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I_A Channels: Diverse Regulatory Mechanisms

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Abstract

In many peripheral and central neurons, A-type K^+ currents, I_A, have been identified and shown to be key determinants in shaping action potential waveforms and repetitive firing properties, as well as in the regulation of synaptic transmission and synaptic plasticity. The functional properties and physiological roles of native neuronal I_A, however, have been shown to be quite diverse in different types of neurons. Accumulating evidence suggests that this functional diversity is generated by multiple mechanisms, including the expression and subcellular distributions of I_A channels encoded by different voltage-gated K^+ (Kv) channel pore-forming (α) subunits, interactions of Kv α subunits with cytosolic and/or transmembrane accessory subunits and regulatory proteins and post-translational modifications of channel subunits. Several recent reports further suggest that local protein translation in the dendrites of neurons and interactions between I_A channels with other types of voltage-gated ion channels further expands the functional diversity of native neuronal I_A channels. Here, we review the diverse molecular mechanisms that have been shown or proposed to underlie the functional diversity of native neuronal I_A channels.

Keywords

Kv4 channels; Kv1 channels; Kv channel accessory subunits; posttranslational regulation of Kv channels; Kv12 channels

Introduction

Rapidly activating and inactivating, A-type K^+ currents (I_A), initially characterized by Connor and Stevens (1971a, 1971b) in invertebrate neurons, are now well recognized as key determinants in the regulation of excitability in a wide variety of vertebrate peripheral and central neurons. In addition, electrophysiological studies have revealed that I_A subserves a variety of physiological roles in neurons, from the regulation of action potential durations and repetitive firing rates to controlling the backpropagation (into dendrites) of action potentials and the modulation of synaptic transmission and synaptic plasticity (Johnston and others 2000; Kim and Hoffman 2008). Considerable evidence now suggests, however, that the detailed biophysical properties, the molecular determinants and the functional roles of I_A

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are actually quite variable in different types of neurons. Here, we review the physiological roles and the molecular and functional diversity of native neuronal I_A channels and discuss the various regulatory mechanisms that have been shown or postulated to contribute to this diversity.

Molecular and Functional Diversity of Native I_A Channels

Studies in heterologous expression systems have demonstrated that at least six of the genes encoding voltage-gated K^+ (Kv) channel pore-forming (α) subunits can generate rapidly activating and inactivating K^+ currents with properties similar to neuronal I_A, suggesting that the functional diversity of native I_A is generated, at least in part, by the expression of different and/or multiple Kv α subunits and Kv α subunit–encoded channels. Indeed, accumulating evidence suggests that the molecular determinants and the functional properties of native neuronal I_A channels are distinct in different types of neurons. The Kv4.2 α subunit, for example, is robustly expressed in hippocampal and cortical pyramidal neurons as well as in cerebellar granule cells and is one of the main contributors to the generation of I_A in these cells (Kim and others 2005; Nadin and Pfaffinger 2010; Nerbonne and others 2008; Norris and Nerbonne 2010; Shibata and others 2000; Yuan and others 2005). In dorsal root ganglion neurons, in contrast, Kv4.2 expression is negligible, suggesting that Kv4.2-encoded channels do not contribute to I_A in these cells (Phuket and Covarrubias 2009). Multiple Kv α subunits, including Kv4.1, Kv4.3, Kv3.4, and Kv1.4, that can generate I_A-type channels, however, are highly expressed in dorsal root ganglion neurons and have been suggested to contribute to the generation of I_A in these cells (Cao and others 2010; Chien and others 2007; Phuket and Covarrubias 2009; Rasband and others 2001).

