactive
(also referred to as Aβ<sup>56</sup>) and had no temporal, spatial, or structural relationship to amyloid fibrils, whereas type 2 AβO recognized by OC antibodies were related to amyloid fibrils temporally, spatially, and structurally and represented the majority of oligomers generated in vivo. The authors concluded that although most of the soluble Aβ in brains with dense core plaques (e.g. AD brains) are type 2 AβO, the bulk of these oligomers are rendered functionally innocuous by their effective containment within plaques. In contrast, they suggested that type 1 AβO may be more directly pathogenic in certain brain regions as they are more finely dispersed than the type 2 AβO (16). Further work is required to reconcile these conclusions with the observations that OC reactivity, not A11 reactivity, correlated with the onset and severity of AD in human brain studies (17, 18) and that only OC-positive oligomers correlated with cognitive decline and promoted tau aggregation and phosphorylation in a different transgenic AD mouse model (18).

Another recent study (19) utilized several oligomer-directed quantitative assays, including a high specificity binding assay based on the affinity of certain AβO for the cellular form of the prion protein (PrP<sup>C</sup>) (PrP-ELISA or PLISA) (20), to assay AβO across brain tissue from multiple AD mouse models and human brain samples. The PrP<sup>C</sup>-interacting AβO represented a distinct population of high molecular weight Aβ assemblies that were as accurate as any other predictor of memory impairment in the AD mouse models and human AD patients. Oligomers interacting with PrP<sup>C</sup> were preferentially recognized by the OC antibody rather than the A11 antibody (21, 22) and thus would appear to correspond to the type 2 AβO (16). Critically, the fraction of PrP<sup>C</sup>-interacting AβO varied greatly between transgenic AD mouse models and likely determines the extent to which PrP<sup>C</sup>-dependent molecular mechanisms contribute to the progression of AD (19). That different transgenic AD mouse models may produce predominantly one (or a few) of the many potential types of AβO present in the human AD brain clearly complicates interpretation of data from the animal models. More work is required to clarify these discrepancies in AβO type and function both between animal models and between the animal models and the human situation. However, the characterization of different AβO species based on antibody or other conformational recognition (e.g. PrP<sup>C</sup> interaction) is a useful criterion with which to help decipher the contribution of particular oligomeric species to AD pathogenesis. In vivo it is highly likely that more than one oligomeric species contributes to toxicity, and thus understanding the temporal and spatial distribution of all AβO types in the brain during the initiation and development of AD, as well as knowing their receptors and mechanisms of toxicity, is essential to progress the field. Although AβO have been proposed to cause neurotoxicity through a variety of mechanisms, including direct interaction with lipids resulting in damage to the membrane through, for example, pore formation, or through intracellular accumulation leading to cytotoxicity (23, 24), here we focus on the binding of Aβ to cell surface receptors.
MINIREVIEW: Aβ Receptors

The “Good” Aβ Receptors

Proteins that bind Aβ (whether monomeric, oligomeric, or fibrillar forms) and reduce the amount available to aggregate into toxic oligomers can in many ways be considered “good” receptors. Such receptors may internalize Aβ into neurons or other cells (e.g. microglia) and target it for lysosomal degradation or remove it from the brain by transcytosis across the blood-brain barrier (BBB) (Fig. 1). One such receptor is the low-density lipoprotein receptor-related protein 1 (LRP1), which binds multiple ligands including monomeric Aβ and is abundantly expressed in various brain cell types. LRP1 has been implicated in mediating Aβ transcytosis across the BBB (25), as well as in the uptake and local clearance of Aβ in vascular smooth muscle cells and neurons (26, 27). Recently, the AD genetic risk factor PICALM, which encodes the phosphatidylinositol-binding clathrin assembly (PICALM) protein involved in the endocytosis of various cell surface receptors, was reported to influence Aβ clearance across the BBB through regulating the function of LRP1 in brain endothelial cells (28). PICALM also has been linked to Aβ transport across the BBB (29). PICALM on endothelial cells bound monomeric Aβ40, and genetic knock-out or the addition of a competing PICALM antibody blocked the transcytosis of Aβ40 in a process that also required LRP1 (29). The low-density lipoprotein receptor (LDLR) is also implicated in neuronal and astrocytic Aβ uptake and BBB transcytosis of Aβ (30). Although not cell surface receptors, the carriers apolipoprotein (apo) E and clusterin (apoJ) bind soluble Aβ and facilitate its uptake through receptors such as LRP1 or LRP2 and LDLR, thereby reducing the amount of Aβ available to aggregate (31). Microglial cells surrounding Aβ plaques express the scavenger receptors SCARA1 and SCARA2, which have a high affinity for soluble and fibrillar Aβ and mediate phagocytosis and clearance of Aβ from the brain (32). The macrophage receptor with collagenous structure (MARCO) binds Aβ and activates the ERK1/2 signaling pathway, leading to reduced inflammation (33). Collectively, these and other receptors and carriers (Table 1) work together, alongside other mechanisms for degrading or inactivating Aβ in the extracellular environment, such as the Aβ-degrading enzymes neprilysin and insulin-degrading enzyme (34), to maintain Aβ at low, manageable, non-toxic levels in the brain.

