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Review

Amyloid-β oligomers synaptotoxicity: The emerging role of EphA4/c-Abl signaling in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is characterized by progressive memory loss and dementia. The strong correlation between cognitive decline and the loss of synapses supports the idea that synaptic damage is a relevant pathogenic mechanism underlying AD progression. It has been shown that amyloid beta oligomers (AβOs) induce synaptotoxicity ultimately leading to the reduction of dendritic spine density, which underlies cognitive damage. However, the signaling pathways connecting AβOs to synaptic dysfunction have not been completely elucidated. In this review, we have gathered evidence on AβOs receptors and the signaling pathways involved in synaptic damage. We make special emphasis on a new AβOs induced axis that involves the tyrosine kinase ephrin receptor A4 (EphA4) and c-Abl tyrosine kinase activation. EphA4 is a key player in homeostatic plasticity, mediating dendritic spine remodeling and retraction. AβOs aberrantly activate EphA4 leading to dendritic spine elimination. c-Abl is activated in AβOs exposed neurons and in AD patient's brain, and the inhibition of activated c-Abl ameliorates cognitive deficits in AD mouse model. The EphA4 receptor activates c-Abl intracellular signaling. Therefore EphA4 is an emerging AβOs receptor and the activation of the EphA4/c-Abl axis would explain the synaptic spine alterations found in AD.

1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia in the elderly and is characterized by the progressive decline of memory and cognitive functions. It starts with deficits in episodic memory, disorientation and impairment of judgment and reasoning. The disease gradually progresses towards profound dementia, affecting daily functions and autonomy, and eventually causing the death of the patient [1]. Despite its dramatic health and social impact there are no effective treatment options for AD [2].

The AD brain is characterized by extracellular aggregates of the amyloid β-peptide (Aβ) called senile plaques, and by neurofibrillary tangles (NTFs), which are intraneuronal aggregates of the hyperphosphorylated microtubule-associated protein tau. Both protein aggregates are linked to atrophy and to the loss of neuronal populations in regions related to memory and cognition [3]. However, neuronal death seems be a late event in the neurodegenerative process. The degeneration of neurons begins with early neuronal dysfunction (decreased synaptic plasticity and neuronal connectivity), followed by loss of synapses and the remodeling of axons and dendrites [4] (Fig. 1).

Senile plaques were first described by Alois Alzheimer while studying brain sections from a patient with dementia [5]. Many years later, the Aβ peptide was identified as the main component of these plaques [6]. Aβ is a ≈4.3 kDa amphiphilic peptide that is produced by proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases [7]. Three main Aβ peptide forms are produced, depending on the sites of γ-secretase cleavage, consisting of 38, 40 or 42 amino acids. $Aβ_{42}$ levels are particularly important because this peptide can oligomerize and form amyloid fibrils more easily than the shorter forms [8] (Fig. 1).

Familial forms of AD represent only 1% of all AD cases and are mainly caused by mutations in the genes that encode APP, presenilin 1(PS1) or presenilin 2 (PS2). PS1 and PS2 form the catalytic core of the γ-secretase complex. Mutations in APP and PS are associated with a

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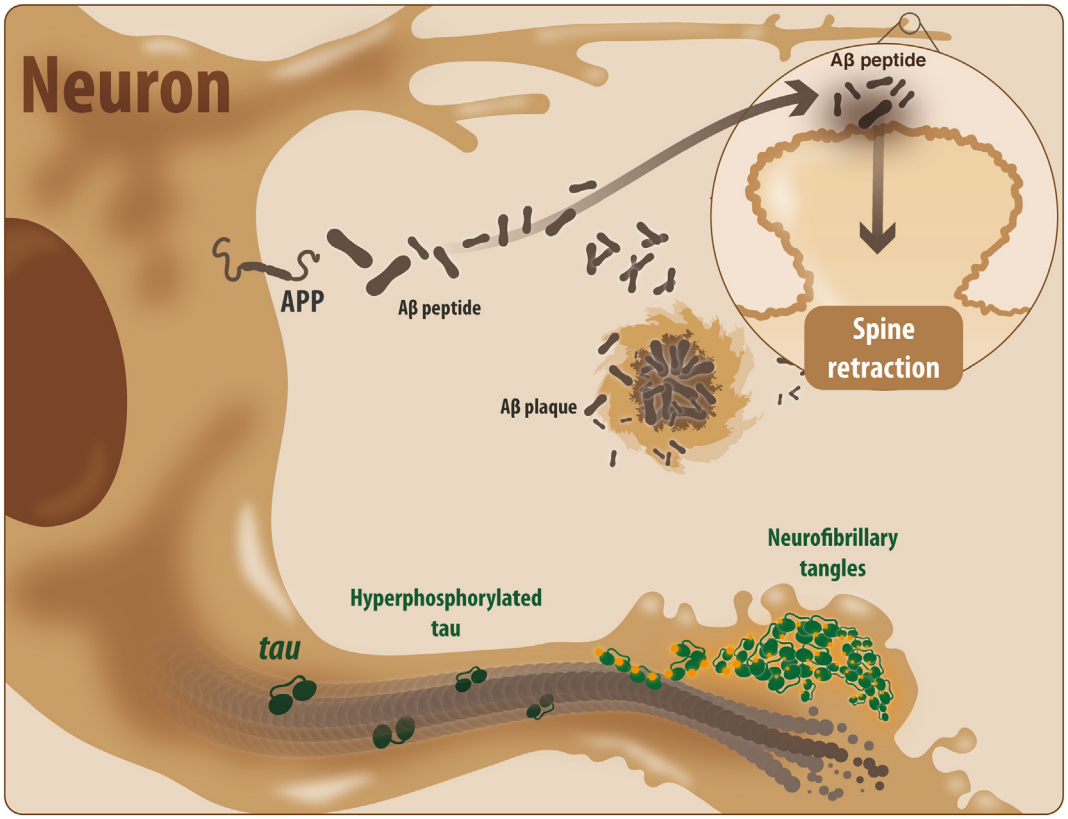

Fig. 1. Synaptic damage induced by Aβ oligomers.
The processing of the transmembrane protein APP by BACE1 and γ-secretase produces the Aβ peptide. The accumulation of Aβ peptide generates oligomeric species and subsequently the fibers that are deposited in the form senile plaques. In parallel, the alteration of kinase/phosphatase activities in neurons triggers the hyperphosphorylation of tau and the formation of neurofibrillary tangles.

higher ratio of $A\beta_{42}/A\beta_{40}$ [9]. Also, some mutations in the Aβ sequence induce oligomerization and stabilization of oligomeric forms of Aβ [10,11]. The initial Aβ aggregation occurs by the formation of toxic soluble oligomers (AβOs). Then, aggregation progresses forming insoluble Aβ fibrils (Aβf) [12] (Fig. 1) and eventually insoluble senile plaques and cerebrovascular amyloid deposits [13].

