Decalmodulation of Ca$_v$1 channels by CaBPs

Jason Hardie and Amy Lee*

Departments of Molecular Physiology and Biophysics; Otolaryngology-Head and Neck Surgery and Neurology; University of Iowa; Iowa City, IA USA

Ca^{2+}-dependent inactivation (CDI) is a negative feedback regulation of voltage-gated Ca$_v$1 and Ca$_v$2 channels that is mediated by the Ca^{2+} sensing protein, calmodulin (CaM), binding to the pore-forming Ca$_v$ α_1 subunit. David Yue and his colleagues made seminal contributions to our understanding of this process, as well as factors that regulate CDI. Important in this regard are members of a family of Ca^{2+} binding proteins (CaBPs) that are related to calmodulin. CaBPs are expressed mainly in neural tissues and can antagonize CaM-dependent CDI for Ca$_v$1 L-type channels. This review will focus on the roles of CaBPs as Ca$_v$1-interacting proteins, and the significance of these interactions for vision, hearing, and neuronal Ca^{2+} signaling events.

Neuronal excitability and synaptic transmission are regulated by a vast array of voltage-dependent ion channels of which voltage-gated Ca$_v$ Ca^{2+} channels are crucial. Inward Ca^{2+} currents mediated by Ca$_v$ channels help shape neuronal firing properties, neurotransmitter release, and synaptic plasticity.[1] Ca$_v$ channels also couple fast electrical signals with slower Ca^{2+}-dependent signaling pathways that can involve Ca^{2+}-release from intracellular stores and phosphorylation by protein kinases.[2] For example, Ca^{2+} influx via Ca$_v$1 (L-type) channels promotes the phosphorylation of the transcription factor, cAMP response element-binding protein (CREB), which plays a role in activity-dependent gene expression.[3,4] Therefore, factors that modulate Ca$_v$ channel output can have a large neurophysiological impact.

Of these factors, Ca^{2+} ions that permeate the channel play a fundamental role in inhibiting further Ca^{2+} entry (Ca^{2+}-dependent inactivation, CDI). CDI was first characterized as greater inactivation of Ca^{2+} currents compared to Ba^{2+} currents in voltage-clamp recordings of Paramecium.[5] CDI has since been observed for Ca$_v$1.2 and Ca$_v$1.3 channels (L-type), as well as Ca$_v$2.1 (P/Q), Ca$_v$2.3 (R-type), and Ca$_v$2.2 (N-type) channels in heterologous expression systems.[6] The mechanism involves calmodulin (CaM), which is constitu-

*Correspondence to: Amy Lee; Email: amy-lee@uiowa.edu

tively tethered to site(s) in the C-terminal domain of the pore-forming Ca$_v$ α_1 subunit. Upon channel activation, CaM binds incoming Ca^{2+} and induces conformational changes that underlie CDI.[7] The hallmark of CDI is a rapid inactivation of Ca^{2+} currents during a prolonged depolarization, which is reduced for Ba^{2+} currents, which undergo primarily voltage-dependent inactivation (**Fig. 1**). The structure/function relationships of CaM regulation of Ca$_v$ channel CDI are summarized in previous reviews.[7-9]

The importance of CDI as a regulatory mechanism in cardiac myocytes was elegantly elucidated by David Yue and colleagues. By expressing dominant negative CaM mutants that cannot bind Ca^{2+}, a maneuver that inhibits CDI of native Ca$_v$1.2 channels in cardiac myocytes, they demonstrated a role for CDI in restricting the duration of the cardiac action potential.[10] Human mutations that affect Ca^{2+} binding to CaM cause long QT syndrome characterized by prolonged myocyte action potentials, arrhythmia, and sometimes cardiac arrest.[11] In collaboration with Al George's group, the Yue lab showed that these long QT-causing CaM mutations suppress CDI of Ca$_v$1.2 channels in transfected HEK293T cells. When expressed in cardiac myocytes, the CaM mutations prolonged action potential durations and caused arrhythmia.[12]

