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Dendritic Spine Loss and Synaptic Alterations in Alzheimer's Disease

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Abstract Dendritic spines are tiny protrusions along dendrites, which constitute major postsynaptic sites for excitatory synaptic transmission. These spines are highly motile and can undergo remodeling even in the adult nervous system. Spine remodeling and the formation of new synapses are activity-dependent processes that provide a basis for memory formation. A loss or alteration of these structures has been described in patients with neurodegenerative disorders such as Alzheimer's disease (AD), and in mouse models for these disorders. Such alteration is thought to be responsible for cognitive deficits long before or even in the absence of neuronal loss, but the underlying mechanisms are poorly understood. This review will describe recent findings and discoveries on the loss or alteration of dendritic spines induced by the amyloid β (Aβ) peptide in the context of AD.

Keywords Alzheimer's disease · Aβ · Aβ oligomers · Dendritic spines · Synaptic loss · Cytoskeleton · Molecular mechanisms

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Dendritic Spines: Sites for Excitatory Synaptic Transmission

Although Camillo Golgi (1843–1926) initially thought that the tiny thorn-like protrusions observed on dendrites after silver impregnation were staining artifacts, follow-up studies by Santiago Ramón y Cajal (1852–1934) demonstrated that these protrusions are genuine structures that constitute dendritic spines [1, 2]. It is now widely accepted that dendritic spines are anatomical specializations on neuronal cells that form distinct compartments that isolate input from different synapses and are essential for excitatory synaptic transmission. Several types of dendritic spines with different shapes (stubby, thin, or mushroom-shaped), volumes (0.001–1 mm^3), and contents (may contain organelles such as smooth endoplasmic reticulum and polyribosomes) have been identified [3]. These differences raise the question of whether spines have distinct functions, a question that is currently the topic of intense research. Modern microscopy such as two-photon laser scanning microscopy (2-PLSM [4]; for a review on applications in neuroscience, see [5]) has been extremely useful to address this question and allowed the imaging of dendritic spines in vivo. Studies using 2-PLSM provided compelling evidence that spines are plastic and undergo remodeling upon synaptic activity [6–9] (for a review, see [10]). Thus, combined in vivo 2-PLSM and ultrastructural analysis by electron microscopy showed the existence of two main types of spines: transient spines, which tend to be thin and small, and persistent spines, which are usually larger [11]. Spines were shown to undergo experience-dependent growth in the barrel cortex upon novel sensory experience induced by whisker trimming in rat. Spine growth was preceded by synapse formation and newly formed spines increased in volume as they became stable [12, 13]. Such change in size implies functional alterations

because the content in postsynaptic density (PSD) proteins and AMPA receptors of spines is modulated by spine head volume [14, 15]. However, the extent and impact of the functional consequences remain undefined, but may be a prerequisite for learning and memory processes.

Changes in the number of dendritic spines, be it new formation or elimination [16, 17], depend on the actin cytoskeleton (reviewed in [18, 19]). Various in vitro studies have examined the signaling pathways leading to remodeling of the cytoskeleton. Similar to most signaling cascades, these pathways are highly complex and rely on activity-dependent interactions of postsynaptic proteins and on actin polymerization and depolymerization (for a recent review about synaptic control of dendritic architecture, see [20]). Of special interest in the field of Alzheimer's disease (AD) is the regulation of actin dynamics by ionotropic glutamate receptors such as AMPA and NMDA receptors, as amyloid β peptide (Aβ) is speculated to exert its influence via these receptors (see the "Aβ-induced disturbance of synaptic signaling" and "Aβ-induced disruption of the cytoskeletal network" sections).

Synaptic Alterations in AD

AD is the most common form of dementia that causes progressive loss of cognitive and intellectual functions. The important role of Aβ in the course of AD and its deposition in the brain as β-amyloid plaques is now widely recognized and was demonstrated by numerous in vitro and in vivo studies (for a review, see [21]). However, a direct link between the amount of β-amyloid plaque deposits and behavioral symptoms has not been clearly demonstrated in transgenic mouse models of AD or in patients. This led to the hypothesis that smaller Aβ assemblies commonly known as Aβ oligomers or protofibrils, which are formed before β-amyloid fibrils, may be involved in the pathology. Several studies have now provided evidence that small Aβ assemblies might indeed be the main neurotoxic species in AD (for recent reviews on the role of Aβ oligomers in AD, see [22, 23]). But despite intense research, the mechanisms of action of Aβ oligomers remain somehow elusive. Better knowledge of these mechanisms and of the processes underlying the devastating deterioration of memory in AD patients is crucial for the development of potential therapies. Thus, the question of how Aβ oligomers influence and disturb signaling pathways involved in learning and memory is currently of high interest in the field. As cognitive deficits in animal models of AD can occur before or even in the absence of neuronal degeneration, it has been hypothesized that synapses rather than neurons are the first structures to be affected by exposure to toxic Aβ oligomers. This review will discuss recent findings suggesting that disturbance of synaptic signaling and loss or alteration of dendritic spines might be one of the first signs of AD pathology.

Synaptic Loss in AD Patients

The presence of β-amyloid plaques and tau pathology are the main criteria for a postmortem diagnosis of AD. The large size of single β-amyloid plaques (up to 100 μm in diameter) and the availability of simple staining techniques have allowed correlative studies of the number of β-amyloid plaques and the severity of premortem cognitive deficits. However, many of these studies revealed little or no correlation. For instance, Terry et al. [24] showed that synapse loss provides a much better indicator for cognitive impairment than β-amyloid plaque burden (for extensive reviews on this topic, see [25–27]). Additional postmortem studies using quantitative electron microscopy (EM) and stereological sampling in mild cognitive impairment (MCI) and early-to-mild AD patients confirmed that synapse loss is an early structural correlate in the process of AD [28, 29]. Biochemical analyses further showed that several presynaptic and postsynaptic proteins are downregulated in the brain of AD patients, in particular synaptophysin, a presynaptic vesicle membrane protein (reviewed in [30]), as well as synaptic membrane and postsynaptic proteins such as for instance synaptobrevin and synaptopodin [31, 32], suggesting substantial synaptic alterations.