The accumulation and aggregation of Aβ peptide is thought to be the main pathological cause of AD [3]. Senile plaques are toxic causing neurons in their vicinity to degenerate and swell, generating dystrophic neurites near to plaque periphery. However, although Aβf are toxic and trigger neuronal dysfunction, cytoskeleton alterations and neuronal death [3], the soluble AβOs are considered the key pathological factors responsible for the early synaptic dysfunction and loss that underlies cognitive decline [14].

2. Synaptic plasticity in health and disease

In the healthy adult brain, synaptic plasticity is critical for learning and memory. Neurons must maintain long-term synaptic connections for the storage of information but at the same time they must remain plastic to create new memories. Thus, the formation, remodeling and elimination of spines and synapses occur as part of activity-dependent changes in neuronal connections. Long-term potentiation (LTP) and long-term depression (LTD) are two forms of functional synaptic plasticity that either increase or decrease the strength of synaptic transmission by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate ionotropic glutamate receptors (AMPARs) [15–17]. The synaptic surface expression of these receptors is regulated by signaling cascades that modulate their traffic and insertion into the synapse, a process that is also under the control of electrical activity [18,19]. In the majority of synapses, NMDAR activation is required and the level and duration of Ca^{2+} influx and the downstream signaling pathways activated, it induces either LTP or LTD.

The synaptic plasticity associated with learning and memory also implies synaptic structural changes. Therefore, although *in vivo* imaging studies show that the overall cell-specific morphology of axons and dendrites is remarkably stable, experience-dependent structural changes at the spine level occur. Boutons and dendritic spines appear and disappear, leading to synapse formation and elimination, and defining the structural plasticity [20–23]. Moreover, retraction and synapse elimination, also known as synaptic pruning, are key processes necessary for neuronal rewiring and require coordinated activity of structural and signaling molecules [24,25]. Particularly important are proteins involved in the regulation of actin filaments, which are the main cytoskeletal component of spines [26].

Functional and structural synaptic changes occur in a wide spectrum of neurodegenerative diseases, such as AD, Parkinson Disease (PD) and Huntington Disease (HD). LTP is disrupted while LTD is promoted, and the weakening of synaptic transmission is linked to synapsis retraction and elimination [27–29] In particular, AD is characterized by dysfunction of the glutamatergic synapses in the hippocampus and neocortex, which correlates with LTP impairment and the memory loss reported in AD [26,30].

3. The role of AβOs in AD synaptic changes

The experimental evidence indicates that early synaptic plasticity impairments and synapse loss are the main events that underlie memory loss and cognitive decline in AD. Indeed, the degree of dementia correlates closely with synapse loss in postmortem brains, especially in hippocampal and cortex regions associated with learning and memory. Synaptic loss in AD was first described by Davies et al.

[31], who carried out a quantitative morphometric analysis from the cortex biopsies of AD patients. They estimated that there was a synaptic loss of 25–35% of total synapses, and a 15–35% loss of synapses per neuron in cortex and hippocampus of AD brains [31]. Synaptic degeneration is observed in patients in early stages of AD, and also in those with mild cognitive impairment (MCI) [32]. Other studies confirmed that synaptic loss in frontal cortex, temporal cortex, and dentate gyrus have the strongest pathological correlation with dementia [32,33], and also revealed a similar loss of pre- and postsynaptic components [34]. Moreover, several studies show that the initial decrease in the number of synapses does not correlate with the subsequent loss of neuronal cell bodies in AD patients and in AD animal models [35,36]. These results show that the pruning of synaptic terminals precedes neuronal loss.

The compelling evidence gathered over recent years indicates that soluble AβOs are the main elements that cause early neuronal dysfunction, cytoskeleton remodeling and synaptic loss [9,37,38]. AβOs induce: i) the impairment of synaptic plasticity in cultured brain slices and in dissociated neurons; ii) a decrease in the number of dendritic spines, and synaptic weakening; iii) the inhibition of synaptic function and learning in animal models and iv) neuronal death [36,39]. Indeed, although the density of senile plaques in the AD brain does not correlate well with the degree of cognitive deterioration [36,39,40], several studies have shown a robust correlation between soluble AβOs levels and the extent of synaptic loss and severity of cognitive impairment. In AD brains AβOs are present surrounding senile plaques [41] and there is evidence that the halo of AβOs around the plaques interfere with synaptic function and causes disruption of neural circuits leading to cognitive impairment [9,14]. AD transgenic mice that overexpress Aβ, show neurological deficits and decrease in the number of synapses before they develop Aβ deposits in the brain [36]. In fact, time-lapse imaging of AD transgenic mice brains revealed that AβOs cause instability of pre- and postsynaptic structures and synaptic loss [12,42,43]. In addition, loss of dendritic spines has also been observed in the absence of senile plaques suggesting that AβOs are the main actors in the early AD stages [21]. Moreover AβOs promote the disruption of axons and dendrite trajectories, cytoskeletal alterations and neuronal loss [43].

Today, the role of AβO in triggering synapse dysfunction and the loss of spines is well recognized. However, the specific AβOs species involved in the pathology, the participating receptor(s), and the molecular mechanisms that are activated by AβOs leading to synaptic dysfunction, are still intensely debated. AβOs bind to mature pyramidal excitatory neurons, but not to GFAP-positive astrocytes. The binding of AβOs induces aberrant changes in the morphology of dendritic spines in hippocampal neurons, where irregular filopodia formation is followed by a decrease in the density of spines in neuronal processes [44,45].

One of the most relevant synaptic changes induced by AβOs is the inhibition of LTP. Soluble Aβ dimers and trimers extracted from the frontal and temporal cortices of AD patients impair glutamatergic synaptic transmission and alter LTP in mouse hippocampal slices in a NMDAR-dependent manner [46]. Moreover, *in vitro* experiments with hippocampal neurons show increased calcium entry [47]. In addition to inhibiting LTP in the cortex, it was demonstrated that AβOs facilitate evoked LTD in the CA1 region of the hippocampus through glutamatergic NMDAR and mGluR (metabotropic receptors) receptors. This induction of LTD is linked to a decrease in the volume of dendritic spines [48].

