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Review Article

Antagonists of the Kv1.5 potassium channel

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CONTENTS

Abstract

Potassium channels are an extensive family of ion channels selectively permeable to potassium ions (K^+). They serve important functions in many crucial physiological processes and their dysregulation is key in several pathophysiological states, including pulmonary arterial hypertension, cancer and cardiac arrhythmias. One subset of K^+ channels is comprised of the voltage-gated K^+ (Kv) channels, of which over 40 isoforms have been identified and shown to serve important roles in cellular processes, such as the maintenance of resting membrane potential, cell contractility, neuronal activity and cell proliferation. The Kv1.5 isoform, encoded by the *KCNA5* gene, has received much attention, with extensive research already carried out into its physiological, biophysical, structural and molecular properties. It is believed to be a potential target in diseases such as atrial fibrillation and pulmonary hypertension. As a result, a wide variety of pathways and pharmacological tools/drugs with modulatory effects on this channel have been identified. This review focuses on inhibitory regulation of Kv1.5 channels and will outline the following aspects: 1) structure, sequence and function; 2) transcriptional regulation; 3) trafficking; 4) occlusion/inhibition; and 5) altered kinetics or biophysical properties.

Introduction

Potassium channels are the most complex family of voltage-gated ion channels. *Shaker*, *Shaw*, *Shab* and *Shal* were the original sequence-related potassium channel genes identified in the fruit fly *Drosophila*, and each now has a human homologue. Despite being widely distributed in membranes of all living cells, it was not until 1987 that the first potassium channel was cloned (1, 2). However, the existence of outward currents driven by potassium ion (K^+) movement was established as far back as the early 1950s (3-5). Hodgkin and Huxley were the first to record K^+ currents using giant squid axons. While initial studies focused on homologues identified in *Drosophila* and giant squid axons, subsequent research has identified K^+ channels in virtually all cell types and species.

Several classes of K^+ channels have been identified in mammalian cells: 1) voltage-gated K^+ channels (Kv); 2) large-, intermediate- and small-conductance Ca^{2+}-activated K^+ channels (BK_{Ca}, IK_{Ca} and SK_{Ca}, respectively); 3) adenosine triphosphate (ATP)-sensitive (or ATP-inhibited) K^+ channels (K_{ATP}); 4) inwardly rectifying K^+ channels (K_{IR}); and 5) two-pore-domain K^+ channels (K_{2P}). Transient receptor potential (TRP) channels and nonselective cation channels (NSCCs) can also pass K^+ ions across the cellular membrane. Of these, the Kv channels in particular are thought to be prominent in the regulation of resting membrane potential, action potentials and cell excitability. Of particular interest are the Kv1.5 channels. The Kv1.5 gene (*KCNA5*) encodes for a *Shaker*-related Kv channel characterized by a delayed rectifier-type current. With a wide tissue distribution, Kv1.5 channels have been shown to play an important functional role in physiological processes, such as neuronal excitability, neurotransmitter release, cardiac action potentials, myocyte contractility, insulin secretion and cell proliferation in cancer (6-9). More specifically, in the cardiovascular system, Kv1.5 has been identified as the channel underlying the ultrarapid rectifying K^+ current (I_{Kur}) in atrial myocytes, the predominant repolarizing current and the sustained outward K^+ currents in pulmonary vascular smooth muscle cells (VSMCs). As such, these channels have become a focal point and target in the treatment of atrial fibrillation and hypoxic pulmonary hypertension.

A multitude of mechanisms can be targeted to impede the correct gating and functioning of K^+ channels. The whole-cell current through Kv channels, $I_{K(V)}$, is determined by the following equation: $I_{K(V)} = N \times P_{open} \times i_K$, where N denotes the total number of Kv channels, P_{open} is

the steady-state open probability of a Kv channel, and i_K is the amplitude of current through a single Kv channel. Based on this equation, the current through the Kv1.5 channels can be reduced by: 1) decreased total number of channel proteins due to transcriptional inhibition of the *KCNA5* gene via its transcriptional silencer elements (*e.g.,* the Kv1.5 repressor element KRE in the promoter region of the gene) (10, 11); 2) decreased number of functional channels in the plasma membrane due to inhibition of channel trafficking by the Kv channel-interacting proteins (*e.g.*, KChIP), an accessory subunit regulating the functional surface expression of Kv1.5 (12), and to inhibition of α-α-subunit assemblying via the cytoplasmic *N*-terminal tetramerization domain (T1) (13); 3) decreased activation and/or increased activation of Kv channels due to association with the regulatory β-subunits (14) and to inhibition of channel activity by protein kinase C (PKC)-mediated phosphorylation of the channel α- and β-subunits (15); 4) pharmacological blockade of the Kv1.5 channel by selective (*e.g.*, 4-aminopyridine, bepridil, correolide) (16, 17) and nonselective (*e.g.,* nicotine, endothelin-1 [ET-1], serotonin [5-HT], fenfluramine, acute hypoxia, dichloroacetate) (18-20) inhibitors; and 5) transcriptional/translational and functional inhibition of Kv1.5 channels by antiapoptotic proteins (*e.g.,* Bcl-2) (21).

This review summarizes inhibitory mechanisms involved in the regulation of Kv1.5 channel expression and activity.

Sequence and structure of the Kv1.5 channel

KCNA5 is the current official annotation for the Kv1.5 channel gene (or the *Shaker*-related Kv channel member 5 gene), which was previously referred to as *HCK1, HK2, HPCN1, Kv1.5, MGC117058, MGC117059* and *PCN1*. Philipson *et al.* (22) were the first to isolate and sequence the K+ channel gene, at the time designated *PCN1*, using a rat brain K+ channel probe to screen a human insulinoma cDNA library for clones encoding the Kv channel. Human *PCN1* had a predicted 6,113-amino-acid protein encoded by an open reading frame of 1839 (Fig. 1). Initial studies in somatic cell hybrids mapped the *Shaker*-related K+ channel *KCNA1* gene to chromosome 12 (23). Several subsequent studies in humans, rats and mice (24, 25) were performed to determine the precise location of the *KCNA5* gene locus on chromosome 12, culminating in a 300-kb cluster in which the genes for *KCNA6*, *KCNA1* and *KCNA5* are located at position 13 (26). The Kv1.5 channel has been identified, sequenced and mapped in many other species in addition to humans,

