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Regulation of actin dynamics during structural plasticity of dendritic spines: Signaling messengers and actin-binding proteins

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ABSTRACT

Activity-dependent plasticity of synaptic structure and function plays an essential role in neuronal development and in cognitive functions including learning and memory. The formation, maintenance and modulation of dendritic spines are mainly controlled by the dynamics of actin filaments (F-actin) through interaction with various actin-binding proteins (ABPs) and postsynaptic signaling messengers. Induction of long-term potentiation (LTP) triggers a cascade of events involving Ca^{2+} signaling, intracellular pathways such as cAMP and cGMP, and regulation of ABPs such as CaMKII, Cofilin, Aip1, Arp2/3, α-actinin, Profilin and Drebrin. We review here how these ABPs modulate the rate of assembly, disassembly, stabilization and bundling of F-actin during LTP induction. We highlight the crucial role that CaMKII exerts in both functional and structural plasticity by directly coupling Ca^{2+} signaling with F-actin dynamics through the β subunit. Moreover, we show how cAMP and cGMP second messengers regulate postsynaptic structural potentiation. Brain disorders such as Alzheimer's disease, schizophrenia or autism, are associated with alterations in the regulation of F-actin dynamics by these ABPs and signaling messengers. Thus, a better understanding of the molecular mechanisms controlling actin cytoskeleton can provide cues for the treatment of these disorders.

1. Introduction

Most excitatory synapses of the mammalian central nervous system are situated on dendritic spines (Gray, 1959), the tiny protrusions (~1 μm) first described by Ramón y Cajal in 1888 as "thorns or short spines"(Ramón y Cajal, 1888; Yuste, 2015). Spines are morphologically and physiologically plastic. They undergo activity-dependent changes that play an essential role in neuronal development and in brain cognitive functions including learning and memory (Yuste, 2010).

Synaptic efficiency can be enhanced in the long-term by an intense stimulation (Bliss and Gardner-Medwin, 1973). This is called long-term potentiation (LTP) and it is considered an excellent molecular/cellular model of learning and memory (Bliss and Collingridge, 1993). LTP can be induced in excitatory pathways of many regions of the brain, including hippocampus, and its molecular mechanisms have been intensely studied (Brown et al., 1988; Cotman and Lynch, 1989; Kennedy, 1989; Lynch and Baudry, 1984; Malinow, 1994; Nicoll et al., 1988; Nicoll and Malenka, 1995; Stevens, 1998). In addition to such "functional plasticity", recent studies have revealed another aspect of synaptic plasticity called "structural plasticity", which is defined as the activity-dependent modification of the morphology of dendritic spines and their internal substructures (Bosch and Hayashi, 2012). Two-photon microscopy techniques combined with fluorescent and light-regulated proteins have enabled us to longitudinally monitor spine structural plasticity in living tissue *in vivo* or *ex vivo* and thus study its molecular mechanisms. These approaches reveal that NMDA receptor (NMDAR)-dependent LTP is associated with the long-term increase of the volume of dendritic spines in hippocampal neurons (Matsuzaki et al., 2004; Okamoto et al., 2004), which we refer structural synaptic potentiation or structural LTP (sLTP). It is also known that the spine volume positively correlates with the area of the post-synaptic density (PSD), with the number of receptors on the spine surface (including functional AMPA receptors –AMPAR) and with the number of docked vesicles in the presynaptic site (Matsuzaki et al., 2001; Nusser et al., 1998; Schikorski and Stevens, 1999). Furthermore, induction of LTP in single spines results in a correlated increase in spine size and AMPAR currents (Matsuzaki et al., 2004). These correlations indicate that the dendritic spine structure is tightly linked to its synaptic function. As a proof of this link, it has been shown that blocking structural spine enlargement interferes with functional LTP induction (K. Kim et al.,

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2015).

Here we briefly review the role that several actin-binding proteins (ABPs), especially CaMKIIβ, and signaling messengers such as cyclic AMP and GMP (cAMP and cGMP), play in the regulation of spine structural potentiation through their effect on the dynamics of the actin filaments. In addition, we briefly review the alterations in spine morphology and ABP regulation found in an exemplar range of brain disorders, such as Alzheimer's disease, schizophrenia and autism spectrum disorder.

2. Actin is the major cytoskeletal protein in dendritic spines

Actin is the most abundant protein in eukaryotic cells. Among the three main isoforms of actin, α, β and γ, the latter two isoforms are found in non-muscle cells such as neurons (Dominguez and Holmes, 2011). Actin exists in a dynamic equilibrium between globular (G)-actin and filamentous (F)-actin, and it is highly enriched in dendritic spines, where it functions as the major cytoskeletal component that governs spine morphogenesis and spine plasticity. Actin is also the main anchoring site for many postsynaptic proteins including NMDAR and AMPAR (Cingolani and Goda, 2008; Dillon and Goda, 2005; Hotulainen and Hoogenraad, 2010; Pontrello and Ethell, 2009; Tada and Sheng, 2006).