The “Bad” Aβ Receptors

In contrast to the “good” receptors described above that promote the transcytosis of Aβ out of the brain, one mechanism of action of the “bad” receptors is to mediate the uptake of Aβ into the brain across the BBB. The receptor for advanced glycation end products (RAGE), present on endothelial cells, mediates the influx of circulating Aβ (35). RAGE also internalizes Aβ into neurons, promoting its intracellular aggregation and accumulation, leading to rapid activation of p38 MAPK and mitochondrial dysfunction (36). Contributing to the accumulation

The “Good” Aβ Receptors

The “Bad” Aβ Receptors

| “Good” receptors | Aβ type/conformation | Other interactors | Reference |
|------------------|----------------------|------------------|----------|
| a7-Nicotinic acetylcholine receptor (α7nAChR) | Aβ42 monomer/LMW oligomers (4–24 kDa) | | 79 |
| Apolipoprotein E (apoE) | Aβ42 monomer | LRP1, LDLR | 31 |
| Clusterin (Apoj) | Aβ40/42 monomer | LRP2 | 80 |
| Complement receptor type 3 (CR3 or Mac1) | Aβ40/42 fibril | SR-A | 81 |
| Formyl peptide receptor (FPR1)/formyl-peptide receptor-like 1 (FPRL1) | Aβ42 | | 81 |
| Heparan sulfate proteoglycan (HSPG) | Aβ40/42 monomer | LRP1 | 82 |
| Low-density lipoprotein receptor (LDLR) | Aβ40/42 monomer | apoE | 83 |
| Low-density lipoprotein receptor-related protein 1 (LRP1) | Aβ40/42 monomer | PICALM, apoE | 25–28 |
| Macrophage receptor with collagenous structure (MARCO) | Aβ40/42 monomer | | 33 |
| Phosphatidylinositol-binding clathrin assembly (PICALM) protein | Aβ40/42 monomer | Clathrin/LRP1 | 28 |
| Prion protein (PrPSc) | | | |
| Scavenger receptors (SCARA1/2) | | | |

| “Bad” receptors | Aβ type/conformation | Other interactors | Reference |
|------------------|----------------------|------------------|----------|
| α7nAChR | Aβ42 oligomers (4–56 kDa) | | 85 |
| AMPA receptor | Aβ42 ADDLs (55–90 kDa) A11-negative | | 86 |
| Amylin 3 receptor (AMY3) | Aβ42 ADDLs (4–96 kDa) | | 87 |
| apoE | Aβ42 oligomers | VLDLR/LRP1 | 31, 88 |
| β2 adrenergic receptor (β2AR) | Aβ42 dimer | GluR1 (AMPAR) | 89 |
| Clusterin (Apoj) | Aβ42 oligomer (8–200 kDa) | | 90 |
| Ephrin A4 (EphA4) | Aβ42 ADDLs (4–100 kDa) | | 91 |
| Ephrin B2 (EphB2) | Aβ42 ADDLs (LMW) | | |
| Fc receptor IIIb (FcγRIIb) | Aβ42 ADDLs (12–96 kDa) | | |
| Frizzled (Fzd) | Aβ42 ADDLs (50–100 kDa) | | |
| Insulin receptor | Aβ42 ADDLs (50–150 kDa) | | |
| Leukocyte immunoglobulin-like receptor B2 (Lirb2)/PirB | Aβ42 ADDLs (5–150 kDa) | | |
| Na+/K+/ATPase neuron-specific α3 subunit (NaKα3) | AβSPD (128 kDa spheres) | | |
| Neuriligin-1 | Aβ42 A11-positive | PSD95 | 95 |
| NMDA receptor | Aβ42 ADDLs (12–96 kDa) | PSD95 | 10, 55, 57 |
| p75 neurotrophin receptor (p75NTR) | Aβ42 ADDLs (LMW) | | 97 |
| P/Q-type calcium channels | Aβ42 globulomers | | 98 |
| PrPSc | Aβ42 ADDLs (70–250 kDa) OC-positive | mGluR5, LRP1 | 80, 21, 43, 48 |
| Receptor for advanced glycation end products (RAGE) | Aβ40/42 monomer | | 99 |
| SCARB2/CD36 | | | 100 |
| Sigma-2/PGRMC1 | | TLR-4, TLR-6 | 74, 77 |
| Toll-like receptor 2 (TLR2) | Aβ42 oligomers (50–75 kDa) | | 81 |
of Aβ in the brain is apoE4, a well established genetic risk factor for the development of late-onset AD. As well as being involved in modulating the clearance and degradation of Aβ in the brain, apoE also slows the transport of Aβ across the BBB in an isoform-dependent manner, with apoE4 having the greatest effect (37). The detrimental effects of apoE4 are further exacerbated by its ability to bind to and stabilize AβO, slowing down their transition to fibrils (37).

When the first AβO were prepared from synthetic Aβ42 peptide, the now widely used Aβ-derived diffusible ligands (ADDLs), it was observed that their binding to hippocampal neurons was abolished by treating the cells with trypsin (7). This observation, coupled with the low oligomer concentration (5 nM) required for neurotoxicity, indicated that one or more high-affinity protein receptors are responsible for AβO binding and subsequent neurotoxicity. To date, several candidate “bad” Aβ receptors that bind AβO at the cell surface and then trigger a variety of downstream signaling pathways that negatively impact on neuronal function and survival have been described (Table 1; supplemental Table 1) (38–41). The role of several of these receptors in mediating AβO neurotoxicity is controversial or yet to be reproduced. The heterogeneity and dynamic nature of AβO preparations as discussed above undoubtedly have led to difficulties in first identifying a particular receptor and then in corroborating its involvement in different model systems and between different laboratories. The use of different and often poorly characterized preparations of AβO, different toxicity measurements on divergent target cell populations under different conditions, and the use of different transgenic AD mouse models at different stages of disease all confuse the picture. The recent report that the proportion of PrP<sup>C</sup>-interacting AβO varies between different mouse models of AD (19) may go some way to explain these discordant observations. Indeed this highlights a fundamental issue in the field; it is very unlikely that all receptors bind to the same oligomeric species of Aβ, and binding of different AβO to an individual receptor may be differentially influenced by other receptors or co-receptors in their vicinity (see below). Many of the signaling pathways initiated by these receptors converge into common downstream targets that are ultimately responsible for neurotoxicity and cell death.

**Dynamic Signaling Platforms Mediate AβO Binding and Action**

Various lines of evidence suggest that AβO binding to neurons may involve multi-protein cell surface receptor complex(es) whose assembly is initiated upon binding of oligomers to one or more of the receptor proteins listed in Table 1. These signaling platforms or signalosomes (5, 39, 42) will be formed from complexes of proteins and lipids in the plane of the plasma membrane, and will be transient in nature and likely involved in both physiological and pathological responses, contributing to both neuroprotection and neurotoxicity. The relative contribution to these two endpoints may depend on multiple factors, including the type and concentration of oligomer species, the compartmentalization of particular receptors and signaling effectors into different signaling platforms, the relative local interaction and concentration of particular receptors, co-receptors, and lipids, the interplay between the various downstream signaling pathways, and the rate of receptor down-regulation/internalization.