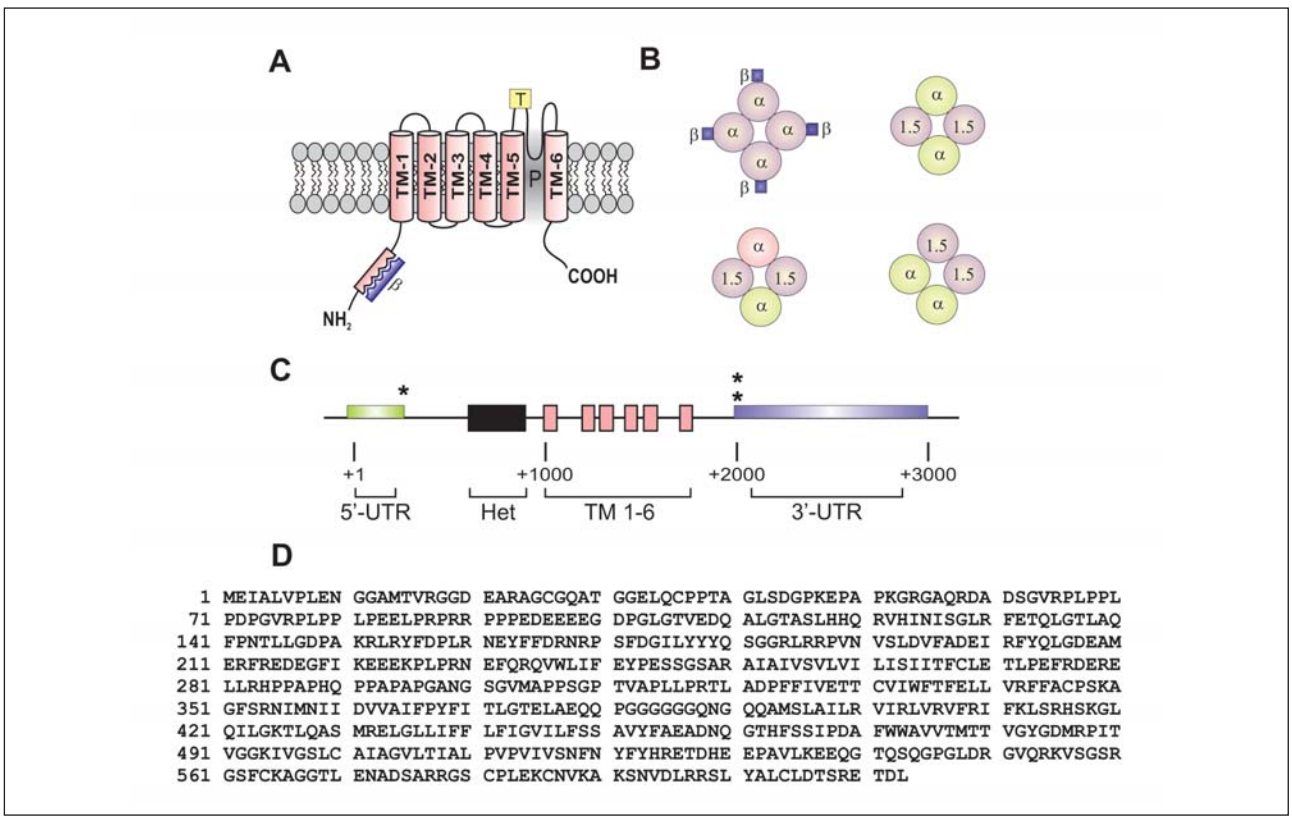

Fig. 1. Sequence and structure of the Kv1.5 channel. **A**: membrane topology of a single Kv α-subunit, for example Kv1.5. TM-1-TM-6 indicate the 6 transmembrane domains, T represents the turret regulator region. A β-subunit is shown to be associated with the *C*-terminus. P indicates the pore-forming loop between the TM-5 and TM-6 domains. **B**: representations of possible α-α- and α-β-subunit co-assembly. Kv1.5 α-subunits may form homotetramers or heterotetramers with other Kv α-subunits, such as Kv1.2 and Kv1.3. **C**: *KCNA5* gene. **D**: amino acid sequence for the whole *KCNA5* gene. * and ** denote the start and end of the gene coding region, respectively.

including rats (located on chromosome 4, q42), mice (also known as MGC25248, located on chromosome 6, 61.0 cM) (24) and dogs (located on chromosome 27).

To date, around 30 single nucleotide polymorphisms (SNPs), including 9 coding SNPs, have been identified in the *KCNA5* gene. Documented functional changes incurred by SNPs include a decrease in sensitivity to channel currents by quinidine (an antiarrhythmic drug) due to two nonsynonymous variants (P532L and R578K) in the *C*-terminus; an additional drug-resistant *C*-terminal α-helix alters the channel secondary structure due to a P532L variant (27, 28). Kv channelopathy associated with atrial fibrillation has been shown to correlate with a mutation (E375X) affecting the S4-S6 voltage sensor, pore region and *N*-terminus. Such a loss of channel function prolonged the action potential and early afterdepolarization in human atrial myocytes (29). SNPs in *KCNA5* may be responsible for decreased currents in pulmonary arterial smooth muscle cells in patients with idiopathic pulmonary arterial hypertension (IPAH) (18).

Studies into the membrane topology showed that the Kv1.5 subunit consists of six transmembrane domains (TM-1-6), intracellular *N*- and *C*-termini and a highly conserved pore loop between TM-5 and TM-6; the membrane topology of a single subunit is featured in Figure 1A. The fourth transmembrane domain (TM-4) contains a preserved region of positive Arg or Lys amino acid residues (repeats of Arg or Lys-Xaa-Xaa$_{(7)}$). The cytoplasmic *C*-terminus differs between Kv channel α-subunits. The cytoplasmic *N*-terminus, however, contains a tetramerization domain (T1-TM-1) comprised of molecular determinants for the formation of functional tetrameric channels from specific α-subunit assembly. This 120-amino-acid domain is highly conserved throughout the Kv channel family and forms a tetrameric structure thought to align with the channels' pore region (13). The tetrameric T1 domain exists as a region distinct from the transmembrane channel, resembling a ball and chain structure (30), and is fundamental in influencing the channel conformation, gating and electrophysical properties. Such regulation may be achieved by interaction with Kv channel β-subunits; a 90-amino-acid region in the *N*-terminal T1 domain of Kv1.5 is essential for interaction with Kvβ1 subunits (31).

Functional channels commonly form octomers by assembling as homo- or hetero-multimers of four α-subunits associated with four regulatory β-subunits (Fig. 1B). Heterotetrameric complexes known to form functional channels with Kv1.5 include Kv1.2 (KCNA2), Kv1.4 (KCNA4) and Kv1.6 (KCNA6) subunits. Varied subunit composition can lead to functionally different heteromeric Kv1.5 channels. For example, a channel comprised of two Kv1.5 and two Kv1.2 subunits may differ functionally from a tetramer consisting of three Kv1.5 and one Kv1.1 subunit; as a consequence, the native Kv currents through these channels are dramatically different in terms of kinetics, amplitude and response to drugs. This creates a great diversity in native Kv1.5 channels.

Indeed, by way of example, Kv1.2/Kv1.5 heterotetramers contribute to setting and maintaining the resting membrane potential in rat cerebral VSMCs (32) and forming 4-aminopyridine (4-AP)-sensitive channels in rabbit portal vein (33). Kv channel currents, or $I_{K(V)}$, in oligodendrocyte progenitor cells are believed to be generated by K^+ efflux through channels formed partly by Kv1.5 subunits (possibly forming heteromultimeric channels with Kv1.6 or other Kv subunits) (34). Responses to drugs and K^+ channel modulators can be dramatically altered by heteromultimeric association, *e.g.,* in macrophages, Kv1.3 and Kv1.5 co-localize to form margatoxin-sensitive channels (35). Heterotetramers formed of Kv1.4 and Kv1.5 subunits and Kv1.5 homotetramers present in GH_3 cells are differentially regulated by the hormone dexamethasone; heterotetramers are somewhat upregulated, whereas homotetramers of Kv1.5 are doubled in expression, altering cellular excitability (36).

Kv1.5-associated subunits

Kv channel β1.2, β1.3, β2 and β3 subunits are known to interact with Kv1.5 to form multimeric complexes. Despite having very disparate lengths, from Kvβ1.2 at approximately 350 kb to Kvβ3 (KCNA3B) at about 7 kb, the exon patterns are very similar and greater than 80% homology is observed in their *C*-termini (329 amino acids). Although β-subunits are not required for the expression and function of the α-subunits, they interact to change the gating behavior and kinetics of Kv1.5 channels (37).

I_{Kur}, an atrial-specific K^+ current in human myocytes principally consisting of Kv1.5 subunits, is actively suppressed by PKC via direct phosphorylation of the channel only when the channel is specifically associated with the Kvβ1.2 accessory subunit (15). In contrast, another study in Chinese hamster ovary (CHO) cells stably transfected with rat Kv1.5 showed no effect for the PKC inhibitors chelyrethrine and PKC19-36 on $I_{K(V)}$; however, the study did describe a direct inhibition of these channels by bisindolylmaleimide (BIM) in a phosphorylation-independent and state-, voltage-, time- and use-dependent manner (38). Conversely, accelerated inactivation by co-association of Kv1.5 with Kvβ1.3 is reduced in the presence of PKA, where phosphorylation of a serine residue (24) in the *N*-terminus of Kvβ1.3 was crucial (39).

