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Regulation of Synaptic Transmission by Presynaptic CaMKII and BK Channels

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Abstract Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the BK channel are enriched at the presynaptic nerve terminal, where CaMKII associates with synaptic vesicles whereas the BK channel colocalizes with voltage-sensitive Ca^{2+} channels in the plasma membrane. Mounting evidence suggests that these two proteins play important roles in controlling neurotransmitter release. Presynaptic BK channels primarily serve as a negative regulator of neurotransmitter release. In contrast, presynaptic CaMKII either enhances or inhibits neurotransmitter release and synaptic plasticity depending on experimental or physiological conditions and properties of specific synapses. The different functions of presynaptic CaMKII appear to be mediated by distinct downstream proteins, including the BK channel.

Keywords Calcium/calmodulin-dependent protein kinase II (CaMKII) · Neurotransmitter release · BK channel · Slo · Slo1 · SLO-1 · Maxi-K channel · Synapsin · $Ca_V2.1$ · Calcium channel · Ryanodine receptor · Synaptotagmin · SNARE

The presynaptic nerve terminal contains a rich variety of proteins. Many of these proteins contribute to the precise control of neurotransmitter release, which is vital to the proper function of the nervous system. Among presynaptic proteins that regulate neurotransmitter release, CaMKII and the BK channel are two prominent players and share the property of being activated by Ca^{2+}. Presynaptic CaMKII and BK channel play important and complex roles in controlling synaptic strength and plasticity through interactions with a variety of other presynaptic components, including channels that provide Ca^{2+} for their activation and proteins that mediate their functions. This review summarizes our current understanding about the functions of presynaptic CaMKII and BK channel in regulating synaptic transmission. Two main reasons prompted me to review the functions of these two proteins in the same article: (1) presynaptic CaMKII and BK channel interact closely in regulating synaptic transmission and (2) the functions of presynaptic CaMKII or BK channel have rarely been the focus of scientific reviews.

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The Function of Presynaptic CaMKII in Controlling Synaptic Strength and Plasticity

Structural and Functional Properties of CaMKII

CaMKII is a serine–threonine protein kinase that is activated by Ca^{2+} and calmodulin. It is a holoenzyme of multiple protein subunits. Electron microscopic analyses suggest that the holoenzyme consists of 12 subunits that form two stacked hexameric rings [1, 2]. Four closely related but distinct genes (α, β, γ, and δ) encode CaMKII subunits in mammals. The holoenzyme may be formed by either one or more isoforms of the CaMKII subunits [3].

Each CaMKII subunit consists of a catalytic domain, a regulatory domain, a variable segment, and an association domain (Fig. 1). The regulatory domain is further divided into two partially overlapping domains: autoinhibitory domain and calmodulin-binding domain [4]. The catalytic domain has intrinsic kinase activity and contains the substrate- and adenosine triphosphate (ATP)-binding sites.

However, under basal conditions, the kinase activity is inhibited by the autoinhibitory domain, which binds the catalytic domain as a pseudosubstrate. Upon Ca^{2+}/calmodulin binding to the calmodulin-binding domain, the autoinhibitory domain dissociates from the catalytic domain, which unmasks the kinase activity. The variable segment differs in length among CaMKII isoforms and may serve to localize CaMKII to specific subcellular domains and to modify the sensitivity to Ca^{2+}/calmodulin. The association domain mediates assembly of the holoenzyme (see [5] for a review).

The activity of CaMKII may be controlled by autophosphorylation of specific residues in the autoinhibitory domain (Fig. 1). Phosphorylation of three threonine residues (T^{286}, T^{305}, and T^{306}, numbered according to their positions in αCaMKII) is of particular importance. T^{286} is trans-autophosphorylated by the catalytic domain of a neighboring CaMKII subunit after the autoinhibitory domain has dissociated from the catalytic domain in response to Ca^{2+}/calmodulin binding [6]. CaMKII autophosphorylated at this residue remains active even after cytoplasmic [Ca^{2+}] falls back to the basal level [7–11]. T^{305} and T^{306} are located in the calmodulin-binding site. They may be autophosphorylated following T^{286} autophosphorylation and Ca^{2+}/calmodulin dissociation from the calmodulin-binding domain. Autophosphorylation at T^{305} and T^{306} blocks subsequent activation of the kinase by Ca^{2+}/calmodulin [12, 13]. Autophosphorylation is potentially an important mechanism in controlling the function of presynaptic CaMKII since synaptic vesicle-associated CaMKII may be similarly autophosphorylated [14] and the autophosphorylation may be enhanced by depolarization [15].

Autophosphorylation of CaMKII may be reversed by dephosphorylation catalyzed by phosphatase 1 (PP1), phosphatase 2A (PP2A), or phosphatase 2C. Although the three phosphatases can dephosphate CaMKII at any of the three threonine residues (T^{286}, T^{305}, and T^{306}) in vitro [13, 16–18]; some specificity appears to exist in vivo. For example, CaMKII in the cytoplasm is primarily dephosphorylated by PP2A whereas that in the postsynaptic density is primarily dephosphorylated by PP1 [18]. This apparent specificity is probably due to the enrichment of distinct phosphatases in different subcellular compartments [18]. It remains to be determined which phosphatase(s) catalyzes the dephosphorylation of presynaptic CaMKII.

CaMKII could also become constitutively active (Ca^{2+}-independent) following oxidation of a pair of methionine residues near the autoinhibitory domain, which was recently shown for δCaMKII [19]. However, it remains to be determined whether βCaMKII and γCaMKII, in which the two methionine residues are conserved, may be similarly modulated by the oxidation.

