

Neuronal and Cardiovascular Potassium Channels as Therapeutic Drug Targets: Promise and Pitfalls

Journal of Biomolecular Screening
2015, Vol. 20(9) 1055–1073
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Automation and Screening
DOI: 10.1177/1087057115601677
jbx.sagepub.com



Edward S. A. Humphries¹ and Caroline Dart¹

Abstract

Potassium (K⁺) channels, with their diversity, often tissue-defined distribution, and critical role in controlling cellular excitability, have long held promise of being important drug targets for the treatment of dysrhythmias in the heart and abnormal neuronal activity within the brain. With the exception of drugs that target one particular class, ATP-sensitive K⁺ (K_{ATP}) channels, very few selective K⁺ channel activators or inhibitors are currently licensed for clinical use in cardiovascular and neurological disease. Here we review what a range of human genetic disorders have told us about the role of specific K⁺ channel subunits, explore the potential of activators and inhibitors of specific channel populations as a therapeutic strategy, and discuss possible reasons for the difficulty in designing clinically relevant K⁺ channel modulators.

Keywords

K⁺ channels, ion channels, channelopathies, cardiac, neuronal, vascular, drug development, review

Potassium Ion Channels

Potassium (K⁺) channels are a large family of integral membrane proteins that form aqueous pores in cell membranes through which K⁺ can flow. They are unique among ion channels in that they are found in virtually all types of cells in all organisms where they perform a range of biological functions. In the human genome, K⁺ channels are by far the largest and most diverse of the ion channel families, with almost 80 different genes encoding the principal pore-forming subunits (**Fig. 1**).^{1–4} In most cells, they play an essential role in maintaining and stabilizing the resting membrane potential. The opening of K⁺ channels, which occurs in response to a range of different signals, leads almost universally to the efflux of K⁺ from the cell, causing the membrane potential to become more negative. In nerve and muscle cells, their ability to repolarize or hyperpolarize the membrane helps them control action potential frequency and duration, while other functions include regulation of neurotransmitter release and hormone secretion, potassium homeostasis, epithelial electrolyte transport, cell proliferation, apoptosis, and tumor progression.^{5–8}

Disruption of genes encoding K⁺ channel subunits and subsequent loss or gain of channel function is linked to a range of human diseases, including hyperinsulinemia, disturbances of the heart rhythm, and some types of epilepsy.^{5,9,10} K⁺ channels can also be subject to pathological inhibition by autoantibodies, leading to diseases such as acquired neuromyotonia¹¹ and certain forms of epilepsy and encephalitis.^{12–15} These disorders

have often helped to clarify the roles of particular channel populations within complex physiological systems and raise the possibility that activation or inhibition of selective K⁺ currents within cells could be a viable therapy. Indeed, K⁺ channel modulators are common medicines in certain diseases¹⁶; for example, in the treatment of diabetes, the oral antihyperglycemics such as glibenclamide, nateglinide, and glipizide all inhibit adenosine triphosphate (ATP)-sensitive (K_{ATP}) channels. Most of the type III antiarrhythmics, including amiodarone, increase the cardiac refractory period by blocking several different types of K⁺ channel.¹⁷ In both epilepsy and hypertension, there are examples of drugs that target K⁺ channels.¹⁶ However, considering the scope for clinical impact, their membrane localization, diversity, and often defined tissue distributions, K⁺ channels remain underexploited as a target in drug discovery. This may be due to a number of factors. The sheer diversity of K⁺ channel subunits and their ability to form heteromultimeric complexes with different pore-forming subunits and accessory proteins means that the precise composition of functional channels within a particular tissue *in vivo* is often

¹Institute of Integrative Biology, University of Liverpool, UK

Received May 31, 2015, and in revised form July 26, 2015. Accepted for publication July 28, 2015.

Corresponding Author:

Caroline Dart, Institute of Integrative Biology, University of Liverpool, Crown Street, Liverpool L69 7ZB, UK.
Email: c.dart@liv.ac.uk

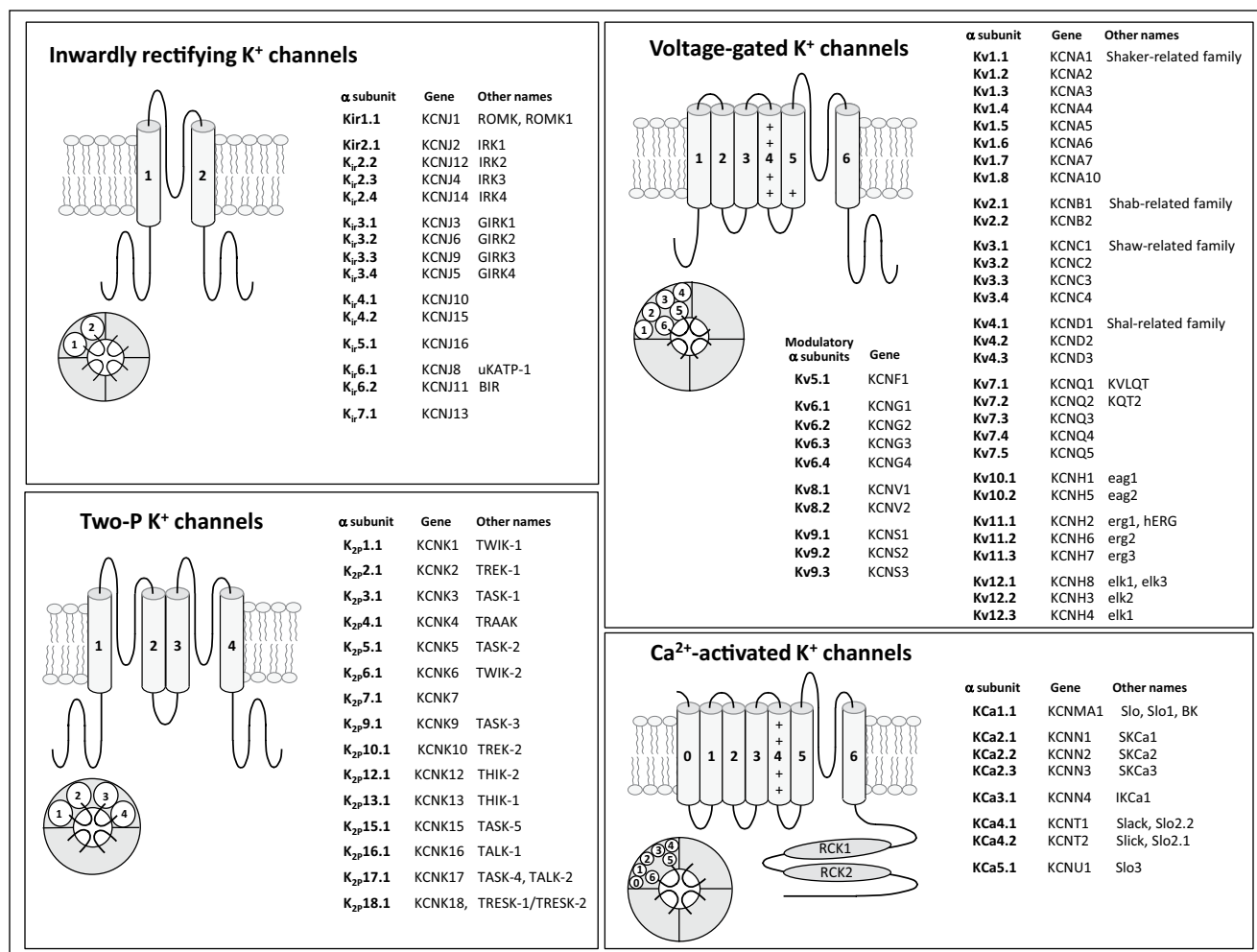


Figure 1. Schematic structure of the four main K⁺ channel classes as described by the International Union of Pharmacology.¹⁻⁴ RCK, regulator of conductance for K⁺.

ill-defined. This makes predicting the functional outcome of channel loss or activation difficult and leads to unpredictable side effects even for specific activators/inhibitors. Drug screening programs also seem to find it difficult to identify selective channel activators. The direct measurement of ion channel activity by manual patch clamping is the best approach for assaying ion channel function but is time-consuming and unsuited to high-throughput screening (HTS). HTS techniques such as ligand binding or ion flux assays, on the other hand, lack the complexity or resolution to detect subtle shifts in channel-gating kinetics that functionally may have profound effects on channel activity. The introduction of screening methods based around fluorometric dyes, which measure changes in ion concentration or cell membrane potential, coupled to fluorescent plate readers with in-built electrical field stimulators, has improved temporal resolution but still represents an indirect measurement of channel activity.¹⁸ More recent advances in automated electrophysiology using planar-array patch-clamp technology circumvent many of the problems of functional resolution and have the potential to screen large

compound libraries,¹⁹ and yet selective compounds remain elusive. One reason for this may be that channel modifiers often need to bind to relatively inaccessible sites within the channel pore or in clefts on or near regulatory domains. These sites may be relatively unforgiving to small structural changes within compounds, making chemical optimization of lead structures difficult. In this context, it is interesting to note that the K⁺ channel family that has the highest proportion of clinically used activators/inhibitors is the ATP-sensitive K⁺ (K_{ATP}) channel family where modifiers appear to work by interacting at exposed peripheral sites on accessory subunits.²⁰

Given their newly discovered roles in regulating cell proliferation and promoting tumor progression, drugs acting on K⁺ channels are likely to be of increasing clinical relevance.^{7,21-23} Here we review what disease-causing genetic disruption of specific K⁺ channel subunits in humans has told us about the functional role of K⁺ channels, explore the potential of selective activators and inhibitors as a therapeutic strategy, and further discuss possible reasons for the difficulty in designing clinically relevant K⁺ channel modulators. Due to the breadth of the

field, we have limited our scope to K^+ channels within cells of the human nervous and cardiovascular systems. A number of excellent recent reviews exist on disease-causing mutations in K^+ channels within tissues such as the pancreas and nonvascular muscle and the role of drugs that target these channels. We will direct the reader to these, and others, throughout.

