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Impaired regulation of synaptic actin cytoskeleton in Alzheimer's disease

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Abstract

Representing the most common cause of dementia, Alzheimer's disease (AD) has dramatically impacted the neurological and economic health of our society. AD is a debilitating neurodegenerative disease that produces marked cognitive decline. Much evidence has accumulated over the past decade to suggest soluble oligomers of beta-amyloid (A β) have a critical role in mediating AD pathology early in the disease process by perturbing synaptic efficacy. Here we critically review recent research that implicates synapses as key sites of early pathogenesis in AD. Most excitatory synapses in the brain rely on dendritic spines as the sites for excitatory neurotransmission. The structure and function of dendritic spines are dynamically regulated by cellular pathways acting on the actin cytoskeleton. Numerous studies analyzing human postmortem tissue, animal models and cellular paradigms indicate that AD pathology has a deleterious effect on the pathways governing actin cytoskeleton stability. Based on the available evidence, we propose the idea that a contributing factor to synaptic pathology in early AD is an A β oligomer-initiated collapse of a "synaptic safety net" in spines, leading to dendritic spine degeneration and synaptic dysfunction. Spine stabilizing pathways may thus represent efficacious therapeutic targets for combating AD pathology.

Keywords

synapse; dendritic spine; glutamatergic; postmortem; genetic; neurodegenerative; animal model; circuit

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, affecting approximately 13% of Americans over the age of 65 (2009). The widespread prevalence of AD has taken a profound toll on our society, physically and economically. Globally, the total estimated costs of dementia account for about 1% of the world's gross domestic product (www.alz.co.uk/research/worldreport2009). Despite the tremendous impact of AD,

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deciphering its cause or developing effective therapeutics for AD remains elusive. Patients suffering from AD experience progressive loss of memory, critical reasoning and other cognitive abilities. Although amyloid deposits, neurofibrillary tangles (NFTs) and cell death remain defining characteristics of AD, the causal relationship between these lesions and their contribution to cognitive impairment is still unclear. However, diverse lines of evidence suggest beta-amyloid (A β) oligomers play a prominent role in AD pathology by inducing synapse degeneration. Here we critically review recent research that implicates synapses as key sites of early pathogenesis in AD. Based on these findings, we propose the idea that synaptic pathology in early stages of AD is, at least in part, caused by the A β oligomer-initiated collapse of a “synaptic safety net” in spines, which then leads to dysgenesis of dendritic spines and loss of functional synapses. This synaptic pathology has a likely consequence of dendrite atrophy and, when combined with tau pathologies, cell death. Therapeutically enhancing spine stabilizing pathways may thus prevent or delay disease progression.

2. Dendritic spines

The vast majority of excitatory synapses within the brain occur on small dendritic protrusions, called dendritic spines. Synaptic strength and neuronal function are greatly influenced by dendritic spine size and number. Activity-dependent spine stability or remodeling contributes to the maintenance or rewiring of neuronal circuits during the lifespan (Alvarez and Sabatini, 2007; Zuo et al., 2005). While spines are highly dynamic early on, stable spines predominate throughout adult life (Grutzendler et al., 2002). Despite the predominance of stable spines in adulthood, imaging studies demonstrate experience-dependent structural alterations of spines in live animals (Alvarez and Sabatini, 2007; Holtmaat and Svoboda, 2009), and spine expression has a salient association with human cognitive function (Ramakers, 2002).

2.1. Regulation of dendritic spines by actin dynamics

Spine stability is conferred by its actin cytoskeleton. Although a relatively small fraction of actin in spines is stable (Kasai et al., 2003), actin stability is dynamically achieved through continuous activity of actin-stabilizing signaling pathways. A host of molecules, most notably small GTPases such as Rac and Rap, regulate actin dynamics. The activity of small GTPases themselves is under the control of GEFs, which serve as activators of small GTPases. Depolymerization of actin leads to spine loss as well as loss of glutamate receptors from synaptic sites (Allison et al., 1998; Halpain et al., 1998). Similarly, interference with the expression or function of upstream regulators of the actin cytoskeleton, including Rac-GEFs, Rac, and Rac targets such as PAK cause spine and synapse loss (Tashiro et al., 2000) (Cahill et al., 2009; Penzes et al., 2003; Xie et al., 2007). Thus the stable component of the actin cytoskeleton confers the structural and functional integrity of the glutamatergic synapse. Conversely, the dynamic fraction of the actin cytoskeleton provides the driving force behind structural remodeling of spines, and contributes to synaptic plasticity (Matus, 2005).