England *et al*. (40) first cloned this novel β-subunit (denoted Kvβ1.3) from human heart muscle. When co-expressed with Kv1.5, Kvβ1.3 had unique functional effects, causing time- and voltage-dependent inactivation, a significant hyperpolarizing shift in channel activation and an increase in deactivation time via an open-channel block of the Kv1.5 channel; Kv1.5, commonly an outwardly rectifying channel, became strongly inwardly rectifying (41). Another β-subunit, Kvβ3, cloned from human left ventricle and mapped to human chromosome 3, similarly accelerated Kv1.5 inactivation, caused a hyperpolarizing shift in activation and slowed activation (42). When co-expressed with Kv1.5, the Kvβ2.1 subunit alters Kv1.5 function (37). Frequently, Kv β-subunit expression with Kv1.5 confers a change in Kv current to

a fast inactivating (A-type) outward current; human Kvβ3.1, which is predominantly expressed in the brain, mediates such a change when co-expressed in CHO cells (43). Kv channel β-subunits belong to an NADPH-dependent oxidoreductase superfamily and their influence on Kv channel activity may involve oxidoreductase activity (44); it is likely that β-subunits play a role in sensing changes in intracellular redox state and oxygen tension. They may confer, in part, the regulatory role in decreasing Kv1.5 channel currents in response to hypoxia specific to oxygen-sensitive tissues and cells, such as pulmonary artery smooth muscle cells (20).

Other accessory subunits currently described include Kv channel-activating (KChAP) or -interacting proteins (KChIP), Src tyrosine kinase and NADPH oxidase. These proteins play important roles in modulating trafficking, subunit co-assembly, cell-surface expression and function of Kv1.5 channels. The chaperone-like protein KChAP, present in cardiomyocytes, can counteract the decreases in Kv1.5 currents caused by co-assembly of Kv.1.5 with Kvβ1.2 subunits (45).

Src family protein tyrosine kinases (PTKs) can bind to both homo- and heterotetrameric Kv1.5 channels via interactions with a proline-rich motif in human Kv1.5 and Src homology 3 (SH3) domains (46-48). Other Kv channel α-subunits that lack the proline-rich motif to bind SH3 domains but are in heterotetrameric complexes including a Kv1.5 subunit may also be phosphorylated by adjacent bound Kv1.5 subunits. SH3-dependent tyrosine phosphorylation is therefore able to inhibit both homo- and heterotetrameric channel currents (48). In astrocytes, while downregulation of Kv1.5 inhibits proliferation, Kv1.5 channel activity is conversely upregulated in proliferating cells due to channel phosphorylation by PTKs (47). Indeed, the tyrosine kinase inhibitor PP2 (47) decreased Kv1.5 phosphorylation, reduced $I_{K(V)}$ and inhibited proliferation, having potentially profound effects on cellular excitability in astrocytes. In contrast, the PTK inhibitor tyrphostin AG-1478 was suggested to exert its rapid and reversible inhibition of Kv1.5 by a direct open-channel block (49).

Transcriptional inhibition of the *KCNA5* gene

The promoter region of the Kv1.5 channel gene (*KCNA5*) has been characterized (11); key transcription factor binding sites and other potential regions of interest in transcriptional regulation of Kv1.5 are indicated in Figure 2. In the intron-less 5'-untranslated region (5'-UTR) of *KCNA5*, a cAMP response element (CRE) consensus is present and cAMP has been shown to decrease both the steady-state *KCNA5* transcript levels and the transcription rate of the *KCNA5* gene in GH_3 cells (11). Mori *et al.* additionally identified a KRE that may play an important role in regulating the cell-specific expression of Kv1.5 channels, possibly by repressing *KCNA5* in specific cell types (10). KRE forms a unique DNA-protein complex to which a nonhistone high-mobility group 1 protein (hHMG1) can bind (10). Other transcription factors located in the potential 5'-promoter region of the *KCNA5* gene that are postulated to be able to directly regulate the transcription of the *KCNA5* gene include: c-Myb, AP-2, NF-κB, SP1-VGF/ERK1, E2A/E bon, creA, C/EBP-ApoB, 2APB-PLCγ, CREB (c-Jun) and γ-IRE (as indicated in Figure 2). The transcription factor SP1, which binds the CACCC nucleotide motif in the promoter region of the murine *KCNA5* gene, has already been studied in VSMCs (50). Inhibition of the interaction between SP1 and *KCNA5* inhibited the promoter activity, and therefore SP1 is potentially influential in the expression of Kv1.5 channels.

The half-life of Kv1.5 mRNA is approximately 30 min, with a protein half-life of 4 h (11, 51). It has been postulat-

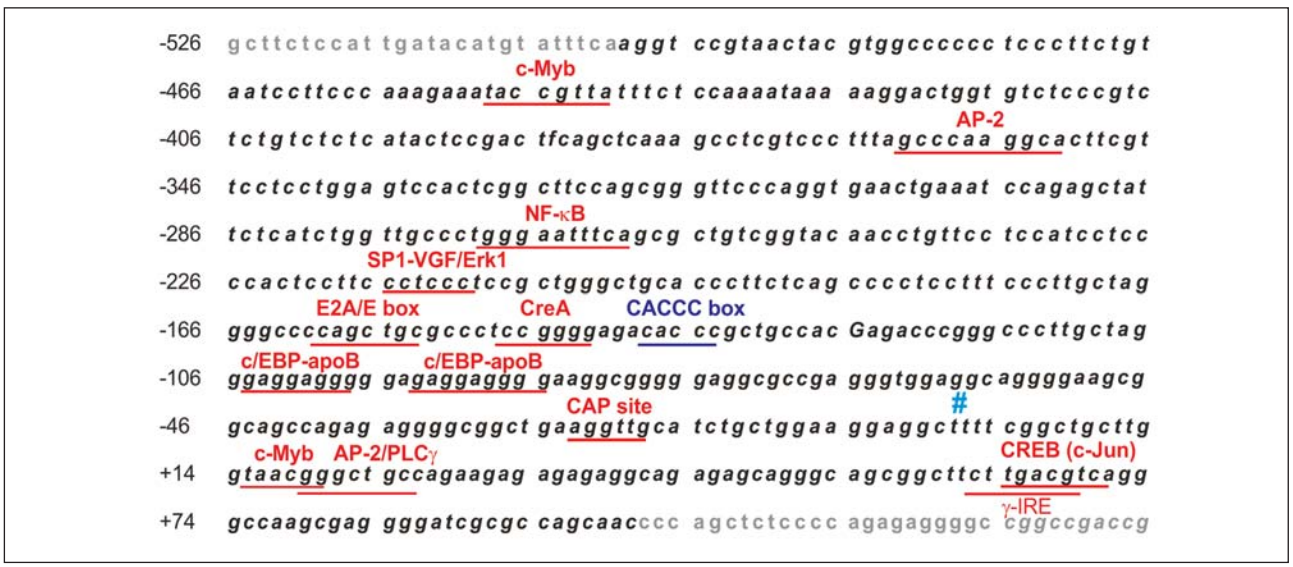

Fig. 2. Potential transcription factor binding sites in the putative promoter region of the *KCNA5* gene. Transcription factor binding sites are indicated by the red lines. # indicates the transcription start site. The gray sequence indicates the start of the gene coding region.

ed that hormones and neurotransmitters may have regulatory effects on Kv1.5 channel gene expression in a matter of hours. While glucocorticoids such as dexamethasone are known to increase mRNA and protein expression in pituitary cells (51) and ventricular myocytes (52), other hormones are associated with a notable inhibition of Kv1.5 expression. Such hormones include the neuropeptides thyroid hormone and thyrotropin-releasing hormone (TRH), which inhibit both gene transcription and protein synthesis in pituitary cell lines. In the heart, thyroid hormone decreases the expression of Kv1.5 mRNA by ~70%, resulting in attenuated electrophysiological properties and contractility, specific to left ventricle myocytes (53). Neurotransmitters such as TRH downregulate Kv1.5 mRNA expression in pituitary cells. This decreased gene transcription occurs in parallel with decreased Kv1.5 channel expression and thus enhances neuronal excitability (54). The proposed mechanism requires Gαq protein activation, but not the associated signaling pathway involving phospholipase C (PLC). Furthermore, neither depletion of intracellular Ca^{2+} nor mechanisms requiring PKC were involved (55).