The postsynaptic actin cytoskeleton is not a static but a highly dynamic structure. Two-photon FRET (Förster resonance energy transfer) live imaging revealed activity-dependent actin polymerization and depolymerization in dendritic spines during synaptic plasticity (Okamoto and Hayashi, 2006; Okamoto et al., 2004). Upon LTP induction, rapid (< 1 min) and persistent actin polymerization occurs in dendritic spines, which results in significant structural enlargement (Okamoto et al., 2004). Honkura and colleagues have demonstrated the presence of different pools of F-actin in the spine: (1) a dynamic F-actin pool with fast turn-over at the periphery of the spine, (2) a stable F-actin pool with slow turn-over at the base of the spine and (3) an “enlargement” pool with slow turn-over that is formed in response to sLTP induction (Honkura et al., 2008).

Thus, there are unique pools of actin that serve to dynamically regulate the cytoskeleton and are crucial for the modulation of the dendritic spine structure and function. This regulation is activity-dependent and carried out by several ABPs.

3. Role of actin-binding proteins in structural synaptic potentiation

The equilibrium between G-actin and F-actin is finely and rapidly regulated during events of synaptic plasticity by a number of postsynaptic ABPs. During LTP induction, specific ABPs are activated/inactivated in sequential phases and in localized regions of the spine to promote polymerization/depolymerization of F-actin. These actin filaments are, in turn, subject to supra-molecular interactions, such as bundling and cross-linking. Briefly, the reorganization of the actin cytoskeleton during LTP goes through two distinct but overlapping phases (Bosch et al., 2014; K. Kim et al., 2015; Okamoto et al., 2009) (Fig. 1). During Phase I (< 5 min after LTP induction), the NMDAR-dependent Ca^{2+}/CaM (calmodulin) signaling activates calcium calmodulin-dependent protein kinase II (CaMKII), which exerts a dual effect in both spine structure and synaptic function (see next section). This phase is characterized by a profound remodeling of the actin cytoskeleton through rapid periods of F-actin disassembly (severing, unbundling) followed by periods of F-actin assembly (polymerization, branching). Phase II (> 5 min after LTP induction) is characterized by the long-term stabilization and consolidation of those changes. In this phase, there is a net increase in actin and new polymerized F-actin in the spine, which is again bundled and crosslinked. All these changes are regulated by several ABPs, including Cofilin, Profilin, Arp2/3, Aip1, Drebrin, α-actinin and CaMKII (α + β) (Fig. 1). The concentration and activity of these ABPs in the spine ultimately determine the status of the actin filaments and therefore the morphology of the spine.

3.1. F-actin disassembly

Cofilin-1 and the related actin depolymerizing factor (ADF) are expressed in neurons and found in the dendritic spine (Yoshimura et al., 2004). Cofilin exerts a bidirectional effect on F-actin depending on its relative concentration to actin. At low concentrations, cofilin promotes F-actin disassembly by cutting the actin filaments (severing) or by facilitating the removal of the actin monomers (depolymerization) (Bamburg and Bernstein, 2010). F-actin severing can actually result in an increased rate of actin polymerization, if there are enough actin monomers available, due to the creation of free barbed filament ends. At high concentrations, cofilin can bind to actin filaments and actually promote their stabilization or even the nucleation of new filaments (Van Troys et al., 2008). During the very initial phase of sLTP induction (~20 s), cofilin undergoes a rapid increase in concentration in the spine (Bosch et al., 2014). Because total actin concentration also increases in the spine during these first seconds/min of sLTP induction (Bosch et al., 2014; Honkura et al., 2008), cofilin severing activity might therefore be one of the key effectors in facilitating F-actin assembly and spine growth. (Bamburg and Bernstein, 2010; Calabrese et al., 2014; Kiuchi et al., 2007). Actin interacting protein 1 (Aip1) selectively binds to cofilin-decorated F-actin and induces the capping (Okreglak and Drubin, 2010; Ono, 2003) or the destabilization of the filaments (Nadkarni and Brieher, 2014). Aip1 concentration also increases at the dendritic spine immediately after sLTP induction (Bosch et al., 2014), suggesting a synergistic interaction with cofilin to initially disassemble actin filaments during these first seconds/minutes of sLTP. Knockdown of cofilin impairs sLTP as well as functional LTP (Bosch et al., 2014; Rust et al., 2010), demonstrating an important function of cofilin in both structural and functional plasticity.

3.2. F-actin assembly

Upon LTP induction, actin is rapidly polymerized into F-actin at the same time the spine volume increases (Okamoto et al., 2004). The length and the complexity of the new actin filaments can be further increased by Arp2/3, the major ABP with polymerizing and filament-branching activities (Ichetovkin et al., 2002; Korobova and Svitkina, 2010). Arp 2/3 is also rapidly translocated to the potentiated spines (Bosch et al., 2014), suggesting a synergistic effect with cofilin on F-actin growth. In contrast, Profilin, another ABP with polymerizing activity (Carlsson et al., 1977), transiently decreases in concentration during sLTP induction (Bosch et al., 2014), suggesting a role in stabilization of spine morphology instead of direct involvement in the induction of spine enlargement (Ackermann and Matus, 2003). Thus, a plausible model for the enlargement of dendritic spines during NMDAR-dependent LTP induction is explained by the rapid recruitment of actin, cofilin, Aip1 and Arp2/3 and their synergistic actions in severing (cofilin, Aip1), capping (Aip1) and branching (Arp2/3) the actin filaments that results in the net growth and remodeling of the actin cytoskeleton and spine size (Fig. 1).