2.2. A role for spine dysregulation in AD

Interestingly, a number of proteins implicated in AD pathology have established roles in synaptic signaling. Furthermore, synapse degeneration is well supported as a major component of AD pathology (Selkoe, 2002). Based on the available evidence, it is likely that spine dysgenesis, induced by A β oligomers, contributes to disrupted neural networks and decline of cognitive function in AD. Thus, continued research into spine destabilization associated with AD is important for understanding the disease process and developing effective therapeutics. Here we discuss the role of dendrite and dendritic spine perturbations

in AD by reviewing neuropathological findings from AD patients, genetic factors that confer susceptibility to AD, evidence from transgenic mouse models, and potential molecular mechanisms underlying the disease process.

3. Synaptic pathology in AD patients

Synapse loss is a prominent and consistent finding in postmortem tissue samples from patients diagnosed with AD (DeKosky and Scheff, 1990; Scheff et al., 1990). Quantitative morphometric analysis of cortical biopsies within 2 to 4 years of clinical AD onset demonstrated reduced numerical density of synapses, ranging from 25% to 36%, and decreased synapse number per neuron (Davies et al., 1987). Numerous studies report dendritic spine loss in the hippocampus (DeKosky and Scheff, 1990; Ferrer and Gullotta, 1990) and throughout the cortex (Catala et al., 1988; Scheff and Price, 1993), the primary brain areas affected by AD-related pathology. Additionally, amyloid plaques found in the brains of AD patients have been associated with dystrophic neurites (Ferrer et al., 1990). It has long been suggested that aberrant structural changes in the cortex and hippocampus could cause cognitive impairment (Scheibel, 1979). Interestingly, cognitive decline has a stronger correlation to synapse and dendrite loss than to NFTs or neuronal loss (DeKosky and Scheff, 1990; Terry et al., 1991). Stereologic sampling of autopsy tissue demonstrated synapse loss in the hippocampus, consisting in a (non-significant) 13% reduction of synapse numbers in mild cognitive impairment (MCI) and a 44% loss in early AD patients (Scheff et al., 2007), indicating that synapse loss represents an early insult in AD that advances with the disease. Furthermore, it has been reported that synapse loss often appears greater than what would be expected from the neuronal death that also occurs with AD, suggesting synapse loss has a central role in AD pathogenesis, rather than just a consequence of cell death (Walsh and Selkoe, 2004). Interestingly, non-demented individuals with a genetic predisposition for developing AD later in life display decreased cortical thickness when compared to control subjects (Apostolova and Thompson, 2008). Findings that indicate synapse deterioration begins early in AD underscore the need to develop better diagnostic tools and enhance our understanding of the neurological changes that take place during the early stages of AD. Approaches to stall or reverse disease progression will likely be most efficacious during this period. That neuropathological studies note putative compensatory changes in the AD brain, such as an increase in the size of remaining dendritic spines, indicates inherent neurological processes capable of combating AD pathology may exist (Fiala et al., 2002; Scheff and Price, 1993). Such mechanisms should be further investigated, as they could represent ideal modifiable pathways suitable for therapeutic targeting to delay disease progression.

4. AD susceptibility genes

4.1. FAD genes: an indirect attack on synapses

Genetic findings have served as an important guide to AD research, but the role specific genes play in contributing to AD pathology remains unclear and convoluted. However, recent findings have identified new candidate susceptibility genes and new roles for established AD associated genes that should merit the focus of future studies. Familial AD (FAD), which has an autosomal dominant form of inheritance, has been associated with mutations in three genes that are involved with the production of A β (Bertram and Tanzi, 2008). Amyloid precursor protein (APP), when cleaved sequentially by β - and γ -secretase, produces the A β peptide. All FAD-associated mutations are found in APP or genes that make up the γ -secretase complex: presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*). Mutations associated with FAD lead to increased production of A β , and much evidence from cellular studies convincingly demonstrate that soluble A β oligomers impair synaptic plasticity (reviewed in (Klein, 2006; Selkoe, 2008)). Studies show that A β oligomers target

dendritic spines thereby inducing spine dysgenesis and reductions in spine density (Lacor et al., 2007; Shankar et al., 2007).