In cortical pyramidal neurons, the Kv4.2, Kv4.3, and Kv1.4 α subunits have all been suggested to contribute to I_A (Norris and Nerbonne 2010), and I_A channels encoded by these different Kv α subunits have been shown to play unique roles in the regulation of the intrinsic excitability of these cells (Carrasquillo and others 2012). Kv4.2-encoded I_A channels, for example, contribute to the input resistances, the current thresholds for action potential generation and the repolarization of action potentials in cortical pyramidal cells. Kv4.3-encoded channels, in contrast, contribute to action potential repolarization without affecting input resistances or current thresholds for action potential generation. I_A channels encoded by Kv1.4 also contribute to the regulation of resting membrane potentials and the current thresholds for action potential generation but do not measurably affect action potential durations. Taken together, these results demonstrate that native neuronal Kv4.2-, Kv4.3-, and Kv1.4-encoded I_A channels in cortical pyramidal cells function over different voltage ranges and differentially regulate resting and active membrane properties (Carrasquillo and others 2012).

Similar to the observations in cortical pyramidal neurons, I_A is also encoded by multiple Kv α subunits in hippocampal pyramidal neurons (Angelova and Muller 2009; Cai and others 2004; Chen and others 2006; Cooper and others 1998; Jenkins and others 2011; Kim and others 2005; Sheng and others 1992; Zhang and others 2010). In addition, the subcellular distribution of I_A channels encoded by each of the different Kv α subunits

is unique (Fig. 1) and has distinct functional consequences. Kv4.2-encoded I_A channels, for example, are expressed in the soma and dendrites of hippocampal pyramidal neurons, in a gradient that increases from the proximal to distal segments (Chen and others 2006; Sheng and others 1992) (Fig. 1A). As a result of this unique subcellular distribution pattern, Kv4.2-encoded I_A channels function to regulate the amplitudes of backpropagating action potentials into dendrites and contribute to the regulation of synaptic integration in these cells (Cai and others 2004; Kim and others 2005). In contrast to the somatodendritic expression of Kv4.2 (Sheng and others 1992), Kv1.4 has been reported to be localized preferentially in axons and presynaptic terminals (Angelova and Muller 2009; Cooper and others 1998; Jenkins and others 2011; Sheng and others 1992), where Kv1.4-encoded I_A channels have been proposed to play important roles in the modulation of neurotransmitter release and presynaptic facilitation (Fig. 1B). Recent studies have also revealed that Kv12.2-encoded channels also contribute to a component of I_A in hippocampal pyramidal cells (Zhang and others 2010). While the subcellular distribution of Kv12.2-encoded channels has not been characterized, electrophysiological experiments have clearly demonstrated that Kv12.2-encoded I_A channels (unlike Kv4.2-encoded I_A channels) contribute to the regulation of somatic resting membrane potentials and repetitive firing rates (Zhang and others 2010), suggesting that Kv12.2-encoded channels are preferentially expressed in the soma of hippocampal pyramidal neurons (Fig. 1C).

Native Channels in Macromolecular Complexes

Accumulating evidence suggests that native neuronal I_A channels function in macromolecular protein complexes comprising one or more Kv α subunit (in the same sub-family) together with cytosolic and/or transmembrane accessory subunits and regulatory proteins that influence channel stability, localization, and properties. Similar to Kv α subunits, there are multiple types of Kv channel accessory subunits that have been suggested, based largely on the results obtained from heterologous co-expression studies, to function in the generation of native neuronal I_A channels. Importantly, however, accumulating evidence suggests that, similar to the Kv α subunits, the physiological roles of I_A channel accessory subunits also vary with cell type. Targeted deletion of the cytosolic accessory subunit K^+ channel interacting protein 2 (KChIP2), for example, reportedly alters the densities, voltage-dependent properties and the recovery from inactivation of I_A in hippocampal neurons, increasing spontaneous firing rates and lowering the current thresholds for repetitive firing (Wang and others 2013). In cortical pyramidal and basolateral amygdala neurons, in contrast, targeted deletion of KChIP2 neither measurably affects I_A nor does it affect the intrinsic resting membrane properties or repetitive firing (Norris and others 2010; Wang and others 2013). Additional studies, however, suggest that the lack of effect of loss of KChIP2 on I_A in cortical pyramidal neurons likely reflects compensatory effects of other members of this family, KChIP3 and KChIP4 (Norris and others 2010). Similar cell-type specificity has been reported for the recently identified Kv4 channel accessory subunit, Navβ1 (Marionneau and others 2012). Loss of Navβ1 increases the excitability of cortical pyramidal neurons but does not measurably affect the excitability of hippocampal pyramidal neurons (Marionneau and others 2012; Patino and others 2009).