Several studies indicate that the loss of dendritic spine density associates with the decrease of key synaptic proteins. Proteomics and immunoblot analyses of tissue from the middle frontal gyrus of AD transgenic mice, showed that levels of NMDAR and AMPAR were significantly reduced compared to control mice [45,49]. More importantly, synaptosomal fractions obtained from AD human brain contain lower levels of NMDAR and AMPAR. In particular, the GluR2 subunits in the postsynaptic density (PSD) decreased to approximately 40% of control brains [50]. Because synaptic scaffolding protein PSD-95 is involved in the anchorage of AMPAR and NMDAR, many studies had focused on establishing the effect of AβOs on post-synaptic structural proteins. Even though no decrease in PSD-95 levels has been observed in synaptosomal fractions from human AD brains or in wild-type neurons acutely treated with AβOs, cultured neurons and synaptosomes from AD mice brains show a reduction in the levels of PSD-95, and decreased expression of the AMPA receptor subunit GluR1 [43,44]. Interestingly, the levels of Shank2 increased, while Shank3 protein levels decreased due to ubiquitination and degradation by the proteasome system in brains from AD transgenic mice [44,45]. In the case of presynaptic proteins, a decrease in synaptophysin has been observed in AD animal models. Interestingly, these changes in synaptic proteins occur simultaneously with the onset of cognitive damage and precede the occurrence of senile plaques.

4. Receptors and signaling pathways involved in AD synaptotoxicity

AβOs bind to dendritic processes with high affinity, suggesting that specific AβOs receptors are present in neuronal dendrites. Multiple AβOs binding partners have been described but the specificity and the relative contribution of these interactions to synaptotoxicity remain to be determined [51]. AβOs bind to various neuronal receptors, including: NMDAR [52], insulin receptor (IR) [53], PrPC receptor (PrPCR) [54], RAGE [55], GM1 ganglioside (GM1) [56], AMPAR [57], Nogo receptor [58], α7-nicotinic AChR [59], $p75^{NTR}$ [60], EphB2 receptor [61] and also the EphA4 receptor [62,63]. All these receptors have been proposed as the AβOs receptor that mediates synaptic damage (Fig. 2). Moreover, several of these receptors are able to bind different Aβ peptide species; including the Aβ monomeric form, dimers, trimers, dodecamers (Aβ*56) and protofibrils. These soluble AβOs induce neuronal death at lower concentrations than Aβf [38].

Natural and synthetic AβOs, at low concentrations, can impair synaptic plasticity and cause loss of dendritic spines in cultured brain slices or in dissociated neurons, while fibrils and monomers are comparatively inert [46,64]. Relevant receptors have been identified by direct binding to different Aβ oligomeric forms; for example AβOs have high affinity (compared with fibrils and monomers) for PrPCR [65]; in contrast, a recent report shows that the monomeric form of Aβ has higher affinity than the $Aβ_{1–40}$ or $Aβ_{1–42}$ oligomeric forms for the GM1 ganglioside [66]. The binding of $Aβ_{1–42}$ to the α7-nicotinic AChR has been well established [59], however the specific forms of Aβ that bind this receptor have not been well defined [55]. Regarding $p75^{NTR}$, it has higher affinity for monomeric Aβ than for the aggregated peptide [60]. The Nogo receptor shows similar affinities for monomeric and oligomeric forms of Aβ [58].

On the other hand, how such a diverse array of molecules is able to bind the same molecular entity is an open question. It is likely that the direct binding of AβOs to one or more of these receptors initiates signaling pathways that promote synaptic damage and elimination in AD. Moreover, because the Aβ peptide is a “sticky” molecule, there is also the possibility that synaptic damage occurs by non-specific binding of AβOs. It also been proposed that AβOs may insert directly into the neuronal membrane, causing the formation of a pore and leading to the loss of ionic homeostasis. Supporting this idea, it was reported that the Aβ peptide potently and quickly induces the perforation of neuronal membranes, triggering an increase in intracellular calcium levels [67]. There is also evidence that AβOs could be taken up by neurons from the extracellular space [68]. AβOs are internalized at the postsynaptic membrane *via* endocytosis mediated by GM1, NGFR, NMDAR, IR, frizzled receptor, PrPCR, and AMPAR [9,45,69]. The vesicular AβOs can be transported through the cytosol and fused with the endolysosomal compartments facilitating their accumulation and aggregation [70]. This situation causes endolysosomal stress and leads to membrane rupture and cell dysfunction [68]. Furthermore AβOs are