Presynaptic CaMKII Modulates Synaptic Strength and Plasticity

CaMKII is enriched at the presynaptic nerve terminal [15, 20], where it mainly associates with the outer surface of synaptic vesicles [21]. At least three isoforms of the CaMKII subunits (α, β, and γ) associate with synaptic vesicles [22]. The function of presynaptic CaMKII in synaptic strength and plasticity has been assessed by a number of studies. Presynaptic CaMKII appears to have complex functions in synaptic transmission. While some studies suggest that presynaptic CaMKII is a positive regulator of synaptic transmission, others suggest that it is a negative or a bidirectional regulator.

Evidence for Presynaptic CaMKII Being a Positive Regulator of Synaptic Transmission

The earliest evidence about the function of presynaptic CaMKII came from analyses of the squid giant synapse, where injection of purified CaMKII into the presynaptic

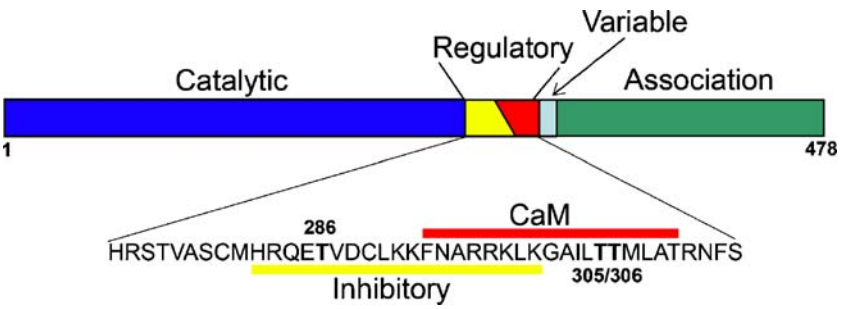

Fig. 1 Schematic representation of domain structures of αCaMKII. The protein may be divided into four functional domains, including the catalytic domain, the regulatory domain, a variable segment that differs between CaMKII isoforms, and the association domain. The regulatory domain is further divided into the autoinhibitory domain and Ca^{2+}/calmodulin (CaM)-binding domain. CaMKII may be autophosphorylated at three threonine residues. Autophosphorylation at threonine 286 (T^{286}) allows the kinase to retain catalytic activity even after Ca^{2+} concentration has returned to basal level, whereas autophosphorylation at T^{305} and T^{306} blocks subsequent activation of the kinase by Ca^{2+}/calmodulin

terminal increases the amplitude and rise rate of evoked postsynaptic potentials and currents (ePSPs and ePSCs), suggesting that presynaptic CaMKII enhances neurotransmitter release [23, 24]. Results of subsequent studies provide further support to the notion that presynaptic CaMKII is a positive regulator of neurotransmitter release. For example, loading of synaptosomes purified from rat cerebral cortices with autophosphorylation-activated CaMKII enhances glutamate release induced by high K^+ or a Ca^{2+} ionophore, whereas loading with a CaMKII inhibitory peptide decreases the release [25]. Application of synthetic CaMKII inhibitory peptides to rat hippocampal brain slices strongly reduces the slope of evoked extracellular field potentials in hippocampal CA1 region without altering postsynaptic receptor sensitivity to glutamate [26]. At the *Drosophila* neuromuscular junction (NMJ), CaMKII inhibitors block the enhancement of dense core vesicle motility caused by tetanic nerve stimulation [27]. In *Xenopus* nerve-muscle coculture, loading of a specific CaMKII inhibitory peptide into the presynaptic neuron but not postsynaptic myocyte blocks the stimulatory effect of neurotrophin-3 on the frequency of miniature spontaneous postsynaptic currents [28]. In cultured mouse hippocampal neurons, brief treatment with glutamate increases the frequency of miniature postsynaptic currents and the number of active presynaptic boutons, which are prevented by the CaMKII inhibitor KN-93 but not its inactive analog KN-92 [29]. These studies suggest that presynaptic CaMKII enhances vesicle motility and facilitates spontaneous as well as evoked neurotransmitter release.

Presynaptic CaMKII also plays roles in long-term potentiation (LTP). At several types of synapses examined, including synapses between *Aplysia* sensory and motor neurons [30], between CA3 neurons in rat hippocampal slices [31], and between cultured mouse hippocampal neurons [29], LTP may be reduced or blocked by injecting a CaMKII inhibitory peptide into the presynaptic neuron. Furthermore, injection of a recombinant αCaMKII into the presynaptic neuron induces LTP if the injection is paired with a weak tetanic nerve stimulation that normally does not induce LTP [29].

Evidence for Presynaptic CaMKII Being a Negative Regulator of Synaptic Transmission

In contrast to the studies described above, several other studies suggest that the function of presynaptic CaMKII is to inhibit synaptic transmission. At the CA3–CA1 synapse of mouse hippocampus, targeted knockout of presynaptic CaMKII enhances neurotransmitter release evoked by repetitive presynaptic stimulation [32]. At the same synapse, universal knockout of αCaMKII enhances synaptic augmentation induced by θ-burst stimulation and decreases synaptic fatigue during repetitive stimulation. Both the augmentation and fatigue are forms of short-term synaptic plasticities. Because the origin of short-term plasticity is largely presynaptic [33–36], these observations led to the suggestion that the function of presynaptic CaMKII is to inhibit synaptic transmission [37]. Interestingly, the effects of presynaptic CaMKII on synaptic augmentation and fatigue appear to be independent of the kinase's catalytic activity [37]. In avian hippocampal slices, long-term depression (LTD) requires a rise of Ca^{2+} in the presynaptic but not postsynaptic neuron and is blocked by the CaMKII inhibitor KN-93 [38]. In rat hippocampal slices, application of the membrane-permeant CaMKII inhibitor KN-62 to the extracellular solution but not infusion into the postsynaptic neuron blocks the LTD induced by low-frequency stimulation of the Schaffer collateral, which led to the conclusion that presynaptic but not postsynaptic CaMKII is needed to induce LTD [39].