In the translated region of the *KCNA5* gene, there are binding domains for factors known to modulate Kv1.5 channel function, trafficking or binding with drugs. The *KCNA5* gene contains 20 PKC phosphorylation consensus sequences in the intracellular regions (56, 57). Associating Kvβ1.2 subunits possess an additional 10 potential PKC phosphorylation sites in their *N*-termini and 27 in their *C*-termini. Although PKC was not implicated in the regulation of *KCNA5* gene transcription (55, 58), other protein kinases are involved in the modulation of Kv1.5 expression. It is worth noting that, although not having a role in transcription, in CHO cells, the specific PKC inhibitor BIM did decrease Kv1.5 current amplitude and inactivation time constants, an effect surmised to be phosphorylation-independent, and state-, voltage-, time- and use-dependent (38). Specific decreases in Kv1.5 mRNA expression were observed when pituitary cells were exposed to the nonspecific protein kinase inhibitor H7 and the (*R*)-diastereomer of adenosine-3',5'-monophosphorothioate, a PKA-specific inhibitor (58), suggesting a requirement for protein kinases in the basal expression of Kv1.5 in these cells.

Other agents known to decrease *KCNA5* gene transcription, cause mRNA instability and decrease $I_{K(V)}$ in pulmonary artery smooth muscle cells and other mammalian cell lines are anorexigenic agents, such as aminorex, fenfluramine, dexfenfluramine, sibutramine and fluoxetine (19). Nonspecific effects of nicotine and smoke from cigarettes also resulted in downregulation of mRNA expression and inhibited protein synthesis in smooth muscle cells, thus decreasing $I_{K(V)}$ (18, 59). Overexpression of the antiapoptotic protein Bcl-2 can downregulate mRNA expression and its antiapoptotic effects have been attributed to the consequential decreased efflux of K^+ via channels, including Kv1.5, in pulmonary artery smooth muscle cells (21).

Post-translational modifications have regulatory roles in the functional expression of Kv1.5 channels. A small ubiquitin-like modifier (SUMO) causes a post-translational modification of Kv1.5 that may potentially alter Kv channel function, with effects particularly on the resting membrane potential and action potential duration. The specific interaction of Kv1.5 with the SUMO-conjugating enzyme UBC9 targets it for modification by SUMO-1, -2 and -3 (60, 61). In addition, PDZ domains reside in both the *C*- and *N*-termini (in the T1 domain) of Kv1.5. Ablation of these domains has regulatory effects on Kv1.5 channel currents and may be implicated in both channel expression and function (62).

Drugs that inhibit Kv1.5 trafficking

The trafficking and steady-state expression of functional Kv1.5 channels in the plasma membrane may also be impeded, decreasing cellular Kv currents. Post-translational modifications and association with regulatory proteins are known to hinder the progression of functional Kv1.5 channels from the endoplasmic reticulum (ER) to the plasma membrane. One such mechanism, post-translational *S*-acylation, regulates trafficking in transfected fibroblasts through modification on both the *N*- and *C*-termini via hydroxylamine-sensitive thioester bonds (63). Targeting of Kv1.5 proteins for degradation, accumulation in intracellular compartments and restricted cell-surface expression were all consequential to inhibition of *S*-acylation, predominantly via actions at the *C*-terminus.

Accumulation of Kv1.5 proteins in the ER where trafficking to the surface membrane is hindered may entail a retrograde trafficking mechanism involving internalization from the plasma membrane into early endosomes. In this instance, the channel is later moved along microtubules by the dynein motor to the membrane, a pathway that is regulated by interactions between Kv1.5 (requiring intact SH3 domains) and the dynein motor complex (64). It may not just be how much, but also where, Kv1.5 is expressed at the cell surface; compartmental expression of the channel in certain membrane regions may also influence the channel activity. A member of the recoverin family of Ca^{2+}-binding proteins, KChIP, has been extensively studied by Li *et al.* (12) and their evidence suggests that association with KChIP2 retards the trafficking of Kv1.5 from the ER to the cell surface. This was largely concluded from evidence in transiently co-transfected HEK293 cells expressing Kv1.5 and KChIP2 or KChIP1, which revealed significantly reduced current densities (approximately 75% and 25%, respectively); however, kinetics were indistinguishable compared to *KCNA5*-encoded channels alone. Furthermore, it is suggested that co-assembly of Kv1.5 with KChIP2 encodes for functional mouse ventricular IK_{slow1} and human atrial I_{Kur}.

Moreover, a precise regulation of the trafficking of specific Kv channel isoforms, including Kv1.5-expressing tetramers, to caveolae has been shown by Martens *et al.* Caveolae are lipid-rich regions of the membrane abundant in signaling complexes and are involved in the rapid integration of cellular signaling events. Kv1.5 channel association with specific lipid rafts targeting caveolae is

reversed by cholesterol and inhibition of sphingolipid synthesis, therefore permitting a targeted, compartmental expression of the Kv1.5 isoform at the plasma membrane (65). Furthermore, a recent study by McEwen *et al*. described a dynamic anterograde and retrograde trafficking of Kv1.5 channel proteins involving internalization to a perinuclear region, co-localization with the early endosomal marker EEA-1 and recycling back to the plasma membrane in myocytes (66).

Electrophysiological properties of the Kv1.5 channel

While ion channel activity can be severely impeded by restricted mRNA production and plasma membrane expression, there are many pharmacologically specific and nonspecific inhibitors that can retard Kv1.5 channel currents once the channel is functionally expressed at the cell surface. To precisely understand the actions of such inhibitors, it is essential to describe the basic characteristics of currents originating from homo- and heteromultimeric Kv1.5 channels.

Voltage-dependent homotetrameric Kv1.5 channels carry a large outward K^+ current which can be characterized by its kinetic profile and conductance. As previously mentioned, heterotetrameric channels may vary in their kinetic profile. Several studies have investigated the electrophysiological properties of the Kv1.5 channel using transfection of cell lines such as HEK293, CHO and *Xenopus* oocytes (18, 37, 67). These electrophysiological properties are summarized in Table I and Figure 3. In HEK293 cells transiently transfected with the human *KCNA5* gene, depolarization to a series of test potentials ranging from –60 to +80 mV revealed a large outward whole-cell current activating around –35 mV, resembling a delayed rectifier-type current (20). The current was sensitive to 4-AP, but relatively insensitive to external tetraethylammonium (TEA) and dendrotoxin (20, 68). However, as shown in Table I, the threshold for activation can range from –20 to –40 mV, half-activation potentials (V_a) from –0.2 to –19 mV and half-inactivation potentials (V_h) from –33 to –9.5 mV; these channels therefore have some heterogeneity in their currents. While such discrepancies may be accounted for by differences in cell lines and techniques, a study by Uebele showed that co-expression with a functional Kvβ2.1 subunit in HEK293 cells altered Kv1.5 function (37). In this study, where Kvβ2.1 was co-expressed, V_a was shifted by 13.9 mV and V_h by 12.5 mV to more negative potentials and the extent of the slow channel inactivation was increased. Similarly, the Kvβ1.3 subunit confers a hyperpolarizing shift in the activation kinetics, along with enhanced slow inactivation and increased deactivation time constants. The changes in inactivation were proposed to involve an open-channel blockade that is allosterically linked to the external pore (40). Furthermore, A-type K^+ currents displaying very rapid inactivation, present in neurons, cardiomyocytes and VSMCs, are blocked by correolide, flecainide and an anti-Kv1.5 antibody and are thought to arise due to co-expression of Kv1.5 with Kvβ1 or Kvβ3 subunits (69).