One such signaling platform is based on PrP<sup>C</sup> (Fig. 2A). PrP<sup>C</sup> was identified to bind AβO, but not monomers or fibrils, with high affinity (K<sub>d</sub> ~0.4 nM) (43, 44) and to selectively interact with high molecular mass assemblies of AβO in AD but not control brains (45). PrP<sup>C</sup> was responsible for the AβO-mediated inhibition of LTP in hippocampal slices (43) and was also required for the manifestation of memory impairments in an AD mouse model (46). AβO binding to PrP<sup>C</sup> leads to activation of Fyn kinase, which in turn phosphorylates the GluN2B subunit of N-methyl-d-aspartate receptors (NMDARs), which was coupled to an initial increase and then a loss of surface NMDARs (20). In addition, the AβO activation of Fyn leads to tau phosphorylation (47). Both mGluR5 (48) and LRP1 (21) have been identified as co-receptors required for the PrP<sup>C</sup>-bound AβO to activate Fyn (Table 1).

PrP<sup>C</sup> localizes to cholesterol- and sphingolipid-rich, detergent-resistant lipid rafts due to the saturated acyl chains in its glycosylphosphatidylinositol anchor and to an N-terminal targeting signal interacting with the heparan sulfate proteoglycan, glypican-1 (49, 50). PrP<sup>C</sup> has been proposed as a key scaffolding protein for the dynamic assembly of cell surface signaling modules (51), and PrP<sup>C</sup>, along with the microdomain-forming flotillin or caveolin proteins, may lead to the local assembly of membrane protein complexes at sites involved in cellular communication, such as cell-cell contacts, focal adhesions, the T-cell cap, and synapses (52). The integrity of lipid rafts is critical for the cell surface binding of AβO and the subsequent activation of Fyn. Treatment of cells with methyl-β-cyclodextrin, which depletes cellular cholesterol and thus disrupts the cholesterol-rich lipid rafts, caused the re-localization of PrP<sup>C</sup> and Fyn from detergent-resistant rafts to detergent-soluble, non-raft regions of the membrane (21). Surprisingly, disruption of the rafts with methyl-β-cyclodextrin significantly reduced (by >80%) the cell surface binding of the AβO, although the cell surface expression of PrP<sup>C</sup> was unaffected, and prevented the AβO from activating Fyn (21). The addition of AβO to neurons caused a large increase of mGluR5 in the detergent-resistant fraction (53), and on binding oligomers, the co-localization of LRP1 and PrP<sup>C</sup> increased (21), suggesting that binding of AβO to PrP<sup>C</sup> causes these co-receptors to cluster together in rafts and activate the signaling complex. This cell-surface, raft-based signaling complex based on PrP<sup>C</sup> may be key in mediating the neurotoxic actions of type 2 AβO (Fig. 2A). Another cholesterol-rich, raft-based platform may involve the presynaptic α7-nicotinic acetylcholine receptor (α7-nAChR) as its AβO-mediated activation was attenuated on disruption of the rafts by cholesterol depletion (54).

Another signaling platform(s) is likely based on NMDARs (Fig. 2B), which are necessary but not sufficient for AβO binding (reviewed in Ref. 5). NMDARs are anchored by PSD95, which acts as a scaffold to organize multiple membrane-associated proteins at synapses and which interacts with other AβO receptors including EphB2 (55). Binding of AβO to postsynaptic density complexes containing NMDARs promoted dendritic spine loss in an NMDAR-dependent manner and abol-
ished NMDAR-dependent LTP (55, 56). Antibodies against the subunits of NMDAR blocked the binding of AβO to neurons, and the NMDAR antagonist Memantine completely protected against AβO-induced reactive oxygen species formation (57), indicating that the receptors are required for binding and downstream action of AβO. However, no direct binding of AβO to NMDAR subunits has been reported. The EphB2 receptor modulates NMDAR by tyrosine phosphorylation and recruits active NMDAR to excitatory synapses. AβO interacted directly with the extracellular fibronectin repeats of EphB2, which led to depletion of surface EphB2 by enhancing its proteasomal degradation and to the internalization of GluN1 subunit-containing NMDARs (58). The 7-nAChR also induces AβO-mediated NMDAR dysfunction and synaptic impairment.

FIGURE 2. Aβ oligomer receptor signaling platforms. AβO induce synaptic impairment and neuronal cell death by interacting with multiple receptor signaling platforms. A, PrPC-based, cholesterol- and sphingolipid-rich lipid raft signaling platform. The co-receptors LRP1 and mGluR5 cluster with PrPC upon AβO binding and lead to activation of Fyn kinase, which phosphorylates NMDAR and tau. pTyr18, phospho-Tyr-18; pTyr1482, phospho-Tyr-1482. B, both 7nAChR and EphB2 bind AβO and induce NMDAR-mediated dysfunction and synaptic impairment. pCREB, phospho-cAMP-response element-binding protein. C, the presynaptic NaK3 binds ASPD oligomers, inducing Ca2+ influx via N-type VGCCs, resulting in mitochondrial dysfunction, tau phosphorylation, and synaptic impairment.

A further signaling platform is based on the Na+/K+-ATPase (Fig. 2C), whose neuron-specific α3 subunit (NaK3) was recently identified to bind amylospheroids (ASPD) (38). ASPD are 15-nm spherical AβO that are distinct from ADDLs, that are not recognized by the A11 conformation-dependent antibody, and that caused selective degeneration of mature human neurons (60). The direct binding of ASPD to NaK3 impaired its activity, resulting in an increase in cytoplasmic Na+ and depolarization of the neuron. This in turn activated N-type voltage-gated Ca2+ channels (N-type VGCC), leading to Ca2+ overload in the cytoplasm and mitochondria, ultimately leading to tau phosphorylation and degeneration of neurons. This signaling platform is localized on the presynaptic membrane (Fig. 1).

