Comparison of K^+ Channel Families

Jaume Taura, Daniel M. Kircher, Isabel Gameiro-Ros, and Paul A. Slesinger

Contents

Abstract

K^+ channels enable potassium to flow across the membrane with great selectivity. There are four K^+ channel families: voltage-gated K (K_v), calcium-activated (K_{Ca}), inwardly rectifying K (K_{ir}), and two-pore domain potassium (K_{2P}) channels. All four K^+ channels are formed by subunits assembling into a classic tetrameric (4x1P = 4P for the K_v, K_{Ca}, and K_{ir} channels) or tetramer-like (2x2P = 4P for the K_{2P} channels) architecture. These subunits can either be the same (homomers) or different (heteromers), conferring great diversity to these channels. They share a highly conserved selectivity filter within the pore but show different gating mechanisms adapted for their function. K^+ channels play essential roles in controlling neuronal excitability by shaping action potentials, influencing the resting membrane potential, and responding to diverse

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physicochemical stimuli, such as a voltage change (K_v), intracellular calcium oscillations (K_{Ca}), cellular mediators (K_{ir}), or temperature (K_{2P}).

Keywords

Calcium-activated · Conductivity · Gating · Inwardly rectifying K · Ion channel · Potassium channel · Selectivity · Two-pore domain potassium · Voltage-gated K

Abbreviations

EKG	Electrocardiogram
GIRK	G protein-gated inwardly rectifying potassium channel
K_{ATP}	ATP-sensitive inwardly rectifying potassium channel
TALK	Two-pore ALkaline-activated K^+ channel
TASK	Two-pore acid-sensitive K^+ channel
THIK	Two-pore halothane-inhibited K^+ channel
TRAAK	TWIK-related arachidonic acid-stimulated K^+ channel
TREK	TWIK-related K^+ channel
TRESK	TWIK-related spinal-cord K^+ channel
TWIK	Two-pore weak inward-rectifying K^+ channel

1 Overview

A key property of all K^+ channels is their ability to selectively allow permeation of K^+ across the membrane at near diffusion limited rates. That is, they discriminate between K^+ and other monovalent cations and anions, with high fidelity, providing a conduit for K^+ to flow in and out of cells. Built on the framework of K^+ selectivity, K^+ channels have evolved different gating mechanisms (i.e., opening and closing) and functions in a variety of cell types. In this chapter, we compare some of the essential features of K^+ channels across the different families and subfamilies.

The voltage-gated K^+ channels (K_v) form the largest gene family in the K^+ channel group, first described by Hodgkin and Huxley (1945) and cloned 36 years ago (Noda et al. 1984). In mammals, K_v channels are encoded by 40 genes, with each gene encoding a corresponding α subunit. Traditionally, K_v channels play a role in cell excitability, where channel opening helps to repolarize excitable cells via efflux of K^+, such as during the action potential (Hille 1986). The K_v channel family is divided into 12 subfamilies (A-González and Castrillo 2011; Abbott et al. 2001) (Fig. 1), based on analyses of the hydrophobic domain containing the six transmembrane segments (S1-S6).

The first evidence of K^+ currents activated by calcium was described by Gardos over 60 years ago, who observed the activation of K^+ selective conductance by

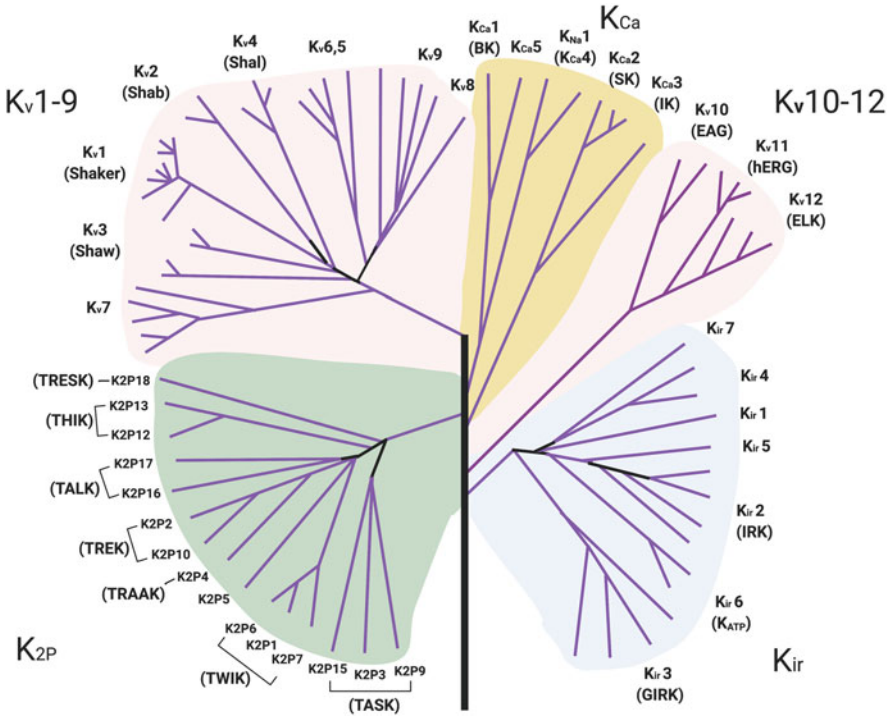

Fig. 1 Potassium channel tree. Dendrogram of the different families of potassium channels

intracellular free calcium in red blood cells (Gardos 1958). The family of calcium-activated (K_{Ca}) channels encompasses a group of K^+ channels with different physiological and pharmacological properties. The calcium sensitivity characteristic of K_{Ca} channels allows them to couple membrane potential changes during the action potential with elevations in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), contributing to activation of the afterhyperpolarization (AHP) and regulation of the action potential (Berkefeld et al. 2010). Based on their single-channel conductance, K_{Ca} channels can be classified as small conductance (SK) K_{Ca} channels, which are $K_{Ca}2.1$-$K_{Ca}2.3$ (4–14 pS) (Kohler et al. 1996), intermediate conductance (IK) K_{Ca} channel, also named as $K_{Ca}3.1$ (32–39 pS) (Ishii et al. 1997), and large conductance (*big* conductance, BK) K_{Ca} channel, also known as $K_{Ca}1.1$ or Slo1 (200–300 pS) (Butler et al. 1993; Kshatri et al. 2018). With a fair degree of sequence homology, the K_{Ca} channel family includes the sodium-activated K^+ channels $K_{Ca}4.1$ and $K_{Ca}4.2$ (also called Slack/Slo2.1 and Slick/Slo2.2, respectively), as well as the pH-dependent $K_{Ca}5.1$ channels (also named as Slo3) (Fig. 1) (Wei et al. 2005).

Inwardly rectifying K (K_{ir}) channels were first described over 70 years ago in skeletal muscle fibers by Bernard Katz (1949), who observed an "anomalous" rectifier inward current in the presence of different extracellular K^+ concentrations. K_{ir} gating appeared to shift with the Nernst potential for K^+. Years later, several

studies explained that the property of inward rectification arises from an asymmetric blockade of the open channel pore by intracellular Mg^{2+} (Matsuda et al. 1987) and polyamines (Lopatin et al. 1994; Oliver et al. 2000). This property of inward rectification enables K_{ir} channels to play a key role in the maintenance of the resting membrane potential and the regulation of the action potential duration in excitable cells (Hibino et al. 2010). The family of inwardly rectifying K^+ channels comprises a variety of channels classified in seven different subfamilies, from $K_{ir}1.x$ to $K_{ir}7.1$ (Kubo et al. 2005) that are encoded by 15 different genes (Kubo et al. 2005) (Fig. 1). From a functional perspective, K_{ir} channels can be classified into four groups: (1) K^+ transport channels, including $K_{ir}1.1$, $K_{ir}4.1$-$K_{ir}4.2$, $K_{ir}5.1$, and $K_{ir}7.1$; (2) Classical K_{ir} channels, comprising $K_{ir}2.1$-$K_{ir}2.4$ channels; (3) $K_{ir}3.x$ or G-protein-gated K_{ir} channels (GIRK), which encompass GIRK1–4; and (4) ATP-sensitive K^+ channels (K_{ATP}), which correspond to $K_{ir}6.1$-$K_{ir}6.2$ (Hibino et al. 2010; Kubo et al. 2005). Due to their divergence in properties from other K_{ir} channels, some are often referred to by their functional name, i.e. GIRK for $K_{ir}3$ and K_{ATP} for $K_{ir}6.2$.

The first two-pore domain potassium (K_{2P}) channel ever described was discovered only 25 years ago in *Saccharomyces cerevisiae*, TOK1 (Ketchum et al. 1995). A year later, dORK ($K_{2P}0$) in *Drosophila melanogaster* (Goldstein et al. 1996)) and finally TWIK1 ($K_{2P}1$) in humans (Lesage et al. 1996) were discovered. K_{2P} channels contribute to a K^+ leak current in excitable and non-excitable cells (Czirjak and Enyedi 2002). This resting or background conductance is critical in motoneurons (Berg et al. 2004; Talley et al. 2000), dorsal root ganglion neurons (Kang and Kim 2006; Pereira et al. 2014), or cerebellar granule neurons (Plant et al. 2002). Whereas "leakage current" typically refers to a non-selective current following membrane damage, K_{2P} channels support a K^+-selective leak that is fairly voltage-independent. At rest, open K_{2P} channels enable K^+ efflux due to K^+ concentration gradient, making the intracellular more negative, limiting further K^+ efflux and suppressing depolarization. Under physiological conditions, neurons display a resting membrane potential (V_m) of −60 to −90 mV, while the equilibrium potential for K^+ (E_K) is approx. −90 mV, with a K^+ concentration of 5 mM outside and 140 mM inside at 37°C. Nevertheless, K^+ leakage contributes more to the V_m. K_{2P} channels affect the frequency, duration, and amplitude of action potentials. K_{2P} are tightly regulated by splicing, post-translational modifications (phosphorylation, sumoylation, glycosylation) and numerous chemical (phospholipid composition, GPCR activation, second messengers) and physical agents (extracellular and intracellular pH, mechanical stretch, temperature) (Gada and Plant 2019; Goldstein et al. 2001; Niemeyer et al. 2016). Currently, the K_{2P} family is composed of 15 different subunits ($K_{2P}1$–15) and encoded by genes numbered KCNK1–18 (no expression has been found for KCNK8, KCNK11, or KCNK14). They have been historically grouped according to structural and functional relatedness in six subfamilies: TREK1-TREK2-TRAAK ($K_{2P}2$-$K_{2P}10$-$K_{2P}4$), TALK1-TALK2 ($K_{2P}16$-$K_{2P}17$), TWIK1-TWIK2 ($K_{2P}1$-$K_{2P}6$), TASK1-TASK2-TASK3-TASK5 ($K_{2P}3$-$K_{2P}5$-$K_{2P}9$-$K_{2P}15$), THIK1-THIK2 ($K_{2P}12$-$K_{2P}13$), and TRESK ($K_{2P}18$). Like K_{ir} channels, K_{2P} channels are also commonly referred to via their functional name.

2 Subunits/Assembly/Topology

Potassium channels share many similarities when it comes to their topology, assembly, and subunit composition. However, there are some key differences, which we will explore here. For voltage-gated potassium channels each K_v channel is a tetramer composed of similar or identical pore-forming α subunits, and in some cases also contains auxiliary β subunits which can alter channel localization and/or function (A-González and Castrillo 2011; Abbott et al. 2006). The α subunits are arranged around a central axis that forms a pore (Coetzee et al. 1999). Each α subunit is a polypeptide with 6 transmembrane domains (S1-S6) and five loops connecting the segments (Fig. 2). The N- and C-terminal regions are cytoplasmic. The pore-forming region of the channel is produced by the S5-S6 linker (P-loop) and contains the K^+ selectivity filter (Heginbotham et al. 1994). The voltage-sensing domain (VSD) is formed by segments S1-S4 that control pore opening via the S4-S5 intracellular loop that is connected to the pore domain (Bezanilla 2000; Cui 2016; Gandhi and Isacoff 2002; Schmidt and Mackinnon 2008). Within each subfamily both homomeric and heteromeric channels may form with a range of biophysical properties (Abbott et al. 2006; Albrecht et al. 1995), leading to a large diversity of channels.