K^+ Channel Diversity

Structurally, K^+ channels form from the association of (usually) four pore-forming α subunits often in association with modulatory accessory subunits. They can be grouped into the following four major classes¹⁻⁴ (**Fig. 1**):

1. **Inwardly rectifying K^+ (K_{ir}) channels.** In terms of structure, the K_{ir} family is the simplest K^+ channel, with each subunit formed of just two transmembrane domains separated by a pore-forming region. These subunits form tetramers (four subunits) to produce functional K_{ir} channels.²⁴ The family consists of the strong inwardly rectifying potassium channels ($K_{ir2.x}$), the G protein-activated inwardly rectifying potassium channels ($K_{ir3.x}$), and ATP-sensitive potassium (K_{ATP}) channels (formed from $K_{ir6.x}$ and accompanying regulatory sulfonylurea receptor [SUR] subunits). Functionally, all members of this family possess some degree of inward rectification, a characteristic asymmetrical K^+ conductance whereby K^+ moves more easily into the cell than out.^{25,26} They tend to be active around E_K and thus help set and maintain the resting membrane potential but close in the face of large depolarizations so as not to oppose membrane excitation. For excellent in-depth reviews on K_{ir} channels, see Ashcroft⁵ or Hibino et al.²⁷
2. **Two-P K^+ channels.** These channels have four transmembrane domains and two pore (P) domains per subunit and are therefore referred to as “tandem” or “twin” pore K^+ channels (K_{2p}). The functional channel probably forms as a dimer. Family members include the TWIK ($K_{2p1.1}$), TREK ($K_{2p2.1}$), TASK ($K_{2p3.1}$), THIK ($K_{2p13.1}$), TALK ($K_{2p16.1}$), and TRESK ($K_{2p18.1}$) channels and constitute “leak” K^+ conductances.²⁸ They are regulated by various stimuli such as pH, O_2 partial pressure, membrane stretch, temperature, G proteins, fatty acid, and inhalation anesthetics.^{29,30}
3. **Voltage-gated K^+ channels.** These include several important subfamilies: the Shaker, Shab, Shaw, and Shal-related K^+ channels ($K_v1.x$, 2.x, 3.x, and 4.x, respectively); the KCNQ channels ($K_v7.x$); and the eag, erg, and elk channels ($K_v10.x$, 11.x, and 12.x, respectively). These channels possess six transmembrane domains per subunit with a voltage sensor on the fourth transmembrane segment (S4), which allows

them to detect and open in response to membrane depolarization.^{31,32} As such, they tend to play roles in repolarizing membranes in nerve and muscle cells, thus controlling action potential frequency and duration. Four α -subunits come together to form the pore-forming region of the channels and α -subunits usually associate with accessory subunits to form functional channels.

4. **Ca^{2+} -activated K^+ channels.** These share a similar structure to the voltage-gated K^+ channels but possess an extra transmembrane domain, named S0, involved in regulation by β subunits. The family consists of Ca^{2+} -activated Slo (BK) channels ($K_{Ca1.x}$, 4.x, 5.x) and the Ca^{2+} -activated SK ($K_{Ca2.x}$) and IK ($K_{Ca3.x}$) channels. These channels are regulated not only by voltage but also by intracellular Ca^{2+} ; BK_{Ca} channels possess a “calcium bowl” region at the C-terminus, while SK/IK_{Ca} channels are modulated by the calcium binding protein calmodulin.^{33,34}

The diversity of K^+ channels and ability for different subunits within a family to associate to form heteromers often makes it difficult to determine the molecular makeup of channel populations in vivo and thus to assign functional roles. This has been aided to some extent by investigations into human channelopathies, a range of diseases where the genetic disruption of channel subunit activity leads to a distinct phenotype.

Neuronal K^+ Channels

Due to the equilibrium potential for K^+ (mammalian cells ~ -85 mV), the opening of K^+ channels generally mediates outward K^+ currents that act to dampen cellular excitability. Loss of function of several types of K^+ channel is thus associated with conditions characterized by neuronal hyperexcitability. This includes several forms of epilepsy (**Table 1**), a disorder characterized by abnormal firing of neuronal networks within the brain due to an imbalance between network excitation and network inhibition.

$K_v1.1$ -Containing Channels

The K_v1 family includes mammalian homologues of the Shaker K^+ channels originally cloned in *Drosophila* where mutation of the Shaker (Sh) gene leads to a characteristic trembling of the legs following etherization.³⁵ $K_v1.1$ is known to associate with other Shaker-related channels ($K_v1.2$, $K_v1.4$) to form heteromeric channel complexes in various regions of the brain where they control neuronal excitability, action potential propagation, and synaptic transmission (**Fig. 2**).⁶ In humans, a single loss-of-function mutation of $K_v1.1$ is associated with episodic ataxia type 1 (EA1), an autosomal dominant neurological condition

Table 1. Neuronal K⁺ Channelopathies.

Protein	Disease	Gene	Effect on Current	Reference
K _v 1.1	Episodic ataxia I	KCNA1	Loss	36
K _v 3.3	Spinocerebellar ataxia type 13	KCNC3	Loss	42
K _v 4.3	Spinocerebellar ataxia type 19	KCND3	Loss	168
K _v 4.2	Temporal lobe epilepsy	KCND2	Loss	46
K _v 7.1	Jervell and Lange-Nielsen syndrome	KCNQ1/KCNE1	Loss	105, 169–172
K _v 7.2/7.3	Benign familial neonatal convulsions	KCNQ2/3	Loss	52–54
K _v 7.3	Autism spectrum disorders	KCNQ3	Loss	55
K _v 7.4	Autosomal dominant nonsyndromic sensorineural hearing loss DFNA2	KCNQ4	Loss	60, 61
K _v 10.1	Temple-Baraitser syndrome	KCNH1	Gain	173
K _{Ca} 1.1	Autism spectrum disorders	KCNMA1	Loss	174
K _{Ca} 1.1	Generalized epilepsy with paroxysmal dyskinesia	KCNMA1	Gain	79
K _{Ca} 4.1	Epilepsy of infancy with migrating focal seizures	KCNT1	Gain	175
K _v 11.1	Epilepsy	KCNH2	Loss	176, 177
K _{ir} 4.1	SeSAME syndrome (EAST syndrome)	KCNJ10	Loss	93–95
K _{ir} 6.2	Development delay, epilepsy and neonatal diabetes	KCNJ11	Gain	97
NA	Acquired neuromyotonia	NA		10

EAST, epilepsy, ataxia, sensorineural deafness, and tubulopathy; NA, not applicable; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance.

characterized by continuous involuntary muscle quivering (myokymia) and bouts of severe contractions of head and limb muscles, leading to loss of coordination and balance.³⁶ Seizures have been linked to dysfunction of neuronal networks within the hippocampus, a region of the brain located in the medial temporal lobe and often associated with epileptic seizure. Channels containing the K_v1.1 subunit have been identified in both the axons and synaptic terminals of hippocampal neurons in the rat, and mutations associated with EA1 in humans cause reduced current amplitude and a positive shift in voltage activation of K_v1.1-containing channels, consistent with reduced channel activity.^{37,38}

K_v1 Modulators as Drugs

Researchers at Wyeth, now part of Pfizer (New York, NY), have published on novel small-molecule inhibitors of protein-protein interactions that act to modulate K_v1.1 activity by blocking channel inactivation.³⁹ In the hippocampus, K_v1.1 is coexpressed with accessory K_vβ1 subunits, which convert K_v1.1 from a slowly inactivating delayed rectifier-type current into a fast inactivating current. This increases neuronal excitability by reducing the sustained hyperpolarizing current that flows through K_v1.1 and increasing the ability of the neuron to fire repetitively. A novel approach to reducing neuronal excitability is therefore to prevent inactivation of K_v1.1 channels. A yeast two-hybrid screen identified a number of small-molecule “disinactivators” that most likely interact with sites on the K_vβ1 N-terminus or its receptor site on K_v1.1 and prevent it binding and inhibiting

K_v1.1 channels.³⁹ It is suggested that drugs based on these disinactivators may ultimately be useful for preventing inactivation of K_v1.1 channels in the brain and thus reducing neuronal hyperexcitability in diseases such as epilepsy. A key advantage of this approach is that, unlike existing anticonvulsants, it would not prevent a neuron from responding to excitatory stimuli but would instead act predominantly to dampen repetitive firing.

There is also therapeutic potential in blocking the activity of functional K_v1 channels and increasing neuronal excitability. The organic compound 4-aminopyridine (4-AP, fampridine) has been used extensively as a pharmacological tool to study the functional properties of K_v1 channels for which it is a reasonably selective blocker.⁴⁰ 4-AP (marketed as Ampyra in the United States and Fampyra in Europe) was approved by the Food and Drug Administration (FDA) in 2010 and licensed in the United Kingdom in 2011 for use in the treatment of multiple sclerosis, having been shown to improve walking speed in patients with multiple sclerosis in two clinical trials. 4-AP's therapeutic effect has not been fully elucidated, but it most likely functions by blocking the prolonged hyperpolarizing currents that flow through K_v1 channels, shortening the relative refractory period and increasing axonal conduction.