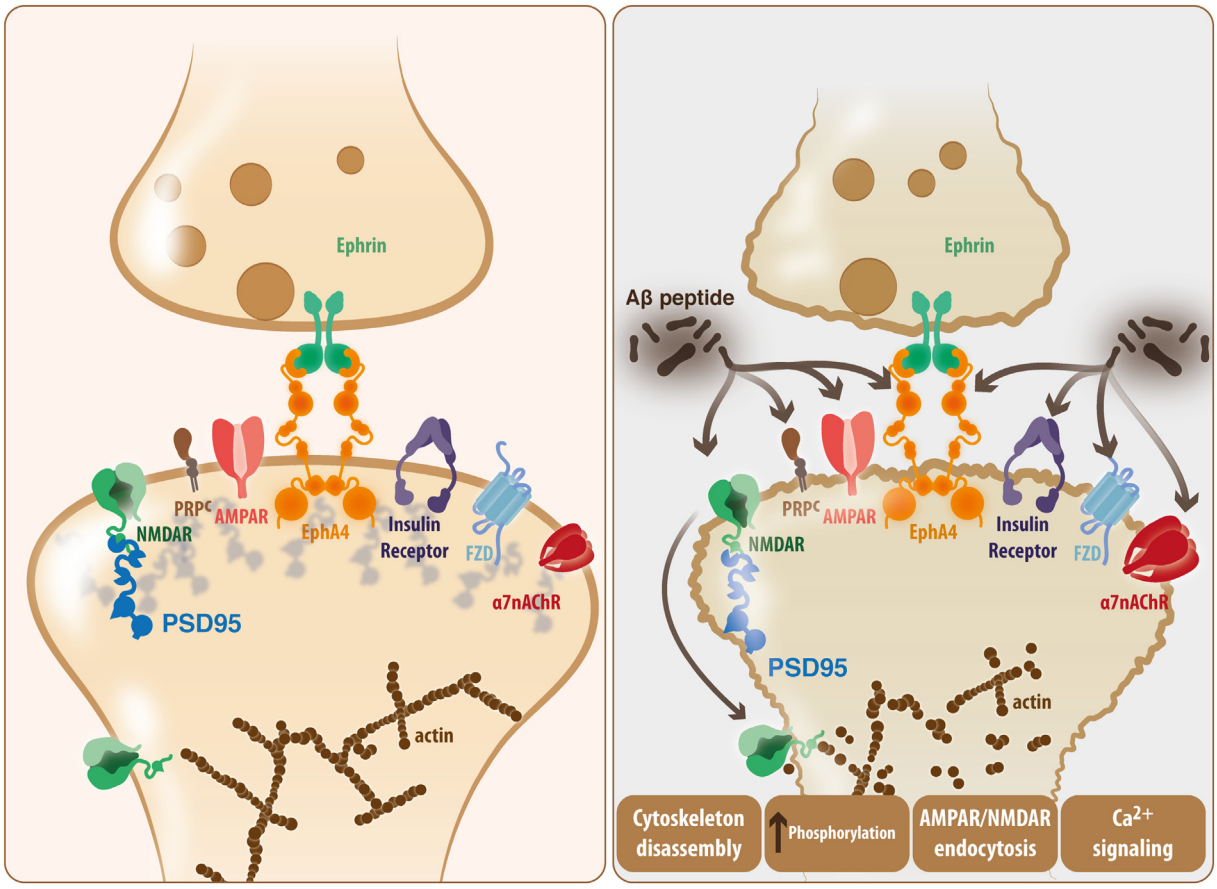

Fig. 2. AβOs bind to specific targets in the synapse.
The binding of AβOs to various receptors modulates several signaling cascades that promote key synaptotoxicity events. AβOs induce synaptic changes that lead to synaptic retraction and its subsequent elimination.

transmitted between neurons using synaptic connections. Indeed, the intracerebral inoculation of Aβ aggregates and brain extracts from AD patient's induce amyloidogenesis in AD mice models [71–73]. Intracellular soluble AβOs are transferred between anatomically connected neurons through synapses, reaching in this way distant areas of the brain [74]. Different AβOs species can propagate between neurons, but not between glial cells [75]. This transmission depends on the direct connection of axons and dendrites [76]. These results support the AD spreading hypothesis, which states that Aβ can be transferred from one area of the brain to another and that could also be transmitted between people [77,78].

However, the prevalent hypothesis is that AβOs bind to specific targets in the synapse, mediating synaptic alterations that appear very early; before any symptoms appear in the AD patients (Fig. 2). In the next section we will analyze glutamate and Eph receptors, which are key AβOs receptors present in glutamatergic synapses of the hippocampus.

4.1. The role of glutamate receptors (NMDAR and AMPAR) in synaptotoxicity

Several studies have examined the synaptic effects of AβOs on glutamate receptors. Direct binding of AβOs to NMDAR subunits has been reported in many studies [45,47,79]. As mentioned above, AβOs induce LTP inhibition and facilitates electrically evoked LTD in the CA1 region of the hippocampus, effects mediated through the NMDAR and AMPAR [13,80]. In hippocampal neurons, NMDAR antagonists prevent the synaptic spine loss and decreased NMDAR levels and activity caused by AβOs [81]. In cortical neurons, it has been described that AβOs promote NMDAR endocytosis resulting in a reduction of their cell surface levels and depression of NMDAR-evoked currents. These processes could happen before synaptic damage becomes irreversible [29].

LTD induction by AβOs appears to require signaling through activated PP2B and GSK-3β [29] and is linked to a decrease in neuronal glutamate uptake, which cause the subsequent activation of the NMDAR. Although synaptic NMDARs have been related to signaling pathways that favor neuroprotection [82], Aβ-induced synaptic dysfunction seems to be dependent on extrasynaptic NMDARs overstimulation that results in aberrant activation of cytoplasmic Ca^{2+} and redox-mediated signaling. In turn, this changes trigger downstream pathways that promote tau phosphorylation, neuronal damage pathways and proapoptotic molecules [83] Consistent with this model of Aβ-induced synaptic loss, Aβ synaptic toxicity causes the activation of caspases, Cdk5, calcineurin/PP2B, PP2A, Gsk-3β, Fyn, cofilin, and CaMKII and the endocytosis of AMPARs as well as NMDARs.

The brain of AD patients show a reduction in AMPAR levels before neurofibrillary tangles appear, suggesting that changes in AMPAR levels could be an early molecular alteration in AD [84]. In primary cultured neurons, AβOs bind to excitatory synapses sequestering into clusters AMPARs that contain GluR5 subunit, and causing local hyperexcitability and calcium increase [80]. Also, Aβ oligomeric forms interact with GluR2-containing AMPARs, inducing their endocytosis through a mechanism that involves calcineurin. The removal of AMPARs from the synaptic surface or their inhibition by antagonists reduces AβOs synaptic binding. The specific loss of GluR2-containing AMPARs causes an increase in Ca^{2+} permeability, which induces aberrant cell signaling [57].

4.2. New players in AβOs synaptotoxicity: The ephrine receptors

The tyrosine kinase ephrine receptors (Eph) are divided into two groups, EphA (1–9 types) and EphB (1–5 types) [85]. The EphA receptor binds with variable affinity to ephrinA ligands (EphrinA 1–5), which are anchored to the cell membrane by a glycosylphosphatidylinositol anchor (GPI). On the other hand, EphB binds to ephrinB ligands (EphrinB 1–3), which unlike ephrinA have a transmembrane domain and a short cytoplasmic region [85].