K_{Ca} channels basic topology is similar to that of K_v channels; in fact, both families belong to the 6/7TM group of K^+ channels (Gutman et al. 2005; Wei et al. 2005). Cryo-EM structures of the full length $K_{Ca}1.1$ channel have provided extensive information about its structure and gating (Hite et al. 2017; Tao et al. 2017) (PDB: 5TJ6 and 5TJI, respectively). Importantly, small and large conductance subfamilies of K_{Ca} channels have two main differences in their structure: $K_{Ca}1.1$ channels have an additional transmembrane domain, S0, and their S4 transmembrane domain is voltage-sensitive (Fig. 2) (Kshatri et al. 2018). Due to the S0, the N-terminus is extracellular, and the large C-terminal domain that comprises around two-thirds of the protein is intracellular (Meera et al. 1997). Like the K_v, the S1-S4 transmembrane segments of the $K_{Ca}1.1$ channel form the VSD (Diaz et al. 1998; Ma et al. 2006) and the S5-S6 segments contain the P-loop with the K^+ selectivity filter (Meera et al. 1997). Another major difference between $K_{Ca}1.1$ channels and $K_{Ca}2.x$/$K_{Ca}3.1$ is the cytoplasmic C-terminal domain, which in $K_{Ca}1.1$ channels contains two regulating conductance of K^+ (RCK) domains, RCK1 and RCK2 (Yuan et al. 2010). X-ray crystal structures of the isolated C-terminus of $K_{Ca}1.1$ have provided valuable structural information about RCK1 and RCK2 (PDB: 3NAF) (Yuan et al. 2011). Both RCK domains possess a high affinity Ca^{2+}-binding site: a string of negatively-charged aspartate residues located at RCK2, labeled as the Ca^{2+}-bowl (Schreiber and Salkoff 1997), and a site containing the residues D362 and D376 in RCK1 (Yuan et al. 2010). Four of these pore-forming subunits of $K_{Ca}1.1$ (α subunit) assemble to form functional homotetramers (Shen et al. 1994).

$K_{Ca}2.1$-$K_{Ca}2.3$ and $K_{Ca}3.1$ channels share with K_v channels the six TM domain (S1-S6) topology (Kohler et al. 1996), with the S5 and S6 TM pore-forming

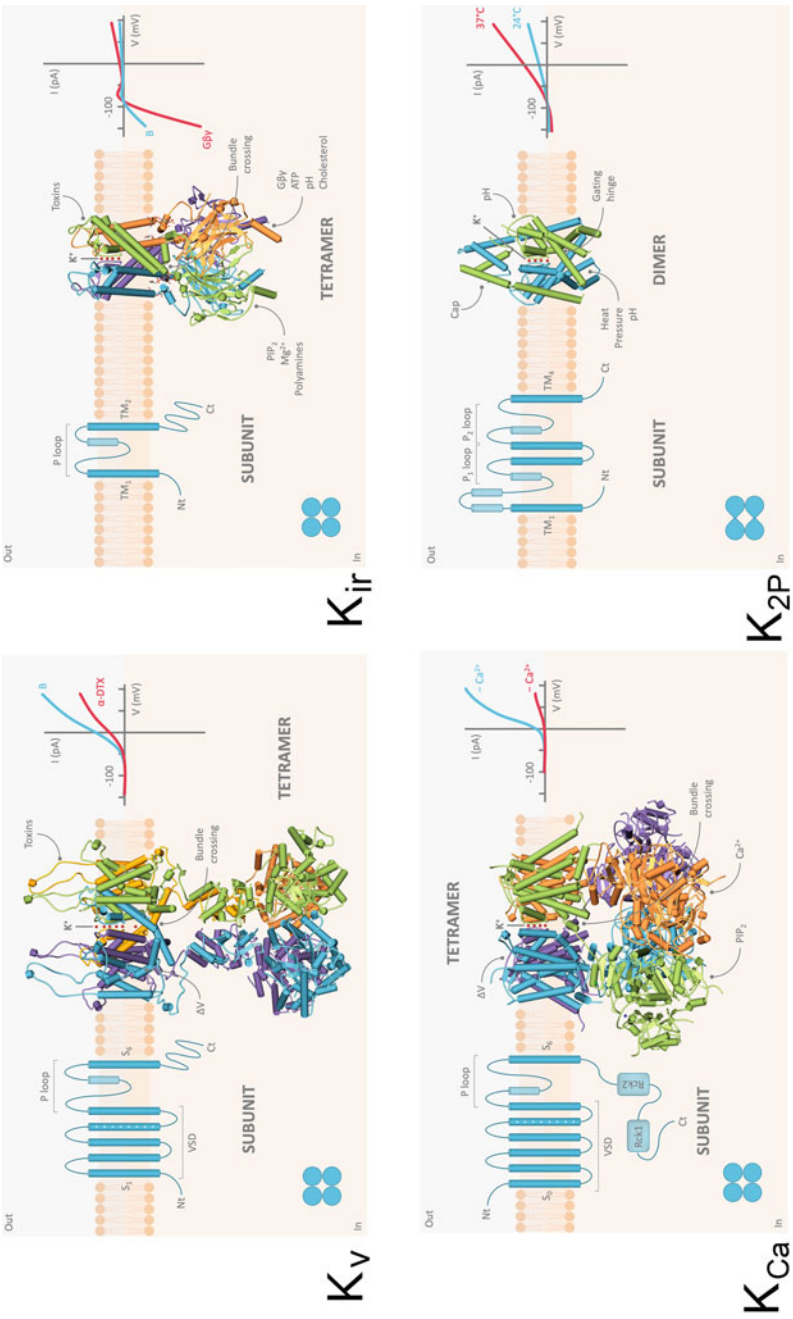

Fig. 2 Potassium channel structure and function. The membrane topology, atomic structure, and typical current-voltage (I-V) plots are shown for the K_V (basal vs α-DTX), K_{Ca} (± Ca^{2+}), K_{ir} (± Gβγ), and K_{2P} (37 ° C vs 24 ° C) channels. Adapted from Yu and Catterall (2004)

domains, and the N- and C-terminal domains facing the cytosol (Kshatri et al. 2018). Unlike K_v and $K_{Ca}1.1$ channels, the S4 domain lacks voltage sensitivity, and therefore gating is membrane potential independent (Hirschberg et al. 1999). In the cytosolic C-terminal domain of small conductance K_{Ca} channels, a calmodulin (CaM) binding domain (CaMBD) (Adelman 2016; Fanger et al. 1999) is located that indirectly confers Ca^{2+} sensitivity (Xia et al. 1998). In general, $K_{Ca}2.1$-$K_{Ca}2.3$ and $K_{Ca}3.1$ assemble in homotetramers to form functional channels (Kohler et al. 1996; Sforna et al. 2018), but $K_{Ca}2.1$-$K_{Ca}2.3$ can also arrange in heterotetramers (Strassmaier et al. 2005).

K_{ir} channels share a relatively simple topology, as compared to K_v and K_{Ca} channels (Fig. 2). They contain two transmembrane domains, TM1 and TM2, separated by a linking pore-forming P-loop sequence that includes the K^+ selectivity filter (Heginbotham et al. 1994). The cytoplasmic N- and C-terminal domains form a characteristic cytoplasmic extended pore structure (Fig. 2) (Nishida et al. 2007). Four subunits associate to form functional homotetramers or heterotetramers. While $K_{ir}1.1$ and $K_{ir}7.1$ can only form homotetramers (Kumar and Pattnaik 2014; Leng et al. 2006), the majority of K_{ir} channels assemble with subunits within the same subfamily (Hibino et al. 2010). $K_{ir}4.x$ forms homotetramers (Pessia et al. 2001), while the formation of functional $K_{ir}5.1$ homotetramers has not been described yet (Hibino et al. 2010). However, $K_{ir}5.1$ can associate with $K_{ir}4.1$-$K_{ir}4.2$ to form functional channels ($K_{ir}4.1$-$K_{ir}5.1$ or $K_{ir}4.2$-$K_{ir}5.1$) (Pessia et al. 2001).

Like K_{ir} channels, K_{2P} channels also contain a simplified topology, compared to K_v and K_{Ca} channels (Fig. 2). K_{2P} channels contain the two pore-forming P loops (P1, P2), where the K^+ selectivity filter can be found, and four transmembrane helices (TM1-TM4). The first pore-forming P-loop sequence (P1) is located in between TM1 and TM2, while the second one (P2) is found between TM3 and TM4. The 2P/4TM topology (2P/8TM for TOK1) is unique among other K^+ channels (1P/6TM for K_v or 1P/2TM for K_{ir}). However, despite differences in the topology, the overall K_{2P} channel structure does not differ much from K_v, K_{Ca}, and K_{ir} channels, due to its pseudo tetrameric architecture. Each protomer (2P) will assemble to form a dimer (2x2P = 4P) to recreate a classic tetrameric K^+ channels configuration (4x1P = 4P) (Gada and Plant 2019; Goldstein et al. 2001; Niemeyer et al. 2016). The P1 and P2 loops share high homology with the K_v channel P-loop (Fig. 3). K_{2P} channels also possess an extracellular cap domain, constituted by the external loop located in between TM1 and P1. The two subunits assemble their helical caps to generate two lateral tunnels where the ions move from the exterior to the pore (extracellular ion pathway). This assembly is stabilized in most K_{2P} channels by a disulfide bond (Lesage et al. 1996; Niemeyer et al. 2003). The cap impedes direct ion transport between the pore and the extracellular medium.

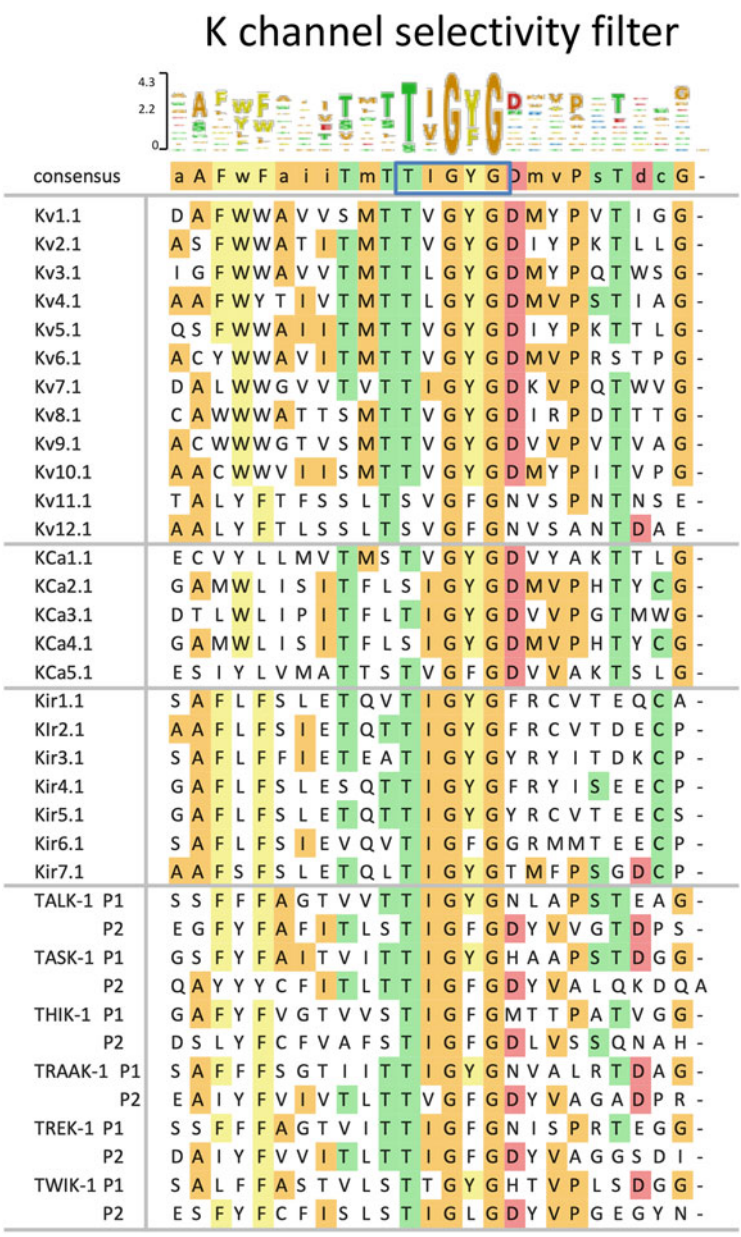

Fig. 3 Potassium channel selectivity filter. Sequence alignment of the P-loop from the indicated human potassium channels

3 K^+ Selectivity

All four families of K^+ channels are highly selective for K^+. This is accomplished through a structure referred to as the selectivity filter (SF), which allows for the discrimination between K^+ and other cations, in particular Na^+ (Hille 1986) (Fig. 3). K_v channels also contain a gate at the bundle crossing on the intracellular side of the membrane, which is responsible for opening in response to a voltage stimulus. Together, these determine when the channel conducts K^+ (Liu et al. 2015). $K_{Ca}1.1$ channels are impermeable to Na^+ and Li^+ (Blatz and Magleby 1984; Tabcharani and Misler 1989), while $K_{Ca}2.x$ and $K_{Ca}3.1$ channels are slightly less selective, allowing some Na^+ and Li^+ permeation (Shin et al. 2005). In some K_{ir} channels, strict K^+ selectivity also involves residues outside the SF that contribute to keep its structure (Makary et al. 2006; Yi et al. 2001). Particularly, Glu139 and Arg149 in GIRK1, Glu152 in GIRK2, or Glu145 and Arg155 in GIRK4 are suggested to form a salt bridge behind the selectivity filter that confers rigidity to its structure, and mutations in these amino acids lead to a substantial loss of K^+ selectivity (Makary et al. 2006). However, $K_{ir}7.1$ exhibits an unusual larger inward conductance of Rb^+ over K^+ (Wischmeyer et al. 2000). K_{2P} channels are also highly selective for K^+. However, TWIK1 can alter its selectivity to Na^+ under hypokalemia, which can lead to depolarization (Chatelain et al. 2012; Ma et al. 2011). Moreover, TASK and TWIK change ion selectivity in response to extracellular acidification (Ma et al. 2012).