K_v3-Containing Channels

Channels in the K_v3 Shaw subfamily activate rapidly at high-voltage thresholds (~10 mV) and have very fast deactivation rates. This allows them to open during the peak of the action potential to speed up membrane repolarization

and enable repetitive neuronal firing at high frequencies.⁴¹ $K_{V3.3}$ is expressed throughout the central nervous system, particularly in cerebellar Purkinje neurons. Mutations in $K_{V3.3}$ cause the autosomal dominant neurological disorder SCA13 (spinocerebellar ataxia type 13), which leads to degeneration of the cerebellum and the spinal cord.⁴² The four main disease-associated mutations in $K_{V3.3}$ lead to either reduced channel expression or channels with altered gating properties when expressed in *Xenopus* oocytes.⁴³ The reduction in protein levels arises due to a reduction in protein half-life as SCA13 mutations generate unstable proteins that are rapidly degraded. Interestingly, mutant $K_{V3.3}$ protein levels could be partially restored by treatment with trimethylamine *N*-oxide, a chemical chaperone that stabilizes the mutant protein and helps folding.⁴³ This suggests that identification of small-molecule chaperones may be a novel approach to partially rescuing channel activity.

K_{V4} -Containing Channels

Channels containing K_{V4} Shal subunits mediate the fast-inactivating “A-type” current in dendrites of hippocampal neurons (Fig. 2).⁴⁴ These channels are active at subthreshold potentials and are believed to regulate firing frequency and the spread of excitability in the dendritic tree. Action potentials initiated in the axon hillock propagate down the axon but also invade the soma and dendrites (back-propagating action potentials) to inform dendritic synapses that the neuron has fired.⁴⁵ Summation of back-propagating action potentials and excitatory synaptic inputs received by the dendritic tree is believed to be the basis of dendritic signal integration. The activity of dendritic A-type channels limits the spread of back-propagating action potentials and the regulation of K_{V4} expression, localization, and kinetics, thus modulates certain aspects of dendritic signal processing.⁴⁴ Truncation of the $K_{V4.2}$ subunit, resulting in a decrease in dendritic A-current density, has been associated with temporal lobe epilepsy.⁴⁶ The most common form, mesial temporal lobe epilepsy (MTLE), arises in the medial aspect of the temporal lobe where the hippocampus, parahippocampal gyrus, and the amygdala are located. A reduction in dendritic A-current would be expected to lower the firing threshold for action potentials as well as increasing the spread of back-propagating action potentials. Interestingly, seizures have been shown to induce surface recruitment of $K_{V4.2}$ subunits in thalamocortical neurons, which relay sensory information to the cerebral cortex, presumably in a feedback response to reduce excitability.⁴⁷ Pharmacologically, K_{V4} currents are selectively inhibited by several spider toxins that modify gating kinetics⁴⁸ and can be activated by the NeuroSearch (Hellerup, Denmark) compound NS5806.⁴⁹ NS5806 increases current flowing through K_{V4} channels by

enhancing peak amplitude and slowing current decay. This latter effect on current inactivation depends on the presence of KChIP2, a cytosolic accessory protein that interacts with the intracellular N-terminus of K_{V4} channels.⁴⁹ Also see the section on cardiac K_{V4} below.

K_{V7} -Containing Channels

Four of the five members of the K_{V7} family are expressed in the nervous system, where they form homomeric and heteromeric K^+ channels. In many regions of the brain, channels composed of $K_{V7.2}$ and 7.3 subunits underlie the slow voltage-gated “M-current,” so called because the current is inhibited by neurotransmitters acting via G_q -coupled muscarinic receptors.⁵⁰ These channels localize predominantly to the axon initiation segment in neurons and are open at membrane potentials (from around -60 mV) that are the subthreshold for most voltage-gated K^+ channels. They do not inactivate and thus generate a steady outward current that stabilizes the membrane in the face of depolarizing currents (reviewed by Brown and Passmore⁵¹). Since their activation is slow, they tend not to contribute to the repolarization phase of the action potential but act to subdue excitability and repetitive firing in neurons. A number of different mutations of $K_{V7.2}$ and $K_{V7.3}$ have been shown to be associated with idiopathic generalized epilepsy, including benign familial neonatal seizures (BFNS), a disorder characterized by recurrent seizures in newborns.^{52–54} Not all the mutations have been functionally characterized, but most result in reduced amplitude of the M-current, which would be consistent with neuron depolarization and increased burst activity. Seizures in BFNS usually spontaneously stop within the first 15 weeks, although the susceptibility to seizures in later life is increased in BFNS-diagnosed infants ($\sim 16\%$ compared with 1% – 2% in the general population⁵²). It is unclear why seizures cease. One possibility is that the expression of K_{V7} subunits is developmentally regulated, and the neonatal brain is most dependent on the stabilizing effect of the M-current.

Loss of function mutation of $K_{V7.3}$ is also associated with autism spectrum disorders (ASD). In this context, it is probably an M-current formed by the association of $K_{V7.3}$ subunits and $K_{V7.5}$ subunits that is important.⁵⁵ The control these channels exert over neuronal excitability may be important in the generation of synchronous oscillations of networks of neurons, which is believed to be involved in memory formation and storage and, potentially, emotional processing and behavioral monitoring, which are all affected in individuals with ASD.^{56–59} The causal gene for autosomal dominant nonsyndromic sensorineural hearing loss (DFNA2) has been identified as *KCNQ4*, which encodes the $K_{V7.4}$ protein.^{60,61} This progressive form of hearing loss is thought to result from a decrease in K^+ efflux from sensory hair

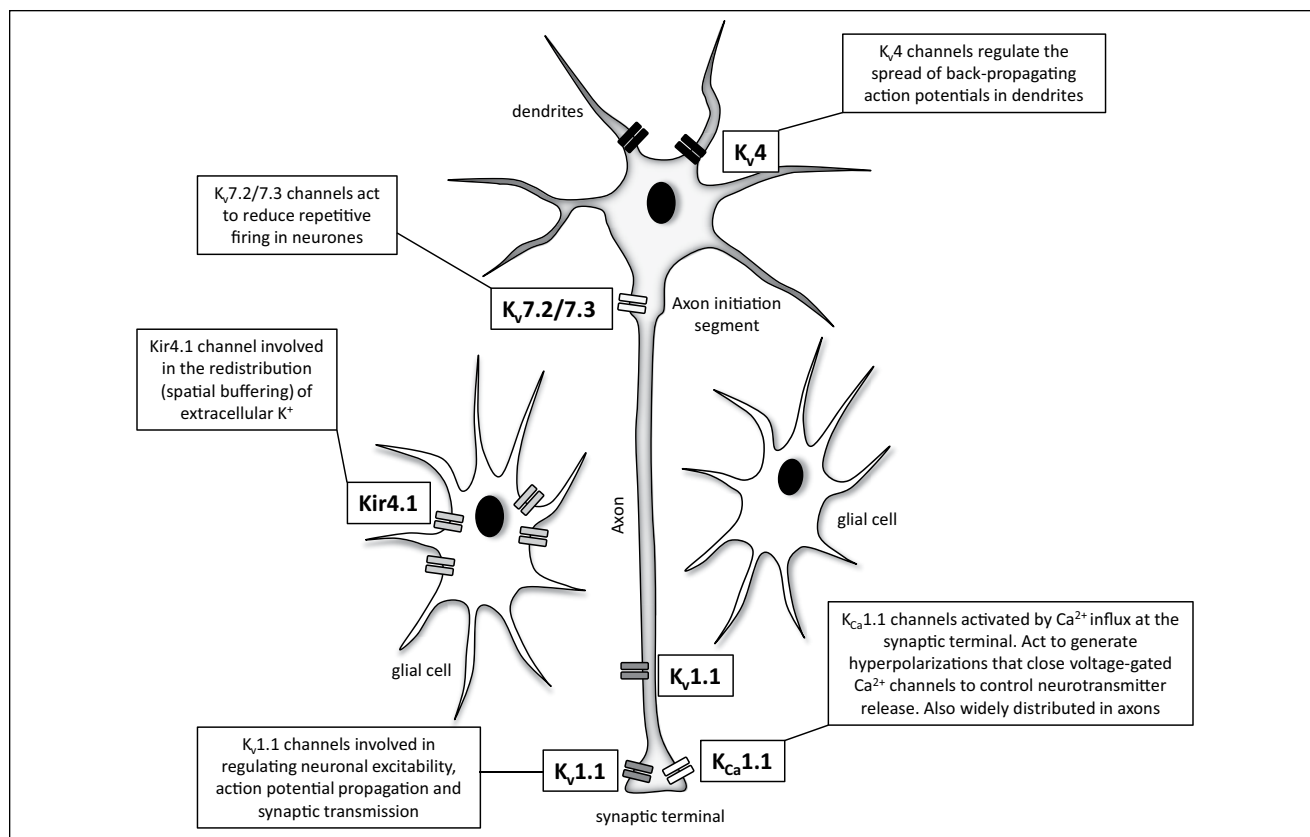


Figure 2. Differential localization of K⁺ channel subtypes in neurons. K_v1.1-containing channels are expressed in the axon and presynaptic terminal, where they regulate neuronal excitability, action potential propagation, and synaptic transmission. K_v4.3-containing channels are expressed in dendrites and are involved in regulating the spread of back-propagating action potentials in the dendritic tree. K_v7.2/7.3 channels, which form the M-current, are expressed in the axon initiation segment and are active at subthreshold membrane potentials where most voltage-gated K⁺ channels are closed. They act to dampen excitability and repetitive firing in neurons. K_{ca}1.1-containing channels are expressed in the presynaptic terminal, where they localize with voltage-gated Ca²⁺ channels. They are activated by the Ca²⁺ influx that occurs in response to action potential-induced terminal depolarization and act to terminate the action potential and generate after-hyperpolarizations that close Ca²⁺ channels and reduce neuronal excitability. K_{ir}4.1-containing channels are expressed in glial cells, where they are potentially involved in the redistribution of K⁺. See text for details.