Dendritic Spine Abnormalities in Transgenic Mouse Models of AD

Given the importance of synaptic loss in AD patients, several transgenic mouse models of AD have been analyzed for dendritic spine anomalies and synaptic loss. These analyses ranged from a simple determination of the level of synaptophysin and other presynaptic and postsynaptic markers, such as for instance PSD95 in brain slices by immunohistochemical staining, to more elaborate measures, such as a counting of dendritic spines in Golgi stained neurons, or the analysis of spine morphology and dynamics by EM or in vivo 2-PLSM. The ensemble of these analyses has provided consistent evidence that, despite differences in Aβ accumulation in the various transgenic mouse models analyzed, synaptic loss occurs consistently in an age-dependent manner in these models. The question of whether such loss occurs before β-amyloid plaque deposition or not, however, remains controversial. In line with the proposed toxic effect of small Aβ assemblies, a significant reduction in spine density was reported in Tg2576 and PDAPP mice long before β-amyloid plaque deposition can be detected [33–35]. Yet a study by Spires-Jones et al. reported normal spine density before β-amyloid plaque deposition in the same Tg2576 mouse model [36], possibly

because of methodological differences and due to the fact that different brain areas were analyzed. Although smaller Aβ assemblies seem to have toxic effects on spines, additional detrimental effects on dendritic morphology caused by β-amyloid plaques cannot be excluded. Indeed, recent studies in Tg2576 and PSAPP AD mouse models showed a spatial correlation between dendritic abnormalities such as spine loss and β-amyloid deposits [37–40] and increased spine elimination in the immediate vicinity of β-amyloid plaques [36]. However, Spires-Jones et al. also described reduced spine density and plasticity less close to β-amyloid plaques, and an increase in aspiny dendrites in young transgenic mice, indicating that the detrimental effects might still be partly because of soluble Aβ. Additional evidence that soluble rather than deposited Aβ is the culprit for synaptic loss has been provided by other groups, reporting synaptic loss in aged plaque-bearing transgenic mice even in regions devoid of extracellular Aβ deposits [39, 41–44]. It should be noted that, in humans, the pathological events leading to AD are by far more complex than that modeled in animals. Thus, besides β-amyloid plaques and Aβ oligomers, neurofibrillary tangles formed from hyperphosphorylated protein tau significantly contribute to the disease and may also participate in synaptic loss. Furthermore, mitochondrial dysfunction has been shown to play an important role in AD pathology (for a recent review, see [45]). Besides an increase in oxidative stress, such mitochondrial alteration might also affect the function and plasticity of spines, as dendritic mitochondrial contributions are essential but limited for the support of synapses [46].

Molecular Mechanisms I: Aβ-induced Disturbance of Synaptic Signaling

Studies on changes in dendritic spine in AD models described so far have addressed morphological and biochemical alterations, but these changes have also been shown to have strong functional consequences. Early disturbance in synaptic processes involved in learning and memory have been reported in several transgenic mouse models (for recent extensive reviews, see [22, 23, 47, 48]). Electrophysiological measurements of long-term potentiation (LTP), a mechanistic model of synaptic strength and plasticity, showed that Aβ oligomers can disrupt or disturb these molecular processes [49–54]. Several reports further demonstrated that infusion of small Aβ assemblies directly into the brain can rapidly disrupt learned behavior and impair cognitive functions but does not lead to any permanent neurological deficit in animal models [55, 56]. These studies suggest a direct negative effect of Aβ oligomers on synaptic signaling, which precise mechanisms remain not fully understood but have recently been further clarified.

Aβ Oligomers Affect the Number and Functions of Neurotransmitter Receptors

Although disturbances of synaptic signaling may result from a general disruption of the membrane provoked by the formation of pores by Aβ [57], growing evidence indicates a direct interaction of Aβ with postsynaptic receptors such as NMDA, AMPA, or α-7 nicotinic acetylcholine (nACh) receptors. Using a preparation of soluble Aβ oligomers known as ADDLs, Klein et al. showed that Aβ oligomers specifically target excitatory synapses containing NMDA receptors in hippocampal neurons [58, 59]. Continued exposure to ADDLs altered spine morphology and decreased spine density. Upon binding to the postsynaptic membrane, ADDLs rapidly decreased the number of NMDA receptors at the membrane [59]. These findings are in line with the demonstration that Aβ can regulate NMDA receptor trafficking and reduce the surface expression of the receptor by increasing endocytosis, an effect that is partially blocked by a nACh receptor antagonist [60]. Further support for the involvement of NMDA receptors was provided by three additional studies [61–63]. One of these studies demonstrated that exposure to physiological concentrations of naturally secreted Aβ oligomers induces a loss of dendritic spines in rat organotypic slices [61]. This loss could be prevented by prolonged application of an NMDA receptor antagonist, which alone had no effect on spine density, indicating that NMDA receptor activity is required for Aβ oligomer toxicity. Structural analyses of presynaptic and postsynaptic morphology of cultured hippocampal neurons incubated with cell-derived Aβ oligomers further revealed a rapid decrease in size and number of presynaptic markers and dendritic spines that was blocked by an antagonist of the NMDA or nACh receptor [62]. Finally, the analysis of the effect of Aβ on the number of NMDA receptors in primary neurons and brain extracts from APP transgenic mice also showed a significant decrease of surface NMDA receptor in postsynaptic density preparations [63]. A similar reduction in the surface expression of the AMPA receptor upon Aβ exposure was also reported [64]. By using an efficient set of transfection assays in organotypic slice cultures, Hsieh et al. demonstrated that Aβ triggers synaptic AMPA receptor endocytosis, which reduces the number of surface AMPA receptors and leads to dendritic spine loss. These findings support previous reports that Aβ reduces the level of AMPA receptor and postsynaptic density protein 95 (PSD-95) in neuronal cultures [65, 66] and in a double knock-in mouse model of AD [67].

These profound alterations in the composition and structure of the postsynaptic compartment have severe functional consequences. Electrophysiological recordings assessing synaptic strength demonstrated a general reduction

in miniature excitatory postsynaptic currents (mEPSCs) amplitude [61, 62, 64], in NMDA receptor and AMPA receptor currents [60, 61, 67], and in calcium influx [61], all indicating decreased synaptic strength. These changes share parallels with long-term depression (LTD), a form of synaptic plasticity that reflects a weakening of synaptic transmission and that has been recently shown to restructure synaptic contacts [68]. Thus, a shift toward synaptic depression, indicative of an inhibitory effect of Aβ, is in line with the observed memory impairment and lower LTP induction in transgenic mouse models of AD. However, a recent report suggested that the effect of Aβ is more complex. APP transgenic mice carrying various familial AD mutations showed an aberrant increase in excitatory neuronal activity leading to nonconvulsive seizures [69], indicating an excitatory effect of Aβ. Yet at the same time, downregulation of functional synaptic AMPA and NMDA receptors and structural changes in inhibitory circuits were observed and interpreted as compensatory inhibitory mechanisms to overexcitation [69]. Although interesting, this hypothesis will need more work to be confirmed.