It has been suggested recently that Kv channel accessory subunits play distinct roles in the functional regulation of I_A channels in different cellular compartments (Fig. 2). The single transmembrane Kv4 channel accessory protein, dipeptidyl peptidase-like protein 6 (DPP6), for example, has been suggested to be critical for generating the characteristic I_A gradient in hippocampal pyramidal neurons (Fig. 2A). Interestingly, targeted deletion of DPP6 reduces I_A densities and alters the amplitudes of backpropagating action potentials in the distal dendrites of hippocampal pyramidal neurons without altering I_A densities or intrinsic excitability in the soma (Sun and others 2011). In cerebellar granule cells, in contrast, acute "knockdown" of DPP6 was shown to drastically reduce I_A densities and to alter intrinsic excitability in the soma (Nadin and Pfaffinger 2010). Whether I_A is functionally expressed in the dendrites of granule cells, however, has not been determined. Taken together, these results suggest distinct functional roles for DPP6 and, in addition, suggest that compartmentalization of function of DPP6 is cell type specific (Fig. 2B). Whether cell type-specific compartmentalization of function is unique to DPP6 or whether this mechanism is important in the functional regulation of I_A channels by other Kv accessory subunits remains to be determined.

Differential modulation of the biophysical properties of native neuronal I_A channels by individual accessory subunits also contributes to the functional diversity of I_A channels. Targeted deletion of KChIP2, for example, shifts the $V_{1/2}$ of steady-state inactivation of I_A to hyperpolarized potentials but does not affect the voltage dependence of channel activation (Wang and others 2013). Acute "knockdown" or targeted deletion of DPP6, in contrast, shifts the voltage-dependences of I_A activation and steady-state inactivation to more *depolarized* potentials (Kim and others 2008; Nadin and Pfaffinger 2010; Sun and others 2011). Similarly, while acute "knockdown" or targeted deletion of DPP6 slows the kinetics of I_A activation and inactivation (Kim and others 2008; Nadin and Pfaffinger 2010; Sun and others, 2011), targeted deletion of KChIP2 or Navβ1 does not measurably affect the kinetics of I_A activation and inactivation (Marionneau and others 2012; Wang and others 2013). The biochemical mechanisms underlying I_A channel modulation by different Kv channel accessory subunits are also distinct. Considerable evidence suggests, for example, that Kv4 protein stability is dependent on the expression of KChIPs and that the expression KChIPs is also dependent on the expression of Kv4 α subunits (Foeger and others 2012; Menegola and Trimmer 2006; Norris and others 2010). Similarly, it has also been reported that Kv4 (and KChIP) protein stability is dependent on the association of Kv4 α subunits with DPP6 (Nadin and Pfaffinger 2010). DPP6 protein expression in the hippocampus, cortex and cerebellum, however, is only mildly reduced after the loss Kv4.2, suggesting that stabilization of the DPP6 protein is independent of Kv4.2 (Nadin and Pfaffinger 2010).