cells, potentially leading to damage over time due to K⁺ overload.^{62–64}

K_v7.2-7.5 Modulators as Drugs

Recently, retigabine (Potiga in the United States and Trobalt in the European Union), a first-in-class K_v7.2-7.5 opener, has been approved for the use of drug-resistant epilepsy with partial-onset seizures.^{65–67} Retigabine is derived from flupirtine, a drug with longstanding use as a nonopioid analgesic with known relaxant/anticonvulsive properties. Retigabine generates a hyperpolarizing shift in the voltage dependence of channel activation, thus enhancing the stabilizing M-current and limiting neuronal excitability. It shows little selectivity between neuronal K_v7.2/7.3 channels and other K_v7.2-7.5 channels and may also affect neurotransmission involving the major inhibitory transmitter gamma-aminobutyric acid

(GABA). Retigabine has been shown to increase the concentration of GABA in the brain, by either enhancing GABA synthesis or blocking GABA metabolism, and increases GABA-induced current in rat cortical neurons.⁶⁸ A concerning side effect of retigabine is bladder voiding possibly due to relaxation of bladder smooth muscle (detrusor muscle) or loss of excitability in sympathetic neurons in the bladder.⁶⁹ Other reported side effects include dizziness,⁶⁵ cardiovascular disorders such as prolonging of the QT interval (see later),⁷⁰ and eye pigmentation color change.^{70,71} Interestingly, studies on the retention of patients taking retigabine in the open-label extension study show 60% discontinuation of retigabine treatment at 28 months.⁷² In somewhat different study cohorts, a trial undertaken at University College London predicted a possible near 100% discontinuation of retigabine treatment at 2 years.⁷³ ICA-27243, a compound from Icagen (Durham, NC), is reported to be a selective K_v7.2/7.3 opener that binds to a site

in the voltage sensor domain.⁷⁴ In the folded protein, the binding pocket appears to be formed from residues in both the C-terminal end of the S2 domain and the N-terminus of the S3 domain, regions of the channel protein with a high degree of variability between K_{V7} subfamily members.⁷⁴ This highlights the need for improved information regarding the 3D structure of K^+ channels to identify variable regions that can be targeted by selective modulators.

$K_{Ca} 1.1$ -Containing Channels

$K_{Ca} 1.1$ (BK) subunits are widely distributed in the axons and at presynaptic terminals of excitatory neurons in the cortex and hippocampus.^{75,76} At synaptic terminals, they are localized in close proximity to voltage-gated Ca^{2+} channels and are activated in response to the Ca^{2+} influx that occurs in response to action potential-induced terminal depolarization.^{77,78} Their activation serves to terminate the action potential and generate after-hyperpolarizations that close Ca^{2+} channels and dampen neuronal excitability. Subunit mutations resulting in loss of channel function would therefore be expected to heighten neuronal excitability consistent with epilepsy. Interestingly, a $K_{Ca} 1.1$ mutation discovered by Du et al.⁷⁹ is a gain-of-function mutation associated with generalized epilepsy with paroxysmal dyskinesia (GEPD). This mutation is thought to cause seizures in two possible ways: either $K_{Ca} 1.1$ -containing channels are expressed in inhibitory neurons, or this gain of K^+ channel function allows quicker release of Na^+ channels from inactivation, therefore increasing burst firing of neurons.^{80,81}

$K_{Ca} 1.1$ Modulators as Drugs

$K_{Ca} 1.1$ channels have proved particularly challenging for drug design (reviewed by Nardi and Olesen⁸²). Clinically prescribed drugs such as hydroflumethiazide (Saluron) and chlorothiazide have antihypertensive effects probably because they activate $K_{Ca} 1.1$ channels in vascular smooth muscle (see later), but these compounds are essentially diuretics that inhibit Na^+/Cl^- reabsorption from the distal convoluted tubules in the kidneys.⁸³ The NeuroSearch activator NS1619 has been used extensively as a pharmacological tool to study $K_{Ca} 1.1$ channel function but has poor potency and many off-target effects, most significantly the inhibition of L-type Ca^{2+} channels.⁸⁴ NS11021 is a more selective activator that functions by shifting the voltage activation curve to more negative potentials.⁸² The activation of neuronal K^+ channels to decrease excitability and neurotransmitter release has been seen as a novel approach for targeting acute ischemic stroke. The activator BMS 204352 (Bristol-Myers Squibb, New York, NY) appeared initially promising and has neuroprotective effects in animal models, significantly reducing cortical infarct volume

in a stroke model in spontaneous hypertensive rats.⁸⁵ It reached phase 3 clinical trials for treatment of acute ischemic stroke but failed to show a significant effect over placebo.⁸⁵

$K_{ir} 4.1$ -Containing Channels

$K_{ir} 4.1$ channel subunits are found primarily on nonneuronal cells within the brain, mostly glial cells within the hippocampus, cortex, thalamus, and brainstem.^{86,87} $K_{ir} 4.1$ can form homomeric channels or complex with $K_{ir} 5.1$ or $K_{ir} 2.1$ to form heteromeric channels. These heteromeric channels show strong inward rectification, unlike the $K_{ir} 4.1$ homotetramer. In common with other inward rectifiers, $K_{ir} 4.1$ controls the resting membrane potential of astrocytes, and their ability to allow K^+ to move reasonably freely both into and out of the cell has led to the idea that they help control the microenvironment around neurons by assisting in spatial K^+ buffering.^{88,89} The restricted extracellular space around neurons means that the repolarization of a single action potential can cause a significant increase in extracellular $[K^+]$, with high-frequency firing potentially raising extracellular K^+ by several millimolar.⁹⁰ Due to the high K^+ permeability of membranes, a prolonged increase in extracellular K^+ would depolarize neurons and alter excitability. Excess extracellular K^+ therefore needs to be efficiently siphoned from the immediate vicinity of the neuron, and it is postulated that $K_{ir} 4.1$ -containing channels allow K^+ influx into glia at sites of high extracellular K^+ . This K^+ is then potentially shuttled via a network of gap junction-connected glia and released by efflux through homomeric $K_{ir} 4.1$ channels at sites of low extracellular K^+ .⁹¹ Disruption of this ability to clear K^+ would have profound effects on neuronal excitability, and there is increasing interest in the role of $K_{ir} 4.1$ in epilepsy. Interestingly, glial cells taken during surgery from patients with intractable epilepsy have reduced K_{ir} currents.⁹² Loss-of-function mutation of $K_{ir} 4.1$ has also been shown to be associated with seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME) and epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST) syndromes.^{93–95} No current modulators are available for these channels.

$K_{ir} 6.2$ -Containing Channels

$K_{ir} 6.2$ is the pore-forming subunit of the neuronal K_{ATP} channel. These channels respond to fluctuations in intracellular levels of adenine nucleotides and are inhibited by ATP but activated by Mg^{2+} -bound nucleotides, particularly $MgADP$.⁹⁶ This ability to sense intracellular ATP/adenosine diphosphate (ADP) levels ensures that changes in cellular metabolism are translated to changes in membrane K^+ permeability and thus membrane potential and excitability. A number of $K_{ir} 6.2$ gain-in-function mutations give rise to a

group of syndromes known as DEND (development delay, epilepsy, and neonatal diabetes).⁹⁷ Twenty percent of DEND patients have neurological disorders such as generalized epilepsy, delay of motor development, and speech and learning disabilities. All characterized mutations share the common feature that they decrease the ability of ATP to close that channel or increase the ability of Mg^{2+} nucleotides to activate it. The role of K_{ATP} channels is perhaps best understood in pancreatic β cells, where they are involved in glucose-dependent insulin secretion.⁹⁸ Due to the subunit composition of these pancreatic channels (believed to be $K_{ir}6.2$ in combination with the regulatory subunit SUR1) and the relatively low $[ATP]/[ADP]$ in pancreatic β cells during fasting, pancreatic K_{ATP} channels are constitutively active under basal conditions and help maintain the β -cell resting membrane potential. Elevation of blood glucose results in increased glucose uptake by β cells and its subsequent metabolism, leading to a rise in the intracellular levels of ATP and a fall of ADP. This closes active K_{ATP} channels, resulting in a reduction of K^+ efflux, depolarization, and activation of L-type voltage-dependent Ca^{2+} channels, which increases Ca^{2+} influx and triggers the Ca^{2+} -dependent secretion of insulin. Increased K_{ATP} activity in pancreatic β cells would reduce insulin secretion, explaining the diabetes in these patients, but how hyperactivity of neuronal K_{ATP} channels induces neurological effects is unclear. K_{ATP} channels are expressed predominately in inhibitory GABAergic neurons, with K_{ATP} channel openers causing decreased firing of pyramidal cells in substantia nigra.^{99,100} Drugs that modulate K_{ATP} channel activity are one of the few K^+ channel clinical success stories and have been extensively reviewed elsewhere.¹⁰¹ K_{ATP} channel blockers include the first-generation antidiabetic sulfonylurea tolbutamide, now largely fallen into disuse due to side effects, and the second-generation antidiabetic sulfonylureas glibenclamide, glipizide, gliclazide, glimepiride, and gliquidone. K_{ATP} channel openers include the antihypertensives diazoxide, minoxidil, pinacidil, and the vasodilator nicorandil, which is largely prescribed for the treatment of angina.