Inactivation of Kv channels can be split into three categories based primarily on the rate at which inactivation occurs. Fast (N-type) inactivation is brought about by occlusion of the inner pore by an NH_2-terminal region referred to as a “ball and chain” structure; slow (C-type)

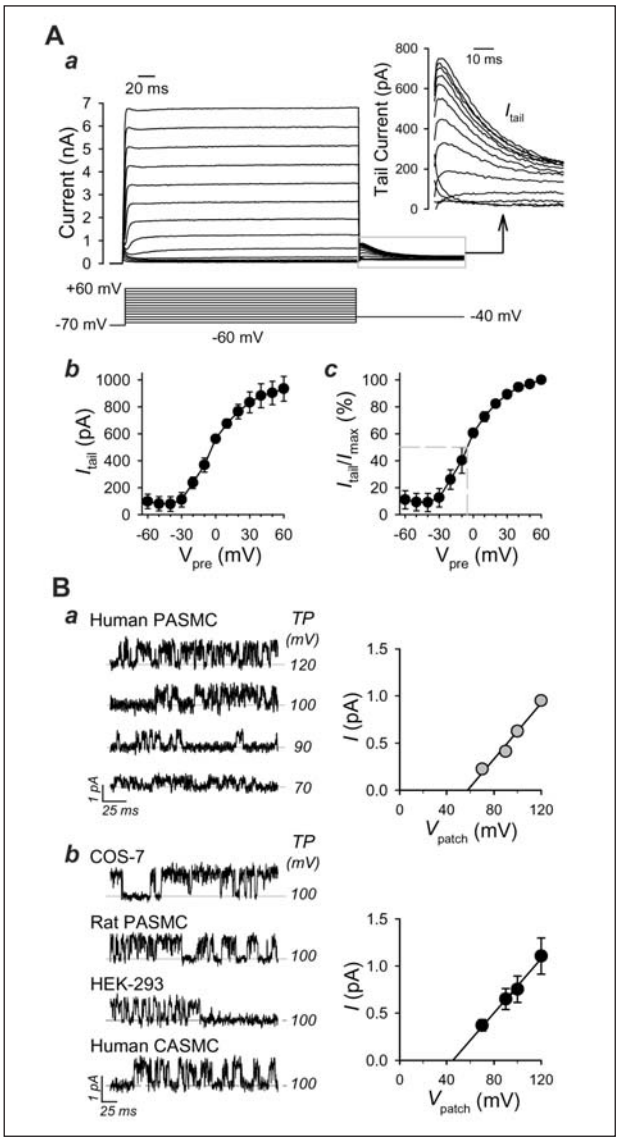

Fig. 3. Electrophysiological properties of the Kv1.5 channel. **Aa**: Representative trace of Kv1.5 expressed in HEK293 cells; the 300-ms steps represent increments of 20 mV from -60 to +60 mV from a holding potential of -70 mV. The tail currents shown in the insert are recorded by repolarization to -40 mV subsequent to each step pulse. Current-voltage relationship for Kv1.5 tail currents (**b**) and normalized tail currents (**c**). **B**: Representative traces for single channel openings of native Kv currents in the cell-attached mode in human pulmonary artery smooth muscle cells (PASMC) (**a**), rat PASMC and human coronary artery SMCs (CASMC) and as homotetrameric Kv1.5 channels expressed in COS-7 and HEK293 cell lines (**b**). TP represents the applied test potential. Current-voltage relationships for single channel openings are shown on the right of each panel. Reproduced with permission from Ref. 18.

Table I: Electrophysiological and pharmacological properties of Kv1.5 channels.

Expression system	Threshold	Act	Inact	4-AP IC_{50}	TEA IC_{50}	Single channel cond.	Ref.
Xenopus oocytes, hPCN1	–25 mV	V_a = –6 mV *k* = 6.4 mV	V_h = –25.3 mV *k* = 3.5 mV				22
CHO cells, hPCN1/ Kv1.5	–30 mV	V_a = –19 mV *k* = 6.5 mV	V_h = –33 mV *k* = 3.9 mV				67
L cells, HK2 gene		V_a = –14 mV *k* = 6.0 mV	V_h = –24 mV *k* = 3.7 mV	75% inhibition (500 μM)	16% inhibition (10 mM)		68
Xenopus oocytes, cKv1.5 cRNA	–40 mV		V_h = –21 mV *k* = 7.0 mV	211 μM	Extracellular > 10 mM Intracellular < 10 mM	9.8 pS	115
MEL cells, hKv1.5		V_a = –14 mV *k* = 12 mV		270 μM	330 mM	8 pS	97
HEK cells, Kv1.5		V_a = –0.2 mV *k* = 6.2 mV	V_h = –9.6 mV *k* = 5.2 mV				37
HEK cells, hKv1.5 (+Kvβ2.1)		V_a = –14.6 mV *k* = 5.6 mV	V_h = –22.1 mV *k* = 5.1 mV				37
HEK cells, COS-7 cells, *KCNA5* gene	–35 mV	V_a = –5.7 mV		> 70% inhibition (5 mM)		14.4 pS	18
HEK cells, hKv1.5	~ –20 mV	V_a = –8.9 mV *k* = 3.6 mV	V_h = –18.6 mV *k* = 4.5 mV				116

V_a, half-activation potential; *k*, time constant of activation/inactivation; V_h, half-inactivation potential.

inactivation involves rigorous constriction of the outer mouth of the channel pore and occurs independent of voltage from –25 to +50 mV (70), and U-type inactivation is caused by a preferential inactivation from channel closed states (during 10-s depolarization) (71, 72). U-type inactivation occurs *in vivo* by truncation of a 209-amino-acid segment in the *C*-terminal of Kv1.5 in cardiac cells, with ~35% greater inactivation (73). Altered gating of the channel imposed by Kv1.5 channels undergoing C- or U-type inactivation can therefore cause distinct changes in Kv1.5 channel function. Interactions of the T1 domain may power U-type inactivation in Kv1.5 channels (13), whereas C-type inactivation may arise due to the presence of a Kv1.5 turret region (74). Using a substituted cysteine accessibility method (SCAM) analysis, a discrete region of the pore turret (the TM-5-P linker) that decreased the current amplitude and increased the rate of inactivation in Kv1.5 was revealed (74). An additional gating mechanism involves the TM-6 segment; mutations in the cytoplasmic side of this transmembrane region drew attention to a highly conserved Pro-X-Pro sequence. Changes in the open state probability influenced the movement of TM-6 during channel gating (75).

Conventional K^+ channel blockers and novel selective inhibitors of the Kv1.5 channel

The most commonly utilized Kv channel blockers are 4-AP, TEA and correolide. As shown in Figure 4, Kv1.5 currents are significantly reduced by both of these agents. Correolide (1-10 μM) is a nortriterpene purified from *Spachea correae* that acts to selectively block the Kv1 family of potassium channels (76). Correolide inhibited Kv currents, particularly those carried by Kv1.5-encoded channels, by approximately 70% at +60 mV in both pulmonary and retinal artery smooth muscle cells (18, 69). 4-AP blocks Kv1.5 channels with high affinity (IC_{50} = 50 μM) from the cytoplasmic side of the membrane (77). Both binding and dissociation of 4-AP from the channel require channel opening, although it may also bind to the closed and resting states subsequent to deactivation. TEA is widely used to study Kv channels; however, it is less selective and used to block both Ca^{2+}-activated K^+ channels and Kv channels. Its inhibition of Kv1.5 is similar to that of 4-AP and involves an intracellular block of the channel pore (77). Alternatively, an extracellular block may arise subsequent to K^+ binding in the pore, causing a conformational change and enabling TEA to bind (78).

Given their functional importance and potential as clinical targets, an array of novel inhibitors have been specifically designed to target Kv1.5 channels. While many more examples may exist, a selection of these drugs is mentioned below.