The selectivity filter is comprised of a highly conserved region in the P-loop, containing the T-I/V-G-Y/F-G consensus sequence (Bichet et al. 2003; Doyle et al. 1998; Heginbotham et al. 1994; Varma et al. 2011; Zhou et al. 2001b) (Fig. 3). This signature sequence creates a narrow conduit that can accommodate multiple unhydrated K^+ ions (Nishida et al. 2007), which transit between the central cavity of the channel and the extracellular solution. The geometry and polarity of these sites mimic the dipoles of water and thermodynamically favor binding of K^+ over Na^+ (Åqvist and Luzhkov 2000; Bernèche and Roux 2001; Noskov et al. 2004; Roux 2005; Shrivastava et al. 2002). In this way, water molecules are stripped from K^+, which passes through in single file through the filter. Na^+ remains bound to water molecules (they have higher dehydration energy) and is energetically unfavorable for passing through the selectivity filter.

Mutagenesis studies on K_v channels first revealed the importance of the selectivity filter (Heginbotham et al. 1994). Some members of the K_{ir} channel family have shown how alterations of the signature sequence lead to loss of K^+ selectivity. Particularly, a serine substitution at glycine-156 in $K_{ir}3.2$ (GIRK2) channels produces a loss of K^+ selectivity, allowing Na^+ entry and inappropriate cell depolarization (Slesinger et al. 1996; Tong et al. 1996) that leads to death, and is responsible for the *weaver* mouse phenotype (Patil et al. 1995). Recently, an L171R mutation near the selectivity filter in human GIRK2 was reported for a patient with a severe hyperkinetic disorder that also eliminated K^+ selectivity (Horvath et al. 2018).

For K_{2P} channels, the selectivity filter is located below the cap domain and is disposed in a convergent fourfold symmetric configuration to emulate hydration of

K^+ ions. Despite some differences, K_{2P} channels exhibit similar sequences to the T-I/V-G-Y/F-G consensus sequence (Schewe et al. 2016) (Fig. 3). Interestingly, the specific sequence composition can confer the channel a change in ion selectivity under certain conditions. For example, the presence of a second threonine (Thr118) within the selectivity filter of TWIK1 enables the channel to support Na^+ leak currents (Ma et al. 2011).

4 Gating Mechanisms

One of the areas where there is a large divergence in K^+ channels is through their different gating mechanisms. The K_v class of channels are voltage-dependent and have evolved to use the power of the electric field that exists across excitable membranes to move charged groups of ions crosswise across the membrane (Ishida et al. 2015; Schmidt and Mackinnon 2008). Voltage-dependent gating of K_v channels involves several molecular processes including: (1) detection of changes in voltage across the membrane by the voltage-sensing domain (VSD). VSD activation results in conformational rearrangement leading to (2) propagation of VSD movements to the ion conduction pore via a helical linker (Khalili-Araghi et al. 2006). Rearrangement of the pore, via VSD-pore coupling, results in (3) pore opening and ion conduction into the cell (Cui 2016). The VSD can adopt a stable conformation in the absence of the rest of the channel (PD) (Chakrapani et al. 2008; Krepkiy et al. 2009). One of the first VSDs defined at the atomic level and considered a native, non-altered structure was part of the mammalian $K_v1.2$ channel (PDB: 2A79) (Long 2005). This structure showed that the VSD interacts with the pore domain of an adjacent subunit where the voltage sensor is latched around the pore of an adjacent subunit and voltage sensing in one subunit would affect the pore region of another subunit (Long et al. 2007).

A key characteristic of the VSD is the presence of basic amino acids, including positively charged arginine and lysine amino acids in the S4 segment, in a repeating motif of one positive charge separated by two hydrophobic residues. The number of positive charges is variable, with some Shaker related channels having as many as seven (Zhou et al. 2001a). Most models of voltage-dependent gating suggest that as transmembrane voltage changes polarity during depolarization, with the cytoplasmic side becoming positive, the energy exerted on the S4 charges is altered and moves the S4 segment. The S4 segment appears to translate and rotate counterclockwise (Ahern and Horn 2005; Larsson et al. 1996). The C-terminal portion of the S4 segment is accessible to the intracellular solution at rest and as depolarization occurs, the charged residues become less accessible to the intracellular solution and instead become more accessible to the extracellular solution, resulting in the S4 segment moving to an external position (Ahern and Horn 2004, 2005; Baker et al. 1998; Broomand and Elinder 2008; Gandhi and Isacoff 2002; Larsson et al. 1996; Lin et al. 2011). The result is channel activation, leading to opening of the water-filled channel and the flow of K^+ down the electrochemical gradient out of the cell. As the

membrane potential repolarizes, the VSD returns to the resting state, which in turn closes the channel and terminates K^+ permeability.

K_v channels can exhibit various types of inactivation, each involving distinct mechanisms. In some channels, inactivation occurs soon after the channel is activated. This fast inactivation, or N-type inactivation, is mainly due to an intracellular block of the channel by the intracellular N-terminus, often referred to as the inactivation particle (Aldrich 2001). A relatively slower form of inactivation termed C-type occurs after tens or hundreds of milliseconds have elapsed following channel activation (Pau et al. 2017). It appears that the pore structure of this class of channels and the permeating ions play a pivotal role in this process; however, it remains the subject of investigation (Hoshi and Armstrong 2013). Modulation of the inactivation process conveys the ability to control the cellular availability of K_v channel currents. In some cases, inactivation is sensitive to the cellular redox environment (Sahoo et al. 2014). A structural component within the N-terminus has been identified that serves as a sensor for the cytoplasmic redox potential (e.g., exposure to oxidizing agents) and leads to inactivation of the channel (Finol-Urdaneta et al. 2006).

Two different gating mechanisms can be observed in K_{Ca} channels: voltage and calcium-dependent gating for $K_{Ca}1.1$ channels, and calcium-dependent for small and intermediate conductance K_{Ca} channels (Fakler and Adelman 2008). Large conductance $K_{Ca}1.1$ channels exhibit voltage sensitivity similar to K_v channels; membrane depolarization and intracellular Ca^{2+} combine allosterically to activate the channel and open the inner pore (Horrigan and Aldrich 2002). Four RCK1-RCK2 intracellular domains of the $K_{Ca}1.1$ tetrameric assembly comprise the gating ring (Hite et al. 2017; Yuan et al. 2011). Upon Ca^{2+} binding to the Ca^{2+}-sensitive sites in the gating ring, an aspartate string in RCK1 and the Ca^{2+} bowl in RCK2, the RCK1-RCK2 tandems rearrange to open the gating ring (Yuan et al. 2011). When Ca^{2+} binding to the intracellular domain of the channel combines with the activation of the VSD by membrane depolarization, the chemical and the electrical energies released additively fuel the conformational change of the PD from the closed to the open state (Hite et al. 2017; Horrigan and Aldrich 2002), in a process that requires the interaction of the gating ring with the VSD (Hite et al. 2017). As the membrane voltage depolarizes, the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) required to activate $K_{Ca}1.1$ decreases (Cui et al. 1997), ranging from 0.5 to 50 mM (Xia et al. 2002). A regulatory Mg^{2+}-binding site, located in RCK1, has also been described for $K_{Ca}1.1$ channels (Shi and Cui 2001), through which Mg^{2+} contributes to channel activation (Xia et al. 2002; Yang et al. 2008).

In contrast to $K_{Ca}1.1$ channels, gating is voltage-independent in $K_{Ca}2.x$ and $K_{Ca}3.1$ channels (Hirschberg et al. 1999). Ca^{2+} activates $K_{Ca}2.x$ and $K_{Ca}3.1$ channels through binding to the highly Ca^{2+}-sensitive protein calmodulin (CaM), which is constitutively associated to α subunits of the channel (Fanger et al. 1999; Sforna et al. 2018; Xia et al. 1998). The binding of Ca^{2+} to $K_{Ca}2.x$ and $K_{Ca}3.1$ channels through CaM accounts for their elevated Ca^{2+} sensitivity compared to submicromolar sensitivity of $K_{Ca}1.1$ channels (Adelman et al. 2012; Xia et al. 1998). $K_{Ca}2.x$ and $K_{Ca}3.1$ channels interact with CaM through a highly conserved CaM binding domain (CaMBD) (Adelman 2016; Fanger et al. 1999) in each α

subunit of the channel, and it has been confirmed by cryo-EM (Lee and MacKinnon 2018). Ca^{2+} binding to the EF-hand domains in the N-lobe of CaM promotes the rearrangement of two CaM-CaMBD dimers into a "dimer of dimers," that leads to the conformational change of the helices forming the pore required for channel opening (Lee and MacKinnon 2018; Schumacher et al. 2001).

For K_{ir} channels, the inward rectification is their most distinctive feature. In fact, different levels of inward rectification can be described in K_{ir} channels, ranging from strong inward rectifiers, such as $K_{ir}2.1$-$K_{ir}2.4$, to medium, e.g. GIRK1-GIRK4, and to weak, such as $K_{ir}1.1$ and $K_{ir}6.1$-$K_{ir}6.2$ channels (Hibino et al. 2010; Walsh 2020). Although K_{ir} channels are not intrinsically voltage-dependent, since they lack the voltage-sensing S4 domain (Hibino et al. 2010), the inward rectification shows an apparent voltage sensitivity. Inward rectification is mediated by intracellular Mg^{2+} (Lu and MacKinnon 1994; Matsuda et al. 1987) and naturally occurring polyamines (e.g., $putrescine^{2+}$, $spermidine^{3+}$, and $spermine^{4+}$) (Lopatin et al. 1994; Nichols and Lee 2018). At membrane potentials positive to the equilibrium potential of K^+ ($E_K \approx -95$ mV), Mg^{2+} and polyamines occlude the inner vestibule, only allowing a small outward current. In contrast, at potentials negative to E_K, Mg^{2+} and polyamines flow out of the channel into the cell, allowing a large inward K^+ current (Lopatin et al. 1995). The affinity of Mg^{2+} and the polyamines for binding sites in the pore-forming TM2 helix (Stanfield et al. 1994; Wible et al. 1994) and the cytoplasmic domain of K_{ir} channels (Kubo and Murata 2001; Taglialatela et al. 1995) dictates the strength of the inward rectification (Baronas and Kurata 2014; Clarke et al. 2010). Besides Mg^{2+} and polyamines, K_{ir} channels K^+ conductance is also influenced by extracellular K^+ concentrations ($[K^+]_o$) (Lopatin and Nichols 1996), being this conductance higher at increasing $[K^+]_o$ (Hibino et al. 2010). $K_{ir}7.1$ is an exception and exhibits only a slight dependence on $[K^+]_o$ due to the presence of a methionine at position 125 in the pore domain, instead of the conserved arginine found in the majority of K_{ir} channels (Doring et al. 1998). The intrinsic gating of K_{ir} channels is controlled by two gating structures: the bundle-crossing region in the TM2 of the transmembrane domain (Sadja et al. 2001; Yi et al. 2001) and the G loop in the cytoplasmic domain (Pegan et al. 2005). The first K_{ir} channel structures to be resolved, involving bacterial K_{ir} channels, such as KscA (Doyle et al. 1998) (PDB: 1BL8) and K_{ir}Bac1.1 (Kuo et al. 2003) (PDB: 1P7B), pointed at TM1 and TM2 as key players in the gating of K_{ir} channels. The gating of some K_{ir} channels depends on other regulators, apart from Mg^{2+}, polyamines, and $[K^+]_o$, such as pH, Na^+, ATP, and/or G proteins (Hibino et al. 2010). For instance, changes in the intracellular pH alter the gating of $K_{ir}1.1$ (Schulte and Fakler 2000), $K_{ir}4.1$-$K_{ir}4.2$ (Pessia et al. 2001), and $K_{ir}5.1$ (Tucker et al. 2000), which are closed upon intracellular acidification, while $K_{ir}7.1$ shows maximal response at pH 7.0 (Yuan et al. 2003). In fact, homomeric $K_{ir}4.1$ and $K_{ir}4.1$/$K_{ir}5.1$ channels exhibit different pH sensitivities (Casamassima et al. 2003). In the case of $K_{ir}2.1$-$K_{ir}2.4$ channels, intracellular alkalization activates $K_{ir}2.4$ (Hughes et al. 2000), while either extracellular or intracellular alkalization enhances $K_{ir}2.3$ activity (Zhu et al. 1999). $K_{ir}6.1$-$K_{ir}6.2$ channels, also called K_{ATP}, are regulated by intracellular ATP, which leads to the inactivation of the channel (Terzic et al. 1995), while intracellular nucleoside