3.3. F-actin stabilization

Actin-binding proteins such as CaMKIIβ, Drebrin, and α-actinin serve as stabilizers of the actin cytoskeleton by crosslinking F-actin in bundles or linking F-actin to PSD proteins (Djinovic-Carugo et al., 1999; Koganezawa et al., 2017; Okamoto et al., 2007; Sanabria et al., 2009; Sjoblom et al., 2008). These ABPs are highly enriched in dendritic spines, and their suppression affects spine formation and morphology (Hayashi et al., 1996; Hodges et al., 2014; Okamoto et al., 2007).

Postsynaptic CaMKIIβ is an abundant ABP in the PSD (Peng et al., 2004). Its central role in both structural and functional potentiation is

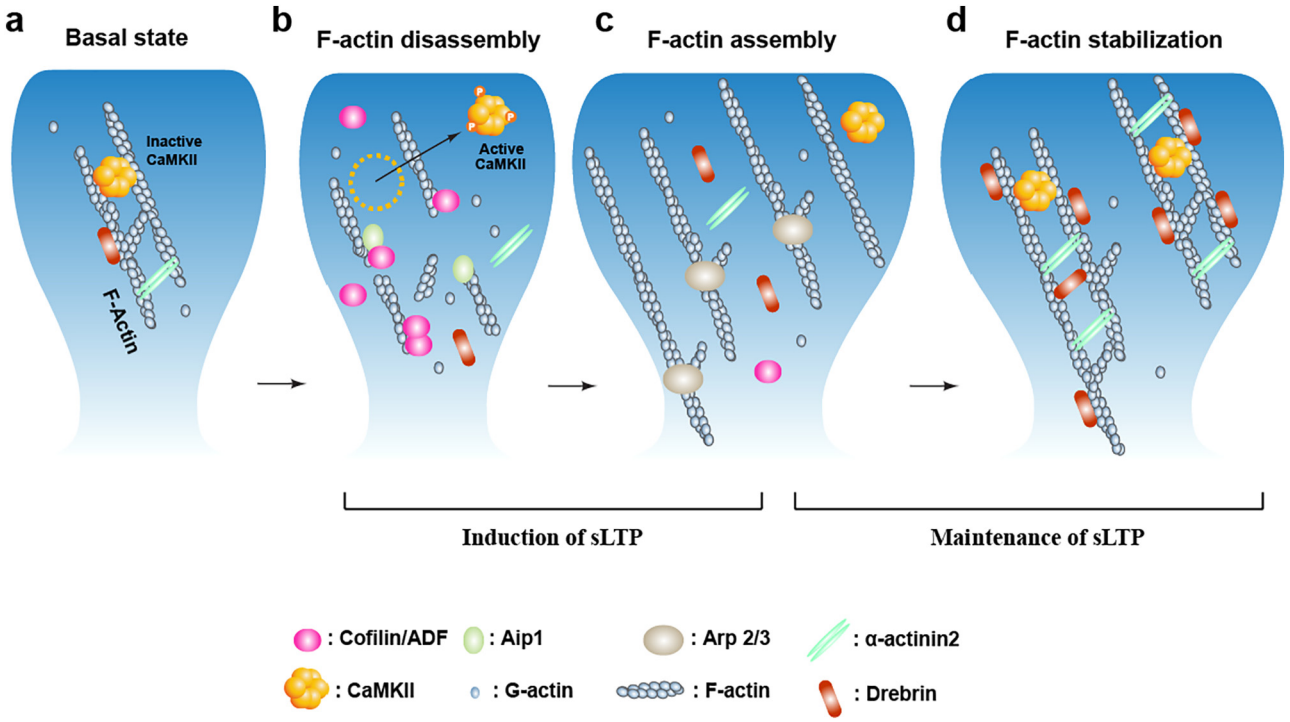

Fig. 1. Schematic of actin cytoskeleton remodeling during structural synaptic potentiation (sLTP). a) In the *basal state*, bundled F-actin maintains a stable spine structure. b) Synaptic signals that induce sLTP activate CaMKII, which detaches from F-actin and unbundles the filaments. Cofilin/ADF rapidly enters the spine and severs those filaments. F-actin stabilizers such as Drebrin and α-actinin reduce their concentration in the spine. This promotes an initial period of *F-actin disassembly*. c) The new free F-actin ends and the high concentration of G-actin result in a net rate of F-actin polymerization. Aip1 and Arp2/3 enter the spine and bind F-actin to cap and branch F-actin, respectively. This subsequent period of *F-actin assembly* extends the size and complexity of F-actin, which results in the enlargement of spine size. d) F- actin stabilizing proteins Drebrin, α-actinin and inactivated CaMKII return to their normal spine concentration, bind to F-actin, re-bundle and cross-link the newly reorganized filaments. This period of *F-actin stabilization* allows the long-term maintenance of the enlarged dendritic spine structure.

explained in the next dedicated section 4.