Further signaling platforms, based on other groupings of the receptors in Table 1, possibly in association with distinct combinations of membrane lipids, may be involved in binding the same and/or other oligomeric forms of Aβ and transducing neurotoxic signals. It should also be noted that although we have described these different signaling platforms as distinct entities (Fig. 2), it is possible that they are not structurally or functionally isolated and that “super” platforms exist which contain multiple receptors interacting with multiple oligomeric forms of Aβ. Furthermore, the protein and lipid composition of these dynamic signaling platforms may alter as a result of electrophysiological activity, oxidative damage, changes in lipids...
such as reduced cholesterol, hypoxia, and other cellular activities, and insults that are known to influence the initiation and/or progression of AD, thus influencing AβO binding and the downstream signaling pathways that are activated.

Does the AβO-promoted clustering of receptors lead to the induction of aberrant neurotoxic signaling (53) or over-stimulation of a physiological pathway (for example, due to prolonged stabilization of an otherwise transient complex involved in normal signaling processes), i.e. gain of toxic function? Or is it the hijacking of the signaling platform by AβO that disrupts normal physiological signaling, i.e. loss of function? Or a combination of these that leads to the neurotoxicity apparent in AD? The amount and/or activity of, and interactions between, individual signaling platform components are likely finely balanced. Either an increase or a decrease in a particular component or an alteration in the interaction between components may be sufficient for AβO to trigger neurotoxicity. It is possible that it is the binding of different AβO to multiple signaling platforms that initiates the complex series of events underlying AD. Following on from this, in the transgenic mouse models that predominantly produce only one type of AβO (19), not all of these signaling platforms will be engaged, resulting in activation of only some of the downstream signaling pathways and thus not recapitulating the complete array of molecular, cellular, and pathological responses seen in the human disease.

Therapeutic Approaches to Blocking AβO Action

AβO and their cell surface receptors provide a multitude of potential therapeutic targets (Fig. 3). For example, the accumulation of the “toxic” AβO could be prevented by blocking their formation, promoting their aggregation into larger order “inert” fibrils or plaques, altering their conformation, or inducing their clearance or degradation (Fig. 3, a–d). Immunotherapy is being actively explored as a potential means to reduce Aβ levels in the brain, although results from several clinical trials have been disappointing (61). Whether natural antibodies or other antibody preparations that bind to conformational epitopes on AβO and are therefore selective for AβO over other forms of Aβ will be more effective than antibodies that recognize peptide epitopes and thus bind both monomeric and oligomeric forms of Aβ awaits to be seen (62–64). The polyphenols, resveratrol and (−)-epigallocatechin-gallate (EGCG) convert soluble AβO into non-toxic aggregates (65, 66) whose binding to PrPC is severely impaired and which no longer activate Fyn (21). Another natural compound, brazilin, has recently been identified to potently remodel mature fibrils, preventing the formation of toxic oligomers by secondary nucleation (67). Sigma-2/PGRMC1 was identified as a receptor mediating the binding of both brain-derived and synaptic AβO (43), mimicking the binding region of this receptor bound to the LTP impairments in a transgenic AD mouse model (72). Recently, the small molecule Chicago Sky Blue 6B was identified in a high-throughput screen to bind to PrPC and inhibit AβO binding (73). Sigma-2/PGRMC1 was identified as a receptor mediating the binding and toxicity of both brain-derived and synthetically prepared AβO following the screening of a library of CNS drug-like small molecules that blocked AβO-induced deficits (74). The compounds identified were ligands for Sigma-2/PGRMC1 and prevented AβO from binding to primary hippocampal neurons and also displaced bound oligomeric species. The small molecule rynchophylline was identified as a novel inhibitor of EphA4, which blocked the ligand-binding domain of EphA4 and rescued AβO-induced deficits (75). Surface epitope masking peptides have recently been shown to prevent AβO binding to PrPC-induced impairments with NaK/ATPase (38). Tetrapiptipeptides mimicking the binding region of this receptor bound to the surface of ASPD, subsequently blocking their interaction with the receptor and preventing ASPD-induced impairments but without affecting the normal function of the Na⁺/K⁺ ATPase (38).

Complete blocking of receptors may have deleterious effects on neuronal function; however, modulating receptor activity is another potential approach to abrogate AβO action (76) (Fig. 3).
MINIREVIEW: Aβ Receptors

3h). Antagonism of the mGluR5 receptor using negative allosteric modulators prevented AβO-induced spine loss and cognitive deficits in transgenic mice (48). The Sigma-2/PGRMC1 ligands also acted as allosteric antagonists for the receptor, preventing aberrant signaling, as well as the subsequent spine loss and cognitive impairments in AD transgenic mice (77). Another approach is to target the downstream signal transduction pathways activated upon AβO binding to its receptors (Fig. 3i). For example, given that AβO binding to PrPSc activates Fyn, a Phase 1b trial of a potent small molecule inhibitor of Src and Fyn for the treatment of AD is underway (78). Ultimately, a combined therapeutic approach, targeting more than one AβO species, its receptor(s), and/or its downstream signaling pathway, will likely be required to alleviate all the neurotoxic effects of the multiple oligomeric forms of Aβ.

Concluding Remarks

Although much progress has been made in identifying Aβ receptors, several questions remain unanswered. How many distinct AβO receptors and signaling platforms are there? What is the contribution of each receptor and signaling platform to AβO-mediated toxicity? What are the individual components in each signaling platform, and how do their compositions, as well as the interactions between them, differ between AD and healthy individuals? Are different AβO signaling platforms involved depending on the initial trigger of disease, and what is their spatial and temporal contribution to disease pathogenesis? Given that there are multiple species of AβO, and that some transgenic mouse models appear to have predominantly one type of AβO, each interacting with a distinct set of receptors, what is the most appropriate animal model? How can we target specific signaling platforms for therapeutic intervention in AD without disrupting the normal physiological roles of these signaling complexes? Answers to these questions will come only from further experimental work comparing the binding of defined AβO preparations (characterized on the basis of biophysical and conformational properties) with each of the identified receptors in situ on cells and in vivo in appropriate animal models. However, the recognition that there are multiple Aβ receptors, binding different forms of Aβ, possibly preferentially in different stages in the development of AD, provides several opportunities for therapeutic intervention as highlighted here. What must also be recognized is that not only are there “bad” Aβ receptors binding oligomeric forms of Aβ and triggering cytotoxicity, but there are also “good” receptors involved in Aβ clearance and metabolism, as well as some like PrPSc that may play dual roles.

