REVIEWS

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# The Roles of CaMKII and F-Actin in the Structural Plasticity of Dendritic Spines: A Potential Molecular Identity of a Synaptic Tag?

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$Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) and actin are two crucial molecules involved in long-term potentiation (LTP). In addition to its signaling function, CaMKII plays a structural role via direct interaction with actin filaments, thus coupling functional and structural plasticity in dendritic spines. The status of F-actin, regulated by CaMKII, determines the postsynaptic protein binding capacity and thus may act as a synaptic tag that consolidates LTP.

## Two Aspects of Synaptic Plasticity: Functional and Structural Changes

One of the fundamental attributes of the brain is the plasticity of its synapses—namely, a positive or negative change in the efficacy of connections between neurons in response to neuronal activity. This feature is essential for the formation and function of neural circuits, and especially for learning and memory. Depending on the specific pattern of stimulation, individual synapses can increase or decrease the strength of their transmission for minutes to months. This long-term potentiation (LTP) or long-term depression (LTD) of synaptic function has been considered a cellular model for the process of learning and has been studied profoundly (9, 10, 13, 23, 57, 72, 76, 90, 91, 131).

Traditionally, changes in synaptic strength are recorded using electrophysiological techniques and defined as "functional plasticity." In the most intensely studied model, the pyramidal neuron of the CA1 region of the hippocampus, this form of plasticity is mainly attributed to the insertion or removal of AMPA-type glutamate receptors (AMPARs) at the postsynaptic membrane, leading to either a potentiation or a depression of synaptic transmission, respectively. However, recent studies have revealed another aspect of synaptic plasticity termed "structural plasticity." Most excitatory synapses in the mammalian brain dwell in tiny protrusions arising from dendrites called spines. Dendritic spines were believed to be morphologically dynamic since their original discovery by Ramón y Cajal (15). Early studies using electron microscopy also proposed that dendritic spines could be plastic structures (29, 43, 44, 143).

Modern advances in live imaging techniques, particularly in two-photon laser scanning microscopy combined with the genetic introduction of fluorescent proteins, have enabled us to monitor morphological alterations of single spines in living tissue directly (FIGURE 1). It has been found that LTP induces the formation of new dendritic spines and increases the volume of existing ones (25, 75, 80, 95). Conversely, induction of LTD leads to the shrinkage or disappearance of dendritic spines (88, 95, 150). Importantly, the size of the spine and the density of AMPARs exhibit a strong positive correlation (44, 69, 79, 92, 137, 147). Although under certain conditions, and in some cellular systems, functional and structural plasticity can be regulated independently (61, 119, 144), the strong correlation between the two suggests that they must share common and overlapping mechanisms.

## CaMKII is Essential for Functional and Structural Plasticity

Since the discovery of LTP, a large number of studies have attempted to unravel its molecular mechanisms. Among the molecules implicated in synaptic plasticity, $Ca^{2+}$/CaMKII has been established as one of the most important postsynaptic components for LTP (67, 68, 127, 128, 132). CaMKII is a ubiquitous serine/threonine protein kinase involved in a vast variety of cellular functions (22, 55, 58, 68, 115–117, 129, 145). It is highly abundant in the brain, especially in the postsynaptic density (102). In mammals, CaMKII is encoded by a family of four genes, α, β, γ, and δ (37, 50). All these isoforms are found in the brain, but α and β subunits are especially highly expressed (7, 102, 141).

CaMKII is necessary and sufficient for the induction of LTP. Extracellular or intracellular application of CaMKII inhibitors such as KN-62 and KN-93, blocks LTP (52, 74, 77, 78). Although these drugs are reported to inhibit also other types of $Ca^{2+}$/calmodulin-dependent protein kinases, such as CaMKI and CaMKIV (111), CaMKII is assumed to be the critical one, since the same effect was observed in animals carrying a genetic disruption of the CaMKII gene (126, 127). On the other hand, injection of an active form of CaMKII increases AMPAR-mediated synaptic transmission and occludes further induction of LTP (70, 125). Viral expression of active CaMKII also enhances transmission by inserting

AMPARs into the synapse, thus mimicking the mechanism for LTP induction (45, 104, 105).

The activity of CaMKII is tightly regulated. In the inactive state, the catalytic core of CaMKII is masked by its own autoinhibitory domain (21, 56). During LTP induction, an influx of $Ca^{2+}$ to the postsynapse through NMDA-type glutamate receptors (NMDARs) leads to the formation of the $Ca^{2+}$-calmodulin (CaM) complex. This complex relieves autoinhibition by binding to the CaMKII regulatory domain located adjacent to the autoinhibitory domain, thereby exposing the catalytic core region. This event is followed by the autophosphorylation of threonine 286 (T286) located within the autoinhibitory domain, which renders the kinase constitutively active even after the intracellular concentration of $Ca^{2+}$ has dropped to the baseline level (21, 51, 56, 86, 118, 140). The significance of this autophosphorylation event was demonstrated when genetically modified animals carrying a mutation at T286 were found to exhibit reduced LTP (38).

