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The Neuronal Kv4 Channel Complex

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Abstract

Kv4 channel complexes mediate the neuronal somatodendritic A-type K^+ current (I_{SA}), which plays pivotal roles in dendritic signal integration. These complexes are composed of pore-forming voltage-gated α -subunits (Shal/Kv4) and at least two classes of auxiliary β -subunits: KChIPs (K⁺-Channel-Interacting-Proteins) and DPLPs (Di-peptidyl-Peptidase-Like-Proteins). Here, we review our investigations of Kv4 gating mechanisms and functional remodeling by specific auxiliary β -subunits. Namely, we have concluded that: (1) the Kv4 channel complex employs novel alternative mechanisms of closed-state inactivation; (2) the intracellular Zn^{2+} site in the T1 domain undergoes a conformational change tightly coupled to voltage-dependent gating and is targeted by nitrosative modulation; and (3) discrete and specific interactions mediate the effects of KChIPs and DPLPs on activation, inactivation and permeation of Kv4 channels. These studies are shedding new light on the molecular bases of I_{SA} function and regulation.

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Keywords

Voltage-gated potassium channel; Gating; Inactivation; Auxiliary β subunits; A-type potassium current; T1 domain

Shal/Kv4 Channels are Highly-conserved Throughout the Animal Kingdom

In the super-family of voltage-gated K^+ channels (Kv channels) of eukaryotes, there are four closely related subfamilies: Kv1 (Shaker), Kv2 (Shab), Kv3 (Shaw) and Kv4 (Shal) [31, 107]. All Kv channels in these subfamilies are tetrameric and share three well-defined domains in the pore-forming α -subunit (N- to C-terminus): the T1 domain (T1), the voltage-sensing domain (VSD) and the pore domain (PD) [49, 75] (Fig. 1). Whereas the transmembrane VSD and PD are found in other Kv channels, the intra-cellular T1 is restricted to the four subfamilies outlined above. However, there are important distinctions between these Kv channels. Kv1, Kv2 and Kv3 channels mediate a broad range of electrophysiological phenotypes, which include fast and slow inactivating outward K^+ currents (A-type and delayed rectifier-type, respectively). In contrast, Shal/Kv4 channels throughout the animal kingdom, exhibit highly conserved primary structure and, with or without auxiliary subunits (see below), the vast majority of them mediate fast A-type K^+ currents [5, 54, 92, 112]. Although Kv4 channels are found in various tissues in mammalian organisms [1, 90, 95], they are broadly found in neurons of primitive and advanced animals [8, 14, 35, 50, 54, 107, 108, 122]. Therefore, Shal/Kv4 channels are likely to determine fundamental electrical properties of neurons.

Numerous studies over the last two decades have focused on investigating bacterial K^+ channels, Shaker-B Kv channels and Shaker-related Kv1 channels. The resulting breakthroughs have revealed the molecular bases of ionic selectivity, voltage-dependent activation gating and open-state inactivation [13, 30, 79, 135]. However, much less is known about the mechanisms that underlie closed-state inactivation, the gating role of the T1 domain and the remodeling/regulatory roles of Kv4 auxiliary β -subunits. The latter is especially important because most Kv channels co-assemble with diverse auxiliary β -subunits to form macromolecular complexes in excitable tissues; and these β -subunits ultimately determine the localization, expression and specific functional properties of the native K^+ conductances [40, 54, 67, 69, 99].

The Somatodendritic A-type K^+ Channel

Since the discovery of the A-type K^+ current in mollusk neurons [28, 39, 89], a wealth of studies have characterized the counterpart in mammalian brain and the nervous system of other organisms [14, 54, 106]. The somatodendritic A-type K^+ current (I_{SA}) is expressed in the soma and dendrites of central neurons; typically, it activates and inactivates rapidly in response to membrane depolarization, operates in the subthreshold range of membrane potentials, is typically inactivated at the resting membrane potential, and its density increases gradually from the soma to the distal dendrites in CA1 hippocampal neurons [42, 113]. In different neuron types, I_{SA} plays many roles; for instance, it prolongs the latency to the first spike in a train of action potentials, slows repetitive spike firing, shortens action