Antiarrhythmic effects were predicted for the furocoumarin derivatives psoralen and oxypeucedanin due to their inhibitory effects on human Kv1.5 channels and prolongation of the action potential duration (79, 80). Oxypeucedanin potently inhibits the open channel in a concentration- and voltage-dependent manner, with an IC_{50} of 76 nM. Since these initial studies, more derivatives have been developed to enhance selectivity and potency against Kv1.5. One derivative with enhanced efficacy inhibited Kv 1.5 channels with an IC_{50} of 27.4 nM in a concentration-, use- and voltage-dependent manner, and it accelerated inactivation and slowed deactivation of the channel (80). Other drugs also conferring an open-channel block with acceleration of inactivation kinetics and slowing of deactivation include: torilin, purified from *Torilis*

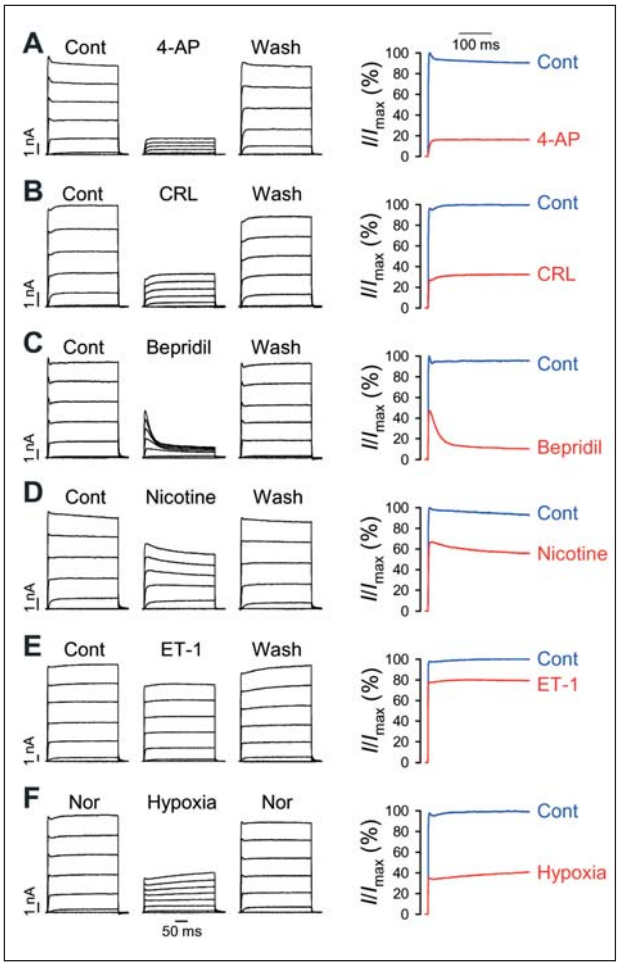

Fig. 4. Pharmacological effects of various drugs and chemicals on the Kv1.5 channel. Traces are elicited by 300-ms step depolarizations from a holding potential of -80 mV and stepping from -60 mV to +60 mV in 20-mV increments. Representative $I_{K(V)}$ traces in control, test and after washout are shown on the left of each panel and normalized currents at a test potential of +60 mV comparing control (blue) and test (red) conditions for each inhibitor as shown on the right for: 4-AP 5 mM (**A**), correolide 1 μM (CRL) (**B**), bepridil 25 μM (**C**), nicotine 100 nM (**D**), ET-1 100 nM (**E**) and acute hypoxia, P_{O2} 22-40 mmHg for 30 min (**F**). **A-E** are homomultimetic Kv1.5 channels expressed in mammalian cell lines, **F** are recorded from human pulmonary artery smooth muscle cells (PASMCs). **B-E** and **F** are reproduced with permission from Refs. 18 and 110, respectively.

japonica, which inhibits the human Kv1.5 channel in a time- and voltage-dependent manner with an IC_{50} value of 2.51 μM at +60 mV (81), and S-9947, which exhibits IC_{50} values 0.42 μM in Kv1.5-transfected CHO cells and of 0.96 μM in human atrial myocytes (82). Open-channel blockade was also the mechanism of action of frequency-dependent Kv1.5 block by diphenylphosphine oxide (DPO) compounds (83); the high potency and resulting prolonged repolarization of these compounds are expected to be useful in the treatment of supraventricular arrhythmias. Finally, NIP-142, with an IC_{50} of 4.75 μM, was likewise shown to prolong the atrial refractory period and to have potential in treating atrial fibrillation; however, NIP-142 differs in its mechanism of action, showing frequency independence, and it may block both the open and closed channel states (84).

Nonselective antagonists of the Kv1.5 channel

In addition to the conventional K^+ channel blockers and selective Kv1.5 channel blockers, many drugs exert inhibitory effects on the Kv1.5 current in addition to their specific targets. For example, extracellular application of nicotine, ET-1, 5-HT, pergolide, loratadine, phenylephrine and bepridil significantly and reversibly reduced Kv1.5 currents, and nicotine and bepridil accelerated the $I_{K(V)}$ inactivation kinetics as well (see Figure 4) (18, 85-90). While it is beyond the scope of this review to discuss each potential inhibitor of Kv1.5 channels in detail, several examples will be discussed below. In addition, Table II provides a comprehensive (although not completely exhaustive) list of known Kv1.5 blockers.

One class of drugs having potent Kv1.5-inhibitory effects are the antiarrhythmics. Class I agents such as quinidine and propafenone, and class III agents such as amiodarone, bertosamil and clofilium, reduce Kv1.5-dependent $I_{K(V)}$, although the mechanisms by which this is achieved are varied. Drug-induced modulation of *KCNA5* expression occurs with chronic amiodarone treatment; Kv1.5 mRNA is significantly downregulated in rat hearts (91). On the other hand, clofilium causes an open-channel blockade of Kv1.5 channels, reducing currents by 80%. It is proposed that the permanently charged compound is trapped within closed channels near the conductivity pore by an “activation trap” mechanism (92, 93). Quinidine, propafenone and its metabolite 5-hydroxypropafenone all produced voltage-dependent block with similar potency (K_D = 0.2-4.4 μM). Studies into their effects on gating currents confirmed an open-channel block (94, 95).

Ca^{2+} channel blockers such as nifedipine (96, 97), diltiazem (98) and bepridil (17), generally used in the treatment of angina and hypertension, all decrease $I_{K(V)}$. When expressed in CHO cells, Kv1.5 channels were inhibited by diltiazem at therapeutic concentrations of 0.01 nM-500 μM in a biphasic manner. Diltiazem also caused a hyperpolarizing shift in both inactivation and activation curves of Kv1.5 currents. All three drugs (nifedipine, diltiazem and bepridil) block Kv1.5 in the open-channel state; diltiazem also binds to the inactive state. It is interesting to note that block of Kv1.5 by nifedipine and C-type inactivation can co-exist, as they are mediated by different mechanisms dependent on the outer pore conformation of the channel (96). Other antianginal agents, such as mibefradil and perhexiline, also decrease Kv1.5 currents when the channel is expressed in mammalian cell lines (99, 100). Both these agents induce a time- and voltage-dependent block and bind to the open-state channel at concentrations within the therapeutic range. When studied on native channels in human atrial myoctes, the effects on the ultrarapid delayed rectifier currents were

Table II: Inhibitors of the Kv1.5 channel.