References

1. Hardy, J. A., and Higgins, G. A. (1992) Alzheimer’s disease: the amyloid cascade hypothesis. Science 256, 184–185
2. Musiek, E. S., and Holtzman, D. M. (2015) Three dimensions of the amyloid hypothesis: time, space and ‘wingmen’. Nat. Neurosci. 18, 800–806
3. Rushworth, J. V., and Hooper, N. M. (2010) Lipid rafts: linking Alzheimer’s amyloid-β production, aggregation, and toxicity at neuronal membranes. Int. J. Alzheimers Dis. 2011, 603052
4. Walsh, D. M., and Selkoe, D. J. (2007) Aβ oligomers: a decade of discovery. J. Neurochem. 101, 1172–1184
5. Ferreira, S. T., and Klein, W. L. (2011) The Aβ oligomer hypothesis for synapse failure and memory loss in Alzheimer’s disease. Neurobiol. Learn. Mem. 96, 529–543
6. Benilova, I., Karran, E., and De Strooper, B. (2012) The toxic Aβ oligomer and Alzheimer’s disease: an emperor in need of clothes. Nat. Neurosci. 15, 349–357
7. Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Kraft, G. A., and Klein, W. L. (1998) Diffusible, nonfibrillar ligands derived from Aβ1–42 are potent central nervous system neurotoxins. Proc. Natl. Acad. Sci. U.S.A. 95, 6448–6453
8. Li, S., Jin, M., Koeglsperger, T., Shepheardson, N. E., Shankar, G. M., and Selkoe, D. J. (2011) Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. J. Neurosci. 31, 6627–6638
9. Lesné, S., Koh, M. T., Kotlikine, L., Kayed, R., Glabe, C. G., Yang, A., Gallagher, M., and Ashe, K. H. (2006) A specific amyloid-β protein assembly in the brain impairs memory. Nature 440, 352–357
10. Shankar, G. M., Li, S., Mehta, T. H., Garcia-Munoz, A., Shepheardson, N. E., Smith, J., Brett, F. M., Farrell, M. A., Rowan, M. J., Lemere, C. A., Regan, C. M., Walsh, D. M., Sahatli, B. J., and Selkoe, D. J. (2008) Amyloid-β protein dimers isolated directly from Alzheimer’s brains impair synaptic plasticity and memory. Nat. Med. 14, 837–842
11. Hepler, R. W., Grimm, K. M., Nahas, D. D., Breeze, R., Dodson, E. C., Acton, P., Keller, P. M., Yeager, M., Wang, H., Shughrue, P., Kinney, G., and Joyce, J. G. (2006) Solution state characterization of amyloid β-derived diffusible ligands. Biochemistry 45, 15157–15167
12. Glabe, C. G. (2008) Structural classification of toxic amyloid oligomers. J. Biol. Chem. 283, 29639–29643
13. Kayed, R., Head, E., Sarsoza, F., Saing, T., Cotman, C. W., Necula, M., Margol, L., Wu, J., Breydo, L., Thompson, J. L., Rasool, S., Gurlo, T., Butler, P., and Glabe, C. G. (2007) Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. Mol. Neurodegener. 2, 18
14. Laganowsky, A., Liu, C., Sawaya, M. R., Whitelegge, J. P., Park, J., Zhao, M., Pensalfini, A., Soriaga, A. B., Landau, M., Teng, P. K., Casadio, D., Glabe, C., and Eisenberg, D. (2012) Atomic view of a toxic amyloid small oligomer. Science 335, 1228–1231
15. Liu, C., Zhao, M., Jiang, L., Cheng, P. N., Park, J., Sawaya, M. R., Pensalfini, A., Gou, D., Berk, A. J., Glabe, C. G., Nowick, J., and Eisenberg, D. (2012) Out-of-register β-sheets suggest a pathway to toxic amyloid aggregates. Proc. Natl. Acad. Sci. U.S.A. 109, 20913–20918
16. Liu, P., Reed, M. N., Kotlikine, L. A., Grant, M. K., Forster, C. L., Qiang, W., Shapiro, S. L., Reichl, J. H., Chiang, A. C., Jankowsky, J. L., Wilmot, C. M., Cleary, J. P., Zahs, K. R., and Ashe, K. H. (2015) Quaternary structure defines a large class of amyloid-β oligomers neutralized by sequestration. Cell. Rep. 11, 1760–1771
17. Tomic, J. I., Pensalfini, A., Head, E., and Glabe, C. G. (2009) Soluble fibrillar oligomer levels are elevated in Alzheimer’s disease brain and correlate with cognitive dysfunction. Neurobiol. Dis. 35, 352–358
18. Chabrier, M. A., Blurtin-Jones, M., Agazaryan, A. N., Arnerus, J. L., Martinez-Coria, H., and LaFerla, F. M. (2012) Soluble AβO promotes wild-type tau pathology in vivo. J. Neurosci. 32, 17345–17350
19. Kostylev, M. A., Kaufman, A. C., Nygaard, H. B., Patel, P., Haas, L. T., Gunther, E. C., Vortmeyer, A., and Strittmatter, S. M. (2015) Prion-protein-interacting amyloid-β oligomers of high molecular weight are tightly correlated with memory impairment in multiple Alzheimer mouse models. J. Biol. Chem. 290, 17415–17438
20. Um, J. W., Nygaard, H. B., Heiss, J. K., Kostylev, M. A., Stagi, M., Vortmeyer, A., Wisniewski, T., Gunther, E. C., and Strittmatter, S. M. (2012) Alzheimer amyloid-β oligomer bound to postsynaptic prion protein activates Fyn to impair neurons. Nat. Neurosci. 15, 1227–1235
21. Rushworth, J. V., Griffiths, H. H., Watt, N. T., and Hooper, N. M. (2013) Prion protein-mediated toxicity of amyloid-β oligomers requires lipid rafts and the transmembrane LRPI. J. Biol. Chem. 288, 8935–8951
22. Nicol, A. J., Panico, S., Freir, D. B., Wright, D., Terry, C., Risse, E., Heron, C. E., O’Malley, T., Wadsworth, J. D., Farrow, M. A., Walsh, D. M., Saibil, H. R., and Collinge, J. (2013) Amyloid-β nanotubes are associated