Compared to cardiac myocytes and heterologous expression systems, CDI is generally weaker for Ca$_v$1 channels in neuronal cell-types. This is most extreme for Ca$_v$1.4 channels in retinal photoreceptors, due to a C-terminal modulatory domain (CTM) in the Ca$_v$1.4 α_1 subunit. The CTM nullifies CDI by competing with CaM binding to the proximal C-terminal domain.[13,14] Prolonged Ca$_v$1.4 Ca^{2+} currents are thought to support tonic glutamate release by photoreceptors in darkness, which is modulated by light stimuli. As in photoreceptors, Ca$_v$1 channels are localized at specialized "ribbon" synapses in inner hair cells (IHCs) – the major sound receptors in the cochlea. Ca$_v$1.3 channels are the predominant Ca$_v$ channels in these cells, and exhibit surprisingly little CDI in IHCs to channels in transfected HEK293T cells.[15,16] Multiple factors may cause the reduced CDI of Ca$_v$1.3 channels in IHCs, such as alternative splicing and editing of RNA,[17,18] and interactions with other proteins.[19,20] In the latter category, a family of Ca^{2+} binding proteins (CaBPs) similar to CaM have emerged as candidate regulators of CDI in IHCs and potentially other neuronal cell-types. Comprised of 7 family members,[21] CaBPs have distinct modulatory effects on Ca$_v$1 and Ca$_v$2 channels in heterologous expression systems.[9,22,23] This review will summarize our current understanding of CaBPs as Ca$_v$1 channel regulators with an emphasis on their neurophysiological significance.
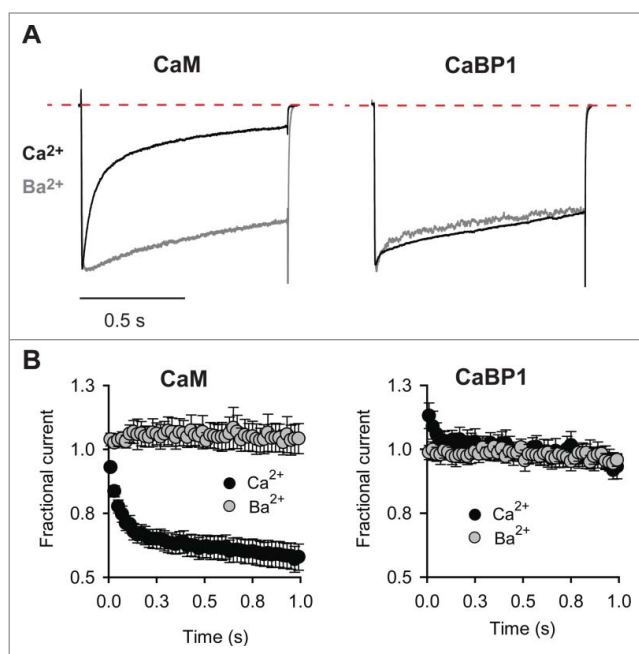
Figure 1. CaBPs antagonize CDI in whole-cell patch clamp recordings of HEK293T cells transfected with $Ca_v1.2$. (**A**) Normalized Ca^{2+} and Ba^{2+} currents evoked by 1-s pulses from -80 mV to $+10$ mV for Ca^{2+} currents or 0 mV for Ba^{2+} currents. Faster decay of Ca^{2+} currents due to CaM (left) is not evident in cells co-transfected with CaBP1 (right). (**B**) Ca^{2+} and Ba^{2+} currents were evoked by 100 Hz-trains of 5-ms pulse from -80 mV to $+10$ mV for Ca^{2+} currents, or 0 mV for Ba^{2+} currents. Fractional current represents current amplitude normalized to that for the first in the train. CDI due to CaM causes rapid declines in Ca^{2+} current (left), unlike the full channel availability maintained at the end of train in cells co-transfected with CaBP1. Adapted from 26.