Altered Downstream Signaling and Immediate Early Genes

Changes in neurotransmitter receptor functions might entail activity changes of various downstream signaling molecules. Calcium-dependent enzymes, in particular, are likely to be affected by Aβ, whether Aβ has excitatory or inhibitory effects on these receptors. Many protein kinases and phosphatases such as calcium/calmodulin-dependent kinase II (CaMKII) and calcineurin belong to this class of enzymes. One of the first steps in signaling cascades involved in learning and memory involves changes in the phosphorylation and activity of various key players. The balance between protein kinases and phosphatases is critical for signal transmission and a shift in this balance has a strong impact on the efficiency of transmission. A substantial change in protein phosphatase activity has been observed in humans and rodents during normal aging and has been associated with AD [70]. The hyperphosphorylation of tau that ultimately leads to the formation of neurofibrillary tangles has raised the possibility that protein phosphatases are also involved in AD etiology through tau. Tau phosphatases such as PP2A are downregulated in AD patients (reviewed in [71]). Although a general decrease in phosphatase activity could account for tau pathology in AD, a more complex role of phosphatases is emerging. Increased activation of calcineurin (also known as PP2B) has been observed in AD patients [72, 73] and the role of this protein phosphatase has recently gained interest. Calcineurin is involved in Aβ-mediated downregulation of NMDA receptors [60], AMPA receptor internalization [64], and spine loss [61]. Consistently, Aβ-mediated inhibition of LTP through calcineurin-dependent mechanisms was reported in rat hippocampal slices [74]. Similarly, protein phosphatase 1 (PP1), a major negative regulator of synaptic plasticity, was recently shown to be involved in Aβ-mediated toxicity in APP transgenic mice, and PP1 inhibition can rescue the negative effect of Aβ on synaptic plasticity [54].

Changes in protein kinase activity have also been linked with AD pathology, in particular with tau hyperphosphorylation. GSK3β, a major tau kinase, is activated by Aβ (reviewed in [75]). It may phosphorylate full-length APP and thereby alter Aβ production [76] and can modulate LTP and LTD [77, 78]. Cyclin-dependent kinase 5 (Cdk5), p21-activated kinase (PAK), and CaMKII are additional protein kinases of major interest in the field of AD. Cdk5 not only phosphorylates tau (reviewed in [79]), but is also involved in the production of intraneuronal Aβ [80]. Furthermore, Cdk5/p25 plays an important role in the regulation of synapse formation, making it an even more interesting candidate for AD. Whether its activity increases the number of dendritic spines and promotes synaptogenesis [81, 82] or causes dendritic spine retraction [83] and NMDA receptor degradation [84] seems however to depend on the cellular context. The activity of PAK is reduced in Aβ oligomer-treated hippocampal neurons and in Tg2576 mice [85] (see the "Aβ-induced disruption of the cytoskeletal network" section). As the loss of PAK in transgenic mice reduces the number of dendritic spines [86], such reduction in PAK activity in AD might contribute to the observed spine loss. CaMKII is another tau kinase whose phosphorylation and activity are decreased in the brain of AD patients and AD mouse models as well as in primary hippocampal neurons exposed to Aβ [54, 87, 88]). The property of CaMKII to act as a primary initiator of signaling cascades underlying LTP (for a recent review, see [89]) may thus contribute to the LTP impairment induced by Aβ.

An alteration in the kinases/phosphatases balance further influences additional downstream factors regulated by protein phosphorylation including the cAMP response element-binding protein (CREB). CREB phosphorylation is decreased by Aβ in AD patients [90], transgenic mouse models [91], as well as in cultured neurons [60, 92, 93] and hippocampal slices [91, 94]. As phosphorylated CREB acts as a transcription factor, reduced phosphorylation can ultimately lead to changes in gene expression. Microarray analyses have revealed long-lasting expression alterations of numerous candidate genes in AD patients and transgenic mouse models (for a review, see [95]). Furthermore, the expression of immediate early genes (IEGs), known to be rapidly induced in an activity-dependent manner during learning and memory, is affected in AD mouse models [96, 97]. The IEG Arc/Arg3.1, in particular, is an established marker of neuronal activity whose expression is robustly

induced upon synaptic activity and its mRNA rapidly transported to dendritic processes for local translation (for a current review, see [98]). Several recent studies demonstrated its importance in synaptic plasticity [99–102]. Arc/Arg3.1 regulates AMPA receptor trafficking by increasing endocytosis which reduces its surface expression and AMPA receptor-mediated synaptic currents (see also [98]). This somewhat counterintuitive effect was postulated to reflect a homeostatic mechanism that maintains synaptic strength within a physiological range after enhanced activity to allow subsequent change in synaptic transmission. Thus, a disruption of Arc/Arg3.1 expression, whether toward an upregulation or downregulation, alters homeostasis and severely impairs memory [98]. It is interesting to note that both phenomena have been observed in relation to AD. Whereas an acute exposure to Aβ oligomers increases Arc/Arg3.1 expression in primary neuronal cultures [58], a long exposure diminishes Arc/Arg3.1 expression in basal conditions and its induction after learning in transgenic mice [54, 69, 97, 103, 104] and AD patients [105].

Molecular Mechanisms II: Aβ-induced Disruption of the Cytoskeletal Network

As spine dynamics is highly dependent on the cytoskeletal network, a change in dendritic spine structures upon Aβ exposure is likely to involve the activity of actin-remodeling proteins (for a recent review, see [10]). One likely candidate is the actin-binding protein cofilin. Binding of active cofilin along actin filaments increases the removal of actin monomers from the sharp end of the filaments and enhances filament severing and depolymerization. Several pieces of evidence point to a role for cofilin in AD pathology. In AD patients and transgenic mouse models, the overall level of cofilin is altered (reviewed in [106]). Furthermore, the expression of an inactivated form of cofilin or a specific competitor for cofilin phosphorylation in culture increases spine density and prevents the loss of dendritic spines upon exposure to Aβ oligomers [61, 107]. Cofilin also forms one of the components of Hirano bodies, intracellular aggregates of actin, and actin-associated proteins which accumulate in the brain of AD patients [108] that may disturb neuronal functions. Although these findings overall indicate that cofilin is associated with AD, it is not known how exactly Aβ affects cofilin function. One potential mechanism may involve protein kinases and phosphatases. Cofilin activity is abolished upon phosphorylation by various kinases including CaMKII and PAK/LIM kinase and restored upon dephosphorylation by the protein phosphatases calcineurin, PP1, and slingshot (reviewed in [20, 106]) whose activities are altered by Aβ (see the "Altered downstream signaling and immediate early genes" section). Cofilin has also recently been shown to be involved in LTP by the demonstration that theta-burst stimulation increases both phospho-cofilin and phosphor-PAK in spines and enlarges synapses in hippocampal slices [109]. Furthermore, the number of spines containing phospho-cofilin increases after exposure to a novel environment [110]. A recent report showing that the synthesis of Arc/Arg3.1 maintains cofilin phosphorylation during LTP [111], further supports the hypothesis that altered signaling affects the actin cytoskeleton.