23. Inoue, S. (2008) *In situ* Aβ pores in AD brain are cylindrical assembly of Aβ protomers. *Am. J. Pathol.* 172, 1439–1450
24. Demuro, A., Smith, M., and Parker, I. (2011) Single-channel Ca2+ imaging implicates Aβ1–42 amyloid pores in Alzheimer’s disease pathology. *J. Neurosci.* 31, 14729–14737
25. Shibata, M., Yamada, S., Kuma, S. R., Calero, M., Bading, J., Frangione, B., Holtzman, D. M., Miller, C. A., Strickland, D. K., Ghiso, J., and Zlokovic, B. V. (2000) Clearance of Alzheimer’s amyloid-β-1–40 peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. *J. Clin. Invest.* 106, 1489–1499
26. Kanekiyo, T., Liu, C. C., Shih, M., Li, J., and Bu, G. (2012) LRP1 in brain vascular smooth muscle cells mediates local clearance of Alzheimer’s amyloid-β. *J. Neurosci.* 32, 16458–16465
27. Kanekiyo, T., Cirrito, J. R., Liu, C.-C., Shih, M., Li, J., Schuler, D. R., Shih, M., Holtzman, D. M., and Bu, G. (2013) Neuronal clearance of amyloid-β by endocytic receptor LRP1. *J. Neurosci.* 33, 19276–19283
28. Zhao, Z., Sugare, A. P., Ma, Q., Li, Li, Halliday, M. R., Kong, P., Kiser, K., Winkler, E. A., Ramana, A., Kanekiyo, T., Bu, G., Owens, N. C., Rege, S. V., Si, G., Ahuja, A., Zhu, D., Miller, C. A., Schneider, J. A., Maeda, M., Maeda, T., Sugawara, T., Ichida, J. K., and Zlokovic, B. V. (2015) Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. *Nat. Neurosci.* 18, 978–987
29. Pflanzner, T., Petch, B., André-Dohmen, B., Müller-Schiffmann, A., Castellano, J. M., Deane, R., Gottesdiener, A. J., Verghese, P. B., Stewart, S., Inoue, S. (2008) Cellular prion protein participates in amyloid-β transcytosis across the blood-brain barrier. *J. Cereb. Blood Flow. Metab.* 32, 628–632
30. Castellano, J. M., Deane, R., Gottesdiener, A. J., Verghese, P. B., Stewart, F. R., West, T., Paolotti, A. C., Kasper, T. R., DeMattos, R. B., Zlokovic, B. V., and Holtzman, D. M. (2012) Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood Aβ clearance in a mouse model of β-amyloidosis. *Proc. Natl. Acad. Sci. U.S.A.* 109, 15502–15507
31. Liu, C. C., Kanekiyo, T., Xu, H., and Bu, G. (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat. Rev. Neurol.* 9, 106–118
32. Wilkinson, K., and El Khoury, J. (2012) Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer’s disease. *Int. J. Alzheimers Dis.* 2012, 489456
33. Brandenburg, L. O., Konrad, M., Wruck, C. J., Koch, T., Lucius, R., and Pufe, T. (2010) Functional and physical interactions between formyl-peptide-receptors and scavenger receptor MARCO and their involvement in amyloid β1–42 induced signal transduction in glial cells. *J. Neurochem.* 113, 749–760
34. Nalivaeva, N. N., Belyaev, N. D., Kerridge, C., and Turner, A. J. (2014) Amyloid-clearing proteins and their epigenetic regulation as a therapeutic target in Alzheimer’s disease. *Front. Aging Neurosci.* 6, 235
35. Deane, R., Du Yan, S., Subramarayan, R. K., LaRue, B., Jovanovich, S., Hogg, E., Welch, D., Manness, L., Lin, C., Yu, J., Zhu, H., Ghiso, J., Francke, B., Stern, A., Schmidt, A. M., Armstrong, D. L., Arnold, B., Lilieniek, S., Nawroth, P. H., Hofman, K., Kindy, M., Stern, D., and Zlokovic, B. V. (2003) RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain. *Nat. Med.* 9, 907–913
36. Takuma, K., Fang, F., Zhang, W., Yan, S., Fukuizaki, E., Du, H., Sosnov, A., McKhann, G., Funatsu, Y., Nakamichi, N., Nagai, T., Mizoguchi, H., Ibi, D., Horii, O., Ogawa, S., Stern, D. M., Yamada, K., and Yan S.-S. (2009) RAGE-mediated signaling contributes to intraneuronal transport of amyloid-β and neuronal dysfunction. *Proc. Natl. Acad. Sci. U.S.A.* 106, 20021–20026
37. Huang, Y., and Mahley, R. W. (2014) Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer’s diseases. *Neurobiol. Dis.* 72, 3–12
38. Ohnishi, T., Yanazawa, M., Sashakawa, T., Kitamura, Y., Hiroki, H., Fukazawa, Y., Kii, I., Nishiyama, T., Kakita, A., Takeda, H., Takeuchi, A., Arai, Y., Ito, A., Komura, H., Hirao, H., Satomura, K., Inoue, M., Muramatsu, S., Matsu, K., Tada, M., Sato, M., Saijo, E., Shimemitsu, Y., Sakai, S., Umetzu, Y., Goda, N., Takino, N., Takahashi, H., Hagiwara, M., Sawa-saki, T., Iwasaki, G., Nakamura, Y., Nabeshima, Y., Teplow, D. B., and Hoshi, M. (2015) Aβ oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent signal transduction pathway. *J. Neurosci.* 107, 796–807
39. Shankar, G. M., Bloodgood, B. L., Townsend, M., Walsh, D. M., Selkoe, D. J., and Sabatini, B. L. (2017) Natural oligomers of the Alzheimer amyloid-β protein induce reversible synaptic loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J. Neurosci.* 27, 2866–2875
40. De Felice, F. G., Velasco, P. T., Lambert, M. P., Viola, K., Fernandez, S. J., Ferreira, S. T., and Klein, W. L. (2007) Aβ oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent signaling pathway. *J. Neurosci.* 27, 183–206.
MINIREVIEW: Aβ Receptors

