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Review

Neuronal voltage-gated K^+ (Kv) channels function in macromolecular complexes

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ABSTRACT

Considerable evidence indicates that native neuronal voltage-gated K^+ (Kv) currents reflect the functioning of macromolecular Kv channel complexes, composed of pore-forming (α)-subunits, cytosolic and transmembrane accessory subunits, together with regulatory and scaffolding proteins. The individual components of these macromolecular complexes appear to influence the stability, the trafficking, the localization and/or the biophysical properties of the channels. Recent studies suggest that Kv channel accessory subunits subserve multiple roles in the generation of native neuronal Kv channels. Additional recent findings suggest that Kv channel accessory subunits can respond to changes in intracellular Ca^{2+} or metabolism and thereby integrate signaling pathways to regulate Kv channel expression and properties. Although studies in heterologous cells have provided important insights into the effects of accessory subunits on Kv channel expression/properties, it has become increasingly clear that experiments in neurons are required to define the physiological roles of Kv channel accessory and associated proteins. A number of technological and experimental hurdles remain that must be overcome in the design, execution and interpretation of experiments aimed at detailing the functional roles of accessory subunits and associated proteins in the generation of native neuronal Kv channels. With the increasing association of altered Kv channel functioning with neurological disorders, the potential impact of these efforts is clear.

Voltage-gated K^+ (Kv) currents are key regulators of neuronal membrane excitability, functioning to control resting membrane potentials [12], spontaneous firing rates [45], the back propagation (into dendrites) of action potentials [18], neurotransmitter release [20], synaptic integration [17,53], and even apoptosis [40]. Neurons typically express multiple types of Kv channels with distinct time- and voltage-dependent properties and subcellular distributions that differentially contribute to the regulation of firing properties and signal integration. Molecular cloning has revealed even greater potential for generating functional Kv channel diversity than was anticipated based on the physiology [10,45]. A large number of Kv channel pore-forming (α)-subunits and a variety of Kv channel accessory subunits have been identified [10,45], and studies in heterologous cells have revealed multiple, sometimes overlapping, effects of accessory subunits on the expression, distributions and properties of Kv α-subunit-encoded channels [25,32]. Electrophysiological and biochemical evidence indicates that native neuronal K^+ currents reflect the functioning of macromolecular K^+ channel complexes comprising four α-subunits, cytosolic and transmembrane accessory subunits, as well as regulatory and scaffolding proteins [25]. Recent proteomic studies, for example, demonstrated that native (mouse) brain Kv4 channel complexes contain many different types of accessory and regulatory subunits [33], each of which may influence channel targeting, trafficking and/or biophysical properties. It has also become clear that the properties of Kv α-subunit-encoded channels and the modulatory effects of channel associated proteins vary in different cellular backgrounds. Thus, studies need to be carried out in neurons to understand the functions of Kv channel accessory subunits in the generation and regulation of native Kv channels. This review focuses on recent advances made in exploring the roles of Kv channel associated proteins in neurons with an emphasis on studies suggesting that Kv channel accessory subunits can serve as points of integration for signaling pathways, as well as link membrane excitability to other cellular processes.

Several recent studies, focused on examining the roles of K^+ Channel Interacting Protein 3 (KChIP3), have highlighted the potential for Kv channel accessory subunits to serve as points of signal integration in the regulation of neuronal function [1,3,51]. KChIP3, like the other members of the Neuronal Ca^{2+} Sensor super family [5], binds Ca^{2+} through multiple EF-hand motifs [31,44]. KChIP3 also promotes the surface expression of heterologously expressed Kv4 channels [56] and regulates the functional expression of neuronal Kv4-encoded currents [29,39]. Exciting recent findings also demonstrate that KChIP3 regulates the voltage dependence of inactivation of Kv4-encoded channels in cerebellar stellate cells in response to Ca^{2+} entry through voltage-gated Ca^{2+} (Cav) channels [3]. In the presence of KChIP3 (but not the other KChIPs), Ca^{2+} entry through Cav3 channels induced a depolarizing shift in the voltage