Posttranslational Modification of Channel Subunits

The functional diversity of native neuronal I_A channels is further expanded by posttranslational modifications of pore-forming and accessory channel subunits, which influence channel properties, densities and subcellular localization. Indeed, considerable evidence suggests that multiple upstream signaling pathways function in concert to fine-tune the properties of I_A, thereby modulating intrinsic neuronal excitability and synaptic transmission/plasticity (Fig. 3). In hippocampal and dorsal horn neurons, for example,

extracellular-regulated kinase (ERK)–mediated phosphorylation of Kv4.2 decreases I_A densities (Hu and others 2003; Hu and others 2007; Yuan and others 2002) (Fig. 3A). Attenuation of I_A increases the excitability of dorsal horn neurons (Hu and others 2007; Hu and Gereau 2003) and increases the amplitudes of backpropagating action potentials in the distal dendrites of hippocampal neurons (Yuan and others 2002). It has also been reported that ERK-mediated phosphorylation of Kv4.2 (at serine 616) is downstream of the activation of the metabotropic glutamate receptor 5 (mGluR5) (Hu and others 2007) and is localized to excitatory neurons in the dorsal horn of the spinal cord (Hu and Gereau 2011). In both hippocampal and dorsal horn neurons, I_A is also regulated by the activation of protein kinase A (PKA) and protein kinase C (PKC) in an ERK-dependent manner (Hu and others 2007; Hu and others 2003; Yuan and others 2002). Direct phosphorylation of Kv4.2 (at Ser 355) by PKA, however, has also been shown to decrease I_A densities in hippocampal neurons (Hammond and others 2008). Interaction of Kv4.2 with the A-kinase anchoring protein 79/150 (AKAP79/150) mediates the anchoring of PKA and regulates Kv4.2 surface expression and excitability in the hippocampus (Lin and others 2011). Interestingly, PKA-mediated phosphorylation of Kv4.2 (at S552) can be driven by neuronal activity and, in addition, promotes the internalization of Kv4.2, resulting in the redistribution of the (Kv4.2) protein from the spines to the dendritic shafts and soma (Hammond and others 2008; Kim and others 2007). The activity-dependent redistribution of Kv4.2 is controlled through clathrin-mediated endocytosis and requires NMDA receptor activation and Ca^{2+} influx (Kim and others 2007). Whether activity-dependent redistribution of Kv4.2 requires the anchoring of PKA by AKAP79/150 remains to be determined.

An upstream signaling pathway that includes the Ca^{2+}/calmodulin-dependent kinase II (CaMKII) has also been identified as a modulator of native Kv4.2-encoded I_A channels in hippocampal neurons (Varga and others 2004) (Fig. 3C). Recent studies in cultured *Drosophila* neurons further suggest that CaMKII-dependent phosphorylation of native I_A channels plays a critical role in synaptic homeostasis (Ping and Tsunoda 2012). In response to a prolonged (24 hours) period of synaptic inactivity, for example, I_A densities are increased in the soma and distal dendrites of excitatory motor neurons and the expression of the *Shal* protein, the Drosophila homolog of mammalian Kv4, is upregulated (Ping and Tsunoda 2012). The homeostatic upregulation of I_A in response to synaptic inactivity stabilizes postsynaptic potentials. Inactivity-dependent increases in I_A are dependent on upregulation of the Drosophila α7 (Dα7) nicotinic acetylcholine receptors (nAChR), increases in Ca^{2+} influx and the activation of CaMKII, suggesting that CaMKII-dependent phosphorylation of I_A channels drives the (inactivity dependent) observed increases in I_A (Ping and Tsunoda 2012) (Fig. 3C). Interestingly, these results are consistent with previous studies demonstrating that the expression of constitutively active CaMKII increases I_A densities and decreases neuronal excitability in mammalian neurons (Varga and others 2004).