Evidence for Presynaptic CaMKII Being a Bidirectional Regulator of Synaptic Transmission

The studies described above suggest that presynaptic CaMKII may either enhance or inhibit synaptic transmission. There are two possibilities for the apparently opposite functions: (1) presynaptic CaMKII has different functions at different synapses and (2) presynaptic CaMKII is a bidirectional modulator of synaptic transmission but one of these two functions predominates under specific experimental or physiological conditions. Results of at least two studies favor the second notion. In mouse hippocampal CA1 region, paired-pulse facilitation is blunted whereas posttetanic potentiation is enhanced by deletion of αCaMKII [40]. Since the origins of both paired-pulse facilitation and posttetanic potentiation are largely presynaptic [33–36], these results led to the suggestion that presynaptic CaMKII is a bidirectional modulator of neurotransmitter release depending on the pattern of presynaptic activation [40]. At the *Caenorhabditis elegans* neuromuscular junction, either gain-of-function or loss-of-function mutation of the CaMKII gene *unc-43* causes a marked decrease in evoked neurotransmitter release [41], suggesting that presynaptic CaMKII is likely a bidirectional modulator of neurotransmitter release [41].

It is worth noting that several commonly used CaMKII inhibitors may have nonspecific effects. For example, the prototypical CaMKII inhibitors KN-93 and KN-62 as well as the KN-93 inactive analog KN-92 potently inhibit voltage-dependent K^+ currents in vascular smooth muscle cells at concentrations that are normally used to inhibit CaMKII [42]. This effect on K^+ currents is independent of CaMKII and Ca^{2+} and is probably due to inhibition of a delayed rectifier K^+ channel [42]. Similarly, both KN-93 and KN-92 potently inhibit the activity of SLO-1 BK

channels expressed in *Xenopus* oocytes (Liu and Wang, unpublished). In addition, KN-93 and KN-62 but not KN-92 can enhance the binding of PKC and calmodulin to A-kinase-anchoring protein 79 (Brooks and Tavalin, 2007 Annual Conference of Society for Neuroscience, presentation number 787.1). Thus, cautions should be taken when interpreting results obtained with these chemicals.

Proteins that Mediate the Functions of Presynaptic CaMKII

Presynaptic CaMKII regulates neurotransmitter release and synaptic plasticity by acting through different downstream proteins. Generally, CaMKII modulates the functions of downstream proteins through phosphorylation. However, there is at least one example showing that the catalytic activity of CaMKII is not required. Presynaptic CaMKII may either enhance or inhibit synaptic transmission, depending on the identities of its downstream proteins.

Synapsin I

Synapsin I is perhaps the first protein implicated in the function of presynaptic CaMKII [23–25, 43]. The mammalian genome contains three distinct genes encoding synapsins (synapsins I, II, and III). Among them, synapsin I is the most abundant in mature neurons [44, 45] and is the only synapsin that may be phosphorylated by CaMKII. Synapsin I has two isoforms (Ia and Ib). These two isoforms differ only at the carboxyl terminal, with Ia having a longer carboxyl terminal than Ib. Synapsins Ia and Ib may be divided into several structural domains (Fig. 2). Domains A, B, and C are also found in synapsins II and III whereas domain D is unique to synapsin I. The distinct carboxyl terminals of synapsins Ia and Ib are named as domains E and F, respectively. The sites of CaMKII phosphorylation are two serine residues in domain D (Fig. 2) [46].

Synapsin I is localized almost exclusively to nerve terminals. The great majority of presynaptic terminals, perhaps all, contain synapsin I [47]. Biochemical studies show that synapsin I primarily associates with synaptic vesicles and accounts for ~6% of total vesicle proteins [47–50]. Synapsin I also associates with the cytoskeletal protein actin [51]. Binding of synapsin I to synaptic vesicle and actin is regulated by CaMKII-dependent phosphorylation. Dephospho-synapsin I binds to synaptic vesicles and actin, whereas phospho-synapsin I dissociates from them [51–53].

A leading hypothesis is that synapsin I tethers synaptic vesicles to the cytoskeleton by associating with actin and synaptic vesicles, and this linkage is disrupted when synapsin I is phosphorylated by CaMKII, resulting in an increase in the number of vesicles in the readily releasable pool [49]. This hypothesis is supported by results of several studies. At the squid giant synapse, injection of dephospho-synapsin I into the presynaptic terminal inhibits neurotransmitter release whereas injection of CaMKII-phosphorylated synapsin I has no effect, and injection of purified CaMKII enhances the release [23, 24]. Similar results are obtained with rat brain synaptosomes (isolated nerve terminals) [25, 43]. At rat hippocampal presynaptic terminals, green-fluorescent-protein-tagged synapsin Ia dissociates from synaptic vesicles and disperses into axons during action potential firing but reassociates with synaptic vesicles after the synaptic activity; the rates of activity-dependent synapsin Ia dissociation–dispersion and of synaptic exocytosis are inhibited by mutations of the two CaMKII phosphorylation sites in synapsin I [54].

Despite the abundance of synapsin I at the presynaptic terminal and its potential importance in synaptic transmission, as suggested by the studies described above, synaptic phenotypes of synapsin I knockout mice are relatively mild. Reported phenotypes include decreases in the size of synaptic vesicle reserve pool [55], in the amplitude of inhibitory postsynaptic currents evoked by isolated action potentials [56], in the number of vesicles exocytosed during brief trains of action potentials [57], and in the size of the total recycling vesicle pool [57]. However, LTP is unchanged and paired-pulse facilitation is increased in synapsin-I-deficient mice [58]. Furthermore, synapsin I deficiency does not alter the amplitude of excitatory postsynaptic currents evoked by isolated stimuli [59, 60].