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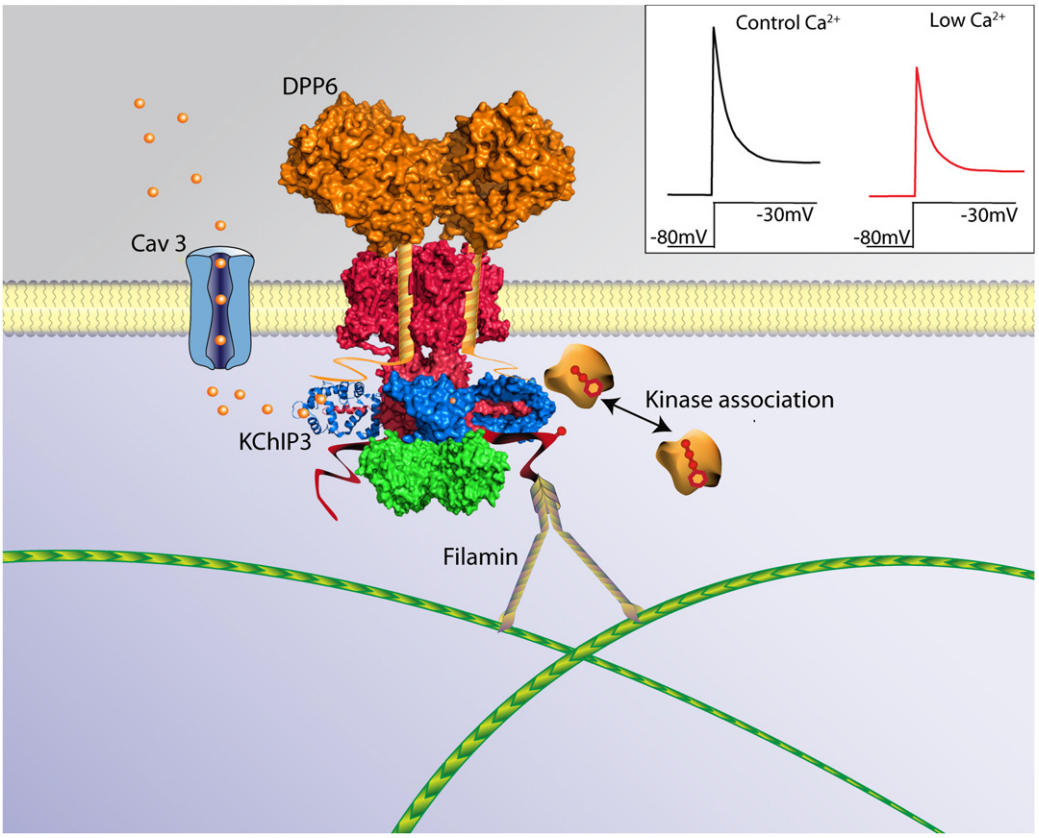

Fig. 1. Multiple components of Kv4 channel macromolecular protein complexes. Schematic representation of Kv4 channel α-subunits (red) bound to Kv β (green), DPP6 (orange) and KChIP3 (blue) accessory subunits. The channel complex is shown anchored to the actin cytoskeleton by filamin via the carboxyl-terminus of one of the Kv4 α-subunits. Kinases also associate with Kv4 channel complexes and phosphorylate α and/or accessory subunits, modifications that can affect channel stability, trafficking and/or properties. It has been reported that association of Kv4 α-subunits with KChIP accessory subunits is required for the modification of channel function by some kinases [51,52]. Cav3 channels can also associate with Kv4 channel complexes by binding to Kv4.2 [2]. In Kv4.2-Cav3 complexes identified in stellate neurons, KChIP3 acts as a Ca^{2+} sensor, and Ca^{2+} entry through Cav3 channels, shifts voltage dependence of Kv4.2 channel inactivation to more depolarized potentials [2,3]. Consistent with a role for Ca^{2+} entry through Cav3 channels in the regulation of Kv4.2 channels, reductions in extracellular Ca^{2+} concentration result in attenuation of Kv4.2 currents (inset) because more Kv4.2 channels are inactive at the holding potential when Ca^{2+} entry is reduced.
Inset adapted with permission from Macmillan Publishers Ltd: Nature Neuroscience copyright 2010 [2].

dependence of Kv4 channel inactivation, thereby linking Kv4 channel availability to local changes in Ca^{2+} concentration [2] (Fig. 1, inset). Together, these observations suggest that KChIP3 may regulate functional Kv4-encoded current densities in neurons, both by controlling the numbers of Kv4 channels expressed at the cell surface and by dynamically regulating Kv4 channel availability in response to changes in Ca^{2+} entry (Fig. 2).