Novel Mechanisms Regulating Native I_A Channels

Local Translation of Kv4.2 in Dendrites

It was recently reported that Kv4.2 is translated locally in the dendrites of hippocampal neurons and that the fragile X mental retardation protein (FMRP), which is an RNA binding protein, regulates the translation and, therefore, the dendritic protein expression, of Kv4.2 by associating with the 3′ and 5′ untranslated regions (UTRs) of Kv4.2 mRNA (Gross and others 2011). Conflicting results have been reported, however, about the net effect of the association of FMRP with the 3′ UTR of Kv4.2 mRNA on dendritic Kv4.2 protein expression (Gross and others 2011; Lee and others 2011). Immunohistochemical and biochemical studies conducted by Gross and others (2011), for example, revealed that targeted deletion of FMRP *decreases* total and cell surface Kv4.2 protein expression in hippocampal and cortical neurons, suggesting that the association of FMRP with Kv4.2 mRNA *promotes* Kv4.2 protein expression. Biochemical and immunohistochemical experiments performed by Lee and others. (2011), however, yielded completely opposite results. These investigators reported that the in vivo loss of FMRP *increases* dendritic Kv4.2 protein levels in hippocampal neurons, suggesting that the association of FMRP with Kv4.2 mRNA *suppresses* Kv4.2 protein expression. Technical differences in the experiments, such as the primary antibodies used for the immunostaining, might underlie the substantive difference in the results reported by these two groups. In spite of these contradicting results, a novel and important finding from both studies is that FMRP associates with Kv4.2 mRNA and that that Kv4.2 is locally translated in the dendrites of hippocampal and cortical pyramidal neurons.

It was also reported by Lee and others (2011) that the 3′ UTR of Kv4.2 mRNA is sufficient for dendritic targeting and that the in vivo loss of FMRP does not affect dendritic targeting of Kv4.2 mRNA. Additional biochemical and pharmacological studies demonstrated that upstream activation of *N*-methyl-D-aspartate (NMDA) receptors results in dephosphorylation of both mammalian target of rapamycin (mTOR) and FMRP in a process that is dependent on phosphoprotein phosphatase 1 (Lee and others 2011). Dephosphorylation of FMRP, in turn, results in increased dendritic Kv4.2 protein expression and in alterations in synaptic plasticity that can be reversed by pharmacologically reducing Kv4-encoded I_A (Lee and others 2011), observations that are clearly consistent with the suggestion that dendritic Kv4.2-encoded I_A channels contributes to synaptic plasticity.

Channel–Channel Macromolecular Protein Complexes

Several recent studies have also suggested that the biophysical properties of native neuronal I_A channels are also modulated through interactions with other types of ion channels. The interaction of voltage-gated Ca^{2+} (Cav) channels encoded by α subunits of the Cav3 subfamily with Kv4.2-encoded I_A channels, for example, has been shown to regulate the biophysical properties of Kv4.2-encoded I_A channels and intrinsic excitability in cerebellar stellate cells (Anderson and others 2010). Although the mechanisms underlying the functional interaction between Cav3- and Kv4-encoded channels are not known, a role for the KChIP3 accessory subunit has been revealed.

It was also demonstrated recently that the voltage-gated Na^+ (Nav) channel accessory subunit, Navβ1, binds to Kv4.2 α subunits and modulates Kv4.2-encoded I_A and intrinsic excitability in cortical pyramidal neurons (Marionneau and others 2012). Similarly, recent reports have demonstrated that "knockdown" of the accessory subunit DPP6 alters the densities and biophysical properties of I_A and also the densities of $I_{K(SO)}$ and the Nav currents (Nadin and Pfaffinger 2010; Nadin and Pfaffinger 2013). Although these studies clearly suggest that Kv4-encoded I_A channels interact biochemically and functionally with other channels in the brain, the structural bases and the physiological roles of these channel–channel interactions remain to be elucidated.