diphosphates, such as ADP, activate the channel through the interaction with SUR, the auxiliary subunits of $K_{ir}6.1$-$K_{ir}6.2$ channels (Hibino et al. 2010; Matsuoka et al. 2000). G-protein gated K_{ir} channels (GIRK) are opened by an interaction of the Gβγ subunit with the βL-βM sheets in the cytoplasmic C-domain of GIRK (PDB: 4KFM) (Finley et al. 2004; He et al. 1999; Ivanina et al. 2003; Whorton and MacKinnon 2013), producing a conformational change that opens the channel pore in a PIP_2-dependent process (Huang et al. 1998; Whorton and MacKinnon 2013). Moreover, the gating of GIRK channels containing GIRK2 or GIRK4 subunits is also influenced by intracellular Na^+ (Ho and Murrell-Lagnado 1999), which promotes the binding of PIP_2 to the channel and activation (Rosenhouse-Dantsker et al. 2008). The structural binding site for Na^+ has been identified in a GIRK2 X-ray structure (PDB: 3SYA) (Whorton and MacKinnon 2011). In this way, the intracellular Na^+ increase after cell depolarization enhances the activity of GIRK channels, bringing the cell back to the resting state.

Like K_v, K_{Ca}, and K_{ir} channels, K_{2P} possesses a gating hinge (Brohawn et al. 2012; Miller and Long 2012; Niemeyer et al. 2016). TM1 and TM3 are located on the outer pore, while the inner helices, TM2 and TM4, play a crucial role in channel activation. The TM4 helix motion, up and down (closer and farther TM2 helix), is a pivotal determinant of the open-close configuration. The interfacial C helix is adjacent to TM4 and movement is transferred to the TM2-TM4 hinge to support pore widening and ion conduction (Brohawn et al. 2012; Miller and Long 2012; Niemeyer et al. 2016). K_{2P} channels are sensitive not only to cytosolic factors, but also to membrane components (and/or alterations). K_{2P} channels also possess intramembrane openings that confer connections between lipid membrane and ion pore. These openings, termed fenestrations, have been named for analogous side portals present in prokaryotic voltage-dependent Na^+ channels (Payandeh et al. 2011). They are located in between the TM2 of one protomer and the TM4 of the other one. The two transmembrane cavities can accommodate acyl chains and influence the channel conductivity (Brohawn et al. 2014).

Although many factors can modulate K_{2P} gating, the extracellular pH (pH_o) is probably the best characterized. Many K_{2P} channels have a histidine located at the entrance of the selectivity filter (TM1-P1) that is protonated upon pH_o decrease. In TASK1 (His98), TASK3 (His98), TWIK1 (His122), and TREK1 (His126), histidine protonation prevents the ion passage. Thus, channel closure is similar to C-type inactivation in K_v channels (Chatelain et al. 2012; Cohen et al. 2008; Kim et al. 2000; Lopes et al. 2001; Rajan et al. 2000). Uniquely, extracellular acidification induces channel activation in TREK2 (His151) and involves a region of the P2-TM4 extracellular loop (Sandoz et al. 2009). Interestingly, TWIK1 switches ion selectivity upon a decrease in pH_o (Ma et al. 2012). Histidine is not the only basic residue in K_{2P} channels that can operate as H^+ sensor. TASK2 lacks the histidine sensor but has an arginine (Arg224) at the second pore domain that confers selectivity filter pH_o-sensing as well. TASK2 is inhibited by acidic pH_o, and surprisingly activated when pH_o increases. In this case, protonation/deprotonation of the side chain of the residue alters the electrostatic stability on the selectivity filter (Niemeyer et al. 2007; Zuniga et al. 2011). Additionally, some K_{2P} channels respond to intracellular pH (pH_i)

alterations. Thereby, K_{2P} channels such as TREK1 or TASK2 switch from low to high activity upon intracellular acidification. The mechanism does not involve any residue in the selectivity filter, but an acidic amino acid in the interfacial C helix (i.e., Glu306 in TREK1), working as an activation gate (Bagriantsev et al. 2011).

In addition to pH, the intracellular C-terminus also supports different gating mechanisms. TREK1 possesses a group of positively charged residues in the C helix that confers the channel the capacity to respond to phospholipids (Chemin et al. 2007). TREK1 also contains a phosphorylation site (Ser348) in the C-terminus that alters channel gating properties, switching the channel from a voltage-independent into a voltage-dependent phenotype (Bockenhauer et al. 2001). The interfacial C helix is also modulated by GPCR activation. TASK2 is closed by direct G protein βγ subunits binding at the Lysine 245 (Anazco et al. 2013; Niemeyer et al. 2016). TASK1 and TASK3 are also closed by G protein α subunit induced diacylglycerol (DAG) generation that is believed to bind the C-terminal domain (Wilke et al. 2014). Physical stimuli such as pressure and temperature also influence K_{2P} gating. Little is known about the specific mechanism but surely involves the intracellular C-terminus (Bagriantsev et al. 2011). For instance, partial deletion of the interfacial C helix in TREK1 lowers heat-induced activation (Maingret et al. 2000). Besides the C-terminus domain that operates as cytosolic gate, K_{2P} channels show an inner gate that modulates the pore conductivity by membrane composition. The current hypothesis sustains that intramembrane fenestration determine TM4 position over TM2, working as a gating hinge and affecting the selectivity filter. Thus, two possible conformations exist: 1) when the lipid acyl chains penetrate into the fenestration up to the cavity located below the selectivity filter, the TM4 helix is in the down conformation and the ion transit is hindered, and 2) in contrast, when the lipid fenestration is empty, TM4 moves up towards TM2 (up conformation), closing the fenestration and releasing the selectivity filter, which can accommodate an extra ion and facilitate ion conduction (Brohawn et al. 2014).

Recent structural determinations support some of these gating mechanisms. TREK2 structure resolved with the inhibitor fluoxetine exhibits a down conformation (PDB: 4XDJ) (Dong et al. 2015). On the other hand, TRAAK crystallization in the presence of the activator trichloroethanol shows the up conformation (PDB: 3UM7) (Brohawn et al. 2014). Moreover, artificially trapping TRAAK into the up state, by a disulfide bridge between TM4 and TM2, induces the channel to a reversible low activity profile. The least understood gating mechanism is the effect of membrane voltage. Although K_{2P} channels lack a specific voltage-sensing domain (i.e., S4 in K_v) and the first leak K^+ channels were initially described as a voltage-independent outward rectifier K^+ channels (Goldstein et al. 2001), some K_{2P} (except for the unphosphorylated TWIK1) can unequivocally alter their activity in response to membrane potential changes. It has been recently proposed that a one-way "check valve" mechanism, in which the selectivity filter acts as a voltage-gate, takes place. Depolarization induces filter opening and outward K^+ flow, whereas at membrane potentials below E_K the non-return valve promotes filter inactivation. The second threonine (i.e., Thr157 in TREK1 or Thr103 in TRAAK) in the selectivity filter of P1 plays a major role in this mechanism. Thus, mutagenesis experiments in TREK1 and

TRAAK turn them into a leak mode (Schewe et al. 2016). Interestingly, TREK1 voltage-gated mode is abolished upon pH_i, pressure and PIP_2 activation (Chemin et al. 2005).

5 Role of Lipids/PIP_2

It has been widely recognized that the lipid bilayer can modulate the function of K^+ channels (Forte et al. 1981; Van Dalen and De Kruijff 2004). One such role is for inactivation of K_v channels, where interaction with the membrane causes prolonged channel closing (Schmidt et al. 2009; Schmidt and Mackinnon 2008). Using $K_v1.2$ as an example, the VSDs are embedded in the membrane, with S4 being mostly shielded away from lipids (Long 2005). The top gating charges found in S4 have been modeled to interact with lipid headgroups, making stable electrostatic interactions with their negatively-charged phosphates (Cuello 2004; Lee and Mackinnon 2004; Long et al. 2007). The mechanical properties of the membrane are dictated by lipid composition, and interaction with the headgroups can facilitate sensor movement and subsequently pore opening.

A version of the K_v channel, lacking a sensor region (PDB: 1K4C), exhibits four immobilized lipids filling and surrounding a crevice between subunits on the extracellular surface of the channel, suggesting affinity for lipids at this region (Santos et al. 2012). Inclusion of lipids with headgroups that coat the extracellular membrane-solution interface with hydroxyl groups (e.g., glycerol and phosphoinositol) drastically increases the probability of finding the channel open (Syeda et al. 2014), suggesting that the pore-forming region of the K_v channels may be transformed into an open conductor of K^+ through interaction with lipid modulators that target either the bundle gate, via direct interaction, or the filter gate, by destabilization of water structure. So, not only are lipids critical for proper protein folding (Valiyaveetil et al. 2002), they also allow for modulation of channel properties. An example of this would be the K_v7 channel, where channel opening requires the membrane lipid PIP_2, which serves as a cofactor that mediates coupling of VSD with the pore gate (Zaydman and Cui 2014).

For K_{Ca} channels, several membrane and cholesterol-related lipids have been shown to modulate the activity of some of these channels. For instance, the membrane lipid phosphatidylinositol-4,5-bisphosphate (PIP_2) influences the activity of small and large conductance K_{Ca} channels. $K_{Ca}1.1$ channels can be either activated or inhibited by PIP_2, depending on the β auxiliary subunits to which they are associated (Tian et al. 2015). Particularly, PIP_2 has an inhibitory effect on $K_{Ca}1.1$ in the absence of auxiliary subunits and when they are in complex with γ1 subunits, while PIP_2 activates the channel when it is complexed with β1 or β4 subunits (Tian et al. 2015). Small conductance K_{Ca} channels are also modulated by PIP_2 (Zhang et al. 2014). This phospholipid acts as a cofactor for $K_{Ca}2.x$ channels activation by CaM upon Ca^{2+} binding, whilst PIP_2 removal leads to channel inhibition (Zhang et al. 2014). Moreover, the regulation of $K_{Ca}2.x$ by PIP_2 is dependent on CaM phosphorylation by casein Kinase 2 (CK2), which phosphorylates the amino acid

T80 in CaM weakening the affinity of PIP_2 for the CaM-$K_{Ca}2.x$ complex (Zhang et al. 2014).