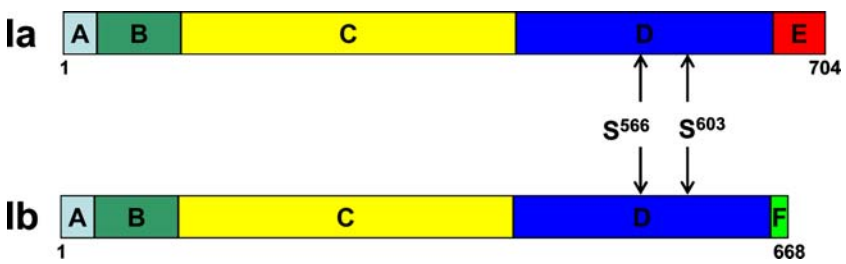

Fig. 2 Schematic representation of domain structures of synapsin Ia and Ib. The two isoforms arise from alternative splicing of a single transcript and differ only at the carboxyl terminal. Each isoform contains five domains. Domains *A*, *B*, *C*, and *D* are common to synapsin *Ia* and *Ib* whereas domain *E* and *F* are unique to *Ia* and *Ib*, respectively. CaMKII phosphorylates synapsin *I* at serine 566 (S^{566}) and serine 603 (S^{603}) in domain *D* [46]

At the calyx of Held synapse, synapsins I and II double-knockout mice show a greater degree of synaptic depression in response to a train of high-frequency stimuli compared with wild type, and this difference between wild-type and mutant mice disappears following injection of either the Ca^{2+} chelator EGTA or a calmodulin inhibitor into the presynaptic terminal, suggesting that Ca^{2+}/calmodulin-dependent phosphorylation of synapsins might be implicated in facilitating neurotransmitter release during high-frequency stimulation. However, there is no evidence for CaMKII involvement. Instead, Ca^{2+}/calmodulin-dependent protein kinase I (CaMKI) was proposed as a candidate that phosphorylates synapsins because all synapsins contain a conserved CaMKI phosphorylation site in domain A [59]. Thus, analyses of synapsin knockout mice suggest that CaMKII-dependent phosphorylation of synapsin I plays only a limited role in controlling neurotransmitter release.

The BK Channel

Presynaptic BK channel (large-conductance Ca^{2+}-activated K^+ channel) is a key negative regulator of neurotransmitter release at the presynaptic nerve terminal (see "The Function of Presynaptic BK Channels in Regulating Neurotransmitter Release"). Several lines of evidence suggest that BK channel function might be modulated by CaMKII. First, BK channels reconstituted into artificial lipid bilayers are activated by ATP and this effect of ATP is blocked by a CaMKII inhibitor [61]. Second, *Drosophila* BK channel (dSlo1) activity is modulated by the protein 14-3-3, which does not interact with dSlo1 directly but via a third protein known as Slowpoke-binding protein (Slob). The binding between 14-3-3 and Slob is modulated by CaMKII [62]. Third, BK channels in glomerular mesangial cells are activated by calmodulin plus ATP in the presence but not absence of CaMKII [63]. Fourth, BK channels contribute to after-hyperpolarization of mouse vestibular nucleus neurons in a CaMKII-dependent manner [64]. Nevertheless, it is unclear from these observations whether BK channel is a direct molecular target of CaMKII phosphorylation and whether CaMKII modulates BK channels at the presynaptic terminal.

Our recent study with *C. elegans* shows that presynaptic CaMKII may modulate neurotransmitter release by phosphorylating the BK channel [41]. In *C. elegans*, neurotransmitter release is greatly reduced in an *unc-43* CaMKII gain-of-function mutant [*unc43*(*gf*)]. This effect of *unc43*(*gf*) is abolished by either blocking or mutating the BK channel SLO-1. Analyses using the *Xenopus* oocyte expression system show that recombinant rat αCaMKII activates SLO-1 by phosphorylating SLO-1 at a threonine residue (T^{425}) in a consensus CaMKII phosphorylation site located in the first regulator of conductance for K^+ (RCK) domain [65]. Expression of SLO-1 ($T^{425}A$) in neurons counteracted the inhibitory effect of *unc-43*(*gf*) on neurotransmitter release in vivo as SLO-1 blockade or mutation did whereas expression of wild-type SLO-1 in neurons had no such effect. These observations suggest that presynaptic UNC-43 may down-regulate neurotransmitter release by phosphorylating SLO-1 at T^{425}. The identified CaMKII phosphorylation site is conserved in mammalian BK channels. However, it remains to be determined whether mammalian BK channels are similarly regulated by presynaptic CaMKII.

$Ca_V2.1$ (P/Q-type) Voltage-Sensitive Ca^{2+} Channel

Neurotransmitter release is triggered by Ca^{2+}. The most important source of Ca^{2+} triggering synaptic exocytosis is influx through VSCCs. Although several types of VSCCs have been implicated in synaptic exocytosis, $Ca_V2.1$ channel appears to be the primary one triggering neurotransmitter release at many mature synapses (for a review, see [66]). A recent study [67] shows that application of CaMKII inhibitors accelerates voltage-dependent inactivation of $Ca_V2.1$ channels, suggesting that a function of CaMKII is to decelerate voltage-dependent inactivation of the channel. Interestingly, this function of CaMKII requires its binding to $Ca_V2.1$ channels but not its catalytic activity. Conceivably, presynaptic CaMKII may be able to enhance neurotransmitter release by decelerating inactivation of $Ca_V2.1$ channels.