potentials and attenuates back propagating action potentials [12, 14, 20, 27, 42, 57, 58, 61, 80, 81, 84, 110, 118, 129]. These roles can influence dendritic excitability, somatodendritic signal integration and long-term potentiation [14, 25, 57, 60]. For instance, I_{SA} controls the propagation of dendritic plateau potentials at branching points by acting as gate-keepers in distal dendrites of hippocampal pyramidal neurons [20]. Most likely, Kv4 pore-forming α -subunits underlie I_{SA} in the central and peripheral nervous systems. Many studies have isolated I_{SA} electrophysiologically and identified Kv4 genes, transcripts and proteins by applying in situ hybridization, single-cell reverse-transcription-polymerase-chain-reaction (RT-PCR) and immunohistochemistry [20, 25, 46, 60, 61, 68; 74, 80, 81, 83, 103, 111, 114, 118, 121]. Furthermore, knock-down, knock-out and over-expression approaches have established the contribution of Kv4 channels to I_{SA} [20, 25, 46, 60, 61, 68, 80, 114]. We will later discuss the additional contribution of at least two classes of specific auxiliary β -subunits to the neuronal Kv4 channel complex.

Inactivation of Kv4 Channels: Two Gates in One?

Inactivation of voltage-gated ion channels is the auto-regulatory time-dependent process that shuts down the corresponding conductances in response to a prolonged or sustained membrane depolarization [41]. In Kv4 channels, inactivation at steady-state is nearly complete; and a relatively fast development of inactivation is a hallmark of all known members of the Shal/Kv4 subfamily [54]. Fast recovery from inactivation at hyperpolarized membrane potentials removes Kv4 channel steady-state inactivation in tens to hundreds of milliseconds. That is in contrast to most other Kv channels, which require seconds to tens of seconds to recover from inactivation. Although inactivation of Shaker-B and Kv1 channels is generally well understood at the molecular level [26, 29, 30, 44, 45, 70, 91, 93, 94, 133, 135], the mechanisms of inactivation of Kv4 channels seem distinct and remain unsolved [54]. In heterologous expression systems and in the absence of auxiliary β -subunits, Kv4 channels may undergo open- and closed-state inactivation [3, 10, 128]. These processes, however, exhibit features inconsistent with the presence of classical N- and P/C-type mechanisms of inactivation, as found in Shaker-B and Kv1 channels [36, 51, 54, 56]. In native Kv4 channel complexes particularly, open-state N-type inactivation determined by the channel's proximal N-terminus is unlikely because KChIPs sequester and immobilize this region constitutively [2, 9, 98, 127].

Another hallmark of native and recombinant Kv4 channels coexpressed with KChIP-1 is that elevated external K^+ accelerates the development of inactivation [59, 63], which appears to contradict the predictions of a “foot-in-the-door” mechanism acting on classical P/C-type inactivation [78, 132]. In this mechanism, K^+ occupies an external pore site and thereby slows inactivation by preventing constriction of the external mouth of the channel. We found that modulation of Kv4 channels by external K^+ involves a saturable site with a K_D of the order of 8 mM; and that this site is possibly located in the selectivity filter because permeant cations are more effective modulators than poor permeant cations ($K^+ = Rb^+ = NH_4^+ > Cs^+ > Na^+$) [59]. We explained these observations quantitatively by assuming that Kv4 channels exhibit profound closed-state inactivation allosterically coupled to the voltage-dependent activation pathway, and a separate set of unstable closed states connected to all states in the activation pathway [59]. The key of this solution is that transiting to this set of unstable

closed states is less likely as the concentration of external K^+ increases (or other permeant cation). These closed states may correspond to vestigial P/C-type inactivation in Kv4 channels. Thus, the Kv4 pore can fluctuate between constricted and conducting conformations before the channel populates a distinct closed-inactivated state at steady-state. In this scenario, acceleration of inactivation by external K^+ results indirectly from the inherent enhancement of the open probability caused by the inhibition of vestigial P/C-type inactivation. An enhanced open probability will promote inactivation from a pre-open closed state because there is no open-state inactivation (in the presence of KChIP-1; see below) and channel closing is significant. This mechanism implies, as proposed before [54], that the structure of the selectivity filter in Kv4 channels is intrinsically more stable than that of Shaker-B, Kv1 and certain bacterial K^+ channels, which allowed alternative mechanisms of closed-state inactivation to evolve.