4.2. AD genetic risk factors alter dendrite and spine expression

The vast majority of AD cases have a late-onset development, sometimes referred to as sporadic AD. Although hundreds of genes have been proposed as AD risk factors, the gene encoding apolipoprotein E (*APOE*) has become established as the most important risk factor (Corder et al., 1993) (Sleegers et al., 2010). Carriers of the $\epsilon 4$ (*APOE* $\epsilon 4$) allele are at higher risk for developing AD, whereas evidence suggests $\epsilon 2$ allele is neuroprotective. Interestingly, recent studies using transgenic mice indicate that ApoE isoforms differentially influence dendrite and dendritic spine morphology. Specifically, reduced spine density was observed in the dentate gyrus (DG) of mice expressing human *APOE* $\epsilon 4$ when compared mice expressing human *APOE* $\epsilon 3$ or WT mice (Ji et al., 2003). The authors also investigated *APOE* $\epsilon 4$ expression in human patients and found an inverse correlation between *APOE* $\epsilon 4$ dose and spine density in the DG. In another study, expression of human *APOE* $\epsilon 4$ in mice lead to reduced dendritic length and branching throughout the cortex and hippocampus (Dumanis et al., 2009). This study did not find that ApoE isoforms affect spine expression in the hippocampus, but the authors did report differences in the cortex. It has also been reported that hippocampal spine loss normally observed in an AD mouse model can be prevented by overexpressing human ApoE2, maintaining spine density at control levels (Lanz et al., 2003). Studies continue to reaffirm the importance of *APOE* as an AD genetic risk factor and although its precise role in AD pathology remains unclear, it is fascinating that differential *APOE* expression can lead to changes in dendrites and dendritic spines, indicating that genetic mutations that lead to the development of AD may impact neuronal structural stability.

Two independent genome-wide association studies (GWAS) recently identified the clusterin gene (*CLU*) as a new susceptibility gene for AD (Sleegers et al., 2010). Clusterin, also known as ApoJ, has many similarities to ApoE, including the ability to bind A β , thus it will be interesting to learn if clusterin also modulates expression of dendrites and dendritic spines. Interestingly, *PICALM*, another novel susceptibility gene identified by GWAS may influence dendrite structure. With a known role in clathrin-mediated endocytosis, *PICALM* can also induce dendritic dystrophy and disrupt vesicle transport when underexpressed in embryonic hippocampal neurons (Sleegers et al., 2010). As new genetic risk factors are identified and manipulated experimentally, it will be important to assess dendrite and dendritic spine phenotypes, and whether genotype alters neuronal structure through a gain-of-function or loss-of-function phenotype. If expression of a specific genetic mutation displays a reduced spine density phenotype, is it due to overproduction of A β or inherently compromising synaptic stability?

5. Dendrite and synaptic pathology in AD mouse models

Based on genetic links identified from the human population associated with developing AD, several transgenic mouse models have been generated to recapitulate specific aspects of AD pathology. Interestingly, rare mutations appear capable of producing the full scope of AD pathology in humans, but when expressed in mice, these transgenes recapitulate only specific aspects of AD (reviewed in (Ashe and Zahs, 2010)). Despite their shortcomings, AD animal models have been extraordinarily instructive. Given that aberrant APP processing is suggested to temporally precede tau alterations and has been directly linked with spine degeneration (Selkoe, 2002), this review will emphasize animal models that mimic amyloidogenesis.