Ryanodine Receptors

The ryanodine receptor (RyR) is a Ca^{2+}-releasing channel in the endoplasmic reticulum (ER) membrane. It is a homomeric complex of four subunits. There are three isoforms of RyRs in mammals: RyR1, RyR2, and RyR3, which are encoded by three different genes. All of them are expressed in the nervous system [68, 69]. The isoforms of RyRs at the presynaptic terminal may vary between synapses. One study shows that presynaptic RyRs are of the RyR2 isoform [70] whereas another study shows that all the three isoforms of RyRs exist at the presynaptic terminal with RyR1 being the most abundant [71]. Pharmacological and genetic analyses suggest that presynaptic RyRs may have several functions in synaptic transmission: (1) promoting spontaneous (i.e., action potential-independent) synaptic exocytosis [72–74], (2) enhancing evoked neurotransmitter release [74, 75], and (3) contributing to short-term and long-term synaptic plasticities [76, 77] (see [66] for a review).

The RyR is mainly activated by Ca^{2+}-induced Ca^{2+} release, a process that links Ca^{2+} influx through VSCCs or receptor-operated Ca^{2+} channels in the plasma membrane to Ca^{2+} release from the ER [78]. CaMKII may modulate Ca^{2+} release from the ER by phosphorylating RyRs, as shown for RyR2. The CaMKII phosphorylation site of RyR2 was initially thought to be serine 2809 (S^{2809}) [79, 80].

However, a subsequent study showed that serine 2815 (S^{2815}) rather than S^{2809} is phosphorylated by CaMKII [81]. Phosphorylation of S^{2815} increases RyR2's Ca^{2+} sensitivity and open probability [81]. Because RyR2 exists at the presynaptic terminal [70, 71], CaMKII could potentially enhance neurotransmitter release by phosphorylating RyR2. However, this possibility has not been experimentally tested.

Synaptotagmin

Synaptotagmin 1 (Syt1) is an integral membrane protein of synaptic vesicles. A large body of evidence suggests that Syt1 is the key Ca^{2+} sensor for the fast and synchronous phase of synaptic exocytosis [82–86] (see [87] and [88] for reviews,). Binding of Syt1 to phospholipids and soluble *N*-ethylmaleimide-sensitive factor attachment receptors (SNAREs) is important to its function [87]. CaMKII may phosphorylate Syt1 at threonine 112 (T^{112}) [89], which increases the interaction of Syt1 with the SNAREs syntaxin and SNAP-25 in vitro, particularly when Ca^{2+} is present [90]. However, substituting T^{112} of Syt1 with either alanine, which cannot be phosphorylated, or aspartate, which is a phosphomimetic, does not alter Syt1's ability of rescuing a secretion defect observed in Syt1-null chromaffin cells, suggesting that CaMKII-dependent phosphorylation of Syt1 does not play an obvious role in exocytosis [91]. Further analyses are needed to determine whether CaMKII-dependent phosphorylation of Syt1 plays a role in regulating neurotransmitter release.

SNAREs

The SNARE proteins include VAMP (synaptobrevin), syntaxin, and SNAP-25. VAMP is also known as *v*-SNARE because it is a vesicle-associated protein whereas syntaxin and SNAP-25 are also known as *t*-SNAREs because they associate with the target (plasma) membrane. These proteins play a central role in synaptic vesicle fusion by forming an α-helical bundle called the SNARE complex or core complex [92]. All three SNARE proteins may be phosphorylated by CaMKII in vitro [93, 94]. However, it remains to be determined whether or not CaMKII-dependent phosphorylation of SNAREs plays a role in regulating synaptic transmission. It has been shown that autophosphorylated CaMKII binds syntaxin in a Ca^{2+}-dependent manner, and microinjection of a short peptide that is identical to the CaMKII binding domain of syntaxin inhibits exocytosis in neurons and chromaffin cells, suggesting that binding of CaMKII to syntaxin is important to synaptic exocytosis [95].

Others

Several other presynaptic proteins are also phosphorylated by CaMKII in vitro, including *N*-ethylmaleimide sensitive factor (NSF), α-soluble NSF attachment protein [94], synaptophysin [96], and rabphilin [97]. These proteins are also implicated in synaptic vesicle cycle. However, it is unknown whether phosphorylation of these proteins by CaMKII regulates synaptic transmission.

Possible Sources of Ca^{2+} for Activating Presynaptic CaMKII

The potential sources of Ca^{2+} for activating presynaptic CaMKII include entry of extracellular Ca^{2+} and release from intracellular stores. However, existing evidence has only implicated Ca^{2+} release from the ER in activating presynaptic CaMKII. At the *Drosophila* NMJ, brief tetanus nerve stimulation causes an increase of dense core vesicle motility, which is dependent on RyR-mediated Ca^{2+} release and CaMKII activation but independent of external Ca^{2+} influx. In this reaction, CaMKII appears to function downstream of RyRs [27]. At the frog NMJ, neurotrophin-3 increases the frequency of spontaneous postsynaptic currents, and this effect of neurotrophin-3 is independent of extracellular Ca^{2+} but may be prevented by inhibiting either inositol 1,4,5-trisphosphate receptors (IP_3Rs) or RyRs or by loading a CaMKII inhibitory peptide into presynaptic motoneurons but not postsynaptic myocytes. These observations led to the suggestion that presynaptic CaMKII is activated by IP_3R- and/or RYR-mediated Ca^{2+} release from the ER [28]. At synapses between *Aplysia* sensory and motor neurons, a form of homosynaptic potentiation involves several synaptic proteins, including presynaptic RyRs and CaMKII [30]. While these observations favor the notion that presynaptic CaMKII is activated by Ca^{2+} release from the ER, it may be premature to exclude potential contributions from Ca^{2+} entry via VSCCs. Further analyses are needed to better understand the source(s) of Ca^{2+} that activates presynaptic CaMKII.