Protein structural studies indicate that CaMKII is an oligomer composed of 10–14 monomers arranged in rotational symmetry (47, 54, 60, 87) (FIGURE 2B). The autophosphorylation at T286 takes place between adjacent monomers of the oligomer in a regenerative way; i.e., even if one subunit is dephosphorylated, the adjacent subunit rephosphorylates it (42, 85, 107, 148). Because of the unique property of CaMKII to become constitutively active, it has been considered an ideal candidate to control the cascade of events that sustain the elevated transmission after LTP induction (66). Recently, conflicting evidence has emerged surrounding the duration of CaMKII constitutive activity during LTP. Biochemical and immunohistochemical studies indicate that the activity of CaMKII remains elevated for several hours after the induction of LTP in hippocampal slices (2, 4, 35, 99, 100). In contrast, a recent elegant imaging study that visualizes CaMKII activity using a fluorescent-resonance energy transfer (FRET)-based probe and fluorescence life-time imaging microscopy (FLIM) found that, when a single spine is potentiated by local flash photolysis of caged glutamate, the activity of CaMKII is transient and decays within a couple of minutes after LTP induction (64). In fact, LTP is not blocked when a CaMKII inhibitor is applied after the induction period (18, 78, 97). Although there is ample evidence indicating that CaMKII is crucial for LTP, the precise temporal and spatial regulation of its activity and the exact mechanisms and pathways that lead to the increase in glutamatergic transmission are not completely known.

CaMKII is also involved in the structural plasticity of spines. Application of the CaMK inhibitor KN-62, or the NMDAR antagonist AP5, prevents glutamate-induced long-term enlargement of the dendritic spine, suggesting that activity-dependent spine growth requires both CaMKII activity and NMDAR influx (80). This begs the question, how does CaMKII activation lead to structural changes at the spine? To answer this, we must first identify the primary mechanisms that regulate the morphology of the dendritic spine.

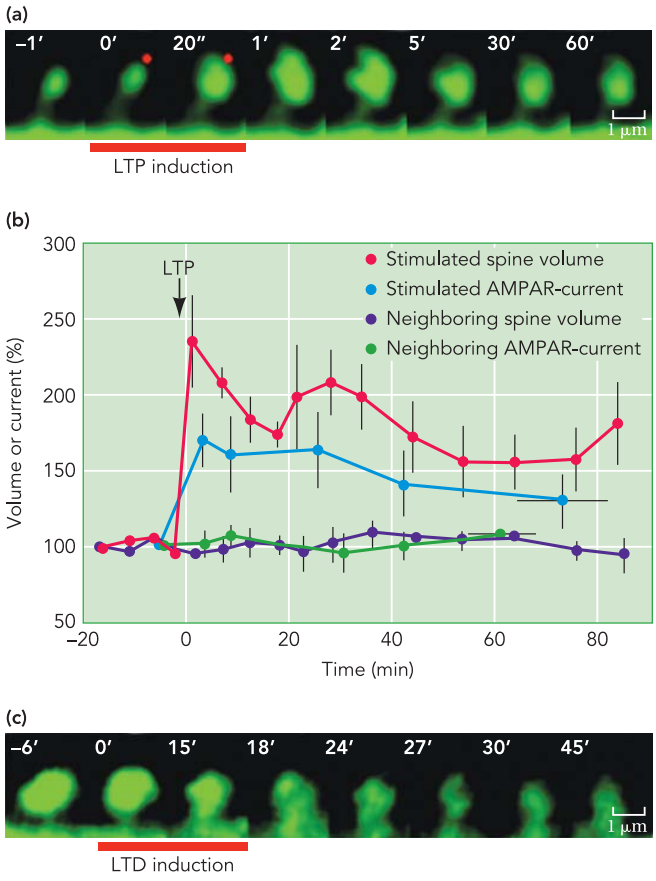


FIGURE 1. **Structural plasticity of dendritic spines**
*a*: Dendritic spines grow after selective induction of LTP by two-photon glutamate uncaging [glutamate pulses at the tip of spine head (red dot) for 1 minute (red bar)] (the authors' unpublished data). *b*: Functional and structural plasticity are correlated. Spine volume and AMPAR currents increase persistently and in parallel to each other after single-spine LTP induction (adapted from Ref. 79). *c*: Spines shrink after electrical induction of LTD [1-Hz stimulation for 15 min (red bar)] (adapted from Ref. 95).