Additional experiments suggest that KChIP3 also regulates Kv4 channel modulation by kinases [52]. The association of G protein-coupled receptor kinases (GRK) with KChIP3, for example, is dependent on Ca^{2+} [51], suggesting that KChIP3 could function to integrate local changes in Ca^{2+} levels with kinase signaling pathways. In addition, the phosphorylation of Kv4 α-subunits has been suggested to be related to surface expression [19,54,61]. The possibility that KChIP3 acts as a point of signal integration to regulate the surface expression of Kv4 channels through multiple pathways is exciting, particularly given the importance of dynamic alterations in Kv4-encoded currents in modulating dendritic integration and synaptic potentiation [8,30]. Interestingly, it has also been reported that KChIPs regulate the surface expression and the functioning of voltage-gated Ca^{2+} channels [57], NMDA receptors [65] and other Kv channels [27], suggesting that these proteins are multifunctional, differentially regulating excitability in different cell types and/or subcellular compartments. Clearly, experiments in which the expression levels of the KChIPs are altered *in situ* are needed to explore these hypotheses directly.

Importantly, KChIP3 has also been demonstrated to function in other cellular processes and has been given additional names reflecting these roles: including regulating gene transcription (downstream regulatory element antagonist modulator or DREAM) [7], modulating the production of amyloid precursor protein by binding to presenilin (calsenilin) [6,28], and regulating gamma secretase activity and apoptosis [21,22]. The possibility that KChIP3 may help coordinate long-term changes, through regulating gene transcription, and short-term changes, in response to alterations in cellular activity (intracellular Ca^{2+} levels and phosphorylation state), in neuronal excitability is intriguing and warrants further investigation.

A number of recent studies also suggest that the inclusion of Kvβ subunits in Kv channel complexes has broad ramifications for channel expression and functioning. Similar to KChIPs, Kvβ subunits also appear to subserve multiple roles including: directly altering the time- and voltage-dependent properties of Kv currents [37,49], regulating the trafficking of Kv1 and Kv4 channels [14,15,64], and modulating changes in Kv currents in response to signaling pathways. Numerous kinases have been shown to phosphorylate Kv1 α-subunits, as well as Kvβ subunits, and thereby modify the effects of Kvβ subunits on Kv1-encoded currents [35]. Interestingly, Kvβ subunits also reportedly associate with Kv4 α-subunits in brain [33], and coexpression of Kvβ subunits with Kv4 α-subunits in heterologous cells alters the cell surface expression of Kv4-encoded channels [62,64]. Little is presently known, however, about the