Table 1. Tissue distribution of CaBPs

CaBP	Region	References
CaBP1/caldendrin	Brain	26,33,35,46
CaBP1, CaBP2, CaBP4, and CaBP5	Cochlea	15,16
CaBP4 and CaBP5	Retina	42,56

Curbing CaM Modulation: CaBPs Antagonize Ca_v1 CDI

CaBPs are ~50% homologous to CaM,[24] and have the following characteristics consistent with roles as Ca_v1 channel modulators in neurons. First, CaBPs (CaBP1, 2, 4, and 5) inhibit CDI when coexpressed with $Ca_v1.2$ or $Ca_v1.3$ channels in transfected HEK293T cells and in *Xenopus* oocytes (**Fig. 1**).[15,16,25-28] This effect results from CaBPs competitively displacing CaM from the Ca_v1 α_1 subunit,[26,29] as well as non-competitive actions that may be due to CaBPs binding to other site(s) on the channel.[30-32] Like CaM, CaBPs have an N-terminal and C-terminal lobe separated by an inter-lobe α-helical linker domain. Each lobe contains 2 EF-hand Ca^{2+} binding domains, at least one of which has amino acid substitutions that would inhibit Ca^{2+} binding.[24] For CaBP1, the key determinants for suppression of $Ca_v1.2$ CDI are the N-terminal lobe and a glutamate residue in the interlobe linker. This glutamate residue (E94), conserved among CaBP family members, abolishes CDI suppression by CaBP1 when mutated to alanine.[27]

Unlike CaM, which is expressed in most cells, CaBPs are expressed primarily in neuronal cell-types in the brain, retina, and inner ear.[15,16,33,34] In each of these tissues, CaBPs are localized in similar cell-types as Ca_v1 channels (**Table 1**), although alterative splice variants of CaBPs may be expressed at varying levels. For example, there are 3 CaBP1 splice variants (CaBP1-S, CaBP1-L, and caldendrin) of which caldendrin is the most abundant in the brain.[33,35] Our understanding of the physiological relevance of CaBPs as Ca_v1 channel modulators has emerged largely from genetically modified mice lacking expression of particular CaBPs, as well as human genetic studies.

CaBP4 and CaBP5 as Modulators of Ca_v1 Channels in the Retina

The first evidence suggesting that CaBP4 is an essential regulator for $Ca_v1.4$ channels in photoreceptor nerve terminals was the similar visual phenotypes of mice lacking CaBP4 or $Ca_v1.4$ (CaBP4 KO and $Ca_v1.4$ KO, respectively). In both strains of mice, there is a loss of synaptic transmission from rod photoreceptors to second-order rod bipolar neurons, which is evident as a diminished "b-wave" in the electroretinogram.[34,36] $Ca_v1.4$ channels containing a CTM exhibit little CDI, even in the absence of CaBPs.[13,14,37,38] However, coexpression of CaBP4 leads to enhanced voltage-dependent activation of the $Ca_v1.4$ in transfected HEK293T cells.[34,39] Thus, $Ca_v1.4$ channels would be expected to activate at more positive voltages in CaBP4 KO mice, which may explain the loss-of function of photoreceptor transmission in these animals. In addition, mutations in the genes encoding CaBP4 and $Ca_v1.4$ cause similar visual phenotypes in humans.[40,41]

Unlike CaBP4, CaBP5 is expressed primarily in bipolar cells in the retina, where it colocalizes with $Ca_v1.2$.[42] In transfected HEK293T cells, CaBP5 causes a modest suppression of CDI, an effect that could explain the reduced rod-mediated ganglion cell responses to light in mice lacking CaBP5.[42]

CaBP2 as a Modulator of $Ca_v1.3$ Channels in Auditory Inner Hair Cells

Cochlear IHCs express CaBP1, CaBP2, CaBP4, and CaBP5,[15,16] which were proposed to serve as suppressors of CDI of the native $Ca_v1.3$ channel. In transfected HEK293T cells, each of these CaBPs except CaBP2 inhibited CDI of $Ca_v1.3$.[15,16] However, subsequent work showed that expression of higher levels of CaBP2 induced strong CDI suppression.[43] Moreover, a mutation that leads to premature truncation of CaBP2 causes moderate to severe hearing loss in humans. When tested in HEK293T cells, the mutant CaBP2 was less effective than the

wild-type CaBP2 in suppressing $Ca_v1.3$ CDI.[43] In individuals affected by the mutation, stronger CDI of $Ca_v1.3$ might impair sound-evoked transmission at the IHC synapse. It is possible that a more severe phenotype is not observed due to potential compensation by the other CaBPs in IHCs.