Cholesterol is another membrane lipid that modulates $K_{Ca}1.1$ activity (Dopico and Bukiya 2017). The cytosolic C-terminal domain of $K_{Ca}1.1$ channels presents a cholesterol recognition amino acid consensus motif (CRAC4) that confers cholesterol sensitivity to the channel (Singh et al. 2012). Cholesterol has shown to inhibit $K_{Ca}1.1$ channels in heterologous expression systems (Wu et al. 2013), although the in vivo effects of cholesterol enrichment or depletion on $K_{Ca}1.1$ channels activity are in some cases contradictory, depending on the tissue where the channel is expressed (Dopico and Bukiya 2017). $K_{Ca}1.1$ channel activity is modulated as well by certain steroid hormones such as 17β-estradiol or dehydroepiandrosterone (DHEA). When co-expressed with β1 auxiliary subunits, $K_{Ca}1.1$ channels are activated by 17-β-estradiol, which exerts no effect on $K_{Ca}1.1$ α subunits alone (Valverde et al. 1999), nor when they are associated with β2 subunits (King et al. 2006). However, the adrenal androgen DHEA is able to activate β2-associated $K_{Ca}1.1$ channels, an effect also exerted by corticosterone (King et al. 2006). The bile acid lithocholate and the non-steroid leukotriene LTB4 are also potentiators of $K_{Ca}1.1$ channels activity in a β1-dependent manner (Bukiya et al. 2007, 2014). Lastly, the omega-3 lipid docosahexaenoic acid activates β1 and β4-associated $K_{Ca}1.1$ channels, exhibiting no effect when the pore-forming α subunits are in complex with β2 or γ1 subunits (Hoshi et al. 2013). The auxiliary subunit-dependent activation of $K_{Ca}1.1$ channels exerted by some of these lipids could be contributing to vascular smooth muscle relaxation and consequently to vasodilation (Latorre et al. 2017).

The activation of all K_{ir} channels is also dependent on PIP_2 (Hibino et al. 2010; Rohacs et al. 2003). The structural mechanism of PIP_2 binding has been elucidated in two X-ray structures for $K_{ir}2.1$ and GIRK2 (PDB: 3SPI and 3SYA, respectively) (Hansen et al. 2011; Whorton and MacKinnon 2011). The presence of this membrane phospholipid in the inner surface of the plasma membrane is essential for K_{ir} activation (Huang et al. 1998; Li et al. 1999), as well as for the activation mediated by the different endogenous gating regulators of K_{ir} channels (Du et al. 2004), like $K_{ir}6.x$ activation by ATP (Baukrowitz et al. 1998) and GIRK activation by Na^+ and Gβγ (Huang et al. 1998; Rosenhouse-Dantsker et al. 2008). Cholesterol is another membrane lipid that modulates the activity of some K_{ir} channels, such as $K_{ir}2.x$, that become inactive at increasing concentrations of cholesterol (Romanenko et al. 2004), and GIRK channels, which in contrast are activated by cholesterol in a PIP_2-dependent and G-protein-independent manner (Glaaser and Slesinger 2017). Other lipids are also involved in K_{ir} activity modulation. For instance, arachidonic acid has shown to increase the current flow through $K_{ir}2.3$ containing channels (Liu et al. 2001), and the intracellular increase of long-chain CoA esters has an opposite effect on $K_{ir}2.1$ and $K_{ir}6.x$ channels, inhibiting the former and activating the latter (Shumilina et al. 2006).

K_{2P} channels are also influenced by surrounding lipids, most likely through the two lateral portals or fenestrations. Many K_{2P} are activated by PIP_2 (i.e., TASK1-TASK3, TREK1, and TRAAK) leading to a leak K^+ conductance mode. Stimulation of G_q/G_{11} coupled receptors such as muscarinic M1 induces PIP_2 hydrolysis and a

subsequent inhibition of TASK1-TASK3, TREK1, and TREK2 (Lopes et al. 2005). However, the relationship between phospholipids and K_{2P} channels can be quite complex in some cases. For example, PIP_2 exerts a dual regulation in TREK1. In transiently transfected cells, intracellular PIP_2 stimulates TREK1 currents in half of the patches and inhibits currents in the other half. Interestingly, pressure, intracellular acidification, and arachidonic acid induced activation are all blocked by the presence of PIP_2. The removal of the C-terminal domain abolished PIP_2-inhibitory capacity, suggesting the implication of this region on the PIP_2-induced gating regulation (Chemin et al. 2007).

6 Trafficking and Accessory Subunits

K_v channels exhibit subfamily-specific patterns of localization within cells (Vacher et al. 2008). For example, in neurons K_v1 channels are expressed at the axon initial segment (AIS). The AIS plays an important role in generating axonal action potentials. K_v1 channels regulate action potential initiation and propagation (Kole and Stuart 2012). Within this channel, specific amino acid sequence motifs act as trafficking determinants (TDs) and direct the initiation, continuation of expression, and localization of these channels to the AIS. TDs are located within the C-terminal domain and act on different interacting proteins (Magidovich et al. 2006). The C-terminal domains are highly conserved in mammalian channels and include a specific motif within the extracellular loop between TM segments S1 and S2 (McKeown et al. 2008) and an acidic motif in the C-terminus of K_v1 α subunits (Manganas et al. 2001). Some K_v subfamily members contain TDs with lower or higher affinity for interacting proteins. The degree of affinity that different subfamily members have for interacting protein leads to trafficking characteristics that are sensitive to co-assembly (Manganas and Trimmer 2000), where localization depends on the TD-interacting protein coupling. TDs also play a role in trafficking from the endoplasmic reticulum (ER). The composition and stoichiometric assembly of K_v1 heterotetrameric channels produces interaction with different proteins and controls ER export of the channel to different loci (Vacher et al. 2007). For example, $K_v1.1$ contains an ER retention signal in its extracellular pore domain that inhibits export from the ER (Manganas and Trimmer 2000; Manganas et al. 2001; Zhu et al. 2001). The retention signal overlaps with the binding site for the neurotoxin α dendrotoxin (DTX), suggesting that $K_v1.1$ retention is due to a DTX-like prototoxin. Phosphorylation also regulates trafficking of $K_v1.2$, with phosphorylation of specific C-terminal tyrosine residues triggering endocytosis of the channels (Nesti et al. 2004). In addition, phosphorylation at a different C-terminal tyrosine residue regulates $K_v1.2$ clustering (Gu and Gu 2011; Smith et al. 2012) and serine phosphorylation sites regulate biogenic trafficking (Yang et al. 2007).

Initial biochemical studies on native K_v1 channels indicated the presence of stoichiometric amounts of copurifying protein components that were initially proposed to be β subunits (Parcej and Dolly 1989). In fact, the majority of K_v1 channels in mammalian brain are associated with $K_v\beta$ subunits (Coleman et al. 1999; Rhodes

et al. 1995, 1996, 1997). There are three genes that encode $K_v\beta$ subunits ($K_v\beta$1-$K_v\beta$3), with various alternative splicing leading to a larger number of functionally distinct isoforms (Pongs et al. 1999). Certain $K_v\beta$ subunits contain a domain in the N-terminus region that confers the rapid "N-type" inactivation to K_v channels (Rettig et al. 1994). The N-terminus region acts like the inactivation particle found in some K_v channels that works to occlude the pore of the activated K_v1 channels.

For K_{Ca} channels, the stable association of the pore-forming α subunits with auxiliary subunits confers versatility in their different physiological roles (Berkefeld et al. 2010). The activity of K_{Ca}1.1 channel is regulated by several β and γ subunits, which are expressed in different tissues and modify the biophysical and pharmacological properties of the channel (Latorre et al. 2017; Li and Yan 2016). Four different β subunits, β1-β4, have been identified, all of them composed of two transmembrane domains linked by an extracellular loop and with intracellular C- and N-termini (Latorre et al. 2017). The stoichiometry of the association between α and β subunits is generally considered to be 1:1 (Latorre et al. 2017), as revealed by cryo-EM studies (PDB: 6 V22) (Tao and MacKinnon 2019). Interestingly, functional channels can operate with less than four β subunits, exhibiting a proportional modification of the channel properties as the number of β subunits increases (Wang et al. 2002). β1 subunits are mainly expressed in the vascular smooth muscle (Knaus et al. 1994a; Latorre et al. 2017) and enhance the apparent voltage and Ca^{2+}-sensitivity of the channel (McManus et al. 1995) and slow down activation and deactivation kinetics (Dworetzky et al. 1996). In addition, β subunits provide K_{Ca}1.1 channel with distinct pharmacological properties, depending on the β subunit to which they are associated (Latorre et al. 2017; Li and Yan 2016). Similarly to β1, β2 subunits increase the apparent Ca^{2+}-sensitivity in the K_{Ca}1.1 channel (Brenner et al. 2000a) and decrease the gating kinetics rate (Brenner et al. 2000a). Moreover, β2 subunits are responsible for K_{Ca}1.1 channel inactivation (Wallner et al. 1999; Xia et al. 2003), in a process where the N-terminal domain of β2 behaves like a peptide ball that occludes the K_{Ca}1.1 channel (Bentrop et al. 2001; Wallner et al. 1999), resembling the ball-and-chain inactivation of K_v channels. In the case of β3 subunits, four different isoforms have been identified (β3a-d) (Uebele et al. 2000), which do not affect K_{Ca}1.1 channel Ca^{2+}-sensitivity (Latorre et al. 2017). Alternately, β3a, β3b, and β3c isoforms exert a partial inactivation of the channel (Uebele et al. 2000), while β3b is also responsible for conferring an outward rectification via the extracellular loop (Uebele et al. 2000; Zeng et al. 2003). On the other hand, β4 subunits are mainly expressed in the brain (Weiger et al. 2000) and slow down the activation and deactivation kinetics of K_{Ca}1.1 channels (Behrens et al. 2000; Weiger et al. 2000). β4 subunits display a dual effect on Ca^{2+}-sensitivity of K_{Ca}1.1 channels: it is reduced in the presence of β4 at low $[Ca^{2+}]_i$, while β4 enhances channel Ca^{2+}-sensitivity at high $[Ca^{2+}]_i$ conditions (Brenner et al. 2000a; Wang et al. 2006).

Four γ subunits have been described (γ1-γ4) (Latorre et al. 2017; Li and Yan 2016), each with a single transmembrane domain and large extracellular leucine-rich repeat N-terminal domain (Yan and Aldrich 2012). Although the stoichiometry of γ association with K_{Ca}1.1 subunits has not been yet fully elucidated (Latorre et al. 2017), experiments investigating different ratios indicate a single γ subunit can

modulate the activity of the α-homotetramer (Gonzalez-Perez et al. 2014). γ1 is the first subunit identified (Yan and Aldrich 2010) and produces a negative shift in the voltage dependence of the activation of the channel (∿140 mV shift) (Yan and Aldrich 2010), leading to the accelerated activation and slower deactivation kinetics, with no effect on Ca^{2+}-sensitivity (Yan and Aldrich 2010). The γ2, γ3, and γ4 subunits also shift the voltage dependence of activation to more negative potentials, although less intensively than γ1 (∿101 mV shift for γ2, ∿51 mV for γ3, and ∿19 mV for γ4) (Yan and Aldrich 2012). Lastly, it has been recently shown that both β2 and γ1 subunits can simultaneously assemble with $K_{Ca}1.1$ homotetramers, endowing the channel with unique gating properties, being active at resting potentials (Gonzalez-Perez et al. 2015).

Apart from the co-assembly with β and/or γ subunits, $K_{Ca}1.1$ channels co-localize in the cell membrane with Ca_V channels forming multiprotein complexes (Berkefeld et al. 2006, 2010; Grunnet and Kaufmann 2004). Given the Ca^{2+}-sensitivity of these channels, in the micromolar range (Berkefeld et al. 2006), they localize close to Ca^{2+} sources in the membrane to achieve these Ca^{2+} concentrations (Augustine et al. 2003; Berkefeld et al. 2006).

For $K_{Ca}2.x$ and $K_{Ca}3.1$ channels, CaM is considered the β subunit of these channels (Berkefeld et al. 2010). CaM is constitutively bound to the pore-forming subunits of the channel with a 1:1 stoichiometry (Fanger et al. 1999) and has been visualized with cryo-EM (PDB: 6CNM) (Lee and MacKinnon 2018). CaM is responsible for K_{Ca} elevated Ca^{2+}-sensitivity (Xia et al. 1998) and has also been implicated in channel assembly and membrane trafficking (Joiner et al. 2001). Apart from CaM, an additional pair of proteins assembles with the $K_{Ca}2.x$-CaM complexes in the membrane to modulate channel activity: CK2 and protein phosphatase 2A (PP2A) (Adelman et al. 2012; Berkefeld et al. 2010). CK2 and PP2A are constitutively bound to $K_{Ca}2.x$ channels, co-assembling with both the CaMBD and the $K_{Ca}2.x$ intracellular N-terminal domain, thus forming together with CaM a multiprotein complex (Allen et al. 2007; Bildl et al. 2004). Instead of phosphorylating the $K_{Ca}2.x$ subunits, CK2 phosphorylates the amino acid T80 of CaM when the channel is closed, decreasing Ca^{2+}-sensitivity of the channel (Allen et al. 2007). On the other hand, PP2A dephosphorylates CaM in the open state of the channel, allowing it to recover its Ca^{2+}-sensitivity (Allen et al. 2007). In terms of kinase modulation, $K_{Ca}3.1$ activity is influenced by 5'AMP-activated protein kinase (AMPK), which interacts through its γ1 subunit with a leucine zipper domain located in the C-terminus of the channel (Klein et al. 2009).