## Actin is Essential for Functional and Structural Plasticity

Actin is the major cytoskeletal protein in dendritic spines, where it serves both as a framework for the mechanical stability of spine structure and as a scaffold for recruiting various other postsynaptic proteins (20, 24, 120). Actin exists in a dynamic equilibrium between two forms, the monomeric globular form (G-actin) and the filamentous form (F-actin). This equilibrium is bidirectionally modulated by several actin-binding proteins (ABPs). Some of them, like actin depolymerization factor (ADF)/cofilin, promote F-actin depolymerization, while others, like profilin, promote actin polymerization. Other ABPs, such as α-actinin or filamin, can cross-link actin filaments to form suprastructures, such as linear bundles or meshwork, respectively (8, 133). Manipulation of ABPs, by

overexpression or knockdown, can significantly affect spine size or spine density (27, 114, 135). Thus, although microtubules can transiently invade the spine (49, 53), spine structure is mainly regulated through the coordinated activity of ABPs on the actin cytoskeleton.

Studies indicate that dendritic spines may contain at least two different pools of F-actin (20, 48). First, a very dynamic pool is believed to exist below the spine surface, interacting directly or indirectly with AMPARs, NMDARs, and PSD scaffolding and signaling proteins. A second more internal and stable pool of F-actin may serve as the main scaffold that supports the overall spine structure. Stable actin filaments have been detected at the core of the spine head, the spine neck, and associated with the spine apparatus (24). Recently, Honkura and colleagues have proposed the existence of a third pool of stable F-actin that is only created after LTP induction. The confinement of this pool in the spine head eventually determines the persistence of LTP-induced structural enlargement. This confinement requires CaMKII activity, as in the presence of KN-62 the pool is released and spine growth is only transient (48).

Disruption of actin filaments by depolymerizing agents, such as latrunculin A, prevents the expression of functional LTP but does not block the short-term potentiation (STP) (19, 59, 62, 63). In a similar way, latrunculin A preferentially inhibits the long-lasting spine enlargement that takes place after LTP induction but not the initial phase (80). Thus, integrity of the actin cytoskeleton is necessary for both functional and structural long-term plasticity.

There have been conflicting reports in the field as to whether actin is polymerized or depolymerized during synaptic plasticity. Studies using fluorescently labeled phalloidin, which specifically binds to F-actin, have reported both an increase (34, 63) and a decrease (36, 41, 46) of F-actin content in the spine following various pharmacological stimulations. Using a FRET-based method to monitor the equilibrium between F-actin and G-actin in response to local electrical stimulation, Okamoto and colleagues demonstrated that LTP shifts the F-actin/G-actin equilibrium toward F-actin, which persists for at least 30 min (FIGURE 3) (95). This shift in equilibrium precedes the accumulation of the total amount of actin, as well as the structural changes to the spine, suggesting that modification of the F-actin/G-actin equilibrium may be required to trigger the morphological reorganization seen during LTP. In contrast, LTD shifts the F-actin/G-actin equilibrium