Due to the profound memory loss associated with AD, it is necessary to test AD mouse models for behavioral deficits indicative of cognitive impairment, especially impairment in reference memory and working memory. Many models display memory impairment as well as aberrant LTP expression (Ashe and Zahs, 2010). Additionally, the prominent synapse pathology observed in AD patients has prompted the investigation of spine morphology and density in AD models. The widely used Tg2576 mouse model (Hsiao et al., 1996), which expresses human APP containing mutations identified in a large Swedish family, display decreased spine density in CA1 and DG much before the formation of amyloid plaques, supporting a role for A β oligomers in mediating at least some AD-related pathology (Jacobsen et al., 2006; Lanz et al., 2003). Interestingly, cognitive impairment also becomes evident in these mice prior to plaque development but around the time when spines become depleted, suggesting that synapse loss can drive cognitive decline. Expressing mutations in *APP* and *PS1* in mice leads to neurons with fewer large spines and various dendritic abnormalities (Knafo et al., 2009). Such dendritic abnormalities include shaft atrophy, neurite breakage, and greater reductions in spine density near amyloid deposits (Grutzendler et al., 2007; Tsai et al., 2004). Similarly, amyloid plaques in Tg2576 mice alter neurites and reduce spine density on dendrites nearby (Spires et al., 2005). Taken together, these studies suggest that both soluble and insoluble amyloid can have deleterious effects on neurons by perturbing synaptic connections as well as dendritic projections. It should be noted, though, that substantial synapse degeneration appears to take place prior to plaque deposition. It will thus be important to explore dendrite and spine phenotypes in newly generated animal models and at time-points before widespread deposition of amyloid plaques. Many AD animal models support the concept that synaptic degeneration is central to the disease and may serve as a driving force, rather than a byproduct, of AD pathology that leads to memory impairment. Importantly, structural alterations have been reported to be reversible pharmacologically, opening new therapeutic directions in AD (Smith et al., 2009).

Despite major advances made possible by the use of animal models, the available models are incomplete and the findings they produce should be taken in conjunction with the limitations of each model. Most models mimic only one or a few components of AD, thus they provide insight about a narrow aspect of the disease, not necessarily the disease as a whole. While genetic manipulations in animals may help identify the role of individual proteins in AD pathogenesis, they could also elucidate important common pathways affected in the disease. Determining the specific pathways disrupted in AD and understanding how they contribute to AD pathology is thus an important next step.

6. Molecular mechanisms of AD pathogenesis

A wealth of genetic data provided evidence that A β has a key role in AD pathogenesis, which has been corroborated by numerous molecular studies and furthered by results showing that A β can mediate its toxic effects by acting on synapses. Given the dramatic synaptic alterations in AD, it is not surprising that AD patients demonstrate altered expression of many synaptic proteins (Arendt, 2009). The presynaptic protein synaptophysin was reported to be reduced by 25–35% in patients diagnosed with MCI or AD (Masliah et al., 2001; Selkoe, 2002). However, since synaptophysin knockout mice lack deficits in synaptic plasticity and cognition, it has been suggested that memory decline in AD involves much more than just synaptophysin loss (Janz et al., 1999; Zhao et al., 2006). Investigation into postsynaptic signaling molecules has revealed a number of intriguing proteins of interest. Although the precise mechanisms that cause spine degeneration in AD remain unknown, recent findings suggest that signaling pathways regulating actin dynamics and receptor expression may be integrally involved.

6.1. AD pathology potentiates synaptic-weakening pathways

The actin binding proteins cofilin and drebrin have contrasting effects on actin stability and their regulated activity works in conjunction to control actin dynamics. Active cofilin induces actin destabilization, and much evidence supports a role for cofilin in neurodegeneration, including AD (Maloney and Bamburg, 2007; Shankar et al., 2007). In contrast, drebrin binds and stabilizes actin in dendritic spines, but reduced levels of drebrin have been reported in the hippocampal formations of patients with AD (Harigaya et al., 1996) and in cortical areas, including the frontal and temporal cortices (Counts et al., 2006). Cofilin and drebrin are direct regulators of actin that are disrupted in AD, but molecules further upstream in actin regulatory pathways are impacted as well.

Just as there are signaling pathways that enhance synaptic strength and regulate synaptic maintenance, other pathways mediate synaptic weakening. Calcineurin (or PP2B) is a calcium sensitive phosphatase that, when activated, can induce a signaling cascade leading to synaptic weakening (Xia and Storm, 2005). Interestingly, calcineurin over-activation has been reported in AD patients and animal models (Liu et al., 2005). Studies have also shown that A β oligomer-induced spine loss and dendritic dystrophies can be prevented by calcineurin inhibition (Wu et al., 2010). Furthermore, a downstream effector molecule of calcineurin, GSK-3 β , experiences increased activation in response to AD-related pathology (Li et al., 2009). Hence over-activation of an NMDAR-calcineurin-GSK-3 β pathway may represent a mechanism by which synapses degenerate in AD.