K_{ir} channels typically associate as homo or heterotetramers without accessory subunits. However, $K_{ir}6.x$ channels function as octamers, composed of four pore-forming $K_{ir}6.x$ subunits, and four auxiliary subunits of the sulfonylurea receptor (SUR1, SUR2A, or SUR2A) (Clement et al. 1997; Shyng and Nichols 1997). The combinations of $K_{ir}6.x$ and SUR auxiliary subunits found in different tissues account for the distinct functional and pharmacological properties of the native channels (Aguilar-Bryan et al. 1998). The intracellular trafficking of some K_{ir} channels is also subjected to protein regulation. Particularly, GIRK channel subunits present trafficking motifs that result in different trafficking patterns of the homo or heterotetramers

(Ma et al. 2002). For instance, GIRK2a (a splicing variant of GIRK2) and GRIK4 present an ER export motif in the N-terminal region and a surface-promoting motif in the C-terminal domain that guide the endosomal exportation of GIRK channels containing these subunits to the cell surface (Ma et al. 2002). In contrast, the lysosomal targeting signal present in GIRK3 downregulates the membrane expression of GIRK3-containing channels (Ma et al. 2002). Sorting nexin 27 (SNX27) also regulates the trafficking of GIRK channels, through the interaction of its PDZ domain with the C-terminal domain of GIRK2c and GIRK3, promoting channel trafficking (Lunn et al. 2007; Munoz and Slesinger 2014). Other PDZ-containing proteins play a role in regulating the localization of some K_{ir} receptors in polarized cells, as is the case of $K_{ir}1.1$ (Yoo et al. 2004), $K_{ir}2.3$ (Olsen et al. 2002), and $K_{ir}4.1$ (Tanemoto et al. 2005).

Few associated proteins have been identified for K_{2P}. The first one is AKAP150, which interacts with TREK channels, both TREK1 and 2. Interestingly, AKAP150 is an A-kinase-anchoring protein, key in the native TREK1 environment that can transform small outward TREK1 currents into big leak K^+ conductance no longer responsive to pressure, intracellular acidification and arachidonic acid induced (Sandoz et al. 2006). New advances in proteomics will surely bring up new K_2P accessory proteins that might be key for its regulation at the activity and trafficking levels. Regulation of K^+ channels by auxiliary subunits is described in more detail in chapter "Control of Biophysical and Pharmacological Properties of K^+ Channels by Auxiliary Subunits".

7 Pharmacology: Blockers and Modulators

The structural and functional diversity among K^+ channels accounts for the wide variety of toxins and small molecules that modulate the activity of these channels. Various toxins exploit different K_v channel characteristics to exert their actions on the channel. One common class of toxins work by occluding the narrow pore of the channel from its extracellular side preventing ion flow and are referred to as "pore blockers." Many of these toxins are composed of a positive lysine and a hydrophobic tyrosine/phenylalanine in a dyad motif (Eriksson and Roux 2002; Gao and Garcia 2003; Miller 1995). With this arrangement the lysine residue occludes the K_v channel selectivity filter and prevents K^+ ions from entering the channel, at the same time the hydrophobic portion of the dyad aids docking and toxin binding to the channel (Dauplais et al. 1997; Gilquin et al. 2002; Savarin et al. 1998; Srinivasan et al. 2002). Examples of this class of toxins include κM-RIIIK and ConK-S1 from cone snails (Al-Sabi et al. 2004; Jouirou et al. 2004) and ShK from a sea anemone (Finol-Urdaneta et al. 2020). Another distinct mechanism is exhibited by "gating modifiers," which bind to the extracellular exposed linker between the TM segments S3 and S4 within the VSD. These toxins inhibit channel function, increasing the energy required to open the channel by shifting the voltage dependence to more depolarized potentials raising the activation threshold. An example of this class is the HaTx toxin from spiders (Tudor et al. 1996). δ-dendrotoxin (DTX), isolated from the green mamba snake venom, is another well-known blocker of K_v channels (Harvey

and Anderson 1985; Harvey and Robertson 2004). Various toxins, in particular conotoxins produced by marine cone snails, have been employed as molecular tools for the study of K_v channels in mammalian targets (Teichert et al. 2015). You can read more on K^+ channel toxins in chapter "Peptide Toxins Targeting K_v Channels".

In addition to toxins, work is currently being conducted to identify small molecule modulators of K_v channels which could prove useful for treating various brain disorders. For example, K_v channel activators could be used to dampen hyperexcitability for treating epilepsy or attention deficit disorder (Wulff et al. 2009). K_v channel inhibitors, on the other hand, could be used to increase excitability in disorders involving reduced neuronal activity, such as multiple sclerosis (MS). For a detailed review of the potential therapeutic utility of K_v modulators, see (Wulff et al. 2009). One example is 4-aminopyridine (4-AP) which is a non-selective K_v channel inhibitor (Wu et al. 2009) which has undergone phase III clinical trials for the treatment of MS (Goodman et al. 2009; Korenke et al. 2008). Another example is dofetilide, a class III antiarrhythmic and inhibitor of $K_v11.1$, that is efficacious in reverting and preventing atrial fibrillation of the heart (Kamath and Mittal 2008).

For K_{Ca} channels, there are different modulators for large, intermediate, and small conductance channels (Kshatri et al. 2018). For example, $K_{Ca}1.1$ channels are blocked by tetraethylammonium (TEA) (Blatz and Magleby 1984; Villarroel et al. 1988), like many K_v channels (Bretschneider et al. 1999), whereas $K_{Ca}2.x$ and $K_{Ca}3.1$ are not affected by this quaternary amine. K_{Ca} subtypes also exhibit different sensitivities to toxins (Kshatri et al. 2018). $K_{Ca}1.1$ channels are classically inhibited by the scorpion venom peptide iberiotoxin (IbTX) (Galvez et al. 1990) and charybdotoxin (ChTX) (Miller et al. 1985). The selectivity of ChTX and IbTX for $K_{Ca}1.1$ channels depends on the type of β subunit associated with the α pore-forming subunit, demonstrating how auxiliary subunits can modify the pharmacological properties of the channel (Latorre et al. 2017). For example, association of $K_{Ca}1.1$ channels in complex with β2/3 or β4 subunits decreases the affinity for ChTX (Meera et al. 2000; Xia et al. 1999), while channels associated with β1 are highly sensitive to ChTX (Hanner et al. 1997). In the case of IbTX, β4-associated $K_{Ca}1.1$ channels are resistant to the blockade by this toxin (Meera et al. 2000). Slotoxin (Garcia-Valdes et al. 2001) and martentoxin (Shi et al. 2008), two scorpion venom toxins closely related to ChTX and IbTX, are potent $K_{Ca}1.1$ blockers. Their affinity for the channel is also dependent on the β subunit composition, with slotoxin weakly blocking $K_{Ca}1.1$ channels assembled with β4 subunits (Garcia-Valdes et al. 2001), while martentoxin exhibits an opposite behavior and selectively blocks α + β4 $K_{Ca}1.1$ (Shi et al. 2008). Other natural toxins that inhibit $K_{Ca}1.1$ channels are the scorpion venom toxin BmP_{09} (Yao et al. 2005), and the fungal alkaloids paxilline, panitrem, and lolitrem B, which have shown to block the channel at low nanomolar concentrations (Imlach et al. 2009; Knaus et al. 1994b). $K_{Ca}2.x$ channels are characterized by their sensitivity to inhibition with the bee venom toxin apamin (to which $K_{Ca}1.1$ are insensitive) (Grunnet et al. 2001; Weatherall et al. 2010). $K_{Ca}2.x$ channels are also inhibited by the scorpion venom toxin tamapin (Pedarzani et al. 2002). Lastly, like $K_{Ca}1.1$ channels, $K_{Ca}3.1$ are blocked by ChTX (Sforna et al. 2018; Wei et al. 2005) and by another scorpion venom peptide toxin, maurotoxin

(Castle et al. 2003), the latter having a high affinity and selectivity for this subfamily of K_{Ca} channels (Castle et al. 2003).

For small molecule modulators of K_{Ca} channels, several activators and inhibitors have been described for the different subfamilies. For example, $K_{Ca}1.1$ channels are activated by the synthetic compounds NS1608 (Strobaek et al. 1996) and BMS-204352 (Gribkoff et al. 2001), which show promise in in vivo models for the treating fragile X syndrome (Hebert et al. 2014). For $K_{Ca}2.x$ channels, the inhibitors UCL1684 (Strobaek et al. 2000) and NS8593 (Strobaek et al. 2006) have been described. Regarding $K_{Ca}2.x$ activators, CyPPA (Hougaard et al. 2007), NS13001 (selective for $K_{Ca}2.2/K_{Ca}2.3$) (Kasumu et al. 2012), and NS309 (Strobaek et al. 2004) are of notice, the latter acting by increasing the Ca^{2+}-sensitivity of the channel. Moreover, the $K_{Ca}2.x$ activator EBIO (Devor et al. 1996) has shown in vivo efficacy as an anticonvulsant (Anderson et al. 2006). Chlorzoxazone is a $K_{Ca}2.2$ activator (Cao et al. 2001) and muscle relaxant that has been approved for the treatment of severe spasticity (Losin and McKean 1966). For $K_{Ca}3.1$ channels, the antifungal drug clotrimazole is a classical small molecule blocker (Wulff et al. 2000), and has been used as scaffold for the development of $K_{Ca}3.1$ inhibitors such as TRAM-34, which exhibits high selectivity for $K_{Ca}3.1$ (Wulff et al. 2000). On the other hand, some $K_{Ca}2.x$ activators also act on $K_{Ca}3.1$ channels to enhance their activity, such as for the benzimidazolones EBIO (Devor et al. 1996), DCEBIO (Singh et al. 2001), NS309 (Strobaek et al. 2004), and SKA-31 (Sankaranarayanan et al. 2009). In short, the strategies that pursue the activation of $K_{Ca}1.1$ and $K_{Ca}2.x$ channels, or the inhibition of $K_{Ca}3.1$ channels, are the most important when it comes to the treatment of diseases involving K_{Ca} channels (Kshatri et al. 2018).

While the biophysical features of K_{ir} channels have been thoroughly studied, their pharmacological modulation remains largely unexplored. Initially, inorganic cations like Ba^{2+} and Cs^{+} were found to block the majority of K_{ir} channels (Hagiwara et al. 1976, 1978), in a voltage- and $[K^{+}]_o$-dependent manner (Quayle et al. 1993). Nevertheless, $K_{ir}7.1$ shows a much lower sensitivity to the blockade by these cations (Krapivinsky et al. 1998). Interestingly, the K_v channel blockers tetraethylammonium (TEA) and 4-aminopyridine (4AP) have little effect on K_{ir} channels (Hagiwara et al. 1976; Oonuma et al. 2002). Several naturally occurring toxins have been described as blockers of some K_{ir} channels (Doupnik 2017). The bee venom peptide toxin tertiapin is a $K_{ir}1.1$ and GIRK channel blocker (Jin and Lu 1998; Kanjhan et al. 2005), as well as its synthetic oxidation-resistant derivative tertiapin-Q (Jin and Lu 1999). Tertiapins are not effective blockers of $K_{ir}2.1$ channels (Jin and Lu 1998). The scorpion venom peptide toxin Lq2, an isoform of charybdotoxin (ChTX), is also a $K_{ir}1.1$ blocker, and again has no inhibitory effect on $K_{ir}2.1$ (Lu and MacKinnon 1997). δ-dendrotoxin (DTX), isolated from the green mamba snake venom, is a well-known blocker of K_v channels (Harvey and Anderson 1985; Harvey and Robertson 2004) that is also a potent $K_{ir}1.1$ inhibitor (Imredy et al. 1998).