Summary, Conclusions, and Future Directions

Substantial progress has been made in recent years in the identification of the molecular mechanisms underlying the generation of I_A in different neuronal cell types and the molecular mechanisms that regulate the biophysical properties, the subcellular distributions, and the functioning of native neuronal I_A channels. It is now clear, for example, that multiple Kv α subunits contribute to the generation of native neuronal I_A channels and that I_A channels encoded by these different Kv α subunits are differentially distributed and play distinct physiological roles in the regulation of intrinsic excitability and synaptic transmission. It is also now known that the association of Kv α subunits with cytosolic and/or transmembrane accessory subunits strongly influences the biophysical properties and the subcellular distributions of native neuronal I_A channels and that posttranslational modifications of Kv channel subunits through multiple upstream signaling pathways further expands and fine-tunes the physiological roles of I_A. Further efforts are clearly needed to fully define the cell type–specific mechanisms that underlie the diversity in the physiological roles and functional compartmentalization of native neuronal I_A channels in different populations of neurons.

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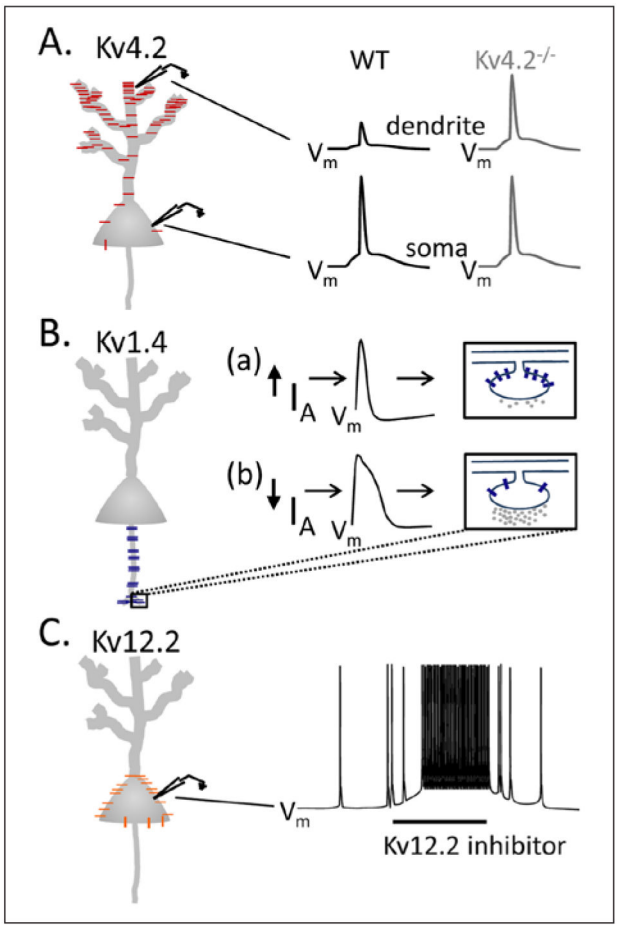

Figure 1.

Functional consequences of the differential (subcellular) distributions of Kv α subunit-encoded native I_A channels in hippocampal pyramidal neurons. Schematic representation of Kv4.2-encoded (red), Kv1.4-encoded (blue), and Kv12.2-encoded (orange) I_A channel distributions in hippocampal pyramidal neurons. (A) Kv4.2-encoded I_A channels (red) are expressed in the soma and dendrites of hippocampal pyramidal neurons, in a gradient that increases from the proximal to distal segments (Chen and others 2006; Sheng and others 1992), and that regulates the amplitudes of backpropagating action potentials (bAPs) in the dendrites. In wild type (WT) neurons, the amplitudes of bAPs in distal dendrites are attenuated, compared with the soma. In ($Kv4.2^{-/-}$) hippocampal neurons lacking Kv4.2, the amplitudes of bAPs are increased (Chen and others 2006). (B) Kv1.4-encoded I_A channels (blue) are localized in axons and presynaptic terminals (Angelova and Muller 2009; Cooper and others 1998; Jenkins and others 2011; Sheng and others 1992). (Ba, Bb) Schematics illustrating model for Kv1.4-mediated modulation of neurotransmitter release. Increased Kv1.4-encoded I_A in presynaptic terminals leads to briefer action potentials and less neurotransmitter release. Decreased Kv1.4-encoded I_A, in contrast, leads to prolonged action potentials and higher neurotransmitter release. (C) Proposed distribution of Kv12.2-encoded I_A channels (orange), with high expression levels in the soma. Bath application of a Kv12.2 inhibitor depolarizes somatic resting membrane potentials and increases repetitive firing rates in hippocampal pyramidal neurons (Zhang and others 2010).