Cardiac K^+ Channels

Disorders of the heart relating to K^+ channel dysfunction mostly involve disruption of the cardiac action potential and thus the rhythmic contraction of the heart muscle. Alteration of K^+ channel function results primarily in repolarization disorders such as long QT syndrome (LQTS) and short QT syndrome (SQTS). The synchronized electrical activity of cells within the heart can be recorded on the body surface as the electrocardiogram (ECG). The time elapsed from the beginning of the QRS complex to the end of the T wave on the surface ECG is defined as the QT interval and is largely determined by the length of the ventricular action

potential (**Fig. 3**). Prolonged QT interval can produce early after-depolarizations, leading to Torsades de Pointes (TdP), which is the typical arrhythmia associated with LQTS; TdP can in turn generate ventricular fibrillation, a lethal arrhythmia. LQTS results from delayed repolarization of ventricular cells due to a reduction in repolarizing (outward) currents or an increase in depolarizing (inward) currents. It is caused by either loss of function of K^+ channels or gain of function of Na^+ or Ca^{2+} channels. SQTS, on the other hand, is caused by gain of function of K^+ channels.¹⁰² Mechanisms underlying loss or gain of function vary. Mutations of K^+ channels have been shown to reduce the number of functional channels at the cell surface by altering trafficking or by affecting the kinetic properties of channel behavior.¹⁰³ LQTS can arise from the disruption of several genes encoding K^+ subunits (see **Table 2**). These mostly involve mutation of subunits encoding the channels involved in repolarization (I_{Ks} , I_{Kr} , I_{K1} ; **Fig. 3**). Repolarization of the atria also involves atrial-specific channels such as $K_{V}1.5$, $K_{ir}3.1/3.4$, and $K_{Ca}2.2/2.3$, which underlie I_{Kur} , I_{KACH} , and I_{SK} respectively. The limited distribution of these channel subtypes makes them interesting and potentially important targets for the development of novel treatment for atrial fibrillation that do not affect ventricle function.

$K_{V}7.1$ -Containing Channels (I_{Ks})

Unlike the other four members of the $K_{V}7$ family, $K_{V}7.1$ is not widely expressed in the CNS but instead is found predominantly in cardiac myocytes and inner ear neurons. In cardiomyocytes, $K_{V}7.1$ ($K_{V}LQT$) combines with the accessory β subunit MinK (KCNE1) to form channels that mediate the slow delayed rectifying K^+ (I_{Ks}) that contributes to the repolarization phase of the cardiac action potential. Loss-of-function mutations of $K_{V}7.1$ lead to long QT syndrome 1 and Jervell and Lange-Nielsen syndrome type 1.^{104,105} These mutations are usually single amino acid missense mutations that cause protein misfolding and early degradation of the channel subunit. In addition to cardiac rhythm defects, patients with Jervell and Lange-Nielsen syndrome have deafness from birth.¹⁰⁵ Mutation of the accessory protein MinK has been shown to be associated with long QT syndrome 5¹⁰⁶ and atrial fibrillation,¹⁰⁷ while gain-of-function mutations of $K_{V}7.1$ are associated with short QT syndrome 2 and familial atrial fibrillation type 3.^{108,109}

$K_{V}7.1$ Modulators

I_{Ks} is a target of interest for the development of antiarrhythmic drugs. Amiodarone, a licensed class III antiarrhythmic, is a nonspecific channel inhibitor that prolongs the cardiac action potential via block of both I_{Kr} and I_{Ks} .¹¹⁰ $K_{V}7.1$ is insensitive to the anticonvulsant retigabine, which activates

Table 2. Cardiac K⁺ Channelopathies.

Protein	Disease	Gene	Effect on Current	Reference
K _V 7.1	Long QT syndrome 1	KCNQ1	Loss	104, 178
K _V 7.1	Jervell and Lange-Nielsen syndrome type 1	KCNQ1	Loss	105, 172
K _V 11.1	Long QT syndrome 2	KCNH2	Loss	115
MinK protein (minimal potassium subunits)	Long QT syndrome 5	KCNE1	Loss	106
MiRP1 (MinK-related peptide 1)	Long QT syndrome 6	KCNE2	Loss	119
K _{ir} 2.1	Long QT syndrome 7 (Andersen-Tawil syndrome)	KCNJ2	Loss	179
K _{ir} 3.4	Long QT syndrome 13	KCNJ5	Loss	140
K _V 11.1	Short QT syndrome 1	KCNH2	Gain	117, 118
K _V 7.1	Short QT syndrome 2	KCNQ1	Gain	108
K _{ir} 2.1	Short QT syndrome 3	KCNJ2	Gain	180
MiRP2 (MinK-related peptide 2)	Brugada syndrome type 6	KCNE3	Gain	131
MiRP1 (MinK-related peptide 1)	Familial atrial fibrillation type 4	KCNE2	Gain	122
K _V 7.1	Familial atrial fibrillation type 3	KCNQ1	Gain	109
K _V 1.5	Familial atrial fibrillation type 7	KCNA5	Loss	133
K _{ir} 2.1	Familial atrial fibrillation type 9	KCNJ2	Gain	181
HCN4	Sick sinus syndrome type 2 autosomal dominant	HCN4	Loss	182
K _V 4.3	Brugada syndrome	KCND3	Gain	128
K _V 4.3	Early-onset persistent lone atrial fibrillation	KCND3	Gain	129
MinK protein (minimal potassium subunits)	Early-onset lone atrial fibrillation	KCNE1	Gain	107
K _{ir} 3.4	Atrial fibrillation	KCNJ5	Loss	183
MiRP2 (MinK-related peptide 2)	Lone atrial fibrillation	KCNE3	Gain	130
MiRP3 (MinK-related peptide 3)	Atrial fibrillation	KCNE4	Gain	184
MiRP4 (MinK-related peptide 4)	Nonfamilial/acquired atrial fibrillation	KCNE5	Gain	185
SUR2A	Paroxysmal Atrial fibrillation	ABCC9	Loss	186

other K_V7 family members, because it lacks a tryptophan residue in the S5 transmembrane domain that is required for retigabine action¹¹¹ (see above). Pharmacologically, K_V7.1 can be selectively activated by the benzodiazepine L-364,373 (R-L3), which is a partial agonist and increases the amplitude of K_V7.1 currents as well as slowing the rate of channel activation and deactivation.¹¹² Interestingly, most mutant channels associated with long QT syndrome 1 respond similarly to wild-type channels, suggesting that the disease-associated channels would be susceptible to activation.¹¹² To our knowledge, the therapeutic benefit of L-364,373 has not been tested. A number of K_V7.1 selective blockers are known, including L-768,673, HMR1556, and JNJ282 (Johnson & Johnson, New Brunswick, NJ). These have generally shown promising results in animal models, prolonging cardiac action potentials and reducing the incidence of arrhythmias, but have also triggered debate regarding the extension of their usage into humans.¹¹³ Potential side effects include hearing loss, inappropriate vasoconstriction (see vascular K_V7.1 below), and the potential to generate TdP and ventricular fibrillation.¹¹³ We are unaware

of any studies investigating selective K_V7.1 blockade in humans.

K_V11.1-Containing Channels (I_{Kr})

K_V11.1 (hERG1a) subunits associate with subunits produced by an alternative transcript of the KCNH2 gene, termed hERG1b, to form channels that mediate the rapid delayed rectifier current (I_{Kr}).¹¹⁴ I_{Kr} represents the most important of the repolarizing currents for action potential termination in the ventricles, atria, and cells of the cardiac conduction system. Loss-of-function mutations of K_V11.1 reduce the amplitude of I_{Kr} and lead to long QT syndrome 2 (LQTS2).¹¹⁵ About 300 different K_V11.1 mutations are linked to LQTS2.¹¹⁶ These mutations cause loss of K_V11.1 channel function by a range of mechanisms, including reducing channel synthesis, suppressing trafficking to the cell membrane, altering channel gating kinetics, or suppressing ion permeation through the channel pore.¹¹⁶ Most mutations appear to affect trafficking. Gain-of-function mutations of K_V11.1 and an increase in repolarizing I_{Kr}

current are associated with short QT syndrome 1.^{117,118} When $K_{v11.1}$ is coexpressed with the β subunit MiRP1 in *Xenopus* oocytes, MiRP1 suppresses $K_{v11.1}$ trafficking to the cell surface and accelerates channel deactivation.¹¹⁹ In the healthy human heart, MiRP1 is predominantly expressed in the conducting Purkinje fibers, although protein levels have been detected in human ventricles.^{120,121} A loss-of-function MiRP1 mutation is associated with long QT syndrome 6¹¹⁹, while gain-of-function mutations of MiRP1 are associated with familial atrial fibrillation type 4.¹²²

$K_{v11.1}$ Modulators

Limitations in the ability of HTS methods to monitor the complex behavior of the channel has restricted the discovery of activators. Several small-molecule activators of $K_{v11.1}$ have, however, been identified. Type 1 activators such as RPR260243 (originally synthesized by Aventis now part of the Sanofi group) increase $K_{v11.1}$ currents by dramatically slowing channel deactivation (reviewed by Zhou et al.¹²³). Type 2 activators such as A935142 (Abbott, Abbott Park, IL), NS1643 (NeuroSearch), ICA-105574 (Icagen), and PD118057 and PD307243 (both Pfizer) primarily impair channel inactivation by binding near the selectivity filter and shifting the voltage dependence of inactivation (reviewed by Zhou et al.¹²³). Mallotoxin, a naturally occurring extract from the tree *Mallotus philippinensis*, and KB130015 in contrast accelerate the rate of channel activation. The therapeutic potential of these activators as antiarrhythmics has not been demonstrated clinically. They appear to have off-target effects and may be proarrhythmic and increase the risk of ventricular fibrillation.¹²⁴ Interestingly, some low-affinity $K_{v11.1}$ blocking agents appear to paradoxically restore I_{Kr} by acting as chaperones to transport mutant $K_{v11.1}$ subunits to the membrane.¹²⁵