4.2.1. The physiological role of ephrine receptors

The Eph family of receptor tyrosine kinases and ephrin ligands, play critical roles in both the developing and the mature nervous system [86–89]. A particular characteristic of the receptors and ligands of the ephrin family is their bidirectional signaling capability, which leads to the activation of downstream signaling pathways. The expression of these proteins in pre- and postsynaptic regions is necessary for the development and stabilization of excitatory synapses [90]. Interestingly, EphB and EphA have opposing roles. EphB receptors promote dendritic spine morphogenesis, favoring the maturation of dendritic filopodial protrusions into dendritic spines [89,91–93]. Thus, the absence of EphB in hippocampal neurons induces defects in the development of dendritic spines, while the activation of EphB2 induces its interaction with NMDAR and the formation of synapses [92,94]. On the other hand, EphA4 regulates the synapse in the opposite direction. Signaling by EphA4, which is expressed on dendritic spines of pyramidal neurons, reduces spine length and density in acute hippocampal slices [95]. In a physiological context, when EphA4 (postsynaptic) is activated by its ligand ephrinA3 (astrocytes) it induces retraction of dendritic spines with the participation of Cdk5 and ephexin1, as part of their pruning. Indeed, EphA4 knockout mice have disorganized, longer, and more numerous spines than wild-type mice. During homeostatic regulation, the activation of EphA4 induces a decrease in the strength of the excitatory synapse *via* Cdk5. Additionally; EphA4 participates in homeostatic plasticity through the regulation of AMPAR levels [95–98].

4.2.2. The ephrine receptors in the pathophysiology of AD

A few years ago the Eph receptors attained relevance in several neuropathologies including AD, becoming possible therapeutic targets [99]. In AD, AβOs have been shown to decrease EphB2 levels in the membrane of hippocampal neurons after 6 h of treatment [45], which could be a direct consequence of the relationship between EphB2 and NMDAR [100]. Interestingly, it was also shown that AβOs bind to the fibronectin repeat domain of EphB2, which leads to receptor endocytosis and degradation in the proteasome. Remarkably, when expression of EphB2 is induced in the dentate gyrus of AD mice, the impairments in LTP and cognitive deficits are prevented [57]. In addition, the overexpression of EphB2 prevents the decrease of AMPAR and NMDAR levels induced by AβOs. This protective effect could be directly related to its PDZ-binding motif [61,101,102]. Recently, it was shown that the small peptide Pep63, which prevents the interaction between EphB2 and Aβ oligomeric species, preserves the levels of EphB2 and GluN2D-NMDA and improves the cognitive performance in the AD mouse model [103].

Unlike EphB2, the receptor tyrosine kinase EphA4 is associated with the loss of dendritic spines under physiological (pruning) and pathological conditions. Indeed, the activation of the EphA4 receptor was initially characterized as being associated with growth cone collapse, and was later connected with dendritic spine wakening and pruning [95,104]. In recent years, EphA4 activity has been shown to be critical for the progression motor neuron degeneration in amyotrophic lateral sclerosis (ALS) [105,106]. The inhibition of EphA4 signaling rescues the axonopathy in motor neuron degeneration models. Interestingly, higher EphA4 expression levels in ALS patients correlates with early disease onset and shorter life expectancy, while loss-of-function mutations in the EphA4 gene are associated with longer survival. Moreover, EphA4 signaling worsen neuronal damage in ischemia-reperfusion [107,108] and experimental autoimmune encephalomyelitis (EAE) models [109].

Remarkably, there is interesting evidence connecting EphA4 with AD. For example, there is a ~2-fold increase in EphA4 mRNA levels in synaptoneurosomes from AD patients. Moreover, there is increased EphA4 expression in the area surrounding senile plaques in human hippocampi [110], and increased levels of active EphA4 in AD brains [111].

We and other groups demonstrated that AβOs induce EphA4 activation, and that the inhibition or absence of this receptor in hippocampal neurons prevents synaptic loss [62,63]. In order to block the binding of AβOs to EphA4 we used a small inhibitory molecule (KYL) that binds efficiently to the ephrin-binding domain of the receptor [112]. We found that pretreatments with KYL protect from the synaptotoxicity induced by AβOs [62]. In addition, Rhynchophylline has been shown to block EphA4 signaling, preventing LTP impairment in the AD mice model. However, there are some questions about the pharmacological specificity of Rhynchophylline on EphA4 and its ability to inhibit its tyrosine kinase activity [113].

Sortilin-related receptor with LDLR class A repeats (SORLA) interacts with the EphA4 and attenuates the ephrinA1 ligand-induced clustering. Recently, has been shown that the SORLA acts as pathological EphA4 modulator, attenuating the synaptotoxic EphA4 activation and the cognitive impairment associated with Aβ-induced neurodegeneration in AD [111]. These works show the therapeutic potential of inhibiting EphA4 for different pathologies, especially AD.

In summary, a variety of specific receptors could be responsible for mediating the synaptotoxicity caused by AβOs in AD (Fig. 2). However, glutamate and Eph receptors can explain most of the pathophysiological defects and structural changes observed in the hippocampus. Nevertheless, further studies are needed to determine the relevance and contribution of each of these molecules to the pathogenesis of this disease.

5. Signaling pathways downstream of the AβOs

As previously mentioned, AβOs can aberrantly initiate intracellular pathways and thereby disrupt normal synaptic function [36]. AβOs bind to receptors in synaptic membranes and modulate downstream signaling pathways.

A characteristic consequence of Aβ aggregation is the remodeling of the cytoskeleton remodeling, which includes axon and dendrite degeneration, the development of dystrophic neurites and tau phosphorylation. These cytoskeletal alterations were reported long ago as hallmarks of AD neurodegeneration [114] and confirm that signaling pathways that regulate the cytoskeleton are important in AD pathology. It is possible that the same deregulated signaling pathways involved in cytoskeletal remodeling and tau phosphorylation are also involved in the loss of synapses and dendritic spines [114].

The most characteristic cytoskeletal alteration of AD is tau hyperphosphorylation, which is linked to the deregulation of Cdk5 and GSK3β kinases activity. The activity of these kinases is increased in AD, and their activation is induced by Aβ damage in cultured neurons [115–118]. Although both tau-phosphorylation kinases are key elements in the regulation of microtubule dynamics [119] they also play an important role in synaptic plasticity, learning and neuronal death [120]. Moreover, their deregulation has serious consequences in synapse maintenance.