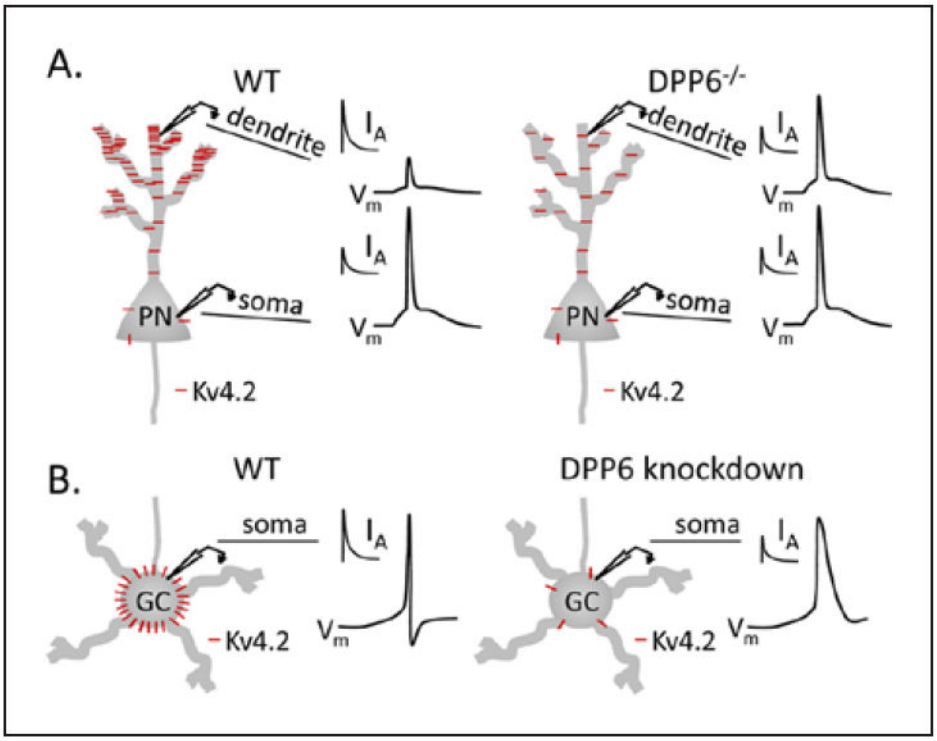

Figure 2.

Cell type–specific modulation of Kv4.2-encoded I_A channels by accessory (dipeptidyl peptidase-like protein 6 [DPP6]) subunits. Schematic representation of Kv4.2 (red) distribution in hippocampal pyramidal neurons (PN) and cerebellar granule cells (GC) in wild type (WT) mice and in mice lacking DPP6. (A) In WT neurons, Kv4.2 (red) expression and I_A densities display a somatodendritic gradient, increasing from the proximal to distal segments (Chen and others 2006; Sheng and others 1992). Targeted deletion of DPP6 (DPP6$^{-/-}$) eliminates the somatodendritic gradient of Kv4.2 expression and I_A densities and increases the amplitudes of bAPs without altering I_A or intrinsic excitability in the soma (Sun and others 2011). (B) In WT cerebellar granule cells, in contrast, I_A is robustly expressed in the soma and acute "knockdown" of DPP6 reduces somatic I_A densities and alters action potential waveforms recorded from the soma (Nadin and Pfaffinger 2010).