$K_{v4.3}$

Channels containing K_{v4} subunits underlie the fast-inactivating "A-type" current I_{to} (Figure 3). I_{to} is formed of fast and slow recovering components, $I_{to1,f}$ and $I_{to1,s}$, respectively.¹²⁶ The channel responsible for $I_{to1,f}$ is formed by assembly of $K_{v4.2}$ subunits, $K_{v4.3}$ subunits, or a combination of the two, while the channel responsible for $I_{to1,s}$ is composed of $K_{v1.4}$ subunits. The extent to which alteration of I_{to} can generate arrhythmic activity in the heart has been difficult to ascertain due to a lack of selective blockers or activators. Dynamic clamp of human atrial myocytes, where a current mimicking I_{to} but of opposite polarity was injected into cells, selectively reduced I_{to} and significantly prolonged atrial action potential duration.¹²⁷ In the same study, reduction of I_{to} by dynamic clamp of rabbit atrial myocytes during β -adrenergic stimulation triggered abnormal membrane potential oscillations (after-depolarizations). These could be abolished by dynamic-clamp increases in I_{to} or by application of the β 1-antagonist atenolol.¹²⁷ This suggests that

changes in I_{to} can potentially provoke arrhythmias. Loss-of-function mutation of the channel subunits underlying I_{to} have not been reported but gain-of-function mutation of $K_{v4.3}$ results in Brugada syndrome¹²⁸ and persistent lone atrial fibrillation.¹²⁹ Mutations of MiRP2, a normally inhibitory β subunit that associates with $K_{v4.3}$, are also linked with lone atrial fibrillation¹³⁰ and Brugada syndrome.¹³¹ Consistent with this, exposure of ventricular myocytes and ventricular wedge preparations from normal canine heart to NeuroSearch's K_{v4} -selective activator NS5806 mimics the symptoms of Brugada syndrome.¹³²

Atrial $K_{v1.5}$ (I_{Kur})

$K_{v1.5}$ underlies the ultrarapid delayed rectifier K^+ (I_{Kur}) current in the atrium involved in the early stages of atrial repolarization (Figure 3). It represents a potentially important target in treating atrial fibrillation (AF), primarily through the prolongation of the atrial effective refractory period (ERP). The ERP represents the period of time after an action potential has been initiated in which a new action potential cannot generate. During this period, depolarization of cells in the myocardium will not produce significant depolarization in surrounding cells, and the ERP thus acts as a protective mechanism to prevent arrhythmias. Antiarrhythmic agents often act to prolong the ERP, but agents designed to treat AF by prolonging the ERP usually also affect the ventricles, inducing other forms of arrhythmia. Functional currents involved in repolarization of the atrium, but not the ventricles, are thus promising new targets for the development of treatments for AF, and several pharmaceutical companies are currently actively exploring this route. It must be mentioned, while many companies are exploring I_{Kur} inhibitors (see below) for treatment of AF, loss-of-function $K_{v1.5}$ mutations have been associated with atrial fibrillation.^{133,134} Loss of $K_{v1.5}$ protein has been detected in chronic AF patients; therefore, inhibiting this remaining current may not produce significant effects on ERP in this particular disease state.¹³⁵

I_{Kur} Modulators

Brivaneess (formerly known as Vernakalant or RSD 1235) is a new antiarrhythmic drug recently approved in Europe that inhibits the atrial-specific channels $K_{v1.5}$ and $K_{ir3.1/3.4}$. It has been shown to be effective in terminating acute-onset atrial fibrillation but is relatively nonspecific and can also have some inhibitory effects on I_{to} and I_{Kr} currents.¹³⁶ Bristol-Myers Squibb has a $K_{v1.5}$ inhibitor BMS-919373 in phase 1 trials to study the effects on atrial ERP in patients with a pacemaker (NCT02153437) and in phase 2 trials to assess the effect of BMS-919373 on the time spent in AF (NCT02156076). Pierre Fabre Medicament (Paris, France) has F373280, a novel docosahexaenoic acid derivative and blocker of $K_{v1.5}$ in phase 2 clinical trials for the treatment of persistent AF (NCT01831856). Xention (Cambridge,

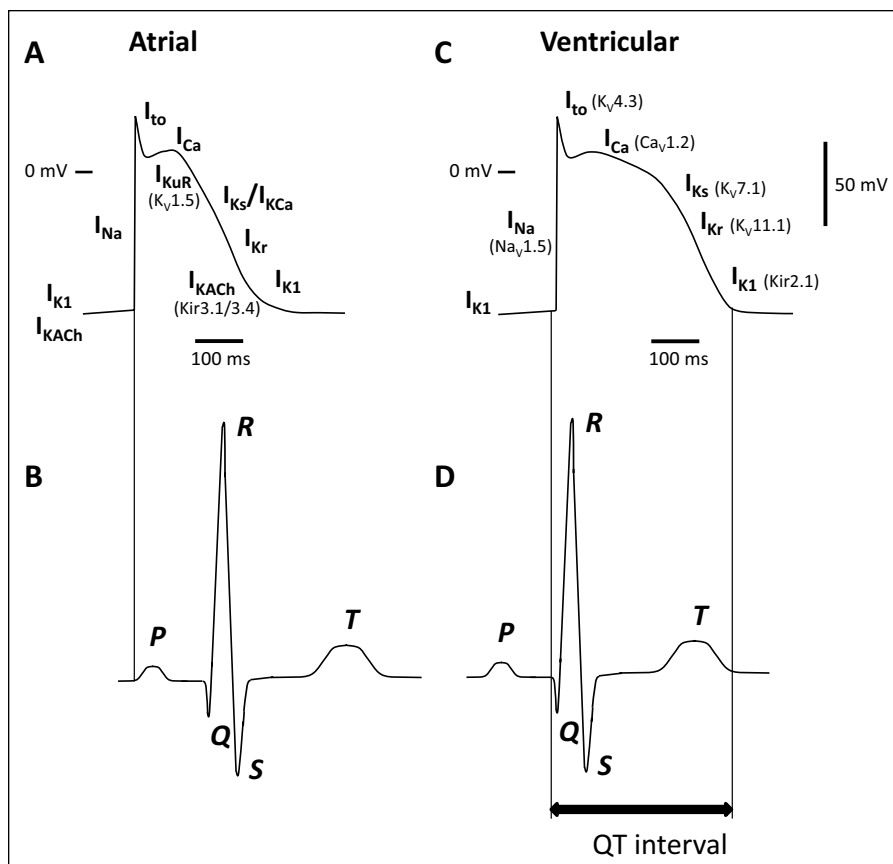


Figure 3. Electrical activity in the atrium and ventricles of the heart. **(A)** Atrial action potential with corresponding underlying currents. Currents similar to ventricle (right) with the exception of atrial-specific currents I_{KUR} (ultra-rapid rectifier K^+ current) mediated by $K_v1.5$ channels, I_{KACh} (acetylcholine-regulated K^+ current) mediated by $K_{ir3.1/3.4}$, and I_{KCa} (calcium-activated K^+ current) mediated by $K_{Ca2.x}$. **(B)** Relationship between atrial action potential and surface electrocardiogram (ECG). **(C)** Ventricular action potential with corresponding underlying currents. I_{Na} (rapid inward Na^+ current) mediated by $Na_v1.5$; I_{to} (transient outward current) mediated by $K_v4.3$; I_{Ca} (inward calcium current) mediated by $Ca_v1.2$; I_{Ks} (slow delayed rectifying current) mediated by $K_v7.1$; I_{Kr} (rapid delayed rectifying current) mediated by $K_v11.1$ and I_{K1} mediated by $K_{ir2.1}$. **(D)** Relationship between ventricular action potential and surface ECG.

UK) has the $K_v1.5$ blocker XEN-D0101 in a phase 1 proof-of-mechanism electrophysiological study and, in partnership with Servier (Neuilly-sur-Seine, France), the more potent and selective XEN-D0103 in two phase 2 clinical studies.

Atrial $K_{ir3.1/3.4}$

The acetylcholine-activated K current (I_{KACh}) carried by $K_{ir3.1/3.4}$ channels is also a candidate for the development of atrial-specific antiarrhythmics.¹³⁷ The novel compound NTC-801 has been shown to inhibit I_{KACh} with a selectivity >1000-fold over other major cardiac currents.¹³⁸ NTC-801 reversed action potential shortening induced by carbachol in isolated guinea pig atrial myocytes but had no effect on ventricular action potential duration. It was also shown to prolong the atrial ERP in a rapid atrial pacing model.¹³⁸ The benzopyrane derivative, NIP-151, is also reported to selectively block I_{KACh} and be capable of atrial-specific ERP prolongation and stopped AF in two animal models of AF.¹³⁹ In contrast, the same study found that dofetilide, a class III antiarrhythmic used in the treatment of AF, significantly prolonged both atrial and ventricular ERP but had little effect in terminating AF in either model.¹³⁹ While I_{KACh} is predominately thought to be an atrial-specific current, recent research has shown involvement of

I_{KACh} in ventricle repolarization, along with a mutation of $K_{ir3.4}$ being associated with LQTS.^{140,141} This may limit the potential of I_{KACh} as a therapeutic target for AF.

Atrial $K_{Ca2.x}$

The calcium-activated K^+ current I_{KCa} mediated by $K_{Ca2.x}$ has recently been shown to be atrial specific in human hearts¹⁴². Blockade of I_{KCa} produces an increase in ERP in sinus rhythm human atrial preparations, whereas in longstanding AF, I_{KCa} blockade has no effect, probably due to the downregulation of $K_{Ca2.2/2.3}$ in longstanding AF.¹⁴² Interestingly, other studies have found an upregulation in $K_{Ca2.x}$ in AF, which leads to speculation that $K_{Ca2.x}$ expression is initially increased in AF before downregulation takes place.¹⁴³ Therefore, inhibition of I_{KCa} in recent-onset AF may prove beneficial, as has been shown in paced guinea pig hearts.¹⁴⁴ To this end, Acesion Pharma (Copenhagen, Denmark) is currently undertaking studies into $K_{Ca2.x}$ modulation for the treatment of AF.