Cdk5 is a small serine/threonine kinase activated by two non-cyclin activators, p35 and p39, and by Tyr15 phosphorylation [121]. It is a key regulator of cytoskeletal remodeling and intracellular signaling cascades in the brain. Thus, Cdk5 plays a critical role in normal mammalian development, and in the adult brain it is essential for maintaining homeostatic synaptic plasticity, learning and memory formation [122]. Indeed, the induction of synaptic plasticity, as well as hippocampus-dependent spatial learning, is affected in Cdk5 knockout

mice and p35/p39 double null mutants [121]. A vast majority of physiological and pathological Cdk5 substrates are associated with the remodeling of the actin cytoskeleton such as Rho GEF ephexin1 and the actin-binding protein WAVE1, which trigger the retraction of dendritic spines. Cdk5 also promotes cleavage and endocytosis of the GluN2B subunit of NMDA receptors, as well as degradation of the postsynaptic scaffold proteins PSD-95 and SPAR. All these effects lead to synaptic transmission reduction [123].

Interestingly, activated EphA4 phosphorylates Cdk5 at Tyr-15 inducing its activation and the downstream ephexin1 dependent RhoA activation that results in the retraction of dendritic spines in response to stimulation by ephrinA1 [97]. In this same line, it has been described that GluN2A is phosphorylated by Cdk5, modifying NMDA receptor conductance [124].

However, Cdk5 activity is deregulated in several neurological disorders, such as Alzheimer's disease, Parkinson's disease, Epilepsy and Huntington's disease, leading to neurotoxicity [125].

Importantly, deregulation of Cdk5 has been shown to be linked to alterations in synaptic functions and memory formation in AD. Cdk5 phosphorylates tau at several AD-specific epitopes, and has been implicated as a crucial element in the progression of neurofibrillary pathology, synaptic alterations and cognitive decline in AD [126]. Cdk5 kinase activity is significantly increased in human AD brains and in hippocampal neurons. Indeed, Aβf treatment induces Cdk5 activation, tau phosphorylation [127], synaptic dysfunction and loss [128].

GSK3β is a proline-directed serine/threonine kinase whose pathological role in AD has been widely reported [129]. GSK3β regulates various cellular processes, including glycogen metabolism, gene transcription and cell death by apoptosis [130]. More importantly, it has been implicated in the regulation of microtubule dynamics, outgrowth of neurites and synaptic plasticity, the absence of GSK3β in neurons induces instability and reduction of dendritic spines [131–133]. Different signaling pathways regulate GSK3β activity. For example, insulin and Wnt signaling inhibits GSK3β activity. In AD, GSK3β activity is deregulated and it has been proposed that loss of Wnt function contributes to AD damage progression [134].

Phosphorylated and activated GSK3β is found in frontal cortex and hippocampus of AD brains [135]. GSK3β activation is also induced by Aβ-neurotoxicity in primary cultured of neurons [136]. GSK3β phosphorylates tau at several phosphorylation sites and, therefore, plays a leading role in the hyperphosphorylation of tau. However, and more interesting for early AD pathology, GSK3β activation is involved in the mechanisms that underlie the observed impairment in learning and memory [129,131]. Moreover, when GSK3β is inhibited with pharmacological or genetic tools, cognitive decline in AD transgenic mice is prevented [137,138]. The inhibition of GSK3β has been proposed as an important target for preventing AD-related damage.

Taken together, these studies suggest that the abnormal AβOs-mediated activation of Cdk5 and GSK3β through the activation of upstream signaling molecules may initially cause synaptic dysfunction and the loss of dendritic spines. These events are followed by axonal and dendritic degeneration, the generation of dystrophic neurites, and tau phosphorylation. Interestingly, EphA4 signaling is upstream of Cdk5 whose activation engages tau phosphorylation, but also synaptic dysfunction and loss and cognitive decline in AD models.

5.1. Tyrosine kinases

Several signaling molecules that transduce receptor-activated signals are localized beneath the postsynaptic membrane where they modulate cell-cell adhesion and anchorage of scaffold proteins. Non-receptor tyrosine kinases such as Fyn and c-Abl kinases, are strategically located at the PSD of glutamatergic synapses [139], and can modulate the effects of Aβ on these synapses. Indeed, it has been described that tau can be phosphorylated at tyrosine residues by tyrosine kinases such as Fyn, Syk and c-Abl in response to Aβ [127,140].

Fyn regulates cytoskeletal dynamics during growth cone movement and the phosphorylation of tau at Tyr18 during early neuronal development. In Aβ exposed neurons Fyn phosphorylates tau at Tyr 18 facilitating the interaction of the NMDAR with PSD-95 [141] promoting the synaptic loss. Thus, the Aβ induced synaptotoxicity is prevented in hippocampal slices from Fyn knockout mice or by reduction of Fyn in AD transgenic mice [142].

6. The role of EphA4/c-Abl pathway signaling in AD synaptotoxicity

Recently, c-Abl, another member of the non-receptor tyrosine kinase family has been implicated in AD. The tyrosine kinase c-Abl is involved in neuronal signaling and cytoskeletal remodeling, playing important roles in cytoskeletal pathology and neuronal death in the AD brain and in other neurodegenerative diseases [143]. Specifically, we showed that c-Abl is activated (phosphorylated) in *in vivo* and *in vitro* AD models. The overexpression of c-Abl induces important damage in mice brains, indicating the important role of c-Abl in neurodegeneration [144].

Phosphorylated c-Abl induces the activation of the transcription factor p73, which in turn regulates proapoptotic gene expression. Additionally, c-Abl directly regulates HDAC2 levels, triggering a decrease in synaptic gene expression in AD [115,127,145,146] (Fig. 3).

6.1. c-Abl structure

The Abl kinase family members, which in mammals include c-Abl and the Abl-related gene (Arg), are key signal transducers activated by extracellular signals including growth factors, extracellular matrix and adhesion receptors activation [60,64], c-Abl kinase regulates cytoskeletal dynamics promoting cell motility and endocytosis and participating in neuronal development, neurogenesis, neuronal migration, axonal extension, and synaptic plasticity [139,147–149].

c-Abl multiple signaling functions relay on the presence of several domains in the c-Abl protein. Indeed, the kinase domain in the N-terminal region (≈60 kDa), has SH3, SH2 and catalytic kinase homology (SH1) domains like Src family members. The SH3 domain mediates the binding to ligands with PxxP motifs and the SH2 domain to phosphotyrosine at NPxY sites. Besides, the SH3 and SH2 domains interact with the kinase domain allowing an auto-inhibited conformation of c-Abl [150]. However, alike other Src tyrosine kinases, c-Abl has a large C-terminal region (90 kDa) with unique domains that includes: three nuclear localization signals (NLS) and one nuclear export signal (NES) that allow the nuclear and cytosolic localizations of this protein; four PxxP motifs and G- and F-actin binding domains (FABD) for cytoskeleton interactions; and a DNA-binding domain related to the regulation of gene expression by c-Abl [151].