Unusual slowing of the apparent rate of macroscopic inactivation as the membrane potential becomes progressively more depolarized is an additional hallmark of Kv4 channels. Particularly, this feature is apparent when Kv4 channels are coexpressed with KChIP-1 or KChIP-3 [9, 52, 59] and has been reported in several studies of neuronal I_{SA} [42, 64, 73, 83]. Such a behavior is a specific central prediction of preferential inactivation from a pre-open closed-state, which has been demonstrated quantitatively for Kv4.3 and Kv4.2 channels coexpressed with KChIP-1 in *Xenopus* oocytes and mammalian cells, respectively [59] (Amarillo et al., J. Physiol., in press). Essentially, the voltage-dependent slowing of the inactivation rate occurs because the concerted opening-closing step of the channel is weakly voltage-dependent. Therefore, as the open probability increases gradually with progressive depolarizations of the membrane potential, the occupancy of the inactivation-permissive pre-open closed state decreases gradually and, consequently, the development of inactivation is slowed in a weakly voltage-dependent manner. Further strong support for a prominent pathway of closed-state inactivation in Kv4 channels comes from recent gating current experiments (Dougherty, De Santiago-Castillo and Covarrubias, J. Gen. Physiol., 131:257–273). We showed that slight—modest depolarizations over a hyper-polarized range of membrane potentials (–110 to –70 mV) induce a profound apparent loss of gating charge (Q-loss). Critically, the kinetics of Q-loss precisely follows the time course of current inactivation in a manner that is independent of the channel's N-terminal region.

In light of the observations summarized above, Kv4 channels are more likely to employ alternative and poorly understood mechanisms of closed-state inactivation. A current working hypothesis proposes that the Kv4 channel inactivation mechanism is analogous to that proposed for closed-state inactivation of HCN channels [54, 56, 59, 115]. Basically, the main internal activation gate of the channel (A-gate) conducts two separate jobs, and therefore, it can control both activation and inactivation. Whether it does one or the other depends on the strength of the electromechanical coupling between the voltage sensor and the A-gate [76]. This coupling is thought to be the mechanism responsible for voltage-dependent Kv channel activation [97]. However, weakening of the underlying molecular interactions over time during a sustained depolarization would promote “dislocation” of the voltage sensor and an apparent Q-loss, rendering the A-gate reluctant to opening (i.e., the A-gate is desensitized to voltage) [115]. Although the collective evidence in favor of a non-N-type and non-P/C-type mechanism of preferential closed-state inactivation in Kv4 channels

is strong, alternative hypotheses have been proposed by others and the problem remains controversial [34, 95, 116, 128].

Gating at the Portals of the K⁺ Pore, the Intracellular T1 Domain of Kv4 Channels