Another major actin-binding protein tightly linked with cofilin is the protein drebrin. Drebrin stabilizes filamentous actin and is required for the accumulation of PSD95. A profound loss of drebrin has been reported in the brains of AD patients, in several transgenic mouse models, and in primary neurons exposed to Aβ oligomers (for a recent review, see [112]). This loss is accompanied by increased binding of cofilin, suggesting a competitive relationship between the two proteins [85, 113]. Drebrin has also been shown to be involved in synaptic targeting of NMDA receptors and downregulation of drebrin in cultured hippocampal neurons reduced spine density and spine widths, indicating an important role of drebrin in spine morphology regulation [114].

Aβ-induced Disturbances are Partially Reversible and can be Prevented by Pharmacological Manipulations

Although the alteration in synaptic signaling and the cytoskeletal network induced by Aβ are profound, these disturbances can be partially rescued, at least at an early stage, using various strategies. Targeting Aβ with antibodies is one of the most promising current therapeutic approaches that are already under evaluation in clinical trials. Several groups including ours have shown a beneficial effect of passive immunization on cognitive functions and LTP in rodents, even after a single antibody administration [54, 115]. Furthermore, active and passive immunization were shown to protect against the progressive loss of synaptophysin [115]. Spine loss in neuronal cultures can be prevented by Aβ-specific antibodies [61, 116], and the simple removal of Aβ from the culture medium by washing has been shown to be sufficient for spine recovery [62, 117]. Moreover, in line with the hypothesis that Aβ oligomers interact with neurotransmitter receptors, recent experiments using NMDA or nACh receptor antagonists confirmed that the initial toxic effect of Aβ is reversible and can be prevented. Whereas a complete blockade of NMDA or nACh receptors prevented Aβ oligomer-mediated spine loss or attenuated their negative effect [60–62], a partial blockade of NMDA receptors was shown to mimic Aβ oligomer toxicity, a phenomenon that

might be explained by the activation of LTD pathways because of lower calcium influx [61]. It is interesting to note that memantine, one of the few currently available drugs for the treatment of AD, acts as an NMDA receptor antagonist. When applied to neuronal cultures exposed to Aβ oligomers, memantine was shown to prevent dendritic spine loss [59, 62], providing a possible mechanism for its beneficial effect in AD patients.

Pharmacological inhibition of proteins further downstream of neurotransmitter receptors has also been reported to protect from Aβ toxicity. The protein phosphatase inhibitors FK506 and cyclosporin can restore or prevent Aβ oligomer-mediated effects [60, 61, 64, 74]. The systemic administration of FK506 in Tg2567 mice has also recently been shown to improve memory formation [118]. Similarly, the pharmacological inhibition of PP1 reverses LTP deficits in APP transgenic mice and genetic PP1 inhibition confers resistance to Aβ oligomer toxicity [54].

Conclusions

Understanding the mechanisms of Aβ-mediated toxicity is a prerequisite for the development of efficient and safe therapeutic approaches to treat AD. The data summarized in this review provide increasing evidence that Aβ exerts its toxic effect by disrupting synaptic signaling, leading to dendritic spine loss and synaptic alterations, which ultimately result in cognitive dysfunctions. Recent findings have proposed a direct interaction of Aβ with postsynaptic receptors, triggering a signaling cascade that shares remarkable similarities with LTD (see Fig. 1). An alteration of the kinases/phosphatases balance upon Aβ exposure could explain some of the changes observed at a synaptic level. Kinases and phosphatases influence the cycling, insertion, and conductance of postsynaptic receptors such as AMPA receptors, affect the activity of actin-remodeling proteins such as cofilin and drebrin, and also exert influence on gene transcription by activating/deactivating transcription factors such as CREB.

When sketched in a simplified view, some of the mechanisms in AD pathology may involve the pathways shown in Fig. 1. LTP is associated with a large influx of calcium, activation of CaMKII via calcium/calmodulin, and phosphorylation of multiple downstream targets. Among these targets, CaMKII-dependent phosphorylation of AMPA receptors alters the receptor's conductance, whereas cofilin phosphorylation prevents its binding to the actin cytoskeleton, and enables drebrin to remain bound and stabilize the cytoskeleton. Phosphorylation of the transcription factor CREB also occurs through various protein kinases including CaMKIV that may depend on calcium/calmodulin or on active CaMKII. Binding of phosphorylated CREB to DNA may then activate the transcription of IEGs, which in turn