Drebrin exists in two isoforms, Drebrin E which is expressed in various tissues, and Drebrin A which is restricted to the nervous system (Koganezawa et al., 2017). Drebrin A accumulates in dendritic spines and creates a stable pool of slow turn-over filaments. In addition to binding to F-actin, Drebrin might also bundle filaments by crosslinking them together (Hayashi et al., 1996; Mikati et al., 2013; Worth et al., 2013). Drebrin associates with other ABPs such as myosins (I, II, V) and gelsolin (Hayashi et al., 1996; Worth et al., 2013) and provides a direct interaction with microtubules (Gordon-Weeks, 2016). Drebrin binding properties are activity-dependent (Koganezawa et al., 2017), thus providing the actin cytoskeleton with a higher degree of stability, complexity and plasticity.

α-actinin forms a dimer containing an actin-binding domain at each N-terminus, which enables crosslinking of actin filaments (Djinovic-Carugo et al., 1999; Sjoblom et al., 2008). Isoforms 1, 2 and 4 are present in the brain, and α-actinin2 is particularly enriched in the PSD of excitatory synapses (Hodges et al., 2014). α-actinin also interact with other PSD proteins, including CaMKIIα, and with synaptic receptors such as NMDAR (Jalan-Sakrikar et al., 2012; Wyszynski et al., 1997). α-actinin4 exerts an interesting molecular role by linking receptor functional activity with spine structure. Kalinowska and colleagues report that α-actinin4 governs metabotropic glutamate receptors (mGluR)-dependent regulation of dendritic protrusions through a CaMKIIβ-dependent process (Kalinowska et al., 2015).

Upon induction of sLTP, the concentration of these ABPs (CaMKIIβ, Drebrin, and α-actinin) in the dendritic spine is transiently reduced for ~1–5 min (Bosch et al., 2014; Sekino et al., 2006). During this time window, therefore, actin filaments can lose their supra-molecular organization (bundling and cross-linking) and allow the access to other actin-binding factors that can reorganize the actin cytoskeleton. The concentration of these three ABPs in the spine progressively returns to basal levels of concentration (Bosch et al., 2014; Mizui et al., 2014), thereby recovering the bundled and cross-linked status of F-actin and promoting the stabilization of the reorganized actin cytoskeleton and the maintenance of the spine enlargement.

4. Role of CaMKIIβ in structural synaptic potentiation

CaMKII is a ubiquitous serine/threonine protein kinase that serves a variety of cellular functions including a key role in postsynaptic LTP and learning/memory (Colbran and Soderling, 1990; Kelly, 1991; Lisman et al., 2002). CaMKII is encoded by a family of four isoforms (α, β, γ and δ) (Tombes et al., 2003). The α and β subunits are the most abundant in the brain (Bennett et al., 1983).

CaMKII activity is tightly regulated by its autoinhibitory domain (Colbran et al., 1989; Kelly et al., 1988). At baseline synaptic conditions, the autoinhibitory domain of CaMKII interacts with its catalytic domain in order to maintain an inactive state. Upon LTP induction, Ca^{2+}/CaM binding disrupts the interaction between autoinhibitory and catalytic domains, and results in autophosphorylation of Thr286 (α subunit) for its autonomous (constitutive) activation and LTP (Colbran et al., 1989; Ikeda et al., 1991; Kelly et al., 1988; Lisman et al., 2002; Miller et al., 1988; Schworer et al., 1988; Thiel et al., 1988). The function of CaMKIIα in LTP has been proposed as a molecular switch essential for learning and memory (Lee et al., 2009; Lisman and Goldring, 1988; Lisman et al., 2002; Lisman, 1985; Silva et al., 1992a; Silva et al., 1992b; Soderling, 1993; Stevens et al., 1994).

Like other ABPs, the β subunit of CaMKII features an F-actin binding domain that targets CaMKIIβ to actin filaments in cells and particularly in dendritic spines (Fink et al., 2003; Okamoto et al., 2004; Okamoto et al., 2007; Shen and Meyer, 1999; Shen et al., 1998). CaMKIIα isoform also binds actin but more weakly, and this interaction reportedly contributes to its localization to the dendritic spine (Khan et al., 2016).