The multifunctional T1 domain of Kv channels encompasses ~100 amino acids within the intracellular N-terminal region of the pore-forming protein. It determines the specificity of subunit assembly within a subfamily [71, 131]; acts as the anchoring site for auxiliary subunits [21, 38]; controls axonal targeting [37, 104]; and regulates activation gating [32, 85, 105, 124, 125]. The T1 domain assembly in the Kv channel appears as a “hanging gondola” connected to the transmembrane core (VSD + PD) via the T1-S1 linkers. These linkers form lateral portals that allow K⁺ ions to access the internal mouth of the channel when the main A-gate opens [65, 75]. Although T1 domains are topologically similar among Kv channels, an important difference between those from Kv1 and non-Kv1 channels (Kv2, Kv3 and Kv4) is that only the latter contain an inter-subunit Zn²⁺ binding site involving the characteristic motif HX(5)CX(20)CC [15, 66, 88] (Fig. 2). While the cysteine doublet and the histidine are from the same subunit at the intersubunit interface, the third cysteine is from the neighboring subunit. This site was first identified in the crystal structure of an isolated Kv3-T1 domain and high-affinity Zn²⁺ binding appeared necessary to maintain the tetrameric quaternary structure [15, 48, 119]. In intact Kv4 channels coexpressed with KChIP-1 and DPPX-S, however, this site is not Zn²⁺-bound constitutively or Zn²⁺ is partially liganded because thiol-specific reagents (e.g., MTSET) can modify the critical cysteines and mild oxidizing conditions readily induce a disulfide-bond across the intersubunit interface [124, 125]. Otherwise, tightly bound Zn²⁺ would have protected all critical cysteines against oxidation. These chemical modifications inhibit channel activity profoundly; and the time-dependent inhibition by MTSET is also state- and voltage-dependent [124, 125]. The accessibility to the Zn²⁺ site cysteines is ~300–400-fold larger in the activated state relative to the resting or inactivated states. In contrast, the cysteine accessibility differs only by ~twofold between resting and inactivated states. Furthermore, the voltage dependence of the accessibility followed the voltage dependence of the peak conductance faithfully. These results were surprising because the Zn²⁺ binding site is apparently distant from VSD and PD elements of the channel that are more directly involved in voltage-dependent gating of the channel. We have proposed that the Kv4-T1 domain undergoes a significant conformational change that is tightly coupled to voltage-dependent gating [124]; and the Kv1-T1 domain may undergo similar rearrangements [32, 85, 105]. A much smaller difference between the cysteine accessibilities of the resting and inactivated states is consistent with the presence of closed-state inactivation in Kv4 channels.

The crystal structures of Kv1 channels and the Kv4-T1 domain [75, 77, 88, 109] suggest a working hypothesis of the putative movements that may underlie the dramatic accessibility changes in the interfacial T1 Zn²⁺ site. For instance, voltage-dependent rearrangements in the VSD may be transmitted to the T1 domain via the T1-S1 linker. This linker begins a few residues downstream from the Zn²⁺ binding motif. Moreover, it is also possible that the space between the T1 domain and the transmembrane domains is narrower when the

channels are closed or closed-inactivated; and, therefore, the lateral intracellular portals are ajar (as suggested by molecular dynamic simulations; Treptow et al., J. Phys. Chem. B., in press). Upon voltage-dependent activation, VSD movements may propagate to the T1 domain. As a result, there is a rearrangement in the interfacial Zn^{2+} site and the T1 and transmembrane domains separate. Then, the internal Agate opens, the lateral portals widen, and the solvent accessibility of the interfacial Zn^{2+} site is dramatically increased. In this scenario, the T1 domain is an integral moving part of the gating machinery in Kv4 channels.

To elucidate the physiological significance of the conformational change in the Zn^{2+} site of the Kv4-T1 domain, we investigated the modulation of the Kv4.1 ternary channel complex (Fig. 1) by nitrosative stress. In a manner analogous to oxidative stress, reactive nitrogen oxide species (RNOS) derived from nitric oxide (NO) metabolism can cause nitrosative stress in proteins [102]. The intra-cellular application of a NO donor (MAHMA-NONOate) to inside-out patches induces rapid inhibition of Kv4.1 channels [126]. To observe this inhibition, it is sufficient and necessary to have two cysteines across the T1 inter-subunit interface (C110 and C132), and intracellular Zn^{2+} antagonizes it [126] (Fig. 2). Furthermore, the addition of reducing reagents (reduced glutathione, GSH; or dithio-threitol, DTT) reverses the NO-induced inhibition. Therefore, we have proposed that the inhibition of the channel by nitrosative regulation results from the formation of a disulfide bond between C110 and C132, which straight-jackets the T1–T1 interface. Supporting this interpretation, these cysteines are only a few Å from each other (Fig. 2), and we detected the reversible formation of high-order oligomers in the presence of NO when C110 and C132 were available only [126]. Straight-jacketing the T1–T1 interface is responsible for the inhibition of the channel by NO because it presumably prevents the inter-subunit T1 displacements associated with activation gating. These results suggest for the first time that the cross-talk between NO and Zn^{2+} [17, 47, 72, 82] may also be critical for redox regulation of I_{SA} in the nervous system.