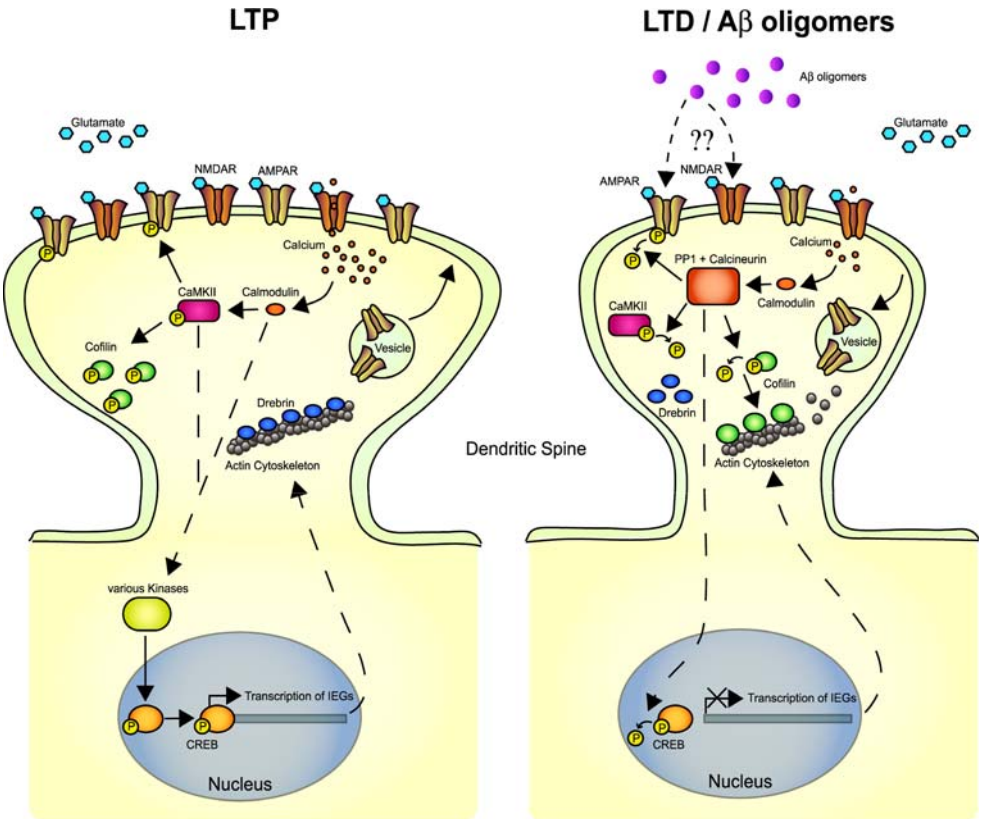

Fig. 1 A simplified schematic representation of major events occurring in dendritic spines upon LTP (*left*) or LTD/Aβ oligomer exposure (*right*). Although there is increasing evidence that Aβ oligomers may trigger signaling cascades similar to LTD, the actual binding partners at the postsynaptic membrane (for instance NMDAR and AMPAR) remain under discussion. For a detailed description of the signaling cascade, see the main text. *LTP* long-term potentiation, *LTD* long-term depression, *CaMKII* calcium/calmodulin-dependent kinase II, *CREB* cAMP response element-binding protein, *IEGs* immediate early genes, *NMDAR* *N*-methyl-D-aspartate receptor, *AMPAR* α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor, *PP1* protein phosphatase 1. *Solid arrows* show direct interaction, *dashed arrows* show indirect or unknown interactions

influence the actin cytoskeleton through yet unknown mechanisms. Finally, LTP-associated conditions enhance the insertion of AMPA receptors into the postsynaptic membrane, resulting in synaptic strengthening.

In contrast, conditions that initiate LTD lead to a mild influx of calcium and the activation of the protein phosphatases calcineurin and PP1. Once active, these phosphatases inactivate CaMKII, reduce the conductance of AMPA receptors, and dephosphorylate CREB, thus blocking the initiation of IEGs transcription. Furthermore, dephosphorylation of cofilin by calcineurin and PP1 promotes its binding to the actin cytoskeleton where cofilin displaces the actin-stabilizing protein drebrin and severs the filaments. These events, together with the increased endocytosis of AMPA receptors, overall weaken synapses and cause spine shrinkage. Although the initial interaction partner or partners of Aβ oligomers have not been identified with certainty, the current data strongly suggest that exposure to Aβ oligomers results in similar pathway as LTD.

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References

1. Glickstein M (2001) Ramón y Cajal, Santiago. Encyclopedia of life sciences. Wiley, Chichester. Available at http://www.els.net
2. Mazzarello P (2001) Golgi, Camillo. Encyclopedia of life sciences. Wiley, Chichester. Available at http://www.els.net
3. Nimchinsky EA, Sabatini BL, Svoboda K (2002) Structure and function of dendritic spines. Annu Rev Physiol 64:313–353
4. Denk W, Strickler JH, Webb WW (1990) Two-photon laser scanning fluorescence microscopy. Science 248:73–76
5. Svoboda K, Yasuda R (2006) Principles of two-photon excitation microscopy and its applications to neuroscience. Neuron 50:823–839
6. Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K (2002) Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420:788–794
7. Grutzendler J, Kasthuri N, Gan WB (2002) Long-term dendritic spine stability in the adult cortex. Nature 420:812–816
8. Mizrahi A, Crowley JC, Shtoyerman E, Katz LC (2004) High-resolution in vivo imaging of hippocampal dendrites and spines. J Neurosci 24:3147–3151
9. Majewska AK, Newton JR, Sur M (2006) Remodeling of synaptic structure in sensory cortical areas in vivo. J Neurosci 26:3021–3029
10. Alvarez VA, Sabatini BL (2007) Anatomical and physiological plasticity of dendritic spines. Annu Rev Neurosci 30:79–97
11. Holtmaat AJ, Trachtenberg JT, Wilbrecht L, Shepherd GM, Zhang X, Knott GW, Svoboda K (2005) Transient and persistent dendritic spines in the neocortex in vivo. Neuron 45:279–291
12. Holtmaat A, Wilbrecht L, Knott GW, Welker E, Svoboda K (2006) Experience-dependent and cell-type-specific spine growth in the neocortex. Nature 441:979–983
13. Knott GW, Holtmaat A, Wilbrecht L, Welker E, Svoboda K (2006) Spine growth precedes synapse formation in the adult neocortex in vivo. Nat Neurosci 9:1117–1124
14. Harris KM, Stevens JK (1989) Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. J Neurosci 9:2982–2997
15. Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen OP (1999) Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nat Neurosci 2:618–624
16. Zuo Y, Yang G, Kwon E, Gan WB (2005) Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex. Nature 436:261–265
17. Zuo Y, Lin A, Chang P, Gan WB (2005) Development of long-term dendritic spine stability in diverse regions of cerebral cortex. Neuron 46:181–189
18. Sekino Y, Kojima N, Shirao T (2007) Role of actin cytoskeleton in dendritic spine morphogenesis. Neurochem Int 51:92–104
19. Matus A (2005) Growth of dendritic spines: a continuing story. Curr Opin Neurobiol 15:67–72
20. Schubert V, Dotti CG (2007) Transmitting on actin: synaptic control of dendritic architecture. J Cell Sci 120:205–212
21. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297:353–356
22. Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 8:101–112
23. Walsh DM, Selkoe DJ (2007) A beta oligomers—a decade of discovery. J Neurochem 101:1172–1184
24. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 30:572–580
25. Scheff SW, Price DA (2006) Alzheimer's disease-related alterations in synaptic density: neocortex and hippocampus. J Alzheimer's Dis 9:101–115
26. Masliah E, Crews L, Hansen L (2006) Synaptic remodeling during aging and in Alzheimer's disease. J Alzheimer's Dis 9:91–99
27. Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. Science 298:789–791
28. Scheff SW, Price DA, Schmitt FA, Mufson EJ (2006) Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 27:1372–1384
29. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ (2007) Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology 68:1501–1508
30. Honer WG (2003) Pathology of presynaptic proteins in Alzheimer's disease: more than simple loss of terminals. Neurobiol Aging 24:1047–1062
31. Reddy PH, Mani G, Park BS, Jacques J, Murdoch G, Whetsell W Jr, Kaye J, Manczak M (2005) Differential loss of synaptic proteins in Alzheimer's disease: implications for synaptic dysfunction. J Alzheimer's Dis 7:103–17, discussion 173–80
32. Ingelsson M, Fukumoto H, Newell KL, Growdon JH, Hedley-Whyte ET, Frosch MP, Albert MS, Hyman BT, Irizarry MC (2004) Early Abeta accumulation and progressive synaptic loss,