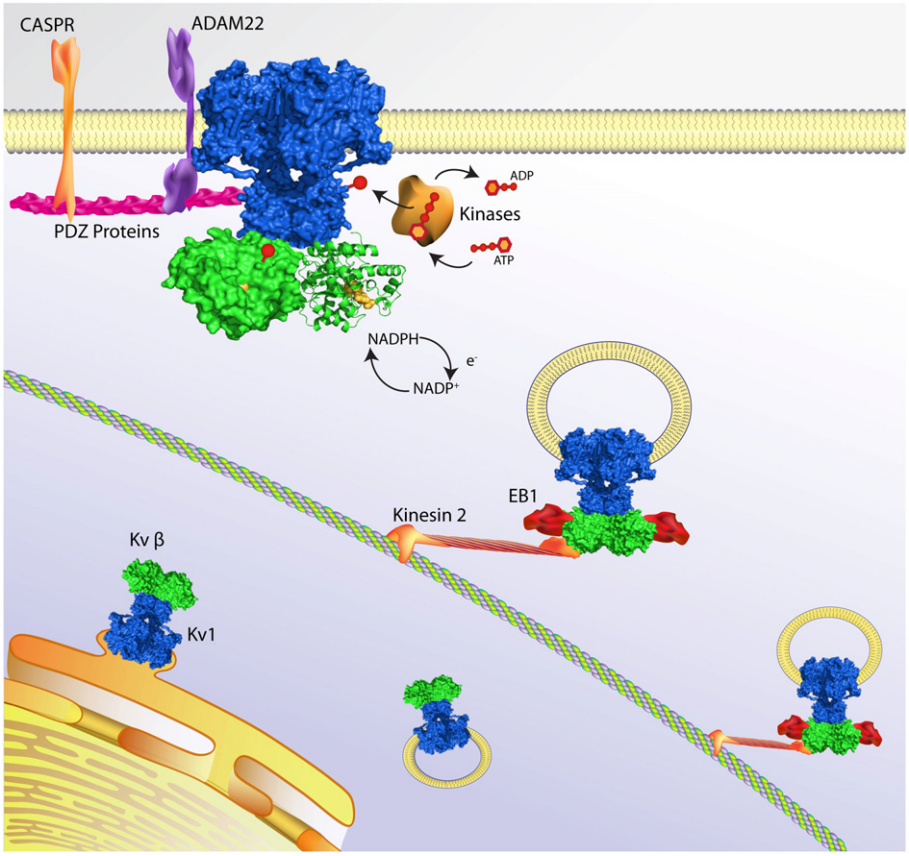

Fig. 2. Kv1 channel complexes targeted to axons. Schematic representation of the assembly and targeting of Kv1 channel macromolecular complexes. Previous studies have shown that Kv1 channel α-subunits (blue) associate with Kv β subunits (green) in the endoplasmic reticulum early during biosynthesis [55]. Through the binding of Kvβ to EB-1 and Kinesin-2 channel complexes then are trafficked down the axon on microtubules. At nodes of Ranvier, Kv1-encoded channels associate with PDZ-domain containing proteins (e.g., PSD-95 and PSD-93) and with the transmembrane proteins, ADAM22 and CASPR. The functioning of Kv1-encoded channels can also be modulated by phosphorylation of both the Kv1 α and the Kvβ subunit [35]. In addition, Kvβ subunits can also regulate channel properties and functioning in response to changes in the oxidation state of the bound co-factor $NADP^+$, providing a potential link between cell metabolism and membrane excitability [42,63].

physiological role(s) of Kvβ subunits in regulating the expression or the properties of native neuronal Kv4 channels.

Given that the Kvβ subunits have a high degree of structural homology to aldo–keto reductases, it is perhaps not surprising that Kvβ2 was crystallized bound to the co-factor nicotinamide adenine dinucleotide phosphate ($NADP^+$) [9,16]. The Kvβ subunits appear positioned, therefore, to serve as sensors of the oxidative state of cells, suggesting a direct link to metabolism [63]. Mutations in the $NADP^+$ binding site have been reported to disrupt Kvβ mediated alterations in the trafficking of Kv1 α-subunits [42]. In addition, changes in the oxidization state of bound $NADP^+$ were shown to result in changes in the expression/properties of heterologously expressed Kv1-encoded currents [26,63]. Interestingly, Kvβ subunits reportedly confer sensitivity to oxygen concentration to heterologously expressed Kv4, but not Kv1-encoded currents [41]. Accumulating evidence also suggests that Kvβ subunits may couple changes in cellular metabolism to the regulation of membrane excitability [58], although a direct link in neurons has yet to be demonstrated.

As highlighted by the results of several recent studies [15,24,36], a number of challenges exist to efforts focused on defining the physiological roles of Kv channel accessory subunits in the generation of native neuronal Kv channels. Recent proteomic studies, focused on Kv4 channel complexes isolated from brain, indicated that Kv4 α-subunits channels interact with multiple different proteins. Many of the proteins traditionally thought of as Kv channel accessory subunits, such as DPP6 and the KChIPs were identified, but several additional, unexpected proteins, such as the GABA receptor subunit, Gabra-6, and the poorly understood metabotropic glutamate receptor, Gpr158, were also found to co-immunoprecipitate with the Kv4.2 protein from brain [33]. Consistent with findings from studies on Kv4.2, other Kv channels have been suggested to interact with scaffolding proteins like ADAM22 and PSD-95. Thus, it seems likely that native Kv channel macromolecular complexes contain numerous accessory and regulatory proteins. In efforts to determine the functional roles of the proteins associated with Kv channels, experiments utilizing heterologous cells will be important, but experiments in native cells will be required to understand fully how each Kv channel accessory subunit functions in the generation of native neuronal Kv channel complexes.