mechanism that is blocked by the Alzheimer disease Memantine. *J. Biol. Chem.* **282**, 11590–11601

58. Cissé, M., Halabisky, B., Harris, J., Devidze, N., Dubal, D. B., Sun, B., Orr, A., Lotz, G., Kim, D. H., Hamto, P., Ho, K., Yu, G.-Q., and Muckle, L. (2011) Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature 467*, 47–52

59. Snyder, E. M., Nong, Y., Almeida, C. G., Paul, S., Moran, T., Choi, E. Y., Nairn, A. C., Salter, M. W., Lombroso, P. J., Gouars, G. K., and Greenberg, P. (2005) Regulation of NMDA receptor trafficking by amyloid-β. *Nat. Neurosci. 8*, 1051–1058

60. Noguchi, A., Matsumura, S., Dezawa, M., Tada, M., Yanazawa, M., Ato, I., Akiola, M., Kikuchi, S., Sato, M., Ideno, S., Noda, M., Fukunari, A., Muramatsu, S.-i., Itozaku, Y., Sato, K., Takahashi, H., Teplow, D. B., Nabeshima, Y.-i., Kakita, A., Imahori, K., and Hoshi, M. (2009) Isolation and characterization of patient-derived, toxic, high mass amyloid β-protein (Aβ) assembly from Alzheimer disease brains. *J. Biol. Chem. 284*, 32895–32905

61. Siemers, E. R., Sundell, K. L., Carlson, C., Case, M., Sethuraman, G., Liu-Seifert, H., Dowsett, S. A., Pontecorvo, M. J., Dean, R. A., and Demattos, R. (2015) Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer’s disease patients. *Alzheimers Dement. 10*, 10106; eja125.2015.06.1893

62. Britschgi, M., Olin, C. E., Johns, H. T., Takeda-Uchimura, Y., LeMieux, A. B., Stutz, S., Akioka, M., Kikuchi, S., Sato, M., Ideno, S., Noda, M., Fukunari, A., Yamasaki, S., Shiomi, T., Yamasaki, S., and Ohyama, J. (2011) Reversing EphB2 depletion rescues cognitive functions in Alzheimer’s disease. *Nat. Neurosci. 14*, 11590–11601

63. Strittmatter, S. M., and Wisniewski, T. (2010) Anti-PrP C monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer’s disease model mouse. *BMC Neurosci. 11*, 130

64. Rammes, G., Hasenjäger, A., Stroka-Saidi, K., Deussing, J. M., and Parsons, C. G. (2011) Therapeutic significance of NR2B-containing NMDA receptors and mGluR5 metabotropic glutamate receptors in mediating the synaptotoxic effects of β-amyloid oligomers on long-term potentiation (LTP) in murine hippocampal slices. *Neuropharmacology 60*, 982–990

65. Izzo, N. J., Staniszewski, A., To, L., Ma, J., Teich, A. F., Saeed, F., Wostein, J., Walko, T., 3rd, Vaswani, A., Warf, D., Syed, Z., Ravenscroft, J., Mozioni, K., Silky, C., Rehak, C., Yurko, R., Finn, P., Look, G., Rishhon, G., Safferstein, H., Miller, J., Johnson, C., Stora, E., Windisch, M., Hutter-Paier, B., Shamloo, M., Arancio, O., LeVine, H., 3rd, and Catalano, S. M. (2014) Alzheimer’s therapeutics targeting amyloid β-42 oligomers I: ApoE4 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits. *PLoS ONE 9*, e111898

66. Nygaard, H. B., van Dyck, C. H., and Strittmatter, S. M. (2014) Fyn kinase inhibition as a novel therapy for Alzheimer’s disease. *Alzheimers Res. Ther. 6*, 8

67. Bodani, R. U., Sengupta, U., Castillo-Carranza, D. L., Guerrero-Muñoz, M. J., Gerson, J. E., Rudra, J., and Kayed, R. (2015) Antibody against small aggregated peptide specifically recognizes toxic Aβ-42 oligomers in Alzheimer’s disease. *ACS Chem. Neurosci. 6*, 1978–1989

68. Izzo, N. J., Staniszewski, A., To, L., Ma, J., Teich, A. F., Saeed, F., Wostein, J., Walko, T., 3rd, Vaswani, A., Warf, D., Syed, Z., Ravenscroft, J., Mozioni, K., Silky, C., Rehak, C., Yurko, R., Finn, P., Look, G., Rishhon, G., Safferstein, H., Miller, J., Johnson, C., Stora, E., Windisch, M., Hutter-Paier, B., Shamloo, M., Arancio, O., LeVine, H., 3rd, and Catalano, S. M. (2014) Alzheimer’s therapeutics targeting amyloid β-42 oligomers II: Aβ42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits. *PLoS ONE 9*, e111898

69. Puzzo, D., Privitera, L., Leznik, E., Farrow, M. A., Sessions, R. B., Saibil, H. R., Clarke, A. R., Asante, E. A., and Shughrue, P. J., and Ray, W. J. (2010) Inhibition of calcineurin-mediated endocytosis and α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptors prevents amyloid-β oligomer-induced synaptic disruption. *J. Biol. Chem. 285*, 7619–7632