Kv4 Channel β -Subunits, Integral Remodeling Parts of I_{SA}

KChIPs (K⁺-Channel-Interacting-Proteins) and DPLPs (Di-peptidyl-Peptidase-Like-Proteins) encompass two distinct families of integral auxiliary β -subunits of neuronal Kv4 channels [54]. KChIPs are cytosolic small-molecular-weight calcium binding proteins related to the neuronal calcium sensor [2, 18, 19]. Since the discovery of KChIPs [2], subsequent studies have reported additional closely related genes and many alternative splice variants [4, 16, 18, 43, 96, 120, 123]. DPLPs are single-pass membrane proteins related to the cell adhesion protein CD26 and the dipeptidyl peptidase IV (DPPIV) [62]. Two distinct DPLPs have been identified as auxiliary β -subunits of Kv4 channels (DPPX and DPPY) and several alternative splice variants have also been discovered [53, 55, 86, 87, 134]. Recent studies have reported crystal structures of KChIP-1 and DPPX [98, 109, 127, 136].

These auxiliary β -subunits produce a plethora of biochemical and functional changes, which influence activation and inactivation gating, and voltage dependence [54]. Promoting the trafficking of Kv4 subunits to the plasma membrane is a common denominator of most KChIPs and DPLPs [2, 54, 55, 87, 134]. KChIP4a is a notable exception that does not promote surface expression [43]. The most common and dramatic effects of KChIPs are to

slow the fast phase of macroscopic inactivation and accelerate the recovery from inactivation. The slowing of fast inactivation results from the tight binding of the cytosolic Kv4 N-terminus to the core of KChIPs (interacting site 1) [4, 21, 98, 101, 127, 136]. The free Kv4 N-terminus may otherwise act as an inactivation domain [36, 51]. Thus, the constitutive sequestration and immobilization of the Kv4 N-terminal inactivation domain (Kv4 NT-ID) is directly responsible for slower inactivation [9, 59]. The molecular bases of accelerated recovery from inactivation are not understood; and the accelerating effects of KChIP-1 on the slow phase(s) of inactivation and channel closing are also intriguing [7, 9, 59]. It is possible that the sequestration of the Kv4 NT-ID by its binding to KChIP-1 relieves a “foot-in-the-door” effect at the A-gate with a dual role on activation and closed-state inactivation (see above). Thus, closing and slow inactivation are eased without the physical interference from the Kv4 NT-ID at the inner mouth of the channel.

KChIPs may also help to stabilize the T1–T1 interface by clamping together two neighboring T1 domains (interacting site 2) [98, 127]. Structural studies suggest that the main role of high-affinity $\text{Ca}^{2+}/\text{Mg}^{2+}$ binding in KChIPs is to maintain their compact tertiary structure, which is necessary for proper coassembly with Kv4 channels [23, 98]. A general dynamic role of Ca^{2+} binding on the functional effects of most KChIPs seems doubtful [96].

Functionally, the common denominator of DPLPs is to shift the voltage dependence of activation and inactivation toward more negative membrane potentials [52, 53, 55, 86, 87, 134]. We hypothesized that this change results from a direct interaction between the DPLPs' single transmembrane segment and the channel's VSD, as suggested by previous reports [100, 134]. To investigate this hypothesis, we implemented a strategy to measure Kv4 gating currents for the first time [33]. This method takes advantage of an engineered charybdotoxin (CTX) binding site in the pore of the Kv4.2 channel. Thus, we isolated the gating currents by blocking the ionic K^+ current upon bath application of CTX. These experiments showed that DPPX-S accelerates the relaxation of the gating currents and shifts the voltage-dependence of gating charge (Q) movement toward more negative membrane potentials; and this shift was quantitatively comparable to that of the peak conductance-voltage relation (–26 mV) [33]. Further kinetic analysis revealed that these observations are readily explained by assuming that DPPX-S destabilizes the resting conformations of the voltage sensors through a catalytic effect that changes the activation pathway's energetic landscape [33]. An attractive possibility that emerges from this study is that the transmembrane segment of DPPX-S evolved to become an integral voltage sensor interacting protein of Kv4 channels. The potent effect of DPPX-S on voltage-dependent gating may also be sufficient to explain acceleration of inactivation coupled to activation [33, 87].