There are, however, a number of potential challenges to the design, execution and interpretation of experiments focused on exploring the functioning of Kv channel accessory subunits in neurons. Among the potential challenges is the fact that many families of Kv channel accessory subunits, including the KChIPs, Kvβs and MinK/MiRPs, have multiple members with properties (and functional effects) that are likely conserved throughout the family. The individual subunits may be able to compensate for the loss of other family members. The disruption of the expression of an individual accessory subunit, therefore, may not reveal defects in the expression or the targeting of α-subunits and/or in the properties of expressed Kv currents dramatic enough to be resolved. Recent studies focused on exploring the contributions of the various KChIPs to the expression of Kv4-encoded channels

in (mouse) cortical pyramidal neurons, in fact, revealed that these cells express KChIP2, 3 and 4 and that when the expression of an individual KChIP was disrupted, the protein expression levels of the remaining two KChIPs are up regulated and Kv4 currents were only modestly affected [39]. Simultaneous RNAi mediated knockdown of all three KChIPs, however, caused a marked reduction in Kv4-encoded current densities [39].

Functional compensation may also occur in other families of Kv channel accessory subunits. There are, for example, three members of the Kvβ family in mammals [46]. Expression of mutant Kvβ subunits has revealed a critical role for Kvβ subunits in the trafficking of Kv1 channels [14]. In animals lacking Kvβ2, the most abundantly expressed β subunit [50], however, Kv1.1 and Kv1.2 α-subunits traffic normally. Mice lacking Kvβ2, however, display cold swim-induced tremors, suffer occasional seizures and have a reduced average lifespan [36], suggesting that the loss of Kvβ2 produces defects that are undetected in the molecular studies focused on examining the effects of Kvβ2 on the trafficking Kv1 channels.

An additional challenge to determining the functional roles of Kv channel associated proteins is the potential for these proteins to interact with multiple channel types and to participate in a number of cellular processes. This point is well illustrated with proteins like the AKAPs and filamins, which interact with specific types of ion channels [13,43], but are also scaffolding proteins generally involved in the formation of macromolecular protein complexes [43,47]. Several Kv channel accessory subunits are also involved in multiple cellular processes. Both KChIP3 and KChIP4, for example, were independently identified as binding partners for the presenilins and were termed calsenilin and calsenilin related protein, respectively, suggesting roles for both proteins in the regulation of gamma secretase activity [6,38]. Disruption of the expression of molecules like the filamins and the KChIPs, therefore, could potentially have numerous consequences for cellular functioning not directly related to Kv channels.

Mutations in K^+ channel α-subunits (for example, Kv7.2 and Kv7.3 in epilepsy [48], and Kv1.1 in Episodic Ataxia Type 1 [4]) have been associated with neurological disorders/diseases. It is perhaps not surprising then that recent results from genetic studies in patient populations and studies using genetically altered mice suggest roles for altered expression and/or functioning of Kv channel accessory subunits in a number of different neurological disorders/diseases. Structural variants of both of the Kv channel accessory subunit genes, *DPP6* and *DPP10*, for example, were identified in a genome-wide association study as candidate genes in autism spectrum disorder [34]. Interestingly, the *DPP6* gene has also been associated with increased risk of progressive spinal muscular atrophy [60] and sporadic amyotrophic lateral sclerosis [11,59]. Mutations in another K^+ channel associated protein, leucine-rich glioma-inactivated 1 (Lgi1), have been linked to multiple epilepsy syndromes [23]. As the functional roles of channel accessory/associated proteins are increasingly appreciated, it seems certain that alterations in the expression and/or properties of these proteins will be linked to more disease states. Clearly, carefully crafted experiments, combining molecular genetic, pharmacological, electrophysiological and biochemical approaches, will be needed to define the roles of Kv channel accessory and associated proteins in the functioning of native neuronal Kv channel macromolecular complexes and to further delineate the contributions of Kv channel accessory subunits to neuronal functioning under normal and pathologic conditions.

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