In addition to toxins, small chemical modulators have been isolated that activate some K_{ir} channels. GIRK channels are activated by small molecules such as the ureas ML297 and GiGA1, which have shown promising anticonvulsant (Kaufmann

et al. 2013; Zhao et al. 2020) and anxiolytic effects (Wydeven et al. 2014). Ethanol, as well as other short-chain alcohols, also activates GIRK channels (Kobayashi et al. 1999), implicating these channels in alcohol motivational and addictive effects (Rifkin et al. 2017). Activators and inhibitors of $K_{ir}6.x$, through the interaction with their SUR auxiliary subunits, have therapeutic applications in human (Hibino et al. 2010). For example, sulfonylureas, such as tolbutamide (Ashfield et al. 1999), glibenclamide (Schmid-Antomarchi et al. 1987), or glimepiride, block the $K_{ir}6.2$/SUR1 channel, stabilizing a conformation of SUR1 that prevents the pore opening (Doyle and Egan 2003). The recent structural determination of the $K_{ir}6.2$/SUR1 complex by cryo-EM (Lee et al. 2017; Martin et al. 2017) has helped in the identification of the sulfonylurea glibenclamide binding site (PDB: 5TWV) (Martin et al. 2017). These drugs have an important clinical use in the treatment of diabetes mellitus II, since the blockade of $K_{ir}6.2$/SUR1 expressed in pancreatic β cells promotes insulin secretion (Ashcroft 2005). Potassium channel openers (KCO), such as nicorandil (Horinaka 2011) and pinacidil (Muiesan et al. 1985), activate $K_{ir}6.x$ channels upon SUR binding and are used in the treatment of myocardial infarction, ischemia-reperfusion injury, and hypertension (Grover and Garlid 2000; Mannhold 2004).

For K_{2P} channels, many different halogenated anesthetics, such as isoflurane or sevoflurane, stimulate the channels (i.e., TREK1, TASK1-TASK3, TRAAK, and TRESK). These volatile anesthetics increase K_{2P} channel open probability and K^+ conductance, resulting in membrane hyperpolarization (Patel et al. 1999; Plant 2012). The mechanism of action, however, is not fully understood but some evidence suggests it involves the C-terminal domain. In addition, halogenated anesthetics could disrupt the inhibitory influence of the G_q/G_{11} (Chen et al. 2006).

Selective serotonin reuptake inhibitors (SSRI) fluoxetine and norfluoxetine inhibit TREK1-TREK2 throughout the lateral portals, as visualized in the TREK2 structure (Dong et al. 2015). Interestingly, some clinical studies have described analgesic activity as a side effect of these antidepressants, which can be explained by their influence on K_{2P} channels (Kennard et al. 2005), which is puzzling to explain since the inhibition of K_{2P} channels is expected to increase pain. For example, fenamates are nonsteroidal anti-inflammatory drugs that selectively activate lipid-sensitive mechano-gated K_{2P} channels, which is, together with the inhibition of pro-excitatory ion channels, the mechanism of analgesic action (Takahira et al. 2005). Fenamates exert their influence by interacting with the N-terminus of K_{2P} channels (Veale et al. 2014). Finally, new compounds, like arylsulfonamide, ML335 and the thiophene-carboxamide ML402, have been reported as activators of TREK1,2/TRAAK (Lolicato et al. 2017).

8 Physiology and Function

Potassium channels support a wide array of functions within the body and the brain. Due to the extensive diversity of the K^+ channel family, a discussion of the roles all these channels play in physiology and function is beyond the scope of this chapter. Instead, we will describe examples for each of the four general K^+ channel families.

K_v channels most notably play a role in the excitability of neurons and help shape action potentials. $K_v1.1$ is one of the most abundant K_v1 subunits expressed in mammalian brain (Trimmer and Rhodes 2004) and often exists as part of a heteromeric channel complex (Rhodes et al. 1997). $K_v1.1$ associates with $K_v1.2$ at axon initial segments (Dodson et al. 2002; Inda et al. 2006; Van Wart et al. 2007), where they control synaptic efficacy via modulation of the action potential (Kole et al. 2007). The role of these channels in controlling neuronal excitability was revealed using venom toxins such as dendrotoxin, which can elicit seizures in rodents (Bagetta et al. 1992). In addition, mice lacking $K_v1.1$ are predisposed to seizures and exhibit spontaneous seizures and changes in CNS structure (Smart et al. 1998). In humans, several loss-of-function mutations have been identified that have been linked to episodic ataxia, myokymia disorders, and partial seizures (Zuberi et al. 1999). In addition to direct loss of $K_v1.1$ channel function, mutations in a protein that co-expresses with $K_v1.1$, the leucine-rich glioma-inactivated protein 1 (LGI1), have been associated with temporal lobe epilepsy (Schulte et al. 2006). In these examples, errant changes in action potential firing frequency can lead to various neurological and psychological disorders such as epilepsy. Targeting $K_v1.1$ subunit containing channels with some form of intervention could rescue the increased likelihood of seizures and epileptiform activity observed in humans with loss-of-function mutations.

$K_v11.1$ channels, often referred to as human ether-a-go-go (hERG) channels (Kaplan and Trout 3rd 1969), are particularly important in heart tissue. There are two kinetically distinct components of the delayed rectifier potassium current observed in cardiac myocytes, referred to as the rapid delayed rectifier (I_{Kr}) and the slow delayed rectifier (I_{Ks}) (Noble and Tsien 1969a, b). These two components are sufficient to account for cardiac repolarization (Noble and Tsien 1969b). I_{Kr} is mediated by $K_v11.1$ and displays a telltale "hook" characteristic of these channels when being recorded during deactivation (Shibasaki 1987). In cardiac cells, the slow activation and deactivation kinetics of $K_v11.1$ coupled with rapid voltage-dependent inactivation and recovery from inactivation make the current that passes through the channels ideal for determining the duration of plateau phase of atrial and ventricular myocyte action potentials (Sanguinetti et al. 1995; Smith et al. 1996) (Fig. 4). The maintenance of this plateau is critical for ensuring sufficient time for Ca^{2+} release from the sarcoplasm to enable cardiac contraction, and $K_v11.1$ current contributes to pacemaking activity of the sinoatrial and atrioventricular node cells (Clark et al. 2004; Furukawa et al. 1999; Mitcheson and Hancox 1999). $K_v11.1$ is the molecular target for most drugs that cause drug-induced arrhythmias (Sanguinetti et al. 1995), many of which require channel opening prior to gaining access to receptor site within the inner cavity of the channel pore (Carmeliet 1992; Kiehn et al. 1996; Yang et al.

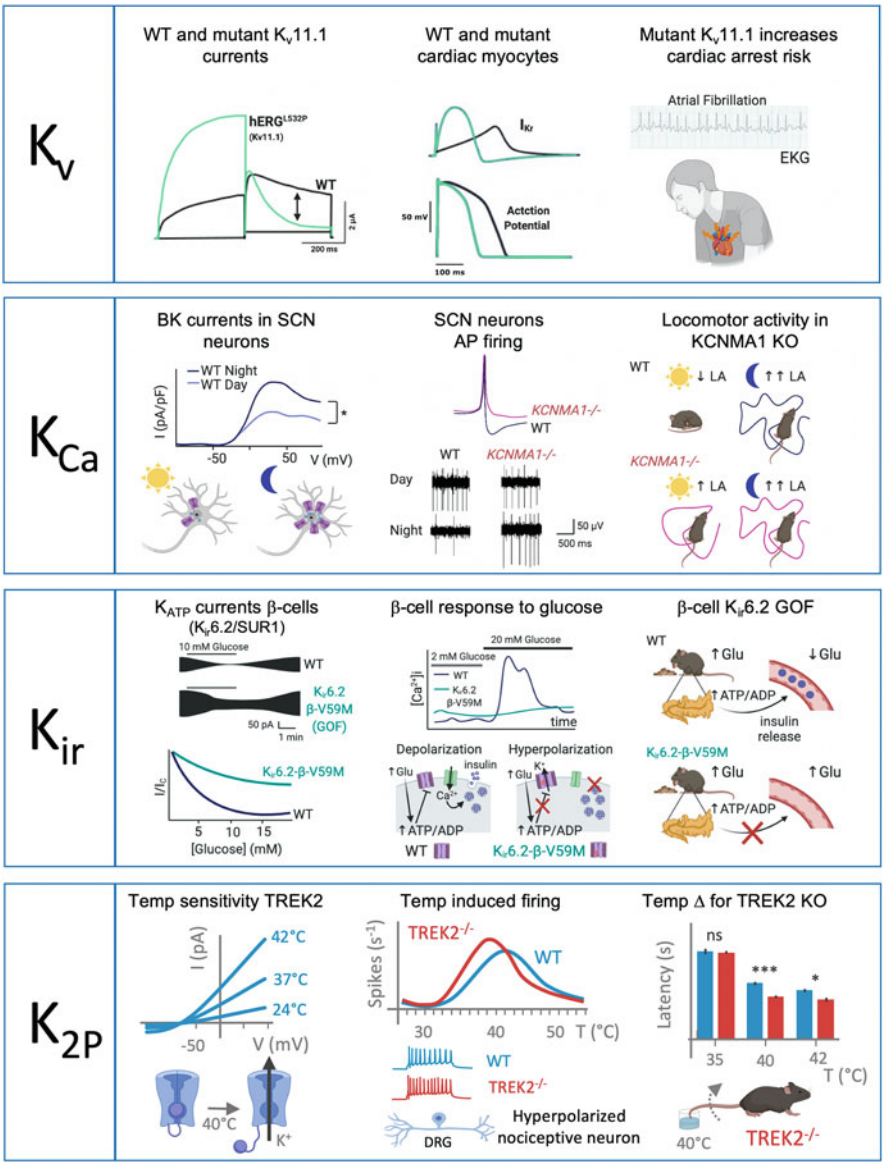

Fig. 4 Examples of physiological role of K_V, K_{Ca}, K_{ir}, and K_{2P} channels. *K_V* Mutant $K_v11.1$ (hERG) in cardiac myocytes (green) exhibits a rapid repolarization as compared to wild type (black) $K_v11.1$ channels. Expression of Mutant $K_v11.1$ results in a change in I_{Kr} and a less sustained action potential in cardiac tissue, an indication of short QT syndrome (SQTS). SQTS produced by the expression of mutant $K_v11.1$ channels can lead to atrial fibrillation and sudden cardiac arrest. *K_{Ca}* $K_{Ca}1.1$ (BK) channels in the suprachiasmatic nuclei (SCN) are essential for the maintenance of the circadian rhythm. The expression of BK channels is enhanced at night, decreasing SNC neuronal activity to keep an activity pattern (high SCN neuronal activity during daytime, and low at nighttime) responsible for circadian rhythmicity. In *$KCNMA1^{-/-}$* mice this neuronal activity pattern is lost, with SNC neurons similarly active during day and night. This leads to an increased locomotor activity of *$KCNMA1^{-/-}$* mice during the day, due to the altered SCN pacemaker function

1995). All clinical compounds developed need to be screened for off-target activity on $K_v11.1$ channel, which could potentially result in arrhythmias. Mutations in the *KCNH2* gene that encodes $K_v11.1$ underlies chromosome 7-associated long QT syndrome (LQTS type 2), accounting for roughly 40% of cases of genetically confirmed LQTS (Fig. 4).

In all genotypes that produce long QT intervals there are some common traits: they occur at an early onset and LQTS carries an increased risk for sudden cardiac arrest (SCA) (Priori et al. 2003). Individuals with LQTS exhibit disruptions in T-wave morphology that are characteristic for different subtypes of LQTS (type 1, 2, and 3) (Moss et al. 1995; Zhang et al. 2000). Disruptions in T-waves may not be apparent at rest, especially in individuals with type 2 LQTS, who develop a bifid or notched T-wave appearance during exercise (Takenaka et al. 2003). It is still unknown why reduced $K_v11.1$ function presents with this bifid or notched T-wave pattern; however, some initial evidence suggests this phenotype may be due to an increase in transmural dispersion of repolarization in cardiac myocytes when $K_v11.1$ current is reduced (Shimizu and Antzelevitch 2000). With LQTS different behaviors are most associated with negative cardiac events or SCA. For type 1, exercise is the primary risk factor (62% of individuals), arousal is the primary trigger (43%) for type 2, and rest or sleep is the most common trigger (49%) for type 3 (Schwartz et al. 2001). While risk factors have been well defined and tools like EKG (Fig. 4) can be used to diagnose individuals, there is still limited understanding of the influence common polymorphisms of the *KCNH2* gene can play in the disorder.