gliosis, and tangle formation in AD brain. Neurology 62:925–931
33. Jacobsen JS, Wu CC, Redwine JM, Comery TA, Arias R, Bowlby M, Martone R, Morrison JH, Pangalos MN, Reinhart PH, Bloom FE (2006) Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 103:5161–5166
34. Wu CC, Chawla F, Games D, Rydel RE, Freedman S, Schenk D, Young WG, Morrison JH, Bloom FE (2004) Selective vulnerability of dentate granule cells prior to amyloid deposition in PDAPP mice: digital morphometric analyses. Proc Natl Acad Sci USA 101:7141–7146
35. Lanz TA, Carter DB, Merchant KM (2003) Dendritic spine loss in the hippocampus of young PDAPP and Tg2576 mice and its prevention by the ApoE2 genotype. Neurobiol Dis 13:246–253
36. Spires-Jones TL, Meyer-Luehmann M, Osetek JD, Jones PB, Stern EA, Bacskai BJ, Hyman BT (2007) Impaired spine stability underlies plaque-related spine loss in an Alzheimer's disease mouse model. Am J Pathol 171:1304–1311
37. Grutzendler J, Helmin K, Tsai J, Gan WB (2007) Various dendritic abnormalities are associated with fibrillar amyloid deposits in Alzheimer's disease. Ann N Y Acad Sci 1097:30–39
38. Dong H, Martin MV, Chambers S, Csernansky JG (2007) Spatial relationship between synapse loss and beta-amyloid deposition in Tg2576 mice. J Comp Neurol 500:311–321
39. Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, Bacskai BJ, Hyman BT (2005) Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. J Neurosci 25:7278–7287
40. Tsai J, Grutzendler J, Duff K, Gan WB (2004) Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat Neurosci 7:1181–1183
41. Alpar A, Ueberham U, Bruckner MK, Seeger G, Arendt T, Gartner U (2006) Different dendrite and dendritic spine alterations in basal and apical arbors in mutant human amyloid precursor protein transgenic mice. Brain Res 1099:189–198
42. Rutten BP, Van der Kolk NM, Schafer S, van Zandvoort MA, Bayer TA, Steinbusch HW, Schmitz C (2005) Age-related loss of synaptophysin immunoreactive presynaptic boutons within the hippocampus of APP751SL, PS1M146L, and APP751SL/PS1M146L transgenic mice. Am J Pathol 167:161–173
43. Moolman DL, Vitolo OV, Vonsattel JP, Shelanski ML (2004) Dendrite and dendritic spine alterations in Alzheimer models. J Neurocytol 33:377–387
44. Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L (2000) High-level neuronal expression of abeta 1–42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci 20:4050–4058
45. Hauptmann S, Scherping I, Drose S, Brandt U, Schulz KL, Jendrach M, Leuner K, Eckert A, Muller WE (2008) Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol Aging (in press)
46. Li Z, Okamoto K, Hayashi Y, Sheng M (2004) The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119:873–887
47. Palop JJ, Chin J, Mucke L (2006) A network dysfunction perspective on neurodegenerative diseases. Nature 443:768–773
48. McGowan E, Eriksen J, Hutton M (2006) A decade of modeling Alzheimer's disease in transgenic mice. Trends Genet 22:281–289
49. Hartley DM, Walsh DM, Ye CP, Diehl T, Vasquez S, Vassilev PM, Teplow DB, Selkoe DJ (1999) Protofibrillar intermediates of amyloid beta-protein induce acute electrophysiological changes and progressive neurotoxicity in cortical neurons. J Neurosci 19:8876–8884
50. Chen QS, Kagan BL, Hirakura Y, Xie CW (2000) Impairment of hippocampal long-term potentiation by Alzheimer amyloid beta-peptides. J Neurosci Res 60:65–72
51. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ (2002) Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416:535–539
52. Wang HW, Pasternak JF, Kuo H, Ristic H, Lambert MP, Chromy B, Viola KL, Klein WL, Stine WB, Krafft GA, Trommer BL (2002) Soluble oligomers of beta amyloid (1–42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus. Brain Res 924:133–140
53. Klyubin I, Walsh DM, Cullen WK, Fadeeva JV, Anwyl R, Selkoe DJ, Rowan MJ (2004) Soluble Arctic amyloid beta protein inhibits hippocampal long-term potentiation in vivo. Eur J Neurosci 19:2839–2846
54. Knobloch M, Farinelli M, Konietzko U, Nitsch RM, Mansuy IM (2007) Abeta oligomer-mediated long-term potentiation impairment involves protein phosphatase 1-dependent mechanisms. J Neurosci 27:7648–7653
55. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, Ashe KH (2005) Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nat Neurosci 8:79–84
56. Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH (2006) A specific amyloid-beta protein assembly in the brain impairs memory. Nature 440:352–357
57. Demuro A, Mina E, Kayed R, Milton SC, Parker I, Glabe CG (2005) Calcium dysregulation and membrane disruption as a ubiquitous neurotoxic mechanism of soluble amyloid oligomers. J Biol Chem 280:17294–17300
58. Klein WL (2006) Synaptic targeting by Abeta oligomers (ADDLS) as a basis for memory loss in early Alzheimer's disease. Alzheimer's and Dementia 2:43–55
59. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, Klein WL (2007) Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J Neurosci 27:796–807
60. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P (2005) Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 8:1051–1058
61. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL (2007) Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci 27:2866–2875
62. Calabrese B, Shaked GM, Tabarean IV, Braga J, Koo EH, Halpain S (2007) Rapid, concurrent alterations in pre- and postsynaptic structure induced by naturally-secreted amyloid-beta protein. Mol Cell Neurosci 35:183–193
63. Dewachter I, Filipkowski RK, Priller C, Ris L, Neyton J, Croes S, Terwel D, Gysemans M, Devijver H, Borghgraef P, Godaux E, Kaczmarek L, Herms J, Van Leuven F (2007) Deregulation of NMDA-receptor function and down-stream signaling in APP [V717I] transgenic mice. Neurobiol Aging (in press)
64. Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R (2006) AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron 52:831–843
65. Almeida CG, Tampellini D, Takahashi RH, Greengard P, Lin MT, Snyder EM, Gouras GK (2005) Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. Neurobiol Dis 20:187–198
66. Roselli F, Tirard M, Lu J, Hutzler P, Lamberti P, Livrea P, Morabito M, Almeida OF (2005) Soluble beta-amyloid1–40