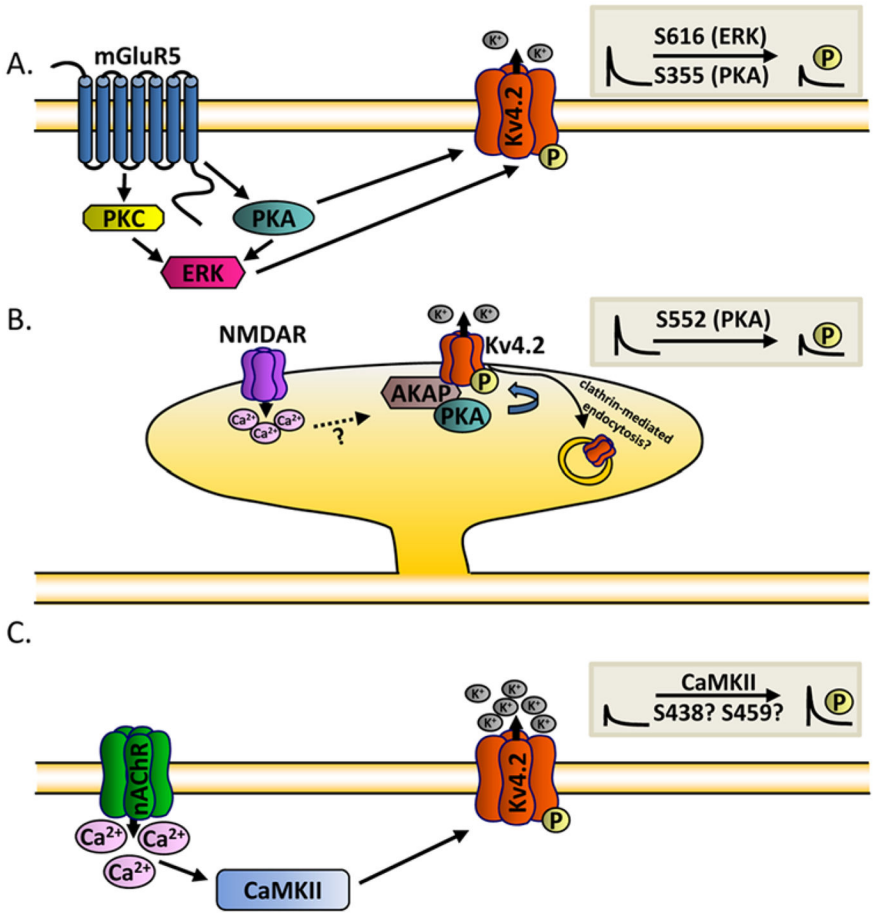

Figure 3.

Multiple upstream signaling pathways function in concert to fine-tune the properties of I_A. (A) Extracellular-regulated kinase (ERK)– and protein kinase A (PKA)–mediated phosphorylation of Kv4.2 is downstream of the activation of the metabotropic glutamate receptor 5 (mGluR5) and decreases I_A densities (Hammond and others 2008; Hu and others 2003; Hu and others 2007; Yuan and others 2002). (B) Interaction of Kv4.2 with the A-kinase anchoring protein (AKAP) mediates the anchoring of PKA and decreases Kv4.2 surface expression (Lin and others 2011). Neuronal activity redistributes Kv4.2 from spines to dendritic shafts and soma through clathrin-mediated endocytosis and requires *N*-methyl-D-aspartate (NMDA) receptor activation and Ca^{2+} influx (Kim and others 2007). (C) Ca^{2+}/calmodulin-dependent kinase II (CaMKII)–dependent phosphorylation of Kv4.2 (*Shal* in *Drosophila*) and increased I_A density (Ping and Tsunoda 2012; Varga and others 2004). Activation of α7 nicotinic acetylcholine receptors (nAChR) and increased Ca^{2+} influx results in downstream CaMKII-dependent phosphorylation of Kv4.2 and in increases in I_A densities.