In contrast to LQTS, short QT syndrome (SQTS) is a disorder with a shortened duration of the QT interval on an electrocardiogram. This disorder is usually accompanied by atrial fibrillation (Patel et al. 2010). Like LQTS, SQTS appears to arise from mutations in the *KCNH2* (Zhang et al. 2011) which result in reduced inactivation and a greater current flow during the plateau of the cardiac potential (Fig. 4), leading to the ventricular and atrial action potential having a shorter duration and a shortening of the QT interval and predispose the individual to sudden cardiac death (Brugada et al. 2004). More on cardiac K^+ channels can be found in

Fig. 4 (continued) (Meredith et al. 2006; Montgomery et al. 2013). K_{ir} $K_{ir}6.2$ is expressed in pancreatic β cells together with its auxiliary subunit SUR1, where it plays a key role in glucose homeostasis: upon food intake and subsequent glucose and ATP increase, the latter inhibits $K_{ir}6.2$/SUR1 channels, promoting cell depolarization, Ca^{2+} intracellular increase, and insulin secretion. The human gain of function mutation β-V59M in $K_{ir}6.2$ leads to a type of neonatal diabetes. Mice bearing this mutation reproduce the human phenotype, exhibiting decreased K_{ATP} currents and glucose response (measured as intracellular Ca^{2+} increase) in β cells (Girard et al. 2009) and impaired insulin secretion upon food intake (Brereton and Ashcroft 2013). K_{2P} TREK2 increases K^+ outflow in response to heat, within the 24–42°C range. Nociceptive expresses TREK2, which regulates non-aversive warmth perception. In a wild-type individual, heat-sensitive c-fibers increase their firing activity gradually as they approach 42°C. The lack of TREK2 in mice significantly increases the number of action potentials by 30% in the 30–40°C range compared to wild type. $TREK2^{-/-}$ mice exhibit hyperalgesia, since tail flick latencies upon 40 and 42°C bath immersion are reduced

chapters "Cardiac K^+ Channels and Channelopathies" and "Cardiac hERG K^+ Channel as Safety and Pharmacological Target".

K_{Ca} channels are widely expressed in both neuronal and non-neuronal tissues, where they play a diversity of physiological roles that are based on their ability to couple membrane potential and the intracellular Ca^{2+} concentration (Berkefeld et al. 2010). Increases in $[Ca^{2+}]_i$ lead to an outward K^+ flux through K_{Ca} channels that contributes to cell hyperpolarization. This helps to maintain Ca^{2+} homeostasis, limiting Ca^{2+} influx either through voltage-gated Ca^{2+} channel inactivation or increasing the activity of Na^+/Ca^{2+} exchangers (Fakler and Adelman 2008). $K_{Ca}1.1$ channels (BK channels) are mainly expressed with β1 subunits in the vascular smooth muscle (Latorre et al. 2017), where these play a key role in the regulation of the vascular tone (Brenner et al. 2000b; Latorre et al. 2017). Ca^{2+} release from the sarcoplasmic reticulum forms Ca^{2+} sparks that activate BK channels, inducing vasodilation (Latorre et al. 2017; Pluger et al. 2000). The dysfunction of $K_{Ca}1.1$ channels or β1 mutations is involved in altered vasoregulation, such as hypertension (Dogan et al. 2019; Latorre et al. 2017). $K_{Ca}1.1$ expression has also been described in the intercalated cells of the kidney, in complex with either β1 or β4 subunits, where they participate in K^+ secretion (Holtzclaw et al. 2011). Importantly, $K_{Ca}1.1$ channels are abundant and broadly found in the CNS (Sausbier et al. 2006), where they mainly associate with β4 subunits (Weiger et al. 2000). In neurons, $K_{Ca}1.1$ channels contribute to different processes involved in neuronal excitability, such as AP repolarization (Storm 1987), mediation of the fast phase of the AHP (Gu et al. 2007; Lancaster and Nicoll 1987; Storm 1987) and shaping the Ca^{2+} dendritic spikes (Golding et al. 1999), as well as to the modulation of neurotransmitter release (Griguoli et al. 2016; Yazejian et al. 2000).

Of particular interest is the role of $K_{Ca}1.1$ channels expressed in the suprachiasmatic nuclei (SCN) in the regulation of the circadian rhythm (Fig. 4) (Meredith et al. 2006; Montgomery et al. 2013; Whitt et al. 2016). $K_{Ca}1.1$ expression and outward currents are increased during nighttime (Montgomery et al. 2013), decreasing SCN neuronal activity at night. This decrease in activity is essential to maintain the high amplitude of the neural activity pattern in the SCN that restricts locomotor activity to the appropriate phase (night) (Montgomery et al. 2013). In *KCNMA1* (gene encoding $K_{Ca}1.1$) knockout mice, the SCN neural activity amplitude is lost, altering the SCN pacemaker function, and making mice more active during daytime (Meredith et al. 2006) (Fig. 4).

$K_{Ca}3.1$ expression has been observed in diverse set of cells, including epithelial, vascular endothelial, vascular smooth muscle cells (Wulff and Castle 2010), hematopoietic cells, such as erythrocytes, lymphocytes, monocytes, and macrophages (Logsdon et al. 1997), and in CNS-resident immune cells, namely microglia (D'Alessandro et al. 2018; Ferreira et al. 2014). $K_{Ca}3.1$ plays an essential role in regulating cellular volume (Sforna et al. 2018), mediating the Ca^{2+}-dependent K^+ efflux that is part of the regulatory volume decrease (RVD) that occurs upon cell swelling (Sforna et al. 2018; Vandorpe et al. 1998). This regulation of cellular volume links $K_{Ca}3.1$ channels with cell migration, since volume increases in one edge for protrusion and decreases for retraction (D'Alessandro et al. 2018).

Interestingly, this role of $K_{Ca}3.1$ channels also accounts for their involvement in glioblastoma multiforme, where $K_{Ca}3.1$ is necessary for cell infiltration, and which expression correlates with worse prognosis (D'Alessandro et al. 2018; Turner et al. 2014).

K_{ir} channels are widely expressed throughout the organism, playing a variety of roles in different cells and tissues. Their characteristic inward rectification accounts for their contribution not only to the maintenance of the resting membrane potential in excitable cells (Hibino et al. 2010), but also to the preservation of ionic gradients in renal tissues (Welling 2016). The ATP sensitivity of $K_{ir}6.x$ channels (Terzic et al. 1995) accounts for their physiological role, coupling the cellular metabolism with the excitability of the membrane (Tinker et al. 2018). Several $K_{ir}6.x$ and SUR subunits combinations are expressed in different tissues (Hibino et al. 2010). Cardiac myocytes and skeletal muscle express $K_{ir}6.2$/SUR2A, where they play a protective role against ischemia-reperfusion (Suzuki et al. 2002) and as linkers to glucose metabolism (Weik and Neumcke 1989), respectively. In vascular smooth muscle, the predominant isoform is $K_{ir}6.1$/SUR2B (Aziz et al. 2014), which participates in the regulation of the vascular tone (Aziz et al. 2014). $K_{ir}6.2$/SUR1 channels have been described in hypothalamic neurons (Ashford et al. 1990), where they play a role in coupling glucose metabolism to glucagon secretion (Miki et al. 2001), and also in pancreatic β cells (Fig. 4). In these cells, $K_{ir}6.2$/SUR1 are key players in glucose homeostasis, linking glucose metabolism to insulin secretion (Ashcroft et al. 1984). An increase in glucose levels elevates intracellular ATP, which binds to SUR1 closing $K_{ir}6.2$ channel pore (Fig. 4) and promoting β cell depolarization, with the subsequent increase of intracellular Ca^{2+} that leads to insulin secretion (Hibino et al. 2010). Importantly, mutations in $K_{ir}6.2$ and SUR1 lead to a range of insulin secretion disorders (Fig. 4) (Remedi and Koster 2010). Gain of function mutations are responsible for different types of neonatal diabetes (Gloyn et al. 2004) (Tinker et al. 2018), while loss of function mutations in both $K_{ir}6.2$ and SUR1 cause congenital hyperinsulinism and hypoglycemia (Nestorowicz et al. 1997; Tinker et al. 2018). Sulfonylureas block $K_{ir}6.2$ channels through their interaction with the SUR subunits and are commonly used for the treatment of diabetes (Ashcroft 2005).

In the case of $K_{ir}4.x$ and $K_{ir}5.1$ channels, $K_{ir}4.1$ homotetramers and $K_{ir}4.1/K_{ir}5.1$ heterotetramers are abundantly expressed in astrocytes (Hibino et al. 2004a) and in retinal Müller glial cells (Ishii et al. 2003), where they play an essential role in the spatial buffering extracellular K^+, helping maintain the osmotic balance (Hibino et al. 2004a; Ishii et al. 2003). $K_{ir}4.1/K_{ir}5.1$ and $K_{ir}4.2/K_{ir}5.1$ channels have also been found in the kidney, particularly in the basolateral surface of renal epithelial cells (Lourdel et al. 2002; Tanemoto et al. 2000), where they contribute to the maintenance of the driving force required for Na^+ reabsorption by recycling K^+ across the basolateral membrane (Huang et al. 2007; Palygin et al. 2017). Moreover, $K_{ir}4.1/5.1$ is also expressed in the cochlea of the inner ear (Hibino et al. 1997, 2004b), contributing to the generation of the endocochlear potential of the inner ear endolymph (Hibino and Kurachi 2006). Mutations in $K_{ir}4.1$ lead to the SeSAME syndrome (Scholl et al. 2009), with a symptomatology characterized by seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME), that correlates with $K_{ir}4.1$ expression in the organism (Scholl et al. 2009).

K_{2P} channels are expressed in motoneurons (Berg et al. 2004; Talley et al. 2000), dorsal root ganglion (DRG) neurons (Kang and Kim 2006; Pereira et al. 2014), cortical, hippocampal, hypothalamic neurons (Fink et al. 1996; Medhurst et al. 2001), cerebellar granule neurons (Plant et al. 2002) and cortical astrocytes (Hwang et al. 2014). In particular, K_{2P} channels in the DRG control the generation of an action potential through thermal-gating of TREK2 (Fig. 4). TREK2 increases K^+ outflow in response to heat, within the 24–42°C range (Kang et al. 2005). Nociceptive neurons in the DRGs that innervate most of the body surface express TREK2, which regulates non-aversive warmth perception. In a wild-type individual, heat-sensitive c-fibers increase their firing activity gradually as they approach 42°C, due to the activation of mainly thermosensitive transient receptor potential (TRP) channels (Caterina et al. 1997). However, in mice lacking TREK2, the number of action potentials significantly increases by 30% in the 30–40°C range compared to wild type. Additionally, $TREK2^{-/-}$ mice exhibit hyperalgesia, since tail flick latencies upon 40 and 42°C bath immersion are reduced (Pereira et al. 2014) (Fig. 4). Overall, the channel, neuron, and animal behavior indicate the following: TREK2 by being active with heat contributes to a hyperpolarizing environment in the nociceptive neurons which dampen nociceptive signals upon non-aversive warmth.

K_2P malfunctioning has been extensively associated to different pain manifestations such as neuropathic pain or migraine. TRESK also contributes to background current in DRG neurons (Plant 2012; Tulleuda et al. 2011). TRESK is downregulated in spared nerve injury (SNI) model of chronic pain in rats. Interestingly, the hyperalgesia and gliocytes activation are reduced after inducing recombinant TRESK gene overexpression (Zhou et al. 2017). TWIK1 and TASK3 are also reduced in SNI. However, their levels are restored after weeks in the case of TWIK1 and months for TASK3 (Pollema-Mays et al. 2013). Multiple TRESK mutations in humans have been associated to migraine with aura (Lafreniere et al. 2010; Rainero et al. 2014). Proximal point mutations in regions close to the pore (i.e., A34V and C110R) lead to smaller TRESK currents (Andres-Enguix et al. 2012). TRESK deletions display dominant-negative phenotype in heterologous systems when is co-expressed with wild-type TRESK (Lafreniere and Rouleau 2011). Together, these studies suggest TRESK as a target for new analgesics.

A noteworthy contribution of the K_2P channels in the brain is their implication on glutamate release from astrocytes. Classically, neurons have been exclusively attributed for fast glutamatergic synaptic transmission. However, recent studies have shown astrocytes induce slow and fast glutamate release, involving mechanisms of neuron-like exocytosis or transporter/channel mediated. Astrocytes display a leaky membrane with a low resistance, attributed to primarily the outwardly rectifier TREK1 (Fink et al. 1996). Activation of TREK1, either directly or upon CB1 activation Gβγ to the N-terminal, induces astrocytic glutamate release (Woo et al. 2012). TREK1 downregulation eliminates glutamate release fast mode but does not affect the slow mode. Interestingly, the "non-functional" TWIK1 is also expressed in astrocytes and forms a functional heteromer with TREK1 (Hwang et al. 2014).

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