induces NMDA-dependent degradation of postsynaptic density-95 at glutamatergic synapses. J Neurosci 25:11061–11070
67. Chang EH, Savage MJ, Flood DG, Thomas JM, Levy RB, Mahadomrongkul V, Shirao T, Aoki C, Huerta PT (2006) AMPA receptor downscaling at the onset of Alzheimer's disease pathology in double knockin mice. Proc Natl Acad Sci USA 103:3410–3415
68. Bastrikova N, Gardner GA, Reece JM, Jeromin A, Dudek SM (2008) Synapse elimination accompanies functional plasticity in hippocampal neurons. Proc Natl Acad Sci USA 105:3123–3127
69. Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, Yoo J, Ho KO, Yu GQ, Kreitzer A, Finkbeiner S, Noebels JL, Mucke L (2007) Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron 55:697–711
70. Mansuy IM, Shenolikar S (2006) Protein serine/threonine phosphatases in neuronal plasticity and disorders of learning and memory. Trends Neurosci 29:679–686
71. Tian Q, Wang J (2002) Role of serine/threonine protein phosphatase in Alzheimer's disease. NeuroSignals 11:262–269
72. Liu F, Grundke-Iqbal I, Iqbal K, Oda Y, Tomizawa K, Gong CX (2005) Truncation and activation of calcineurin A by calpain I in Alzheimer disease brain. J Biol Chem 280:37755–37762
73. Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, Landfield PW, Kraner SD (2005) Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. J Neurosci 25:4649–4658
74. Chen QS, Wei WZ, Shimahara T, Xie CW (2002) Alzheimer amyloid beta-peptide inhibits the late phase of long-term potentiation through calcineurin-dependent mechanisms in the hippocampal dentate gyrus. Neurobiol Learn Mem 77:354–371
75. Kaytor MD, Orr HT (2002) The GSK3 beta signaling cascade and neurodegenerative disease. Curr Opin Neurobiol 12:275–278
76. Rockenstein E, Torrance M, Adame A, Mante M, Bar-on P, Rose JB, Crews L, Masliah E (2007) Neuroprotective effects of regulators of the glycogen synthase kinase-3beta signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. J Neurosci 27:1981–1991
77. Peineau S, Taghibiglou C, Bradley C, Wong TP, Liu L, Lu J, Lo E, Wu D, Saule E, Bouschet T, Matthews P, Isaac JT, Bortolotto ZA, Wang YT, Collingridge GL (2007) LTP inhibits LTD in the hippocampus via regulation of GSK3beta. Neuron 53:703–717
78. Zhu LQ, Wang SH, Liu D, Yin YY, Tian Q, Wang XC, Wang Q, Chen JG, Wang JZ (2007) Activation of glycogen synthase kinase-3 inhibits long-term potentiation with synapse-associated impairments. J Neurosci 27:12211–12220
79. Mazanetz MP, Fischer PM (2007) Untangling tau hyperphosphorylation in drug design for neurodegenerative diseases. Nat Rev Drug Discov 6:464–479
80. Cruz JC, Kim D, Moy LY, Dobbin MM, Sun X, Bronson RT, Tsai LH (2006) p25/cyclin-dependent kinase 5 induces production and intraneuronal accumulation of amyloid beta in vivo. J Neurosci 26:10536–10541
81. Samuels BA, Hsueh YP, Shu T, Liang H, Tseng HC, Hong CJ, Su SC, Volker J, Neve RL, Yue DT, Tsai LH (2007) Cdk5 promotes synaptogenesis by regulating the subcellular distribution of the MAGUK family member CASK. Neuron 56:823–837
82. Fischer A, Sananbenesi F, Pang PT, Lu B, Tsai LH (2005) Opposing roles of transient and prolonged expression of p25 in synaptic plasticity and hippocampus-dependent memory. Neuron 48:825–838
83. Fu WY, Chen Y, Sahin M, Zhao XS, Shi L, Bikoff JB, Lai KO, Yung WH, Fu AK, Greenberg ME, Ip NY (2007) Cdk5 regulates EphA4-mediated dendritic spine retraction through an ephexin1-dependent mechanism. Nat Neurosci 10:67–76
84. Hawasli AH, Benavides DR, Nguyen C, Kansy JW, Hayashi K, Chambon P, Greengard P, Powell CM, Cooper DC, Bibb JA (2007) Cyclin-dependent kinase 5 governs learning and synaptic plasticity via control of NMDAR degradation. Nat Neurosci 10:880–886
85. Zhao L, Ma QL, Calon F, Harris-White ME, Yang F, Lim GP, Morihara T, Ubeda OJ, Ambegaokar S, Hansen JE, Weisbart RH, Teter B, Frautschy SA, Cole GM (2006) Role of p21-activated kinase pathway defects in the cognitive deficits of Alzheimer disease. Nat Neurosci 9:234–242
86. Hayashi ML, Choi SY, Rao BS, Jung HY, Lee HK, Zhang D, Chattarji S, Kirkwood A, Tonegawa S (2004) Altered cortical synaptic morphology and impaired memory consolidation in forebrain- specific dominant-negative PAK transgenic mice. Neuron 42:773–787
87. Zhao D, Watson JB, Xie CW (2004) Amyloid beta prevents activation of calcium/calmodulin-dependent protein kinase II and AMPA receptor phosphorylation during hippocampal long-term potentiation. J Neurophysiol 92:2853–2858
88. Townsend M, Mehta T, Selkoe DJ (2007) Soluble abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. J Biol Chem 282:33305–33312
89. Mayford M (2007) Protein kinase signaling in synaptic plasticity and memory. Curr Opin Neurobiol 17:313–317
90. Yamamoto-Sasaki M, Ozawa H, Saito T, Rosler M, Riederer P (1999) Impaired phosphorylation of cyclic AMP response element binding protein in the hippocampus of dementia of the Alzheimer type. Brain Res 824:300–303
91. Gong B, Cao Z, Zheng P, Vitolo OV, Liu S, Staniszewski A, Moolman D, Zhang H, Shelanski M, Arancio O (2006) Ubiquitin hydrolase Uch-L1 rescues beta-amyloid-induced decreases in synaptic function and contextual memory. Cell 126:775–788
92. Tong L, Thornton PL, Balazs R, Cotman CW (2001) Beta-amyloid-(1–42) impairs activity-dependent cAMP-response element-binding protein signaling in neurons at concentrations in which cell survival Is not compromised. J Biol Chem 276:17301–17306
93. Vitolo OV, Sant'Angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M (2002) Amyloid beta-peptide inhibition of the PKA/CREB pathway and long-term potentiation: reversibility by drugs that enhance cAMP signaling. Proc Natl Acad Sci USA 99:13217–13221
94. Puzzo D, Vitolo O, Trinchese F, Jacob JP, Palmeri A, Arancio O (2005) Amyloid-beta peptide inhibits activation of the nitric oxide/cGMP/cAMP-responsive element-binding protein pathway during hippocampal synaptic plasticity. J Neurosci 25:6887–6897
95. Reddy PH, McWeeney S (2006) Mapping cellular transcriptosomes in autopsied Alzheimer's disease subjects and relevant animal models. Neurobiol Aging 27:1060–1077
96. Dickey CA, Gordon MN, Mason JE, Wilson NJ, Diamond DM, Guzowski JF, Morgan D (2004) Amyloid suppresses induction of genes critical for memory consolidation in APP + PS1 transgenic mice. J Neurochem 88:434–442
97. Dickey CA, Loring JF, Montgomery J, Gordon MN, Eastman PS, Morgan D (2003) Selectively reduced expression of synaptic plasticity-related genes in amyloid precursor protein + presenilin-1 transgenic mice. J Neurosci 23:5219–5226
98. Tzingounis AV, Nicoll RA (2006) Arc/Arg3.1: linking gene expression to synaptic plasticity and memory. Neuron 52:403–407
99. Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, Worley PF (2006) Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. Neuron 52:445–459
100. Plath N, Ohana O, Dammermann B, Errington ML, Schmitz D, Gross C, Mao X, Engelsberg A, Mahlke C, Welzl H, Kobalz U, Stawrakakis A, Fernandez E, Waltereit R, Bick-Sander A,