The Function of Presynaptic BK Channels in Regulating Neurotransmitter Release

Structural and Functional Properties of the BK Channel

BK channel (Slo1) is a member of the *Slo* family of K^+ channels, which has four members in mammals, including Slo1, Slo2.1 (also known as Slick), Slo2.2 (also known as Slack), and Slo3 [98]. BK channel was first cloned from *Drosophila*, in which the channel is encoded by the *slowpoke* (*slo*) locus [99–101]. BK channel has large single-channel conductance (often >200 pS) and is activated by membrane depolarization and elevation of cytoplasmic free [Ca^{2+}]. The central components of a BK channel are four α-subunits. Each α-subunit contains seven putative membrane-spanning domains (S0–S6). A pore domain exists between S5 and S6,

and three positively charged residues occur at regular intervals in the putative S4 voltage sensor [99, 102, 103]. The carboxyl terminal following S6 is located on the cytoplasmic side and contains two RCK domains and a "Ca^{2+} bowl" located within the second RCK domain (Fig. 3) [65, 104, 105]. Both RCK domains, including the Ca^{2+} bowl, are important for Ca^{2+}-dependent channel gating [65, 104–107]. Mammalian BK channel may also contain a second protein called the β-subunit, which has two membrane-spanning domains (Fig. 3). Four different BK channel β-subunits have been identified [108–111]. The β-subunits may modulate several properties of the channel, including the apparent Ca^{2+} sensitivity [111, 112], inactivation [108, 110, 113], and sensitivities to charybdotoxin and iberiotoxin [113, 114] (for a review on the *Slo* family of K^+ channels, see [98]).

BK Channels are Enriched at the Presynaptic Terminal

Many electrophysiological analyses show that the presynaptic terminal contains a K^+ channel with hallmarks of the BK channel, including large single-channel conductance (>200 pS), voltage and Ca^{2+} dependence, and blockade by charybdotoxin or iberiotoxin [115–125]. Besides the BK channel, the presynaptic terminal often contains several other voltage-gated K^+ (K_V) channels (for a review, see [126]). It is sometimes necessary to block other voltage-gated K^+ channels to unmask BK channel function [116, 118, 121].

The existence of BK channels at the presynaptic terminal has been confirmed by immunocytochemistry and labeling with biotin-conjugated charybdotoxin. In rat brain, immunostaining with BK-channel-specific antibodies shows that specific immunoreactivity is concentrated in axons and nerve terminals [127, 128]. At the frog NMJ, labeling with biotin-conjugated charybdotoxin reveals a banding pattern of BK channel distribution at the presynaptic terminal, which mirrors the distribution pattern of α-bungarotoxin-labeled postsynaptic acetylcholine receptors [129]. At the *Drosophila* NMJ, immunostaining with a BK-channel-specific antibody shows that BK channels are enriched in synaptic boutons [62]. At excitatory synapses of rat hippocampus, immunoelectron microscopy analyses show that BK channels are localized to the presynaptic plasma membrane facing postsynaptic glutamate receptors [130]. In cultured rat hippocampal neurons, immunostaining shows that heterologously expressed human BK channels are initially targeted to the axonal surface membrane but become localized in presynaptic terminals with further development [128].

BK channels colocalize with VSCCs at the presynaptic nerve terminal. For example, at the frog NMJ, presynaptic BK channels and N-type Ca^{2+} channels show an identical and overlapping banding pattern of distribution [129]; blocking N-type Ca^{2+} channels with ω-conotoxin GVIA inhibits neurotransmitter release as well as BK channel currents [123]. At the presynaptic site of frog saccular hair cells, BK channels and VSCCs cluster together in the active zone [124], with each cluster containing on average 40 BK channels and 90 VSCCs [131]. The colocalization allows activation of presynaptic BK channels by the Ca^{2+} microdomains or nanodomains resulting from Ca^{2+} entry via neighboring VSCCs (see [66, 132] for reviews on Ca^{2+} microdomains and nanodomains). This property has been explored by using BK channel activity to track Ca^{2+} dynamics at the presynaptic terminals of *Xenopus* NMJs [133] and frog saccular hair cells [131].

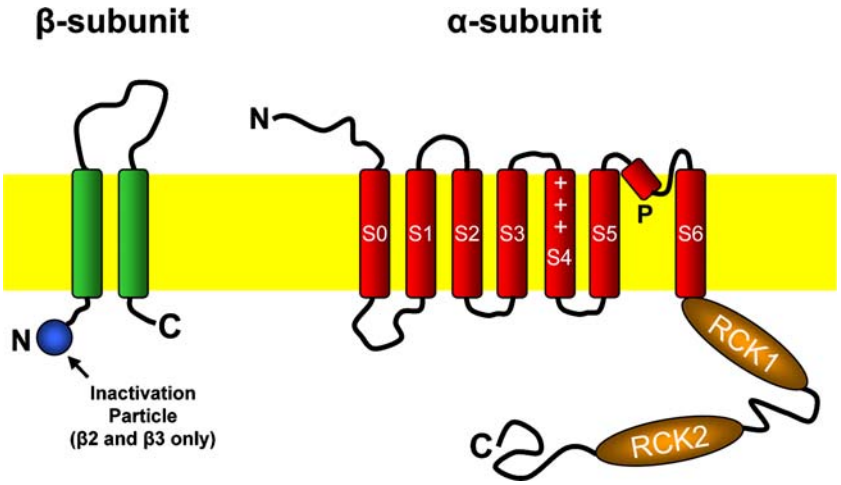

Fig. 3 Diagram showing the structure of BK channel α- and β-subunits. The α-subunit contains an extracellular amino terminal, seven membrane-spanning domains (S0 to S6) linked by intracellular and extracellular loops, a pore domain (*P*) between *S5* and *S6*, and a long cytosolic carboxyl terminal following *S6*. The putative voltage sensor *S4* contains three arginine residues (indicated by the *plus* signs). The carboxyl terminal contains two RCK domains. The β-subunit has two putative membrane-spanning domains, an extracellular loop between the membrane-spanning domains, and intracellular amino and carboxyl terminals. The amino terminals of β2- and β3-subunits contain sequences that cause channel inactivation