Inhibitor	Action on Kv1.5	Cell/tissue	Ref.
Transcriptional			
Bcl-2	$\downarrow I_{K(V)}$, downregulates mRNA	Rat pulmonary artery smooth muscle cells (PASMCs)	21
Survivin	$\downarrow I_{K(V)}$	PAH pulmonary arteries	109
Membrane depolarization (extracellular KCl)	Downregulates mRNA, inhibits gene transcription and protein synthesis	Clonal pituitary cells	117, 118
Anorexigenic agents (aminorex, phentermine, dexfenfluramine, sibutramine, fluoxetine)	$\downarrow I_{K(V)}$, inhibits gene transcription and mRNA instability	PASMCs and mammalian cell lines	19
Nicotine and cigarette smoke	$\downarrow I_{K(V)}$, downregulates mRNA, inhibits protein synthesis	Rat bronchial SMCs *in vivo* and PASMCs	18, 59
Kv1.5 repressor element (KRE)	Regulation of cell-specific expression of Kv1.5	GH_3 clonal pituitary cells	10
Thyrotropin-releasing hormone (TRH)	Downregulates mRNA and protein expression	Clonal pituitary cells	54, 55
Thyroid hormone	Downregulates mRNA	Cardiac myocytes	53
Trafficking			
KChIPs	$\downarrow I_{K(V)}$ and $\downarrow$trafficking to plasma membrane	Transiently transfected HEK cells	12
S-Acylation	$\downarrow$trafficking to plasma membrane	Transfected fibroblasts	63
Subunit co-assembly			
Kvβ1.2 subunit	$\downarrow I_{K(V)}$	*Xenopus* oocytes	45
Kvβ1.3 subunit			
Kvβ2.1 subunit	Changes Kv1.5 α-subunit function	HEK293 and mouse L cells expressing hKv1.5	37
Kvβ3.1 subunit	Changes Kv1.5 α-subunit function, A-type currents	CHO cells	43
Src tyrosine kinase	$\downarrow I_{K(V)}$	Human myocardium and astrocytes expressing cloned and native hKv1.5	46-48
Conventional Kv inhibitors			
4-Aminopyridine	$\downarrow I_{K(V)}$, direct open-channel block	HEK cells, rabbit portal vein myocytes	33, 77, 115
TEA chloride	$\downarrow I_{K(V)}$, direct open-channel block	HEK cells expressing hKv1.5	77
Nonselective Kv1.5 inhibitors			
Ions			
Nickel (Ni^{2+})	$\downarrow I_{K(V)}$, preferentially in the resting or inactivated state	CHO cells	108
Zinc (Zn^{2+})	$\downarrow I_{K(V)}$ and gating shift (actions in external mouth of the pore)	HEK cells	106, 107
Internal Mg^{2+}	$\downarrow I_{K(V)}$, voltage-dependent current decay at strongly depolarized potentials - open-channel block	HEK and mouse Ltk^- cells	105
Phosphorylation			
Tyrphostin AG-1478, a potent protein tyrosine kinase (PTK) inhibitor	$\downarrow I_{K(V)}$, open-channel block and acceleration of inactivation decay	CHO cells stably transfected with rat brain Kv1.5	49
Bisindolylmaleimide (BIM), a protein kinase C (PKC) inhibitor	Phosphorylation-independent $\downarrow I_{K(V)}$	CHO cells	38

Continuation

Table II (Cont.): Inhibitors of the Kv1.5 channel.

Inhibitor	Action on Kv1.5	Cell/tissue	Ref.
Toxins			
Sarafotoxin S6c, an ET_B agonist	$\downarrow I_{K(V)}$, gradual	PASMCs	104
Resiniferatoxin (CHTX, DTX, NTX, KTX)	$\downarrow I_{K(V)}$, variable IC_{50}	MEL cells stably transfected with hKv1.5	97
Receptor agonists/antagonists			
ET-1	$\downarrow I_{K(V)}$	PASMCs	18
Phenylephrine, an α-adrenoceptor agonist	$\downarrow I_{K(V)}$	Human atrial myocytes	85
5-HT (serotonin)	$\downarrow I_{K(V)}$	PASMCs and Ltk^- cells	86
Pergolide, a dopamine D1 and D2 agonist	$\downarrow I_{K(V)}$	Isolated perfused rat lung, rat and human PASMCs	87
Loratadine, ebastine, terfenadine, rupatadine (H_1 antagonists)	$\downarrow I_{K(V)}$, enhances $I_{K(V)}$ decay, $\downarrow$open frequency	HEK or mouse Ltk cells stably expressing Kv1.5	88-90
Anesthetics			
Benzocaine	$\downarrow I_{K(V)}$	Cardiac hKv1.5 channel cloned from human ventricle	119
Bupivacaine	$\downarrow I_{K(V)}$, stereoselective open-channel block	Mouse Ltk cells transfected with cardiac hKv1.5	102, 120, 121
Ca^{2+} channel antagonists			
Diltiazem	$\downarrow I_{K(V)}$, at therapeutic concentrations	CHO cells	98
Nifedipine	$\downarrow I_{K(V)}$, direct open-channel block		96, 97
Bepridil	$\downarrow I_{K(V)}$, action potential repolarization delay	Rat atrial myocytes and HEK cells stably transfected with cardiac hKv1.5	17
Antiarrhythmics			
Amiodarone	$\downarrow I_{K(V)}$, downregulates mRNA, action potential repolarization delay	Papillary muscles, rabbit/guinea pig ventricular cells	91
Clofilium	$\downarrow I_{K(V)}$, accelerates inactivation	CHO cells, *Xenopus* oocytes	92, 93
Quinidine	$\downarrow I_{K(V)}$, voltage-dependent, direct open-channel block, modulated by Kvβ1.3	HEK cells expressing hKv1.5	94, 115, 122
Propafenone and 5-hydroxypropafenone	$\downarrow I_{K(V)}$, concentration-, voltage-, time- and use-dependent	Cardiac hKv1.5-transfected mouse Ltk cells	95
Bertosamil	$\downarrow I_{K(V)}$, direct open-channel block, acceleration of inactivation	CHO cells	113
Antianginal agents			
Mibefradil	$\downarrow I_{K(V)}$, concentration-, voltage-, time- and use-dependent	CHO cells stably expressing cardiac hKv1.5	99
Perhexiline	$\downarrow I_{K(V)}$	HEK cells	100
Antifungal agents			
Ketoconazole (fungicide) and terfenadine	$\downarrow I_{K(V)}$	*Xenopus* oocytes	123
Clotrimazole and ketoconazole, cytochrome P-450 inhibitors	$\downarrow I_{K(V)}$, clotrimazole (open-state block) and ketoconazole (closed-state block)	Rabbit portal vein myocytes expressing native and cloned Kv1.5	124
Fatty acids			
Long-chain polyunsaturated fatty acids, *e.g.*, arachidonic acid, docosahexaenoic acid	$\downarrow I_{K(V)}$, direct open-channel block	Cardiomyocytes	125

Continuation

Table II (Cont.): Inhibitors of the Kv1.5 channel.

Inhibitor	Action on Kv1.5	Cell/tissue	Ref.
Fatty acids			
Linoleic acid	Increased current activation and current inhibition rates - outer pore effects	CHO cells	126
Others			
Papaverine, a vasodilator	$\downarrow I_{K(V)}$, voltage- and time-dependent	Cardiac hKv1.5-transfected Ltk cells	101
Riluzole, a neuroprotectant	$\downarrow I_{K(V)}$, voltage- and time-dependent, accelerated deactivation kinetics	CHO cells	127
Cytochalasins A and B, actin-disrupting agents	$\downarrow I_{K(V)}$	Ltk cells and human atrial myocytes stably expressing hKv1.5	128
FCCP, mitochondria	$\downarrow I_{K(V)}$	PASMCs	129, 130
Novel selective Kv1.5 inhibitors			
Psoralen, a furocoumarin derivative	$\downarrow I_{K(V)}$, open-channel block, action potential repolarization delay	Ltk^- cells, rat atrial muscles stably expressing cardiac hKv1.5	79, 80
Torilin	$\downarrow I_{K(V)}$, voltage- and time-dependent, accelerated deactivation kinetics, open-channel block	Cardiac hKv1.5-transfected Ltk cells	81
S-9947	$\downarrow I_{K(V)}$, action potential repolarization delay	Rat ventricular and human atrial cardiomyocytes	82
ortho,ortho-Disubstituted bisaryl compounds	$\downarrow I_{K(V)}$, direct channel block	*Xenopus* oocytes	131
Diphenylphosphine oxide (DPO) compounds	$\downarrow I_{K(V)}$, concentration-dependent, open-channel block	CHO cells, human atrial myocytes and *Xenopus* oocytes expressing hKv1.5	83
NIP-142	$\downarrow I_{K(V)}$	HEK cells expressing hKv1.5	84
Correolide	$\downarrow I_{K(V)}$	PASMCs	18, 76

somewhat slower, with a steeper dependence on voltage; this effect may be due to inhibition of more than one Kv channel isoform present in these cells (100). Papaverine, a vasodilating agent, inhibited native and expressed Kv1.5 channels in a time- and voltage-dependent manner, with an IC_{50} value of 43.4 μM at +60 mV, due to an open-channel block and a potential role in altering cardiac excitability (101).