Therstappen E, Cooke SF, Blanquet V, Wurst W, Salmen B, Bosl MR, Lipp HP, Grant SG, Bliss TV, Wolfer DP, Kuhl D (2006) Arc/Arg3.1 is essential for the consolidation of synaptic plasticity and memories. Neuron 52:437–444

101. Shepherd JD, Rumbaugh G, Wu J, Chowdhury S, Plath N, Kuhl D, Huganir RL, Worley PF (2006) Arc/Arg3.1 mediates homeostatic synaptic scaling of AMPA receptors. Neuron 52:475–484
102. Rial Verde EM, Lee-Osbourne J, Worley PF, Malinow R, Cline HT (2006) Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission. Neuron 52:461–474
103. Chin J, Palop JJ, Puolivali J, Massaro C, Bien-Ly N, Gerstein H, Scearce-Levie K, Masliah E, Mucke L (2005) Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. J Neurosci 25:9694–9703
104. Palop JJ, Chin J, Bien-Ly N, Massaro C, Yeung BZ, Yu GQ, Mucke L (2005) Vulnerability of dentate granule cells to disruption of arc expression in human amyloid precursor protein transgenic mice. J Neurosci 25:9686–9693
105. Ginsberg SD, Hemby SE, Lee VM, Eberwine JH, Trojanowski JQ (2000) Expression profile of transcripts in Alzheimer's disease tangle-bearing CA1 neurons. Ann Neurol 48:77–87
106. Maloney MT, Bamburg JR (2007) Cofilin-mediated neurodegeneration in Alzheimer's disease and other amyloidopathies. Mol Neurobiol 35:21–44
107. Heredia L, Helguera P, de Olmos S, Kedikian G, Sola Vigo F, LaFerla F, Staufenbiel M, de Olmos J, Busciglio J, Caceres A, Lorenzo A (2006) Phosphorylation of actin-depolymerizing factor/cofilin by LIM-kinase mediates amyloid beta-induced degeneration: a potential mechanism of neuronal dystrophy in Alzheimer's disease. J Neurosci 26:6533–6542
108. Gibson PH, Tomlinson BE (1977) Numbers of Hirano bodies in the hippocampus of normal and demented people with Alzheimer's disease. J Neurol Sci 33:199–206
109. Chen LY, Rex CS, Casale MS, Gall CM, Lynch G (2007) Changes in synaptic morphology accompany actin signaling during LTP. J Neurosci 27:5363–5372
110. Fedulov V, Rex CS, Simmons DA, Palmer L, Gall CM, Lynch G (2007) Evidence that long-term potentiation occurs within individual hippocampal synapses during learning. J Neurosci 27:8031–8039
111. Messaoudi E, Kanhema T, Soule J, Tiron A, Dagyte G, da Silva B, Bramham CR (2007) Sustained Arc/Arg3.1 synthesis controls long-term potentiation consolidation through regulation of local actin polymerization in the dentate gyrus in vivo. J Neurosci 27:10445–10455
112. Kojima N, Shirao T (2007) Synaptic dysfunction and disruption of postsynaptic drebrin-actin complex: a study of neurological disorders accompanied by cognitive deficits. Neurosci Res 58:1–5
113. Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, Rostaing P, Triller A, Salem N Jr, Ashe KH, Frautschy SA, Cole GM (2004) Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron 43:633–645
114. Takahashi H, Mizui T, Shirao T (2006) Down-regulation of drebrin A expression suppresses synaptic targeting of NMDA receptors in developing hippocampal neurones. J Neurochem 97 (Suppl 1):110–115
115. Buttini M, Masliah E, Barbour R, Grajeda H, Motter R, Johnson-Wood K, Khan K, Seubert P, Freedman S, Schenk D, Games D (2005) Beta-amyloid immunotherapy prevents synaptic degeneration in a mouse model of Alzheimer's disease. J Neurosci 25:9096–90101
116. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, Klein WL (2007) Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem 282:11590–11601
117. Shrestha BR, Vitolo OV, Joshi P, Lordkipanidze T, Shelanski M, Dunaevsky A (2006) Amyloid beta peptide adversely affects spine number and motility in hippocampal neurons. Mol Cell Neurosci 33:274–282
118. Dineley KT, Hogan D, Zhang WR, Taglialatela G (2007) Acute inhibition of calcineurin restores associative learning and memory in Tg2576 APP transgenic mice. Neurobiol Learn Mem 88:217–224