BK channels are activated by Ca^{2+} entry through VSCCs. However, identities of VSCCs performing this function appear to vary from cell to cell. In pyramidal neurons of rat hippocampal CA1 region, BK channel activity coincides with the opening of N-type Ca^{2+} channels, suggesting that BK channels are activated by colocalized N-type Ca^{2+} channels [134]. In sympathetic neurons of rat superior cervical ganglia, blocking either BK channels with charybdotoxin or L-type Ca^{2+} channels with nifedipine increases the half width of action potentials whereas blocking other VSCCs has no such effect, suggesting that Ca^{2+} entry via L-type channels selectively activates the BK channel [135]. In rat cerebellar Purkinje neurons, blocking P/Q-type Ca^{2+} channels suppresses afterhyperpolarization [136], which is mainly contributed by the BK channel [137], suggesting that Ca^{2+} entry via P/Q-type channels may activate the BK channel. In rat medial vestibular nucleus neurons, the ratio of evoked firing rate to input current is reduced by increasing extracellular Ca^{2+} and increased by lowering extracellular Ca^{2+}, blocking BK channels or blocking T-type Ca^{2+} channels; blocking BK channels occludes the firing response gain via the T-type but not other VSCCs, suggesting that BK channels are activated by Ca^{2+} entry via T-type Ca^{2+} channels [138]. In plasma-membrane-enriched fractions prepared from rat whole brain, subunits of several Ca^{2+} channels, including $Ca_V1.2$ (L-type), $Ca_V2.1$ (P/Q-type), and $Ca_V2.2$ (N-type), are copurified with BK channels [139]. When BK channels are coexpressed with $Ca_V2.1$ or $Ca_V2.2$ channels in *Xenopus* oocytes and analyzed in inside-out patches, a large outward BK current is preceded by a small inward Ca^{2+} current at each voltage step above the activation threshold of Ca^{2+} channels; normalized current–voltage relationship of the BK channel is bell-shaped and mirrors that of the Ca^{2+} channel but at an inverted direction [139]. The diversity of Ca^{2+} channels that may mediate BK channel activation suggests that activation of BK channels by colocalized Ca^{2+} channels is not a unique property of a specific type of VSCC; rather, the apparent specificity of coupling reflects the identity of VSCCs that are coexpressed and colocalized with the BK channel.

Relatively little is known about the identity of VSCCs that activates BK channels at the presynaptic terminal. At frog NMJs, N-type Ca^{2+} channels play an important role in triggering neurotransmitter release [121, 123, 140–142]. At this synapse, blocking N-type Ca^{2+} channels with ω-conotoxin GVIA significantly inhibits BK currents [121, 123], suggesting that Ca^{2+} entry through N-type channels has the dual functions of triggering synaptic exocytosis and activating colocalized BK channels.

Presynaptic BK Channels Regulate Neurotransmitter Release

Neurotransmitter release is triggered by action potentials and the resultant Ca^{2+} entry through presynaptic VSCCs. BK channels are especially suited to serving as a negative regulator of neurotransmitter release because they colocalize with VSCCs at the active zone and are activated by membrane depolarization as well as elevation of cytosolic free $[Ca^{2+}]$. Indeed, such a function of presynaptic BK channels has been shown by a number of studies. For example, blocking BK channels with charybdotoxin and/or iberiotoxin increases Ca^{2+} entry into the presynaptic terminal as well as the amplitude of end-plate potentials at frog NMJs [129, 143]. The stimulatory effect of charybdotoxin on neurotransmitter release is prevented by pretreatment with 1,2-bis(2-amino-5-fluorophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid tetrakis(acetoxymethyl) ester (BAPTA-AM) but not ethyleneglycol-bis(β-aminoethyl)-*N,N,N′,N′*-tetraacetoxymethyl ester (EGTA-AM) [129]. These two agents are membrane-permeant Ca^{2+} chelators. Each molecule of BAPTA-AM or EGTA-AM has four ester groups attached to the Ca^{2+}-binding site. The ester groups confer membrane permeability and keep the Ca^{2+} chelator inactive. BAPTA-AM and EGTA-AM become active and are trapped inside the cells once the ester groups are removed by intracellular esterases [144]. Although BAPTA and EGTA bind Ca^{2+} with similar affinities ($K_d \approx 160$ nM), BAPTA has a 100-fold faster on-rate and a greater effect at the mouth of Ca^{2+} channels than EGTA [145, 146]. Thus, the blockage of charybdotoxin's effect by BAPTA but not EGTA suggests that presynaptic BK channels are located very close to VSCCs at frog NMJs. In *C. elegans*, the amplitude of ePSCs at the NMJ is increased in *slo-1* loss-of-function mutant but decreased in *slo-1* gain-of-function mutant [41]. At hippocampal excitatory synapses between CA3 and CA1 neurons and between CA3 and CA3 neurons, blocking BK channels increases the amplitude of ePSPs or ePSCs [130, 147]. In addition, blocking BK channels decreases paired-pulse ratio of ePSPs or ePSCs, especially at synapses with high release probabilities [130, 147], which is also a sign of elevated neurotransmitter release probability [126, 148, 149]. Because blocking BK channels causes spike broadening in neurons [130, 147, 150–152], including the presynaptic terminal [118], presynaptic BK channels likely downregulate neurotransmitter release by shortening the duration of depolarization that allows Ca^{2+} entry through VSCCs.