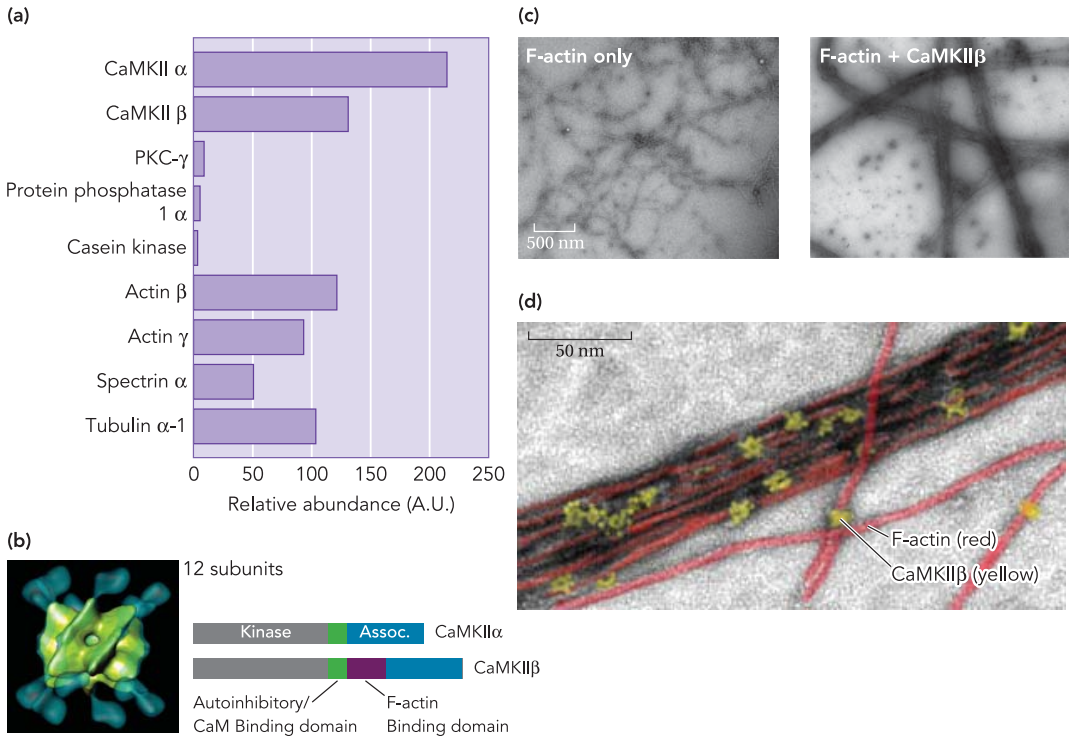


FIGURE 2. **CaMKIIβ bundles actin filaments together**
*a*: The relative abundance, in arbitrary units (A.U.), of various postsynaptic proteins in the PSD, as determined by systematic mass spectrometric assay, shows that CaMKII is more abundant than cytoskeletal proteins and at least one order of magnitude or more abundant than other kinase/phosphatase proteins. Original data are from Ref. 102. *b*: Three-dimensional structure of a CaMKII oligomer of 12 subunits (original data from Ref. 60) and schematic drawings of the domain structure of CaMKIIα and β. Only the β subunit has an F-actin binding domain. *c*: Electron micrographs of bundled F-actin in the presence (*right*) but not in the absence (*left*) of purified CaMKIIβ in vitro (adapted from Ref. 96). *d*: False-colored electron micrograph where bundled F-actin filaments are highlighted in red and CaMKIIβ oligomers in yellow (image from Ref. 110).

toward G-actin. These observations demonstrate that the F-actin/G-actin equilibrium is a key locus of plasticity that bidirectionally regulates the function and structure of the dendritic spine.

*"However, the precise molecular connection between the initial LTP stimulus and the induction or maintenance of spine growth is not yet clear, but several mechanisms have recently been proposed."*

## Possible Role of F-Actin as an LTP-Specific Synaptic Tag

Strong stimulation of the postsynaptic neuron—by means of multiple stimulation trains or stimulation in the presence of enhancers such as brain-derived neurotrophic factor (BDNF) or dopamine (16, 32, 71)—induces a long-lasting synaptic potentiation that can be dissociated into two phases: an early phase that lasts for 1–4 h and does not depend on new protein translation, and a late phase (≥4 h) that requires the synthesis of new proteins. Weak stimulation can only induce the early phase of LTP, but this outcome can be promoted to the late phase if a strong heterosynaptic stimulation occurs in a short time window (≤2–3 h) (33). How the newly synthesized proteins in the soma can selectively find the potentiated synapses is explained by the "synaptic tagging and capture" hypothesis (32, 33). A "tag" is formed at those synapses that are either weakly or strongly stimulated. Newly synthesized "plasticity-related proteins," induced only by the strong stimulation, are "captured" by all tagged synapses, leading to the long-term consolidation of the potentiated state.

The molecular identity of the synaptic tag is still largely obscure, but it has to fulfill several criteria. First, it has to be formed specifically at the potentiated synapses. Second, it does not require synthesis of new proteins. Third, it must last at least 1 h or so. Fourth, it should be a structure able to recruit the newly synthesized plasticity-related proteins.

The new F-actin complex formed at the dendritic spine during LTP induction actually fulfills all of these features. The polymerization of actin does not require new protein translation, and it is induced in a synapse-specific manner. Furthermore, it lasts for at least 30 min and possibly beyond (34, 95), and it can serve as a major docking site for postsynaptic proteins that directly and indirectly bind to F-actin. Hence, the increased number of binding sites conferred by the formation of new F-actin might be the mechanism that selectively captures the LTP-related proteins synthesized in the cell body and transported into dendrites.

Indeed, it has been recently reported that synaptic tagging, but not the synthesis of new plasticity proteins, can be prevented by pharmacologically disrupting F-actin during LTP induction (106), which strongly supports the hypothesis that F-actin is an essential part of the LTP-specific tag. On the other hand, inhibition of CaMK by KN-62 also prevents the establishment of the LTP-specific synaptic tag (109). These observations suggest that there must be a way by which CaMKII activity controls the status and content of F-actin, which ultimately allows the structural plasticity of the spine and the formation of the synaptic tag.