70. Chen, E., Ji, Y., Sun, Y., Kascak, R. J., Kascak, R. B., Mehta, P. D., Strittmatter, S. M., and Wisniewski, T. (2010) Anti-PrP C monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer’s disease model mouse. *BMC Neurosci. 11*, 130

71. Risse, E., Nicoll, A. J., Taylor, W. A., Wright, D., Badoni, M., Yang, X., Farrow, M. A., and Collinge, J. (2015) Identification of a compound that disrupts binding of amyloid-β to the prion protein using a novel fluorescence-based assay. *J. Biol. Chem. 290*, 17020–17028

72. Chung, E., Ji, Y., Sun, Y., Kascak, R. J., Kascak, R. B., Mehta, P. D., Strittmatter, S. M., and Wisniewski, T. (2010) Anti-PrP C monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer’s disease model mouse. *BMC Neurosci. 11*, 130
ways. *J. Biol. Chem.* **287**, 18820–18830

88. Garai, K., Verghese, P. B., Baban, B., Holtzman, D. M., and Frieden, C. (2014) The binding of apolipoprotein E to oligomers and fibrils of amyloid-β alters the kinetics of amyloid aggregation. *Biochemistry* **53**, 6323–6331

89. Wang, D., Govindaiah, G., Liu, R., De Arcangelis, V., Cox, C. L., and Xiang, Y. K. (2010) Binding of amyloid β peptide to β2 adrenergic receptor induces PKA-dependent AMPA receptor hyperactivity. *FASEB J.* **24**, 3511–3521

90. Killick, R., Ribe, E. M., Al-Shawi, R., Malik, B., Hooper, C., Fernandes, C., Dobson, R., Nolan, P. M., Lourdusamy, A., Furney, S., Lin, K., Breen, G., Wroe, R., To, A. W., Leroy, K., Causevic, M., Usardi, A., Robinson, M., Noble, W., Williamson, R., Lunnon, K., Kellie, S., Reynolds, C. H., Bazenet, C., Hodges, A., Brion, J. P., Stephenson, J., Simons, J. P., and Lovestone, S. (2014) Clusterin regulates amyloid-β toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway. *Mol. Psychiatry* **19**, 88–98

91. Vargas, L. M., Leal, N., Estrada, L. D., González, A., Serrano, F., Araya, K., Gysling, K., Inestrosa, N. C., Pasquale, E. B., and Alvarez, A. R. (2014) EphA4 activation of c-Abl mediates synaptic loss and LTP blockade caused by amyloid-β oligomers. *PLoS ONE* **9**, e92309

92. Kam, T. I., Song, S., Gwon, Y., Park, H., Yan, J. I., Im, I., Choi, J. W., Choi, T. Y., Kim, J., Song, D. K., Takai, T., Kim, Y. C., Kim, K. S., Choi, S. Y., Choi, S., Klein, W. L., Yuan, J., and Jung, Y. K. (2013) FcRIIB mediates amyloid-β neurotoxicity and memory impairment in Alzheimer’s disease. *J. Clin. Invest.* **123**, 2791–2802

93. Magdesian, M. H., Carvalho, M. M., Mendes, F. A., Saraiva, L. M., Juliano, M. A., Juliano, L., Garcia-Abreu, J., and Ferreira, S. T. (2008) Amyloid-β binds to the extracellular cysteine-rich domain of Frizzled and inhibits Wnt/β-catenin signaling. *J. Biol. Chem.* **283**, 9359–9368

94. De Felice, F. G., Vieira, M. N. N., Bomfim, T. R., Decker, H., Velasco, P. T., Lambert, M. P., Viola, K. L., Zhao, W.-Q., Ferreira, S. T., and Klein, W. L. (2009) Protection of synapses against Alzheimer’s-linked toxins: insulin signaling prevents the pathogenic binding of Aβ oligomers. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 1971–1976

95. Kim, T., Vidal, G. S., Djurisic, M., William, C. M., Birnbaum, M. E., Garcia, K. C., Hyman, B. T., and Shatz, C. J. (2013) Human LibrR2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer’s model. *Science* **341**, 1399–1404

96. Dinamarca, M. C., Weinstein, D., Monasterio, O., and Inestrosa, N. C. (2011) The synaptic protein neuropilin-1 interacts with the amyloid β-peptide. Is there a role in Alzheimer’s disease? *Biochemistry* **50**, 8127–8137

97. Hashimoto, Y., Kaneko, Y., Tsukamoto, E., Frankowski, H., Koyama, K., Kita, Y., Niikura, T., Aiso, S., Breiden, D. E., Matsuoka, M., and Nishimoto, I. (2004) Molecular characterization of neurohybrid cell death induced by Alzheimer’s amyloid-β peptides via p75NTR/PLAIDD. *J. Neurochem.* **90**, 549–558

98. Nimmrich, V., Grimm, C., Draguhn, A., Barghorn, S., Lehmann, A., Schoemaker, H., Hillen, H., Gross, G., Ebert, U., and Bruehl, C. (2008) Amyloid β oligomers (Aβ1–42 globulomer) suppress spontaneous synaptic activity by inhibition of P/Q-type calcium currents. *J. Neurosci.* **28**, 788–797

99. Origlia, N., Bonadonna, C., Rosellini, A., Leznik, E., Arancio, O., Yan, S. S., and Domenici, L. (2010) Microglial receptor for advanced glycation end product-dependent signal pathway drives β-amyloid-induced synaptic depression and long-term depression impairment in entorhinal cortex. *J. Neurosci.* **30**, 11414–11425

100. Stewart, C. R., Stuart, L. M., Wilkinson, K., van Gils, J. M., Deng, J., Halle, A., Rayner, K. J., Boyer, L., Zhong, R., Frazier, W. A., Lacy-Hulbert, A., El Khoury, J., Golenbock, D. T., and Moore, K. J. (2010) CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nat. Immunol.* **11**, 155–161