Vascular K^+ Channels

The primary role of K^+ channels in the vasculature is to control the resting membrane potential and thus the activity of

Table 3. Vascular K⁺ Channelopathies.

Protein	Disease	Gene	Effect on Current	Reference
K _V 1.5	Pulmonary arterial hypertension	KCNA5	Loss	148
β-1 Subunit K _{Ca} 1.1	Low prevalence of diastolic hypertension	KCNMB1	Gain	157
K _{2P} 3.1 (TASK1)	Pulmonary arterial hypertension	KCNK3	Loss	165

voltage-gated Ca²⁺ channels, a major Ca²⁺ influx pathway.¹⁴⁵ In vascular smooth muscle cells, loss or reduction of K⁺ channel activity results in membrane depolarization, increased open probability of voltage-gated Ca²⁺ channels, increased Ca²⁺ influx, and thus contraction and increased vascular tone. An array of different K⁺ channels from all the major families contributes to this role of regulating tone through membrane potential, with channel type and distribution varying markedly with vascular bed and vessel diameter. Mutations in a number of K⁺ channel subunits have been linked with human disease (Table 3).

K_V1.5-Containing Channels

The major voltage-gated K⁺ channels expressed in the vasculature are K_V1.2, K_V1.5, K_V2.1, and K_V7.4/7.5.^{146,147} Their distribution varies considerably with vascular bed, and there is some controversy over their relative contribution to the regulation of the resting membrane potential. Inhibited gene transcription and/or decreased stability of K_V1.5 mRNA has been implicated in the reduction of functional K_V current in pulmonary artery smooth muscle cells (PASMCs) from patients with primary pulmonary hypertension (PPH).^{148,149} PPH is a relatively rare disease characterized by increased pulmonary vascular resistance and arterial pressure that can ultimately lead to right heart failure. Dependent on the contribution of K_V1.5 to the resting membrane potential in PASMCs, channel dysfunction might be expected to lead to a membrane depolarization and increased Ca²⁺ influx via activated voltage-gated Ca²⁺ channels. Given the role of K_V1.5 in the atrial ERP (see above), it seems unlikely that systemically targeting these channels with activators, which would be expected to reduce the ERP, would have significant beneficial effects in these patients over more traditional Ca²⁺ channel-blocking strategies. In this context, it is interesting that targeted introduction of K_V1.5 into the rat pulmonary circulation by nebulization of an adenovirus carrying the human K_V1.5 gene reduced pulmonary hypertension.¹⁵⁰

K_{Ca}1.1 Channels

Increases in intravascular pressure induce a graded depolarization of the smooth muscle cell membrane, which increases the activity of voltage-gated Ca²⁺ channels, raising global

Ca²⁺ and initiating contraction.¹⁵¹ Although in smooth muscle, the precise mechanism is unclear, Ca²⁺ influx through voltage-gated Ca²⁺ channels also activates ryanodine-sensitive Ca²⁺ release channels (RyRs) located on regions of the sarcoplasmic reticulum in close proximity to the inner side of the plasma membrane.¹⁵² Localized Ca²⁺ release from single or tightly clustered groups of these channels (subsurface Ca²⁺ sparks) can increase contractility by directly contributing to global Ca²⁺ or by increasing Ca²⁺ entry through membrane depolarization by activating Ca²⁺-activated chloride channels. Ca²⁺ sparks also have a significant negative-feedback effect that acts to limit pressure-induced vasoconstriction.¹⁵³ This is achieved through the activation of plasma membrane K_{Ca}1.1 channels. Increases in K_{Ca}1.1 channel activity and resultant outward current (spontaneous transient outward currents or STOCs) induce membrane hyperpolarization, which decreases Ca²⁺ entry via voltage-gated Ca²⁺ channels, lowering global Ca²⁺ and exerting a vasorelaxing effect.¹⁵² A recent study reports that K_{Ca}1.1 current density and STOC activity are significantly decreased in vascular smooth muscle cells from patients with hypertension.¹⁵⁴ While K_{Ca}1.1 levels are similar in normotensive and hypertensive individuals, mRNA and protein levels of the β1 subunit KCNMB1 are reduced in arterial tissue from patients with hypertension. This is consistent with previous animal models of hypertension where similar findings have been reported.¹⁵⁵ Population-based genetic epidemiological studies have also revealed essential hypertension-related genetic variants in the human KCNMA1 gene.¹⁵⁶ Although no functional deficiency in the K_{Ca}1.1 protein was found to explain the association of KCNMA1 genetic variation with an increased risk of systolic severe hypertension, one polymorphism potentially disrupts a binding site for proteins regulating translation and may affect K_{Ca}1.1 mRNA levels.¹⁵⁶ Interestingly, a single-nucleotide substitution in the KCNMB1 gene, leading to a channel gain of function through increased Ca²⁺ sensitivity, is associated with a decreased prevalence of diastolic hypertension.¹⁵⁷ As mentioned above, the clinically prescribed diuretics hydroflumethiazide (Saluron) and chlorothiazide have off-target antihypertensive effects because they activate K_{Ca}1.1 channels in the vascular smooth muscle.⁸³ Modulators against these channels would clearly have clinical value, but their broad distribution and history of failed drug design may ultimately make them less attractive targets.⁸¹

$K_{Ca}2.3$ and $K_{Ca}3.1$ Channels

A link between genetic variation in the Ca^{2+} -activated SK ($K_{Ca}2.x$) and IK ($K_{Ca}3.x$) genes and cardiovascular disease is not well established. These channels are particularly important in the endothelium, where their opening mediates vasorelaxation via the endothelium-derived hyperpolarizing factor (EDHF) pathway (reviewed by Edwards et al.¹⁵⁸). Here, a rise in endothelial Ca^{2+} induced by the binding of vasodilating mediators to endothelial receptors opens $K_{Ca}2.3$ channels on the endothelial cell surface and $K_{Ca}3.1$ channels located on endothelial projections that protrude through small holes in the internal elastic lamina to make contact with the underlying smooth muscle.¹⁵⁹ The K^+ currents that flow out through these open channels induce endothelial hyperpolarization that can spread to subadjacent smooth muscle via myoendothelial gap junctions¹⁶⁰; alternatively, the effluxing K^+ can activate inwardly rectifying K^+ (Kir) channels or Na^+/K^+ -ATPase on smooth muscle cells to induce smooth muscle hyperpolarization and ultimately vasorelaxation.¹⁶¹ Selective activation of these channels thus has therapeutic potential for the treatment of conditions such as hypertension, although due to subunit expression in tissues such as the heart (see Atrial $K_{Ca}2.x$ section), there are likely to be significant issues with systemic activation. Population analysis has identified several single-nucleotide polymorphisms (SNPs) in both coding and noncoding regions of the $K_{Ca}2.3$ and $K_{Ca}3.1$ genes.¹⁶² Currently, the only suggestion of genetic linkage to cardiovascular dysfunction is the finding that an intronic SNP in the $K_{Ca}3.1$ gene was significantly less prevalent in a cohort of 313 Japanese patients who had myocardial infarctions than in a control group.¹⁶³

$K_{2P}3.1$ (TASK1) Channels

A number of members of the K_{2P} family, including TASK-1/2, TREK1/2, TWIK1/2, THIK-1, and TRAAK, have been shown to be present in the vasculature.¹⁶⁴ These channels are believed to underlie the poorly defined “leak” or background currents and are subject to extensive regulation. Whole-exome sequencing of members of a family with pulmonary arterial hypertension without identifiable mutations identified a novel missense variant in KCNK3, which encodes $K_{2P}3.1$ (TASK1).¹⁶⁵ Five further missense variants in KCNK3 were subsequently identified in unrelated patients with familial pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension.¹⁶⁵ Functional studies revealed that all these missense mutations resulted in loss of channel function, which could be reversed in most mutants by application of the channel activator, and phospholipase A2 inhibitor, ONO-RS-082. Drugs that pharmacologically inhibit TASK channels include bupivacaine, methanandamide, and Sanofi-Aventis (Paris, France) A293, but as yet there has been little development of selective

activators, although a number of patents have been filed focusing on screening and assays using the channel proteins.¹⁰¹ The K_{2P} family is a relatively recent discovery and as such represents an area of considerable scope and opportunity for the development of therapeutics.