6.2. c-Abl and tau

In addition to the regulation of actin dynamics in neurons; c-Abl kinase phosphorylates Tau at tyrosine 394 controlling Tau function. Moreover, tau phosphorylated at Tyr394 is present in pre-tangle neurons in AD brains supporting a pathogenic role of c-Abl in AD [152]. Furthermore, c-Abl could also modulate tau by the regulation of other tau kinases. c-Abl modulates Cdk5 kinase function during neurodevelopment [127] and we have shown that c-Abl activates Cdk5 in AD models [127]. Cdk5 is phosphorylated at tyrosine 15 (Tyr15) by c-Abl, stimulating p35/Cdk5 kinase activity [127,149]. The adaptor protein cables mediates the interaction of c-Abl and Cdk5, and this interaction seems to be fundamental for the activation of Cdk5 [149].

The changes in tau phosphorylation that occur in hippocampal neurons treated with Aβ fibrils are linked to Cdk5 activation [127]. Indeed, it has been shown that c-Abl activity is necessary for the phosphorylation of tau induced by Aβ aggregates; additionally, the interaction between Cdk5 and c-Abl increases concomitantly with the

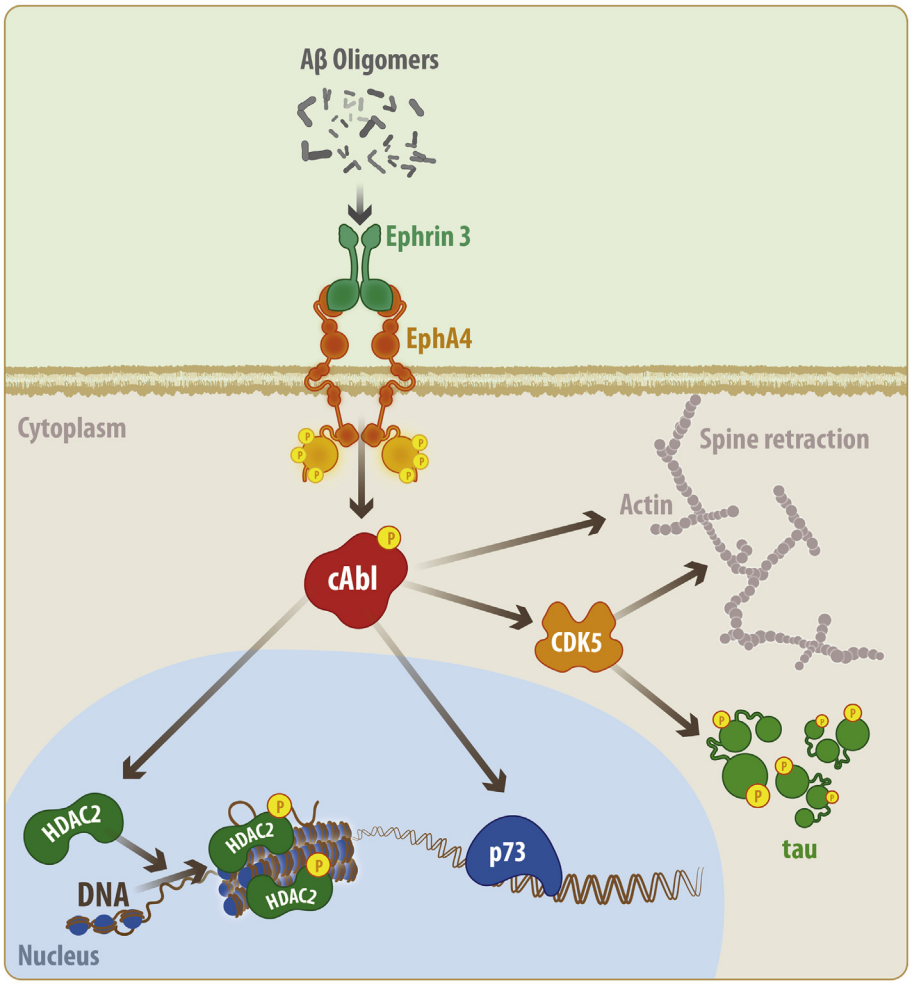

Fig. 3. AβOs bind to EphA4 leading to c-Abl intracellular signaling and synaptic loss.
The activation of EphA4/c-Abl signaling is a crucial event that mediates the synaptic damage induced by AβOs. The inhibition of EphA4 and c-Abl prevents the synaptic loss and LTP inhibition caused by Aβ oligomers. Phosphorylated c-Abl induces the activation of transcription factor p73, which in turn regulates proapoptotic gene expression. Additionally, it has been described that c-Abl directly regulates HDAC2 levels, triggering a decrease of synaptic neuronal gene expression in AD.

phosphorylation of Cdk5 by c-Abl. Moreover, when c-Abl is inhibited with Imatinib (c-Abl inhibitor) in AD mice, the levels of tau phosphorylation and phospho-Cdk5 decreased. These results indicate the main role of c-Abl in Cdk5 activation induced by Aβ neurotoxicity and tau phosphorylation in AD pathology [145].

6.3. *Effects of c-Abl on synaptic structure and function*

Relevant to synaptic plasticity, recent evidence shows that the ability of the c-Abl kinase family members to regulate neuronal cytoskeleton dynamics could be key in the regulation of synaptic structure and function [139,153]. c-Abl and Arg are widely expressed in the adult mouse brain, and both proteins are particularly concentrated in synapse-rich regions. Electrophysiological studies have suggested a role for c-Abl in the efficiency of neurotransmitter release from the presynaptic terminal, since hippocampal pulse paired-facilitation in c-Abl knockout mice is reduced [139].

Moreover, receptors and adhesion molecules that regulate c-Abl activity have been classified as key modulators of the formation and stabilization of the synapse. Adhesion molecules, such as cadherins, modulate signaling pathways in the presynaptic and postsynaptic terminals [154].