## Structural Role of CaMKII as an F-Actin-Bundling Protein

LTP, as well as in vivo sensory experience-driven potentiation, has been demonstrated to deliver AMPARs to the synapse (45, 124, 136). CaMKII has also been observed to translocate to the synapse after synaptic activation (98, 121, 122, 149). Using the expression of various mutant forms of CaMKIIα, it has been demonstrated that this translocation is triggered by the interaction with $Ca^{2+}$/CaM but interestingly does not require functional kinase activity or autophosphorylation at T286 (42, 121, 122). Rather, kinase activity and T286 autophosphorylation are both required for retention of CaMKII at the synapse after translocation (121). CaMKII self-association and interaction with the

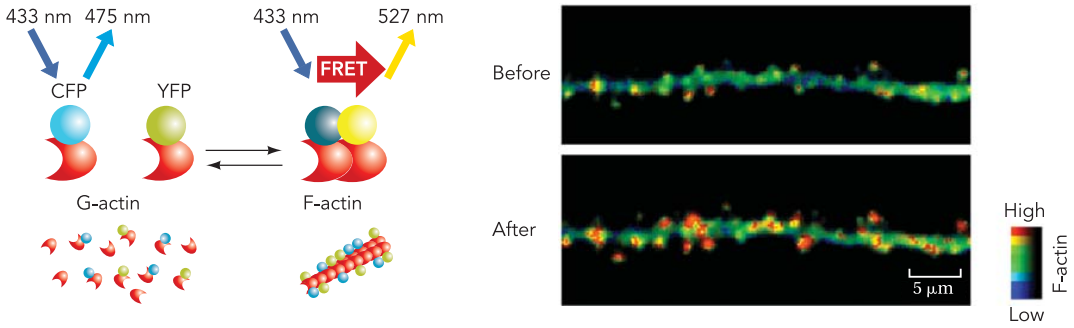


FIGURE 3. **Visualization of F-actin/G-actin equilibrium in spines**
*Left*: strategy for detecting the F-actin/G-actin equilibrium using FRET. *Right*: imaging the F-actin/G-actin equilibrium in dendrites before and after tetanic stimulation. Warmer hues indicate higher F-actin ratios (adapted from Ref. 95).

NR2B subunit of NMDARs are also regulated by T286 phosphorylation and may contribute to the specific localization of CaMKII to the synapse (5, 6). These finely regulated temporal and spatial patterns of trafficking and activity highlight the important role of CaMKII as a signal transduction molecule at the synapse. Interestingly, CaMKII constitutes about 10–30% of the postsynaptic density (PSD) and is much more abundant than any other signal transduction molecule, such as PKC (FIGURE 2A) (26, 102). In fact, this number is comparable to the abundance of structural proteins found in the PSD, such as actin. This observation has led to the speculation that CaMKII might have a structural function in addition to its signaling activity (94).

The β-subunit of CaMKII possesses a unique domain that the α-subunit lacks, which provides the capacity of binding to actin filaments (FIGURE 2B). This F-actin binding domain is involved in delivering CaMKII from the cytosolic fraction to the postsynaptic cytoskeletal structure (95, 123). Overexpression of CaMKIIβ increases the number of neurite extensions and the formation of new synapses, which is also detected as an increase in miniature EPSCs in dissociated neuronal cultures (30, 139). These effects are not seen, or even reversed, after overexpression of the α-subunit of CaMKII (139). Reduction of endogenous CaMKIIβ, but not α, using specific shRNA significantly affects the shape of mature spines, turning them into immature filopodia-like structures (96). Expression of full-length CaMKIIβ, or CAMKIIβ mutants that lack the kinase domain, can rescue the structure of spines to their mature form.

The α- and β-subunits of CaMKII actually coexist in neurons, where they can associate and form hetero-oligomers (11, 123). The β-subunit constitutes about 30% of the total amount of CaMKII in the adult forebrain and 80% in the cerebellum (84). Therefore, in the forebrain, among the 10–14 subunits that constitute one CaMKII hetero-oligomer, an average of 3–4 subunits are CaMKIIβ. In fact, the existence of oligomers made of pure α-subunits but not of pure β-subunits has been reported (12). Hence, the actual proportion of β-subunits in the hetero-oligomers may be even higher. This suggests that CaMKII hetero-oligomers might bind simultaneously to different actin filaments through multiple β-subunits and, thus, might confer on CaMKII the ability to bundle actin filaments together. Confirming this idea, F-actin has been found to forms thick bundled structures in vitro in the presence of the β-subunit of CaMKII but not in the presence of the α-subunit (FIGURE 2, C AND D) (93, 96, 110). Phosphorylation of CaMKII reduces this bundling activity, suggesting that this property can be regulated by synaptic activity (96). Furthermore, Okamoto and colleagues found that CaMKIIβ stabilizes the actin cytoskeleton in spines. Overexpression of CaMKIIβ slows the turnover of GFP-actin dynamics almost twofold. Interestingly, mutants that lack the kinase activity also produce the same effect (65, 96), suggesting that the F-actin bundling property of CaMKIIβ is independent of its kinase activity. These findings clearly point to an essential structural function that CaMKII, through the β-subunit, plays in dendritic spines, with important implications on the reorganization of the actin cytoskeleton during plasticity events.