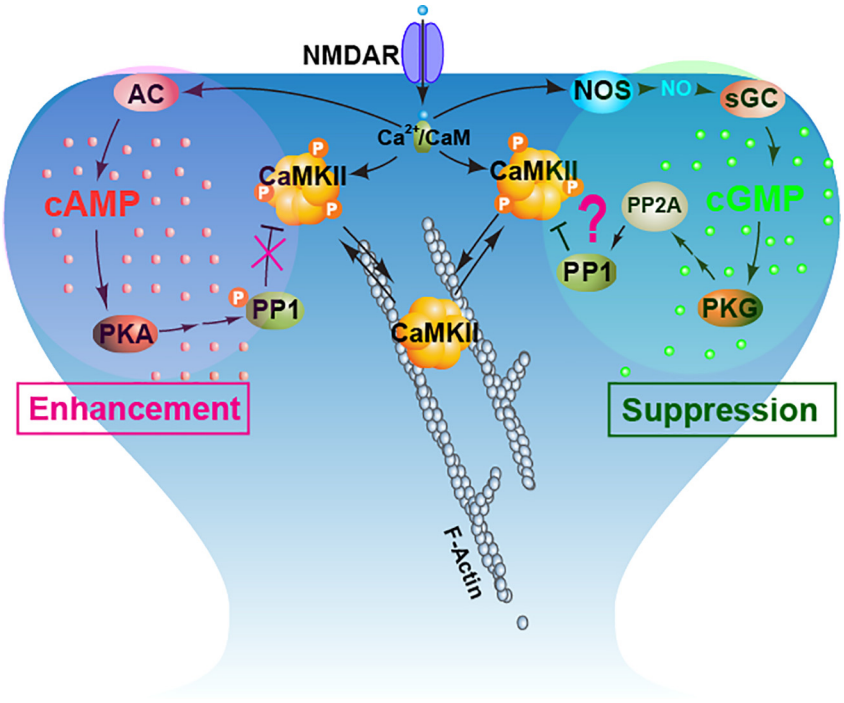

Fig. 2. Proposed pathway of cAMP and cGMP interaction in structural plasticity.
Strong synaptic stimulation leads to postsynaptic activation of CaMKII by Ca^{2+} influx and a concomitant synthesis of cAMP by adenylate cyclase (AC). cAMP-dependent PKA inactivates protein phosphatase 1 (PP1), which normally dephosphorylates and inactivates CaMKII, therefore prolonging the time of CaMKIIβ activation during synaptic plasticity. This results in an increase of structural potentiation (*enhancement*, left) likely by extending the duration of actin cytoskeleton remodeling.
Alternately, NO-dependent synthesis of cGMP by sGC results in cGMP-dependent activation of PKG, which may carry out its downstream effects through PP2A phosphatase-dependent activation of PP1 and subsequent inactivation of CaMKIIβ (*suppression*, right). In this model, cGMP leads to suppression of active CaMKII and actin polymerization directly opposing the action of cAMP through the effects on PP1 phosphatase.

CaMKIIβ does not only bind to actin, but also has the property of bundling actin filaments together (O'Leary et al., 2006; Okamoto et al., 2007; Sanabria et al., 2009) through the formation of hetero-oligomers with the CaMKIIα subunit (Brocke et al., 1999). These properties allow CaMKII to play a key role in the preservation of spine structure (Okamoto et al., 2007).

In addition to its role as an ABP, CaMKII enzymatic activity is also essential for structural synaptic plasticity (Matsuzaki et al., 2004; Okamoto et al., 2004). The inhibition of kinase activity abolishes long-term spine enlargement following stimulation that would otherwise induce sLTP (Matsuzaki et al., 2004). Furthermore, activity-dependent interaction of CaMKIIβ with actin is critical in controlling not only structural, but also functional plasticity (K. Kim et al., 2015). This implies that CaMKII is an essential component in the mechanisms that tightly links structural with functional plasticity in the spine.

CaMKIIβ binding to F-actin in its basal state (Okamoto et al., 2007) limits the binding of other actin-binding molecules (K. Kim et al., 2015). During LTP induction, the CaMKIIβ/actin interaction is abolished by Ca^{2+}/CaM binding (Shen et al., 1998) and the activation of CaMKIIβ (~1 min) results in the detachment and release of unbundled F-actin. This opens a brief time window where other ABPs have access to bind to F-actin, and to profoundly remodel the filaments (Bosch et al., 2014; Okamoto et al., 2009). The subsequent inactivation of CaMKIIβ results in re-bundling of the polymerized F-actin and re-stabilization of the new dendritic spine structure. Blocking the detachment of CaMKIIβ from F-actin without affecting kinase activity results in a deficit of both structural and functional potentiation (K. Kim et al., 2015), highlighting the crucial dual function of CaMKII enzyme in signaling/kinase activity and dendritic spine morphology during synaptic plasticity.

Although the role of CaMKII during the initial stages of plasticity is now well described and accepted, there is some debate about its function in LTP maintenance and its direct role in memory. Chang and colleagues recently proposed that $CaMKII^{T286A}$ phosphorylation promotes the induction of LTP and integration of calcium signals but is not essential for plasticity maintenance (Chang et al., 2017). This result is in agreement with another report where a photoactivatable CaMKII inhibitor negatively impacts plasticity only when stimulated within 1–2 min of LTP induction (Murakoshi et al., 2017). However, if CaMKII is inhibited > 1 min after plasticity induction, it no longer inhibits LTP, suggesting that CaMKII activation is involved in LTP induction but not necessary for the maintenance. In contrast, another group utilized the "erasure test" to show that the expression of a dominant-negative CaMKII after learning significantly impairs the previously formed memory (Rossetti et al., 2017), suggesting that CaMKII plays a key role in maintenance of plasticity and memory, potentially through re-consolidation at the time of recall (Cao et al., 2008).

In conclusion, postsynaptic CaMKII is crucial for structural and functional synaptic potentiation underlying learning and memory. In addition to Ca^{2+}-dependent direct regulation, other signaling molecules such as cAMP indirectly regulate CaMKII activity during LTP (Blitzer et al., 1998; Brown et al., 2000).