Possibly, the functional diversity and specificity among DPLPs is in part dictated by their intracellular N-terminal region. For instance, it has been suggested that the proximal N-terminus of DPPY-a determines voltage-dependent ultra-fast inactivation of Kv4.2 channels coexpressed with this auxiliary subunit [53]. Also, we have found that acidic amino acids within the N-terminus of DPPX-S may confer higher unitary conductance to Kv4.3 and Kv4.2 channels (Kaulin, Rocha, Rudy and Covarrubias, unpublished). This result is significant because the unitary conductance of Kv4 channels coexpressed with DPPX-S

agrees closely with that of the neuronal native counterpart (6–8 pS) [11, 24, 42, 117] and is about 50–100% larger than that of the Kv4 channels expressed alone [9, 43, 56].

Perspective

The cloning and characterization of the first *Shal* gene from *Drosophila melanogaster* was reported in 1990 [130]. Subsequently, the first mammalian homologues were also identified, cloned and characterized [5, 92, 112]; and evidence of putative Kv4 auxiliary β -subunits was published in 1993 and 1994 [22, 111]. In the last 10 years, however, we have learned most of what we know about Kv4 channels and their auxiliary β -subunits in brain, heart and smooth muscle. It is now generally accepted that the neuronal Kv4 channel complex is composed of at least three distinct classes of subunits: the pore-forming α -subunit Shal/Kv4, and two auxiliary β -subunits (KChIPs and DPLPs). These auxiliary β -subunits are integral components of the native complex, and therefore, their functional effects in heterologous expression systems suggest a constitutive overhaul or remodeling of the channel rather than modulation (as it would be with other signaling proteins). Accordingly, ternary Kv4 channels including these subunits have electrophysiological features that for the first time truly begin to resemble those of native Kv4 channels that underlie the I_{SA} [81, 87]. Therefore, only by investigating the mechanism that govern the function of ternary Kv4 channel complexes [6] (Amarillo et al., J. Physiol., in press), we will begin to understand how they work, how they are modulated by signaling processes (e.g., phosphorylation/dephosphorylation, arachidonic acid, NO, Zn^{2+} , etc.), how they impact critical physiological processes, and how they could be involved in disease states. In the immediate future, we hope to learn more about the molecular mechanism of closed-state inactivation, the gating role of the T1 domain, and the specific mechanisms governing the actions of KChIPs and DPLPs. Also, we expect important advances at both ends of the biological spectrum, which may reveal more about the atomic structure of the Kv4 channel complex and its role in complex neuronal processes.

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Fig. 1.

Structural model of the Kv4 channel complex. This model combines the crystal structures of the DPPX dimer (blue-green, extracellular C-terminal domains only), Kv 1.2 tetramer (blue and red, VSD and PD domains, respectively; S4 and S4S5 linker is light blue) and the T1-KChIP-1 octameric complexes (green and orange, T1 and KChIP-1, respectively); and assumes an overall dodecameric stoichiometry. The dotted line represents the putative location of the DPPX transmembrane segment and intracellular N-terminus. Note that KChIP-1 sequesters and immobilizes the N-terminus of the Kv4 channel (*Note: For interpretation of the references to color in this figure legend, the reader is referred to the online version of this article*)

Fig. 2. Stereo view of the interfacial Zn^{2+} binding site in the T1 domain of the Kv4.1 channel. A stick representation of the coordinating residues is shown. C131, C132 and H104 are from the same subunit, and C110 is from the neighboring subunit. The *blue* sphere represents a Zn^{2+} ion in the binding site. Although the isolated T1 domain oligomer is typically Zn^{2+} -bound, the T1 domain in the intact Kv4.1 channel appears to be Zn^{2+} -free or partially liganded (see text) (*Note:* For interpretation of the references to color in this figure legend, the reader is referred to the online version of this article)