## Functional Role of CaMKII as a Signal Transduction Molecule that Remodels the Actin Cytoskeleton

In addition to its direct interaction with actin filaments, CaMKII also triggers alternative pathways, via its kinase activity, that regulate F-actin dynamics (FIGURE 4). These pathways mainly converge on the Rho family of small GTPases such as RhoA, Rac1, or Cdc42. The activity of GTPases is bidirectionally controlled by guanine-nucleotide-exchange factors (GEFs) and GTPase activating proteins (GAPs). GEFs trigger GTPase activity, whereas GAPs suppress it. These signaling pathways are potent regulators of F-actin dynamics and have been directly implicated in spine morphogenesis and plasticity (40, 89, 134).

One of these GEF proteins is kalirin-7, whose activity is reported to be essential for spine enlargement

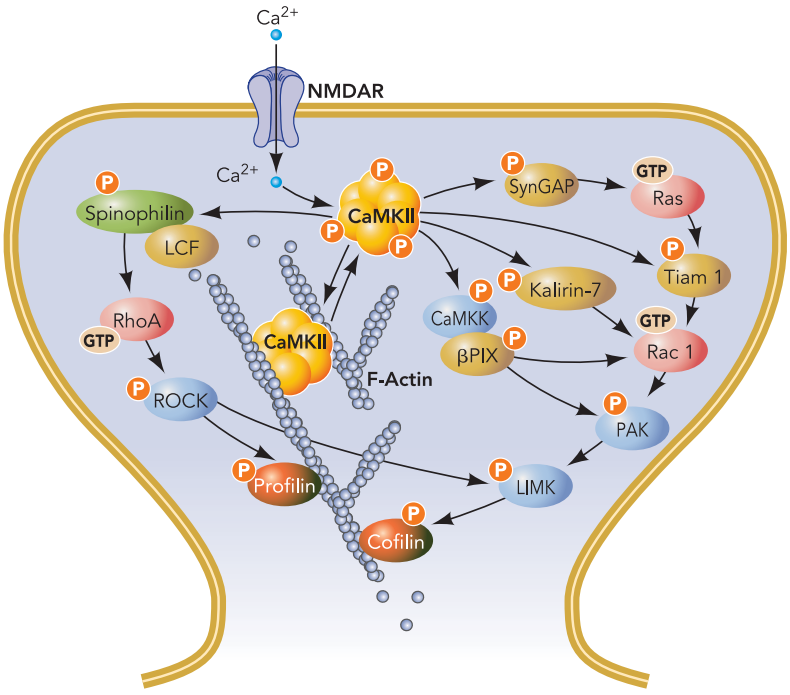


FIGURE 4. **Signaling pathways triggered by CaMKII kinase activity that indirectly regulate the actin cytoskeleton**
NMDAR-dependent calcium influx activates CaMKII. Other than its "direct" bundling action on F-actin, CaMKII kinase activity regulates the signaling cascades involving several other kinases and members of the Rho family of small GTPases. These multiple cascades modulate the activity of the actin-binding proteins cofilin and profilin, which eventually polymerize or depolymerize the actin filaments.

and for GluR1-containing AMPAR trafficking to the synapse (103). After activation of NMDARs, CaMKII phosphorylates kalirin-7 and increases its GEF activity. This leads to the activation of the GTPase Rac1, which in turn activates the cascade of LIM kinase (LIMK) through p21-activated kinase (PAK). LIMK ultimately modulates the activity of cofilin (146).

Cofilin promotes the depolymerization of F-actin by severing actin filaments and by promoting the dissociation of G-actin from the pointed end of F-actin (112). LIMK phosphorylates cofilin at Ser-3 and promotes its dissociation from F-actin and its functional inactivation. The dissociation event allows other F-actin-binding proteins, like drebrin A, to stabilize actin filaments (81). Studies in vivo have shown that both LTP and exploratory learning induce the phosphorylation of cofilin in the hippocampus (19, 28, 34, 83). On the other hand, preventing cofilin phosphorylation by blocking LIMK activity results in spine shrinkage (82, 150). At high concentration, however, cofilin promotes actin filament nucleation and thus enhances actin polymerization in cells (3). Hence, cofilin regulates the G-actin/F-actin equilibrium in a complex variety of ways.