5. Postsynaptic cAMP-dependent regulation of structural plasticity

Cyclic adenosine monophosphate (cAMP) is a ubiquitous second messenger with a variety of cellular functions (Beavo and Brunton, 2002). In dendritic spines, cAMP is synthesized by adenylate cyclase (AC) in response to various receptor-signaling pathways, including NMDAR, mGluR and dopamine receptors (Chetkovich et al., 1991; Chetkovich and Sweatt, 1993; Conn and Pin, 1997; Gilman, 1987; Seeman, 1980). The cAMP pathway plays an important role in synaptic plasticity, specifically in the late-phase of LTP (L-LTP) (Berkowitz et al., 1989; Deisseroth et al., 1996; Enna and Karbon, 1987; Frey et al., 1993; Greengard et al., 1991; Kandel, 2012; Walton et al., 1999). Postsynaptic cAMP activates the cAMP Responsive Element Binding (CREB) transcription factor and upregulates specific transcripts during L-LTP (Berkowitz et al., 1989; Deisseroth et al., 1996; Walton et al., 1999). Membrane-permeant analogues of cAMP have mimicked the increased synaptic potentiation effects of LTP, suggesting that increases in cAMP may lead to L-LTP (Frey et al., 1993). Pharmacological application of the potent AC activator forskolin during synaptic activation shows that cAMP is involved in the structural enlargement of spines (Govindarajan et al., 2011; Otmakhov et al., 2004). These findings suggest that, in addition to its role as a signaling molecule for LTP, cAMP plays a structural role in dendritic spines.

Our recent results show a rapid and protein synthesis-independent

postsynaptic cAMP mechanism in enhancing structural potentiation of spines (Luyben et al., 2016) (Fig. 2 left). Strong synaptic stimulation leads to postsynaptic activation of CaMKII by Ca^{2+} influx while triggering the cAMP/PKA pathway at the same time. As PKA inactivates protein phosphatase 1 (PP1), which dephosphorylates and inactivates CaMKII, an increased presence of cAMP in the spine may prolong the time of CaMKII activation during synaptic plasticity (Blitzer et al., 1998). This effect will result in an increased degree of spine structural potentiation (Luyben et al., 2016), likely by extending the duration of actin cytoskeleton remodeling.

6. Postsynaptic cGMP-dependent regulation of structural plasticity

In the mammalian brain, cyclic guanosine monophosphate (cGMP) is synthesized in response to activation of various receptors including NMDAR, cholinergic and dopamine receptors (Altar et al., 1990; Chalimoniuk et al., 1996; de Vente et al., 2001). The cGMP signaling pathways are thought to play a significant role in modulating synaptic plasticity (Chetkovich et al., 1991; Chetkovich and Sweatt, 1993; Conn and Pin, 1997; Seeman, 1980). In the cerebellum, the cGMP cascade is required for long-term depression (LTD) (Ito, 1989; Kawaguchi and Hirano, 2013). However, the role of cGMP in LTP in hippocampal CA1 pyramidal neurons remains elusive. Originally, the function of cGMP in LTP was thought to be presynaptic, through retrograde NMDAR-dependent nitric oxide (NO) signaling (Zhuo et al., 1994), but other evidence indicates an additional postsynaptic NO/cGMP function in LTP (Garthwaite and Boulton, 1995; Monfort et al., 2002; Son et al., 1998).

The exact role of postsynaptic cGMP in NMDAR-dependent structural potentiation of spines is not known, but signaling molecules which modulate spine structure are known to be downstream of the cGMP pathway, including vasodilator-stimulated phosphoprotein (VASP) (Applewhite et al., 2007; Nikonenko et al., 2013). Indeed, cGMP-dependent protein kinase G (PKG) phosphorylates VASP during synaptic potentiation (Wang et al., 2005). cGMP is also found to modulate a Rho GTPase (RhoA), which stimulates actin polymerization *via* the ROCK LIM-kinase-cofilin pathway (Wang et al., 2005). These results suggest that cGMP signaling has the capacity to directly influence synaptic structural plasticity through its interaction with actin modulating proteins. We found that cGMP is involved in the depotentiation of cAMP-dependent structural enhancement (Borovac et al., 2017) (Fig. 2 right). These results suggest a bidirectional regulation mechanism for structural modification of dendritic spines by postsynaptic cAMP and cGMP signaling pathways.

Bidirectional cAMP and cGMP regulation has been shown in axon/dendrite formation (Shelly et al., 2010). The interactive mechanisms between cAMP and cGMP signaling are not known, but cGMP-dependent activation of cAMP hydrolysis by phosphodiesterases (Beavo, 1995; Zaccolo and Movsesian, 2007), and competitive phosphorylation substrate sites between PKG and PKA (Horstrup et al., 1994) may be involved in the process. cAMP/cGMP signaling may also converge downstream of their kinases through PP1, which in turn impacts CaMKII/F-actin interaction and affects spine morphology (Fig. 2). CaMKII activity is negatively regulated by PP1, which is controlled by cAMP/cGMP-dependent phosphorylation/dephosphorylation of a PP1 inhibitory subunit, inhibitor 1 (I1) (Huang and Paudel, 2000; Mulkey et al., 1994). In conclusion, postsynaptic cAMP/cGMP signaling may indeed play a key role in the regulation of structural synaptic plasticity.