The importance of presynaptic BK channels as a negative regulator of neurotransmitter release is well

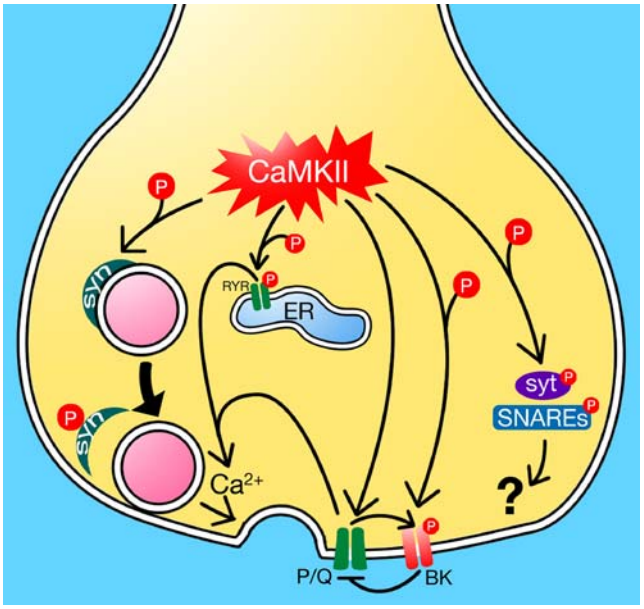

Fig. 4 Diagram showing molecular mechanisms of presynaptic CaMKII and BK channel functions. Presynaptic CaMKII may modulate neurotransmitter release through several possible mechanisms. First, CaMKII may promote synaptic vesicle translocation from the reserve pool to the readily releasable pool by phosphorylating synapsin I (*SYN*). Dephospho-synapsin I binds to synaptic vesicles and keeps SVs in the reserve pool by associating with actin in the cytoskeleton whereas phosphor-synapsin I dissociates from actin and SVs, allowing SVs to translocate to the readily releasable pool. Second, CaMKII may increase Ca^{2+} entry by decelerating $Ca_V2.1$ (P/Q-type) channel inactivation. This effect of CaMKII is independent of its catalytic activity. Third, CaMKII may phosphorylate ryanodine receptors (RYR) to enhance Ca^{2+} release from the endoplasmic reticulum (ER). Fourth, CaMKII may downregulate neurotransmitter release by phosphorylating and activating the BK channel. Several other presynaptic proteins, including synaptotagmin (syt) and SNAREs, are also phosphorylated by CaMKII in vitro; however, the physiological significance is unclear. Presynaptic BK channel is activated by membrane depolarization and Ca^{2+} entry through colocalized voltage-sensitive Ca^{2+} channels (e.g., the P/Q-type channel). The BK channel downregulates neurotransmitter release by shortening the duration of action potentials that allow Ca^{2+} entry through voltage-sensitive Ca^{2+} channels. For clarity, CaMKII, syt, and SNAREs are depicted as stand-alone proteins although they normally associate with SVs or the plasma membrane

illustrated by a genetic screen in *C. elegans*. In a genetic screen designed to isolate mutants that suppress the lethargic phenotype of a hypomorphic syntaxin mutant, which restricts neurotransmitter release, six *slo-1* loss-of-function alleles but no mutants of other K^+ channel genes were identified [153]. Given that there are approximately 70 K^+ channels in *C. elegans* [154], the isolation of only *slo-1* mutants from this whole-genome-based genetic screen suggests that presynaptic SLO-1 plays an important, if not unique, role in regulating neurotransmitter release.

The function of presynaptic BK channels in regulating neurotransmitter release may vary from synapse to synapse. While blocking or mutating BK channels alone is sufficient to enhance neurotransmitter release at frog and *C. elegans* NMJs, and, at glutamatergic synapses between hippocampal CA1 and CA3 neurons [41, 129, 147, 153], addition of 4-aminopyridine to inhibit other K^+ channels is a prerequisite for BK channel blockers to increase neurotransmitter release at hippocampal CA3–CA3 synapses [130]. One potential cause for the differential dependence on 4-aminopyridine between CA1–CA3 and CA3–CA3 synapses is a difference in experimental conditions, as suggested by others [126].

Surprisingly, blocking BK channels decreases the amplitude of excitatory postsynaptic currents evoked by light at salamander rod synapses [155] and by direct nerve stimulation in frog nerve-muscle coculture [156], suggesting that the function of presynaptic BK channels is to facilitate neurotransmitter release. The apparent positive role of presynaptic BK channels in neurotransmitter release might reflect unusual synaptic properties or nonphysiological experimental conditions. For example, salamander rod photoreceptors are nonspiking neurons; special structural properties of the rod synapse might allow BK channels to enhance Ca^{2+} entry and neurotransmitter release by increasing extracellular K^+ concentration in the synaptic cleft, as speculated by the authors [155]. Frogs NMJs in culture may be different from those in vivo or in situ in some functional properties, as suggested by the opposite effects of BK channel blockers on frog neuromuscular transmission in situ [129] and in culture [156].

Concluding Remarks

The studies discussed above indicate that presynaptic CaMKII and BK channel play important roles in regulating synaptic transmission. The molecular mechanisms of presynaptic CaMKII and BK channel functions are summarized in a diagram (Fig. 4). Some major questions remain to be answered about presynaptic CaMKII and BK channel. For example, what are the molecular bases of localizing CaMKII to synaptic vesicles and BK channels to the presynaptic nerve terminal? Is the presynaptic localization of CaMKII or BK channels regulated by synaptic activity? What factors determine whether the predominant function of presynaptic CaMKII is to enhance or inhibit neurotransmitter release under physiological conditions? What is the physiological significance of CaMKII-dependent phosphorylation of some presynaptic proteins that may

be phosphorylated by CaMKII in vitro? How are the functions of presynaptic CaMKII and BK channel regulated under physiological conditions? An elucidation of the functions of presynaptic CaMKII and BK channel will help us to understand how neurotransmitter release and synaptic function are precisely controlled.

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