Although c-Abl kinase has been involved in neurogenesis, neuronal migration, and dendritic and axonal extension, there are few studies on its role in synaptic structure and function. However, compelling evidence places c-Abl signaling as a main regulator of the most important signaling pathways that regulate synapsis and neuronal homeostasis during synaptic plasticity. Indeed, we described that c-Abl kinase regulates PSD-95 clustering (by phosphorylating PSD95 at Y533) [155] and Cdk5 kinase activation [127]. c-Abl participates in the clustering of the acetylcholine receptor in response to Agrin through the activation of Cdk5 [156]. In adittion, Abl-interacting molecules (Abi) participate in the signaling downstream of agrin which is important for establishing morphology and number of dendritic spines [157,158]. Moreover, c-Abl function connects with several of the most important signaling proteins that regulate actin cytoskeleton and receptor trafficking. Two relevant c-Abl targets, RhoA and Cdk5 are involved in receptor and synaptic complexes endocytosis and in the shrinking and elimination of dendritic spines during synaptic plasticity [93,97]. c-Abl binds to the GluN2D subunit of NMDARs [159]. More recently, it has been shown that c-Abl regulates the morphology of dendritic protrusions and accelerates dendritic filopodial motility [153].

It has been demonstrated that signaling from transmembrane receptors such as Eph regulates the synaptic density and the morphology of dendritic spines [62,97]. Recently, we described that AβOs induce the loss of dendritic spines through EphA4 receptor and c-Abl kinase (Fig. 3). We showed for the first time the activation of EphA4 in synaptotoxicity observed in AD models. EphA4 tyrosine phosphorylation and activation were increased in cultured neurons and synaptoneurosomes exposed to AβOs, and also in AD transgenic mouse brains [62,63]. Furthermore, we demonstrated that activation of the EphA4/c-Abl pathway is a crucial signaling event that mediates the synaptic damage induced by AβOs. We also showed that the EphA4 antagonist peptide KYL and the c-Abl inhibitor Imatinib prevent: i) dendritic spine reduction; ii) blockage of LTP induction; and iii) activation of p73, which regulates proapoptotic gene expression, induced by AβOs and c-

Abl activation. Moreover, EphA4−/− neurons or sh-EphA4-transfected neurons showed reduced synaptotoxicity triggered by AβOs [62]. In addition, our results show that AβOs bind to cells overexpressing EphA4, suggesting that they may bind directly to the EphA4 receptor. Together, these results suggest that the EphA4/c-Abl signaling pathway could be relevant in the early cognitive decline observed in AD [62,63] (Fig. 3).

7. The role of c-Abl in other neurodegenerative diseases

In addition to Alzheimer's disease, we found activation of c-Abl in Niemann Pick type C disease (NPC), a neurodegenerative lipidosis [160,161]. In NPC, the c-Abl/p73 signaling pathway is activated in the cerebellum, where most of the damage occurs. We observed that in the NPC mice model there is increase in the expression of p73 pro-apoptotic targets genes. NPC mice symptoms such as weight loss, neurological damage and cerebellar apoptosis were attenuated when the mice were treated with the c-Abl inhibitor Imatinib [160]. In NPC, c-Abl activation is associated with oxidative stress triggered by the lysosomal accumulation of cholesterol [161,162].

Recently, our laboratory described that the inhibition of c-Abl by Imatinib reduces the blood load of AβO in AD transgenic mice, possibly by modulating the processing of APP Interestingly, in the case of NPC pathology we described that c-Abl activity induces specific amyloidogenic processing of APP by promoting the APP-BACE1 interaction [163,164]. c-Abl activity also triggers increased HDAC2 levels that induce neuronal gene repression in NPC models, while its inhibition induces a decrease in HDAC2 levels [165].

c-Abl is also involved in PD [166,167], ALS [168] and in neurotoxicity caused by Prion [169]. Remarkably, a small clinical trial carried out at Georgetown University Medical Center showed that the Nilotinib, a c-Abl inhibitor, improves cognition, motor skills and non-motor function in PD patients [170].

Therefore, abnormal activation of c-Abl is a common pathological mechanism that appears to be present in a number of neurodegenerative diseases. We have shown that c-Abl is a key integrator of cellular signals in response to neuronal damage and that EphA4/c-Abl signaling is relevant in the synaptotoxicity events observed in AD. Thus the EphA4/c-Abl signaling has emerged as a potential target for the development of new therapeutic options for AD patients.

8. Conclusions

AβOs-mediated damage to synapses includes binding to synaptic structures and decreased expression of receptors and structural proteins. This synaptotoxicity is primarily responsible for synaptic damage in the early stages of AD. The mechanisms involved in AD synaptotoxicity have focused on the search for receptors and/or channels that can generate adverse signaling cascades and promote synaptic loss. Several lines of evidence suggest that AβOs bind specifically and with high affinity to dendritic processes of hippocampal neurons, through AβOs receptors such as NMDAR, α7nAchR, the insulin receptor, EphB2, PrPCR, AMPAR and more recently the EphA4 receptor. These receptors bind AβOs with variable affinities and could mediate different downstream signaling cascades critical in the process of synaptic loss.

Several studies have shown the participation of intracellular signaling mediated by tyrosine kinases in the etiopathogenesis and progression of AD. Current knowledge on EphA4 and c-Abl support the idea that this pathway may have a role in synaptic damage induced by AβOs by increasing Aβ production, tau phosphorylation, loss of synaptic structures, LTP impairment and finally apoptosis. EphA4/c-Abl axis would be important aberrantly induced by AβOs, and be responsible for the widespread deregulation of synapse, dendritic spine density reduction, and neuronal death in late stages of the disease, in the areas responsible for learning and memory.

Abbreviations

AD	Alzheimer's disease
Aβ	amyloid β-peptide
NTF	neurofibrillary tangles
AβOs	amyloid beta oligomers
APP	amyloid precursor protein
Aβf	Aβ fibrils
LTP	long term potentiation
LTD	long term depression
PD	Parkinson Disease
HD	Huntington Disease
ADDL	amyloid beta-derived diffusible ligand (Aβ star 56)Aβ*56
Eph	Ephrine receptors
sNMDAR	synaptic NMDA receptors
eNMDAR	extrasynaptic NMDA receptors
IR	tyrosine kinase insulin receptor
PrP^{c}	The Prion receptor
PrP^{Sc}	infectious conformation of the prion protein
EPSCs	excitatory postsynaptic currents
nAChRs	nicotinic acetylcholine receptors
ADF	actin-depolymerizing factor

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Competing interests

The authors declare no competing interests.

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