6.2. AD pathology disrupts pathways regulating synaptic maintenance

A critical regulator of actin assembly and subsequent spine modulation in neurons is p21-activated kinases (PAK), which signals downstream of Rac (Penzes et al., 2003; Zhao et al., 2006). In the hippocampus of AD patients, and animal models of AD, total PAK is reduced with an even greater reduction in active PAK (Zhao et al., 2006). AD-related pathology also mislocalizes PAK in neurons, followed by loss of F-actin in dendrites and dendritic spines (Ma et al., 2008). Furthermore, pharmacological inhibition of PAK in adult mice was sufficient to cause memory impairment, cofilin pathology and drebrin loss (Zhao et al., 2006). Interestingly, kalirin, a key regulator of spine morphogenesis and an upstream activator of PAK in spines, was found to have consistently underexpressed protein and mRNA levels in the hippocampus of AD patients, suggesting a role for the kalirin-Rac-PAK pathway in AD-associated spine pathology (Xie et al., 2007; Youn et al., 2007). Studies investigating protein expression in AD patients continue to reveal aberrant expression of signaling molecules that regulate spine dynamics. Another small RhoGTPase that influences synaptic plasticity by regulating cytoskeleton dynamics called RhoA was also recently described to have reduced expression and altered localization in AD brain hippocampus (Huesa et al., 2010).

6.3. Dysregulation of excitatory transmission in AD

Just as the pathways governing spine plasticity are dysregulated in AD, so too are many receptors that mediate synaptic transmission, causing impairments in functional activity. As dendritic spines serve as sites for most excitatory communication in the brain, numerous studies have investigated the effect of AD pathology on the receptors that mediate glutamatergic transmission. Interestingly, A β reduces surface expression of NMDARs and AMPARs, resulting in dendritic spine loss (Hsieh et al., 2006; Snyder et al., 2005). Not surprisingly, various studies have shown that A β oligomers inhibit LTP (Lambert et al., 1998; Walsh et al., 2002). An important modulator of NMDAR activity, Fyn, a tyrosine kinase, has been reported to be upregulated in AD (Chin et al., 2005). Moreover, overexpressing Fyn concomitantly with A β exposure produces neuronal and cognitive dysfunction in mice, whereas Fyn depletion prevents the neurotoxic effects of A β (Lambert

et al., 1998; Venkitaramani et al., 2007). Interestingly, a recent study demonstrated postsynaptic targeting of Fyn is mediated by tau and that sequestration of Fyn to the soma was sufficient to ameliorate pathology in an AD mouse model (Ittner et al., 2010). AD pathology also appears to affect metabotropic glutamate receptors (mGluRs). Recently, A β oligomers were shown to cluster mGluR5 thereby inhibiting its synaptic diffusion, which led to increased intracellular calcium and synaptic degeneration (Renner et al., 2010). As determining the molecular processes underlying synapse degeneration in AD is critical for understanding the disease and for developing effective therapeutics, the precise signaling cascades underlying synapse loss and cognitive decline need to be further elucidated.

7. Conclusions: impaired “synaptic safety net” in spines

Synapse degeneration is now well established as a major early step in AD pathology. Synapse loss tightly correlates with cognitive decline, and AD-associated etiologic factors have been shown to adversely affect dendritic spines *in vitro* and *in vivo*. The fact that AD is a disease of aging, could suggest impairment in spine maintenance. Postmortem neuropathological findings, along with animal models and cellular studies, indicate that the pathways regulating the stability and remodeling of the actin cytoskeleton are impaired in AD. Disruption of actin regulatory pathways appears to occur at varying levels of the signaling cascade, including direct regulators of actin as well as molecules further upstream, such as GEFs and small GTPases. As the actin cytoskeleton provides the structural scaffold for spines and synapses, and anchors neurotransmitter receptors at the synapse, degeneration of signaling that maintains spines will ultimately lead to collapse of spines and loss of synapses (Allison et al., 1998; Halpain et al., 1998). A stable synaptic cytoskeleton may serve as a “synaptic safety net” that could protect spiny synapses from elimination, and prevent the loss of their glutamate receptor content. Thus maintaining the functional integrity of this “synaptic safety net” could be crucial in preventing or delaying synapse loss. We propose that by therapeutically enhancing actin stability one may be able to delay synapse loss when targeted early in disease progression, even in prodromal stages. While cell surface receptors are the most easily targeted proteins, several components of the intracellular pathway that regulates the actin cytoskeleton, such as GEFs or kinases, might have favorable druggability properties.