7. Alterations of dendritic spine structure and F-actin dynamics in brain disorders

Brain disorders such as Alzheimer's disease (AD), schizophrenia and autism spectrum disorder (ASD), are associated with abnormalities in dendritic spine morphology (Forrest et al., 2018). Given the tight relationship between structure and function in nervous circuits, cells and synapses, it is not clear if these structural abnormalities are the consequence or rather the cause of the physiological impairment. It is therefore of extreme interest to elucidate the alterations in the regulation of F-actin dynamics by ABPs and/or signaling messengers and their contribution to alterations in spine morphology and to synaptic function.

7.1. Alzheimer's disease (AD)

AD is a devastating condition, which presents with significant and progressive memory loss, deposition of amyloid (Aβ) oligomers, and synaptic and neuronal dysfunction (Selkoe, 2000, 2002). As the disease progresses, significant loss of synapses occurs predominantly in the cortex and the hippocampus, which is paralleled with the progression of cognitive decline (Dekosky and Scheff, 1990; Jacobsen et al., 2006; Roy et al., 2016; Shankar et al., 2007; Walsh and Selkoe, 2004).

In Familial Alzheimer's disease (FAD), Aβ oligomers are produced as a result of dysfunctional cleavage of Amyloid precursor protein (APP) by γ-secretase due to mutations in APP and PSEN1/PSEN2 genes (Penzes and Vanleeuwen, 2011). Excessive levels of Aβ in dendritic spines can have detrimental effects on synaptic function. cAMP-dependent synaptic potentiation is inhibited by Aβ deposits (Shankar et al., 2008; Vitolo et al., 2002) and the cGMP pathway is also impaired by Aβ in hippocampal slices (Monfort and Felipo, 2010). Besides altering these signaling messengers, Aβ also causes significant damage to the dendritic spine morphology by interfering with actin modulators. In one report, the treatment of hippocampal neurons with Aβ significantly increases the levels of phosphorylated LIMK and ADF/cofilin, resulting in dramatic remodeling of F-actin and eventually neuronal death (Heredia et al., 2006). Actin/cofilin rod formation is also increased in the AD brain resulting in detrimental synaptic dysfunction (Bamburg and Bernstein, 2016; Rahman et al., 2014). These findings suggest that actin/cofilin dysregulation plays a key role in the synaptic and cognitive dysfunction associated with AD. Another key modulator of actin assembly, PAK, is compromised in AD due to mislocalization in neurons, which leads to loss of F-actin in dendrites and spines (Ma et al., 2008). Kalirin, which is upstream of PAK, was also reported to be under-expressed in AD (Youn et al., 2007), which suggests that the Kalirin-Rac-PAK signaling cascade is involved in AD progression. Finally, RhoA was found to be decreased in AD synapses and has been considered a promising therapeutic target for the treatment of AD (Aguilar et al., 2017; Huesa et al., 2010).

The Aβ–induced spine loss can be blocked by inhibition of calcineurin (PP2B), which is a calcium sensitive phosphatase commonly associated with synaptic weakening (Wu et al., 2010). This finding is consistent with previous reports of calcineurin over-activation in AD (Liu et al., 2005), which is accompanied with dysregulation of synaptic signaling homeostasis.

In sporadic or late-onset AD, another focus of investigation has been the gene encoding apolipoprotein E (APOE) (Sleegers et al., 2010) which has either detrimental or protective effects on the dendritic spine, depending on the allele (APOE ε4 and APOE ε2, respectively) (Dumanis et al., 2009; Lanz et al., 2003). Furthermore, genes such as clusterin (APOJ) and PICALM affect Aβ aggregation and clearance, therefore impacting dendritic spine morphology and disease progression (X. Li et al., 2014; Xu et al., 2015). More research is needed to fully understand the therapeutic potential of targeting these genes.

7.2. Schizophrenia

Schizophrenia is associated with abnormal activity-dependent plasticity with evidence of decreased striatal spine volume (Roberts et al., 1996). Diminished dendritic spine density or spine loss associated with schizophrenia has been reported in various areas of the brain including pre-frontal cortex and the hippocampus (Glantz and Lewis, 2000; Kolomeets et al., 2005; Sweet et al., 2009), which is thought to be

caused by accelerated pruning of synapses during adolescence (Moyer et al., 2015).

The DISC1 gene is associated with mental illness and has been linked to the regulation of spine structure through Rac1, a small GTPase that controls spine cytoskeleton reorganization (Edwards et al., 1999). Reportedly, DISC1 blocks Rac1 activation by inhibiting Kal-7 access to Rac1, therefore affecting the maintenance of the dendritic spine structure (Hayashi-Takagi et al., 2010).

Furthermore, Yan and colleagues have suggested that the synaptic impairments associated with schizophrenia are a result of dysregulation of the actin cytoskeleton through altered expression of key actin regulators including Cdc42, Kalirin and Arp2/3 (Yan et al., 2016). It was also recently reported that expression of the Arp2/3 complex, the actin filament nucleator downstream of Rac1, is significantly lower in the pre-frontal cortex of schizophrenic patients (Datta et al., 2017). Loss of Arp2/3 subunit ArpC3 in forebrain excitatory neurons leads to impaired structural plasticity and loss of dendritic spines *in vivo* (Kim et al., 2013). These Arp2/3 mutant mice respond to haloperidol antipsychotic treatment (I.H. Kim et al., 2015), which strongly suggests a link between Arp2/3 complex regulation and the mechanism of psychiatric disorders such as schizophrenia.