Local anesthetics such as bupivacaine reduced the peak amplitude of Kv1.5 currents in a stereoselective manner, with a block of ~30% and 80%, respectively, and K_D values of 27.3 and 4.1 μM, respectively, for the (–)-(*S*)- and (+)-(*R*)-enantiomers (102). Benzocaine has interesting actions; at lower nanomolar concentrations, Kv1.5 currents are enhanced, whereas micromolar concentrations induce blockade. By performing a series of mutations in the inner mouth of the pore (*e.g.,* T477S, T505A, L508M and V512M), the blocking effects of benzocaine were increased, suggesting a low-affinity binding site in this region. Furthermore, when benzocaine and bupivacaine were combined, the Kv1.5 currents were attenuated as compared to in the presence of bupivacaine alone (103).

Many toxins derived from the venoms of scorpions, snakes and spiders have potent inhibitory effects on ion channel currents. Toxins with the ability to decrease Kv1.5 channel currents include sarafotoxin, charybdotoxin, dendrotoxin, resiniferatoxin, netusistoxin and kaliotoxin (97, 104). Ions themselves can also be effective in preventing the efflux of K^+ ions through Kv1.5 channels. Intracellular Mg^{2+} blocks Kv1.5 channels, particularly at more depolarized potentials, causing acceleration of C-type channel inactivation. At an increased internal Mg^{2+} concentration, a voltage-dependent open-channel block occurs where Mg^{2+} restricts access of K^+ into the selectivity filter (105). In Kv1.5, Zn^{2+} binds to one of two independent binding sites, one of which results in a reduction of current and the other in a shift in the channel gating (106, 107), and Ni^{2+} can decrease $I_{K(V)}$ by preferentially binding to the channel in the resting or inactivated state (108).

Conclusions

Given the crucial functional roles that Kv1.5 channels play in neurons, cardiac myocytes and VSMCs (Table III), it is of utmost importance that the mechanisms involved in regulating the expression, structure, function, gating and inhibition of Kv1.5 channels are fully understood. Kv1.5 channels are of notable importance in pulmonary arterial hypertension (109, 110), cancer (111, 112) and cardiac arrhythmias (84, 113, 114) and have great

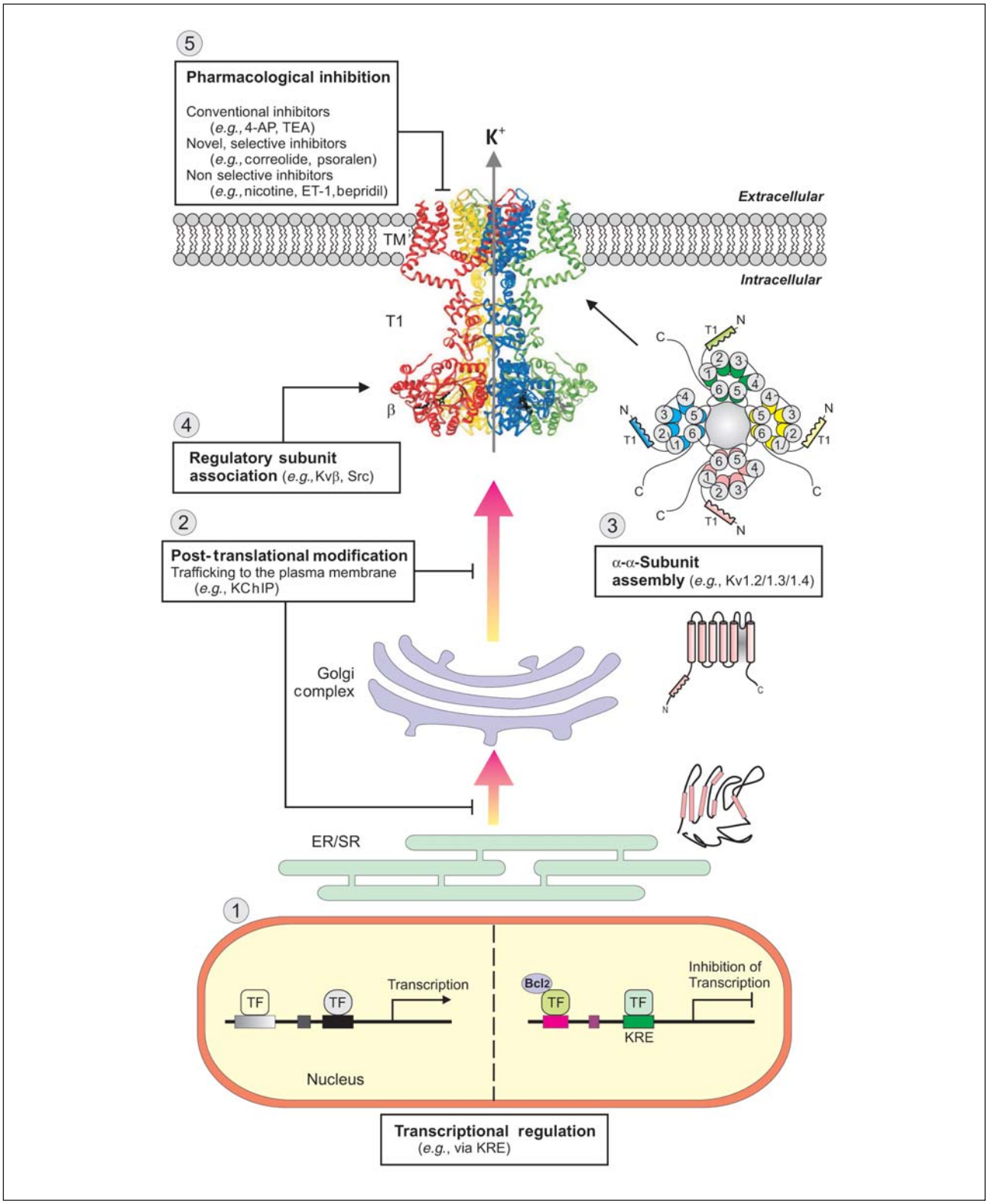

Fig. 5. A diagrammatical representation of possible inhibitory regulation of Kv1.5 channels. Expression of Kv1.5 channels can be modified by: **1**) inhibition of transcription through binding of KRE or the antiapoptotic protein Bcl-2; **2**) post-translational modifications retarding transport of the protein from the endoplasmic reticulum (ER)/Golgi complex to the plasma membrane; **3**) α-α-subunit assembly; Kv1.5 may associate in a functional tetramer with Kv1.2, Kv1.3 or Kv1.4 α-subunits; **4**) regulatory subunit co-assembly with Kv β-subunits or Src tyrosine kinase; and **5**) pharmacological inhibition. Pharmacological inhibition may occur through several mechanisms, including decreasing conduction and open probability, increasing inactivation or increasing activation threshold.

Table III: Pathological rolse of the Kv1.5 channel.

Disease	Expression	Function	Location	Ref.
Idiopathic pulmonary arterial hypertension (IPAH)	Decrease	Decrease	Pulmonary artery smooth muscle cells (PASMCs)	18, 132
Atrial fibrillation	Decrease	Decrease	Atrial myocytes	29, 133, 134
Paroxysmal atrial tachycardia	Transient increase		Atria	135, 136
Hyperthyroidism	Increase	Increase	Atria, ventricle	137, 138
Gliomas	Increases with increased severity			112
Colonic cancer	Increase			111

promise as targets for the treatment of many pathophysiological disorders, particularly atrial fibrillation and arrhythmias. As can be seen from this review, there are many potential pathways and inhibitors currently available to regulate Kv1.5 channel function.

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Online links

Subscribers to the on-line version of *Drugs of the Future* and/or Integrity® can access the animation: Role of K^+, Na^+ and Ca^{2+} Channels in the Propagation of Neuronal Action Potentials.

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