8. Unanswered questions and future directions

Although much progress has been made regarding spine dysmorphogenesis in AD, many questions still need to be addressed. How do A β oligomers exert their effect on synapses? While studies demonstrate A β oligomers do bind dendritic spines, their mode of action on the cytoskeleton is unknown. Future studies should address the missing links between A β oligomer binding to spines and cytoskeletal alterations. It will be valuable to know whether A β binding is mediated by high affinity interactions with specific regions of the cell membrane or if a specific receptor exists that facilitates A β toxicity.

What are the key synaptic signaling pathways disrupted in AD and how are they connected to other AD-related pathology, such as tau pathology and cell death? A number of signaling molecules that regulate synapse function have been shown to be dysregulated in AD, but it will be important to differentiate affected proteins from those that mediate pathology. Furthermore, the mechanisms induced by A β -oligomers that lead to synapse degeneration are becoming known, with a strengthening causal link to tau pathology, including a potential role in dendrite degeneration (Ittner et al., 2010; Zempel et al., 2010). Progress has been made toward reconciling the relationship between synaptic pathology and neuronal loss but it remains a lingering issue that needs resolution.

What role do genetic risk factors play in AD-related spine destabilization? The $\epsilon 4$ allele of *APOE*, which stands as the strongest genetic risk factor for developing sporadic AD, has been shown to alter dendrite and dendritic spine expression (Dumanis et al., 2009; Ji et al., 2003). However, the mechanism by which ApoE exerts its dendritic effects remains unknown and warrants further investigation. Moreover, recent genetic studies provide compelling evidence for newly identified AD susceptibility genes, which represent exciting new opportunities to decipher the molecular basis of AD pathology.

Can synapse degeneration be prevented or reversed? Addressing the questions above will hopefully lead to windows of opportunity for intervention. Discovering the key players in spine destabilization will engender approaches to synapse protection and restoration. Synapse loss likely precedes cell loss, thus, discovering means to slow or halt synapse degeneration may also preserve cell health. Many studies indicate that synapse degeneration contributes to cognitive decline and so mitigating spine loss may also ameliorate cognitive impairment.

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Figure 1.

Depiction of dendrites and dendritic spines found on cortical neurons. **(A)** Representative cultured cortical neuron expressing green fluorescent protein (GFP). Dendrites extend from the soma and exhibit extensive branching, composing the neuron's dendritic arbor. Dendritic spines protrude from dendrites allowing neurons to make synaptic connections. Notice that the axon is thinner than dendrites and does not have spines. **(B)** Magnified image of a dendrite expressing GFP. Dendritic spines have a bulbous head, which serves as the site of synaptic contact, and a thinner neck connected to the dendrite. **(C)** Model of a dendritic spine synapsing with an axon. The postsynaptic density (PSD) anchors synaptic proteins, including glutamate receptors (e.g. NMDARs and AMPARs), at the synapse. The dynamic actin cytoskeleton confers much of the structure and function of the dendritic spine.

Figure 2.

AD-related pathology causes synaptic dysfunction. (A) Cultured cortical neuron over-expressing kalirin-7 (green), stained for drebrin (blue) and treated with fluorescent A β oligomers (also called ADDLs, red). White indicates co-localization, demonstrating ADDLs bind excitatory synapses. (B) Dendrite and spines of a cortical neuron (green) treated with fluorescent ADDLs (cyan). A β oligomers clearly bind dendritic spines, with co-localization shown in white (indicated by grey arrows). (C) Soluble A β oligomers downregulate many of the key molecular players responsible for maintaining the actin cytoskeleton, and also upregulate the activity of proteins that weaken the actin cytoskeleton (loss of the “synaptic safety net”). As a result, the mechanisms regulating synaptic plasticity become dysregulated whereby increased actin destabilization could precipitate collapse of the dendritic spine and ultimately loss of functional synapses.