CaBP1/caldendrin as a Potential Modulator of $Ca_v1.2$ and $Ca_v1.3$ Channels in the Brain

While CaBP2, CaBP4, and CaBP5 are largely restricted in expression to the retina and inner ear, CaBP1 splice variants including caldendrin (CaBP1/caldendrin) are also expressed in the brain.[15,34] CaBP1/caldendrin is localized to subgroups of neurons known to express $Ca_v1.2$ and $Ca_v1.3$ channels, such as in the cerebral cortex and hippocampus. Within these neurons, $Ca_v1.2$ and CaBP1/caldendrin are localized primarily to somatodendritic regions.[33,35,44,45] CaBP1/caldendrin strongly suppresses CDI of $Ca_v1.2$ and $Ca_v1.3$ in transfected HEK293T cells and Xenopus oocytes.[15,16,26,46] In the brain, Ca_v1 channels are important regulators of neuronal excitability. These channels have roles in shaping incoming synaptic inputs, sustaining regenerative dendritic spikes, and activating Ca^{2+}-dependent K^+ currents that curtail cell excitability.[47-49] Some forms of hippocampal synaptic plasticity and learning and memory depend on Ca_v1 channels, particularly $Ca_v1.2$.[50] Thus, CaBP1/caldendrin could have important roles in regulating diverse Ca_v1 functions in the brain.

Since data are not yet available regarding the neurophysiological phenotypes of mice lacking CaBP1/caldendrin,[33] one can only speculate on the potential role of CaBP1 in modulating Ca_v1 channels in neurons. During a train of depolarizations at 100 Hz, a physiologically relevant frequency often used for inducing synaptic plasticity in brain slices,[51] CaM-dependent CDI causes a robust depression of Ca^{2+} influx through $Ca_v1.2$ channels at the end of the train in transfected HEK293T cells. This effect is completely blocked by coexpression of CaBP1, such that channel availability remains as strong at the end of the train as it was at the beginning (**Fig. 1**).[26] Thus, during high frequency bursts *in vivo*, CaBP1 may help support postsynaptic $Ca_v1.2$ Ca^{2+} signals that are involved in synaptic plasticity, activity-dependent gene transcription, and learning and memory.[52] The coexistence of CaM and CaBP1/caldendrin in neurons may allow for a push-pull modulation to fine-tune plasticity involving Ca_v1 channels.

Conclusions

Ca_v channels are essential and versatile regulators of Ca^{2+} signals in excitable cells. Compared to the molecular diversity within the family of voltage-gated K^+ channels, there are relatively few genes encoding the pore-forming subunit of Ca_v channels. The interaction of Ca_v channels with proteins that can modulate their function represents another route by which the activity of Ca_v channels can be adjusted according to cell-type.[53] The opposing regulation of Ca_v channels by CaM and CaBPs represent 2 extremes on the modulatory spectrum. As in the heart, Ca_v channels in some neuronal cell-types may require CDI to control neuronal excitability.[54] However, in other cells, such as IHCs in the cochlea, sustained Ca^{2+} currents due to CaBP1/caldendrin-modulated $Ca_v1.3$ channels may be required for faithful transmission of sensory input.

Studies of how CaBPs oppose CDI of Ca_v1 channels in heterologous expression systems have revealed major insights into the molecular and biophysical mechanisms controlling CDI (reviewed in 7 and 9). However, direct evidence that CaBPs do indeed suppress CDI of Ca_v channels is currently lacking. While phenotypes in the CaBP4 and CaBP5 KO mice are consistent with roles for these CaBPs in regulating Ca_v1 channels in vivo, voltage clamp recordings of Ca_v1 currents in retinal photoreceptors and bipolar cells have not been done to confirm that there is indeed a loss of CaBP modulation in these cells. A definitive role for CaBP1/caldendrin in suppressing CDI of neurons in the brain awaits similar recordings of neurons from CaBP1 KO mice. It also is important to note that CaBPs can interact with partners other than Ca_v channels.[55-60] Therefore, phenotypes in CaBP KO mice might not necessarily arise from altered Ca_v1 channel regulation. Detailed studies of CaBP knockouts, or knock-in Ca_v mutants with disrupted CaBP but not CaM binding, will provide further clues as to the physiological role of CaBPs as modulators of neuronal Ca_v1 channels.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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