CaMKII mediates other signaling mechanisms involving kinases like CaMK kinase and CaMKI, which regulate the GEF activity of β-PAK-interacting exchange factor (β-PIX) (111). This GEF protein modulates both Rac1 and PAK activity and eventually controls cofilin activity (101). Rac1 is also regulated by Tiam1, another GEF protein that is activated by CaMKII either through direct phosphorylation (14, 31) or indirectly through SynGAP and Ras activity (17) to ultimately remodel spine structure (17, 142).

Another small GTPase, RhoA, also controls F-actin dynamics through its actions on cofilin and profilin II. Profilin II is a G-actin-binding protein that facilitates polymerization by promoting the addition of actin monomers to the growing end of actin filaments. This pathway is initiated by CaMKII-mediated phosphorylation of spinophilin (neurabin II). Similar to CaMKIIβ, spinophilin has the property to detach from F-actin after phosphorylation (39). In neurons, this

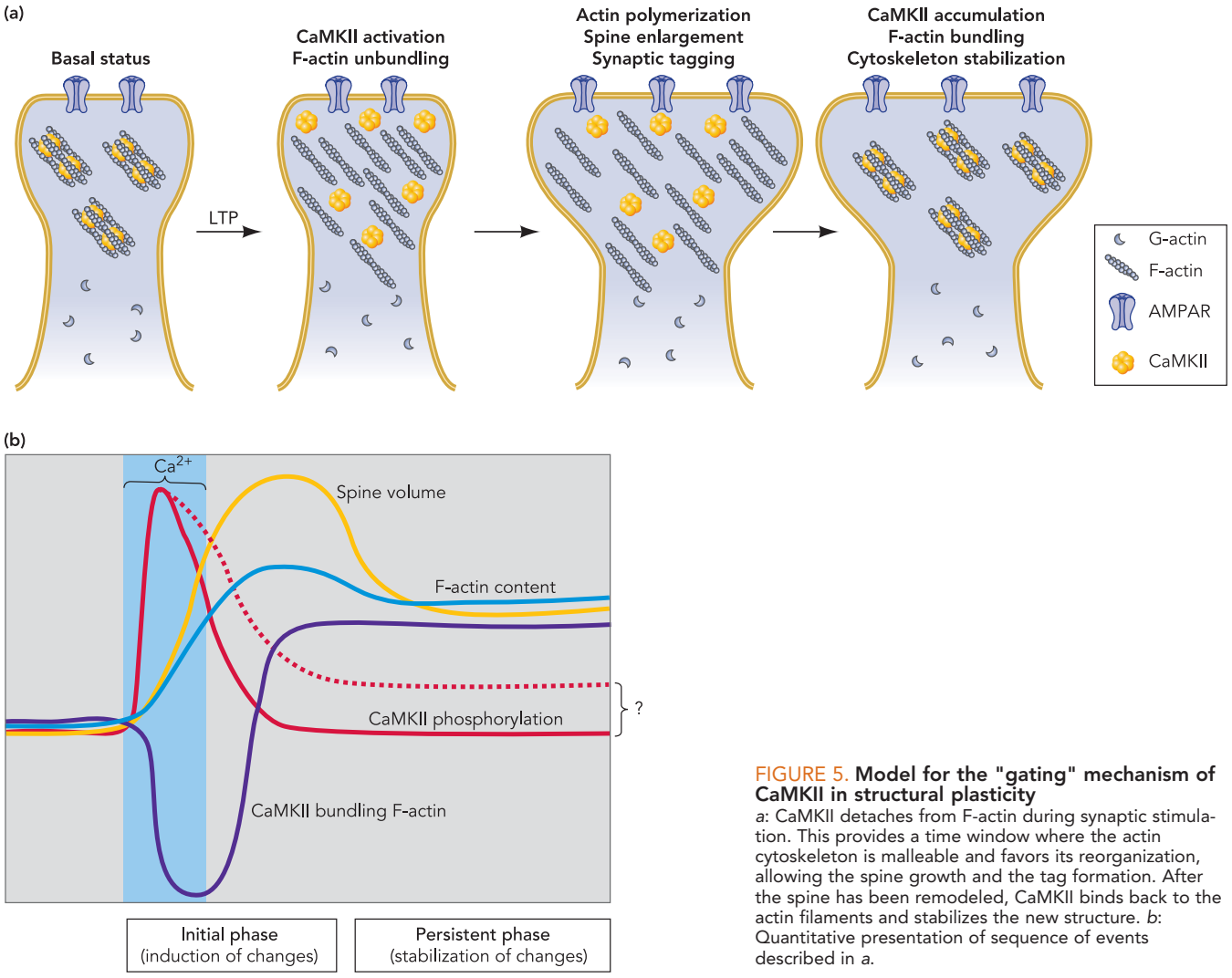


FIGURE 5. **Model for the "gating" mechanism of CaMKII in structural plasticity**
*a*: CaMKII detaches from F-actin during synaptic stimulation. This provides a time window where the actin cytoskeleton is malleable and favors its reorganization, allowing the spine growth and the tag formation. After the spine has been remodeled, CaMKII binds back to the actin filaments and stabilizes the new structure. *b*: Quantitative presentation of sequence of events described in *a*.