Disruption of cAMP specific phosphodiesterase (PDE4B) gene was also reported in the brain of patients with schizophrenia (Fatemi et al., 2008; Millar et al., 2005), suggesting the involvement of cAMP signaling pathway in this psychiatric disorder.

7.3. Autism spectrum disorder (ASD)

Unlike schizophrenia and AD, ASD is associated with a significant overabundance of dendritic spines. Postmortem studies in patients of ASD show an increased spine density in the frontal, parietal and temporal lobes, which negatively correlates with cognitive function (Hutsler and Zhang, 2010; Martinez-Cerdeno, 2017). In Fragile X syndrome, both patients and transgenic animal models exhibit an exaggerated number of dendritic spines in cerebral cortex and, on average, those spines appear to be longer immature structure (Comery et al., 1997; Irwin et al., 2001; Martinez-Cerdeno, 2017). This phenotype suggests an impairment of spine development, with lack of stabilization and/or pruning, involving the dysfunction of several actin regulatory factors.

There are a number of autism-associated risk genes that encode synaptic scaffolding proteins and actin regulatory proteins (Joensuu et al., 2018). Of particular interest are Shank genes that encode the scaffolding proteins located at the PSD of excitatory glutamatergic synapses (Jiang and Ehlers, 2013). Reportedly, Shank3 deficient mice show reduced F-actin levels associated with decreased Rac1 activity as well as reduced activity of its downstream effectors PAK and LIMK, which are known to facilitate actin filament assembly (Duffney et al., 2015). Over-expression of Shank3 is associated with higher F-actin levels achieved through the interaction with the Arp2/3 complex (Durand et al., 2012), which is consistent with the role of Shank3 in mediating ASD through changes in synaptic architecture. The mutations of α-actinin4 have been found in ASD patients (Joensuu et al., 2018; J. Li et al., 2014), suggesting the involvement of actin cytoskeleton in ASD.

Deficiency of cAMP levels has also been shown in patients and mouse models of Fragile X and autism (Kelley et al., 2008), suggesting a defect in cAMP signaling may also be involved in the progression of ASD. Further studies of cAMP pathways can significantly contribute to strategic development of new therapeutics and markers. Besides proteins regulating the actin cytoskeleton, which are highlighted in this review, alterations in other key genes encoding scaffolding proteins, glutamate receptors, calcium signaling molecules and cell adhesion molecules also contribute to the development and progression of these neuropsychiatric disorders (reviewed in (Forrest et al., 2018).

8. Conclusions

Dendritic spine structure is tightly coupled with synaptic function in basal conditions and during the events of plasticity. Postsynaptic actin filaments are the major regulator of spine morphology. The precise regulation of the multiple actin-binding factors and signaling messengers that modulate F-actin ultimately allows for the precise control of the morphology of each individual spine and consequently the modulation of the physiology of each individual synapse.

Induction of LTP promotes the enlargement of the spine size through the growth of the actin cytoskeleton. This growth is carried out by the coordinated localization and activation of various messengers and ABPs. By combining published results, a model emerges to explain the molecular mechanisms of this structural enlargement. During an initial phase (~1 min), NMDAR-dependent Ca^{2+} signaling detaches CaMKIIβ from F-actin, which unbundles the actin filaments, allowing the binding and action of other ABPs. CaMKIIβ detachment also permits the auto-phosphorylated CaMKIIα/β oligomers to freely diffuse and phosphorylate other target molecules to trigger LTP cascades. Cofilin enters the spine and transiently severs the filaments, which creates free ends that polymerize and branch to increase the amount and complexity of the actin cytoskeleton. During the next ~5 min, F-actin stabilizers (including CaMKIIβ, Drebrin and α-actinin) are transiently depleted in the spine head, facilitating the F-actin remodeling. The growth of F-actin explains the enlargement of the spine. In the subsequent stabilization phase (> 5 min), inactivated CaMKIIβ and other stabilizing ABPs re-bundle and crosslink the new polymerized F-actin. The stabilization of this new reorganized actin cytoskeleton can explain the long-term maintenance of the structural changes.

At the same time, postsynaptic cAMP and cGMP specifically modulate structural synaptic potentiation. Strong NMDAR-dependent activation induces cAMP/PKA signaling that prolongs CaMKIIβ activity through PP1 inactivation and enhances the enlargement of dendritic spines. On the other side, postsynaptic cGMP prevents cAMP effects on structural potentiation, suggesting a bidirectional modulation. cAMP/cGMP signaling is not required for the induction of spine enlargement but rather provides an additional feedback mechanism for the consolidation of the structural changes.

Many brain disorders are associated with an aberrant regulation of F-actin dynamics, ABP localization and function, and impaired signaling of messengers including cAMP/cGMP. These alterations likely underlie the aberrant spine morphology found in these disorders. The manipulation of the mechanisms controlling the actin cytoskeleton has the potential to rescue dysfunction. Further studies on the mechanisms of structural plasticity of dendritic spines will provide new therapeutic targets and methods for the treatment of neuropsychiatric disorders.

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