phosphorylation recruits spinophilin together with the GEF protein Lcf to the spine membrane (108), which in turn, promotes the localization of RhoA, RhoA-specific kinase (ROCK), and profilin II close to the PSD, where they promote the formation of new actin filaments (1, 113). At the same time, the RhoA-ROCK complex activates LIMK and modifies actin filaments via cofilin (73, 113).

Altogether, CaMKII is able to modify F-actin through multiple mechanisms. However, the precise molecular connection between the initial LTP stimulus and the induction or maintenance of spine growth is not yet clear, but several mechanisms have recently been proposed. Since CaMKII inhibitors block the sustained phase of spine enlargement during LTP but not the initial and transient phase (80), CaMKII kinase activity must be involved in the long-term stabilization but not necessarily in the initiation of structural changes. Kopec and colleagues suggest that the incorporation of the GluR1 subunit of AMPARs to the synapse promotes the formation of a protein interaction or a complex through the PDZ domain of its COOH terminus. This interaction does not induce spine growth per se but is necessary and sufficient to maintain the long-lasting stabilization of spine enlargement (61). On the other hand, Steiner and colleagues (130) found that PSD-95 signaling is necessary for both the transient and the long-lasting phases of structural plasticity. After LTP induction, a growth-promoting complex may form between PSD-95 and other proteins. Phosphorylation of Ser73 by CaMKII induces the destabilization of this complex and the termination of the initial growth phase (130). In addition, the long-lasting persistent phase of spine growth can be further enhanced by stimulating new protein synthesis, either by application of BDNF or by pairing postsynaptic spikes with glutamate uncaging in single spines (138).

## CaMKII and F-Actin Links Functional and Structural Plasticity

CaMKII stabilizes the actin cytoskeleton and preserves spine structure without the involvement of its kinase activity. However, this kinase activity is essential for structural plasticity (80, 95), because its inhibition abolishes long-term spine enlargement. What, then, is the function of CaMKII kinase activity in structural plasticity? Activity of CaMKII initiates multiple signaling pathways through phosphorylation of targets such as GluR1 or PSD-95 and through activation of the Rho family of small GTPases that regulate the G-actin/F-actin equilibrium. However, because of the abundance of CaMKII in the spine, the main target of its kinase activity may actually be CaMKII itself. Activation of one subunit leads to rapid phosphorylation of the other subunits intra- or inter-molecularly. This phosphorylation status in turn regulates the ability of CaMKII to bind directly to F-actin. In the basal condition, actin filaments are bundled by CaMKII through the β-subunit, thereby maintaining the stability of spine structure (FIGURE 5). NMDAR activation and the resultant $Ca^{2+}$ influx trigger the kinase activity of CaMKII, inducing its autophosphorylation and, thereby, its detachment from actin filaments. The mobilized CaMKII can freely diffuse and phosphorylate other signaling or scaffolding targets. At the same time, the detachment from F-actin allows for additional transient flexibility of the actin cytoskeleton and for subsequent remodeling of the dendritic spine structure.

After CaMKII activity returns to the basal state, phosphatases may take over the signaling cascades and dephosphorylate its targets. Simultaneously, CaMKII associates again with newly reorganized actin filaments, bundles them, and consolidates the remodeled spine morphology. The increased amount of F-actin and its newly remodeled organization provides new binding sites for many other postsynaptic proteins. Newly synthesized LTP-related proteins can be captured at those sites, sustaining the potentiated state for the long term. Thus F-actin is a plausible candidate as the spine-specific synaptic tag that consolidates the late phase of LTP.

In conclusion, there is a great deal of evidence suggesting that CaMKII is a multifunctional molecule that may work as a "gating" mechanism, keeping the spine structure constant at resting $Ca^{2+}$ levels, allowing and promoting modifications when $Ca^{2+}$ levels increase, and eventually preserving new modifications for the long term. The duration of its activated state gives a time window wherein the actin cytoskeleton can be significantly remodeled. In this way, CaMKII plays a dual role in excitatory synaptic plasticity: a signaling role during transient periods of neuronal activity, and a structural role during the basal state, thereby linking functional and structural plasticity. ■

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