Summary

In conclusion, K^+ channels occupy distinct physiological niches within the human body and have an accessible cell surface location, considerable subunit variability, and often tissue-defined distribution yet have largely evaded successful drug discovery. With the exception of the antidiabetic sulfonylureas and antihypertensives that target K_{ATP} channels, most K^+ channel modulators in clinical use today are poorly selective and have significant off-target toxicities. One of the reasons for this comparative failure in drug discovery is that these protein complexes are not easy to study. They often gate very quickly, have complex inactivation kinetics, and can be subject to elaborate regulation by voltage and intracellular and extracellular ion concentrations. Many HTS methods rely on indirect measurement of channel activity (ion flux, fluorometric dyes, luminescence) and lack temporal resolution over a physiologically relevant range. The introduction of automated planar-array patch-clamp technology has significantly improved the capacity to track physiological channel activity in response to compound libraries, but potent selective modulators remain elusive. Optimization of lead structures appears difficult, perhaps due to structural restraints imposed by modifiers binding to relatively inaccessible or spatially restricted sites in the channel pore, in regulatory domains, or at the interface with modulatory subunits. Here, *in silico* modeling and advances in structural biology techniques to crystallize channel proteins within lipid matrices to mimic *in vivo* open and closed states should generate important data. In addition, crystals of ion channels in complex with modulatory ligands/accessory subunits may reveal key interaction sites and interfaces that can be targeted in drug design. Indeed, targeting interaction interfaces with compounds that either mimic or disrupt the regulatory influence of accessory subunits (see, e.g., the $K_v1.1$ “disinactivators”³⁹) may ultimately be a more fruitful approach to modulating channel behavior than directly targeting the ion-conducting subunit. It is also worth noting that most disorders associated with loss-of-function mutations in K^+ channel genes originate not from direct defects in channel activity but from problems with protein folding that lead to early degradation and a reduction in functional channels at the cell surface. An alternative approach may be to identify chaperone agents that stabilize these mutant subunits and allow enhanced trafficking to the membrane. In this context, recent applications have been filed to the FDA and European Medicines Agency (EMA) for a combination therapy for cystic fibrosis using lumacaftor and ivacaftor. Lumacaftor promotes folding of mutated cystic

fibrosis transmembrane conductance regulator (CFTR) subunits and increases expression of this Cl⁻ channel at the cell surface. Ivacaftor then acts to increase Cl⁻ conductance in CFTR channels by increasing their open probability.¹⁶⁶ The applications follow on from two successful phase 3 studies (TRAFFIC and TRANSPORT) that demonstrated significant and sustained improvement in lung function in people with the most common (F508del) form of cystic fibrosis.¹⁶⁷ The opportunity and need for novel, effective ion channel modulators exists but now need to be matched with innovative design and discovery.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: E.S.A.H. is funded by the British Biotechnology and Biological Sciences Research Council (BBSRC). C.D. is funded by the British Heart Foundation (BHF).

References

- Wei, A. D.; Gutman, G. A.; Aldrich, R.; et al. Nomenclature and Molecular Relationships of Calcium-Activated Potassium Channels. *Pharmacol. Rev.* **2005**, *57*, 463–472.
- Gutman, G. A.; Chandy, K. G.; Grissmer, S.; et al. International Union of Pharmacology: LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassium Channels. *Pharmacol. Rev.* **2005**, *57*, 473–508.
- Goldstein, S. A. N.; Bayliss, D. A.; Kim, D.; et al. International Union of Pharmacology: LV. Nomenclature and Molecular Relationships of Two-P Potassium Channels. *Pharmacol. Rev.* **2005**, *57*, 527–540.
- Kubo, Y.; Adelman, J. P.; Clapham, D. E.; et al. International Union of Pharmacology: LIV. Nomenclature and Molecular Relationships of Inward Rectifying Potassium Channels. *Pharmacol. Rev.* **2005**, *57*, 509–526.
- Ashcroft, F. M. ATP-Sensitive Potassium Channelopathies: Focus on Insulin Secretion. *J. Clin. Invest.* **2005**, *115*, 2047–2058.
- Jan, L. Y.; Jan, Y. N. Voltage-Gated Potassium Channels and the Diversity of Electrical Signalling. *J. Physiol.* **2012**, *590*, 2591–2599.
- Stühmer, W.; Alves, F.; Hartung, F.; et al. Potassium Channels as Tumour Markers. *FEBS Lett.* **2006**, *580*, 2850–2852.
- Wickenden, A. K(+) Channels as Therapeutic Drug Targets. *Pharmacol. Ther.* **2002**, *94*, 157–182.
- Schmitt, N.; Grunnet, M.; Olesen, S.-P. Cardiac Potassium Channel Subtypes: New Roles in Repolarization and Arrhythmia. *Physiol. Rev.* **2014**, *94*, 609–653.
- Benatar, M. Neurological Potassium Channelopathies. *QJM* **2000**, *93*, 787–797.
- Hart, I. K.; Waters, C.; Vincent, A.; et al. Autoantibodies Detected to Expressed K⁺ Channels Are Implicated in Neuromyotonia. *Ann. Neurol.* **1997**, *41*, 238–246.
- Majoie, H. J. M.; de Baets, M.; Renier, W.; et al. Antibodies to Voltage-Gated Potassium and Calcium Channels in Epilepsy. *Epilepsy Res.* **2006**, *71*, 135–141.
- McKnight, K.; Jiang, Y.; Hart, Y.; et al. Serum Antibodies in Epilepsy and Seizure-Associated Disorders. *Neurology* **2005**, *65*, 1730–1736.
- Thieben, M. J.; Lennon, V.; Boeve, B. F.; et al. Potentially Reversible Autoimmune Limbic Encephalitis with Neuronal Potassium Channel Antibody. *Neurology* **2004**, *62*, 1177–1182.
- Vincent, A.; Buckley, C.; Schott, J. M.; et al. Potassium Channel Antibody-Associated Encephalopathy: A Potentially Immunotherapy-Responsive Form of Limbic Encephalitis. *Brain* **2004**, *127*, 701–712.
- Shieh, C. C.; Coghlan, M.; Sullivan, J. P.; et al. Potassium Channels: Molecular Defects, Diseases, and Therapeutic Opportunities. *Pharmacol. Rev.* **2000**, *52*, 557–593.
- Riera, A. R. P.; Uchida, A. H.; Ferreira, C.; et al. Relationship among Amiodarone, New Class III Antiarrhythmics, Miscellaneous Agents and Acquired Long QT Syndrome. *Cardiol. J.* **2008**, *15*, 209–219.
- Huang, C.-J.; Harootunian, A.; Maher, M. P.; et al. Characterization of Voltage-Gated Sodium-Channel Blockers by Electrical Stimulation and Fluorescence Detection of Membrane Potential. *Nat. Biotechnol.* **2006**, *24*, 439–446.
- Dunlop, J.; Bowlby, M.; Peri, R.; et al. High-Throughput Electrophysiology: An Emerging Paradigm for Ion-Channel Screening and Physiology. *Nat. Rev. Drug Discov.* **2008**, *7*, 358–368.
- Gribble, F. M.; Reimann, F. Sulphonylurea Action Revisited: The Post-Cloning Era. *Diabetologia* **2003**, *46*, 875–891.
- Arcangeli, A.; Crociani, O.; Lastraioli, E.; et al. Targeting Ion Channels in Cancer: A Novel Frontier in Antineoplastic Therapy. *Curr. Med. Chem.* **2009**, *16*, 66–93.
- Hemmerlein, B.; Weseloh, R. M.; Mello de Queiroz, F.; et al. Overexpression of Eag1 Potassium Channels in Clinical Tumours. *Mol. Cancer* **2006**, *5*, 41.
- Pardo, L. A.; Contreras-Jurado, C.; Zientkowska, M.; et al. Role of Voltage-Gated Potassium Channels in Cancer. *J. Membr. Biol.* **2005**, *205*, 115–124.
- Bichet, D.; Haass, F. A.; Jan, L. Y. Merging Functional Studies with Structures of Inward-Rectifier K(+) Channels. *Nat. Rev. Neurosci.* **2003**, *4*, 957–967.
- Lopatin, A. N.; Makhina, E. N.; Nichols, C. G. Potassium Channel Block by Cytoplasmic Polyamines as the Mechanism of Intrinsic Rectification. *Nature* **1994**, *372*, 366–369.
- Matsuda, H.; Saigusa, A.; Irisawa, H. Ohmic Conductance through the Inwardly Rectifying K Channel and Blocking by Internal Mg²⁺. *Nature* **1987**, *325*, 156–159.
- Hibino, H.; Inanobe, A.; Furutani, K.; et al. Inwardly Rectifying Potassium Channels: Their Structure, Function, and Physiological Roles. *Physiol. Rev.* **2010**, *90*, 291–366.
- Enyedi, P.; Czirájk, G. Molecular Background of Leak K⁺ Currents: Two-Pore Domain Potassium Channels. *Physiol. Rev.* **2010**, *90*, 559–605.
- Bittner, S.; Budde, T.; Wiendl, H.; et al. From the Background to the Spotlight: TASK Channels in Pathological Conditions. *Brain Pathol.* **2010**, *20*, 999–1009.
- Goonetilleke, L.; Quayle, J. TREK-1 K⁺ Channels in the Cardiovascular System: Their Significance and Potential as a Therapeutic Target. *Cardiovasc. Ther.* **2012**, *30*, 23–29.

31. Bezanilla, F. The Voltage Sensor in Voltage-Dependent Ion Channels. *Physiol. Rev.* **2000**, *80*, 555–592.
32. Long, S. B.; Campbell, E. B.; Mackinnon, R. Voltage Sensor of Kv1.2: Structural Basis of Electromechanical Coupling. *Science* **2005**, *309*, 903–908.
33. Bao, L.; Kaldany, C.; Holmstrand, E. C.; et al. Mapping the BKCa Channel's "Ca²⁺ Bowl": Side-Chains Essential for Ca²⁺ Sensing. *J. Gen. Physiol.* **2004**, *123*, 475–489.
34. Maylie, J.; Bond, C. T.; Herson, P. S.; et al. Small Conductance Ca²⁺-Activated K⁺ Channels and Calmodulin. *J. Physiol.* **2004**, *554*, 255–261.
35. Tempel, B. L.; Papazian, D. M.; Schwarz, T. L.; et al. Sequence of a Probable Potassium Channel Component Encoded at Shaker Locus of *Drosophila*. *Science* **1987**, *237*, 770–775.
36. Browne, D. L.; Ganchar, S. T.; Nutt, J. G.; et al. Episodic Ataxia/Myokymia Syndrome Is Associated with Point Mutations in the Human Potassium Channel Gene, KCNA1. *Nat. Genet.* **1994**, *8*, 136–140.
37. Geiger, J. R. P.; Jonas, P. Dynamic Control of Presynaptic Ca²⁺ Inflow by Fast-Inactivating K⁺ Channels in Hippocampal Mossy Fiber Boutons. *Neuron* **2000**, *28*, 927–939.
38. D'Adamo, M. C.; Imbrici, P.; Sponcichetti, F.; et al. Mutations in the KCNA1 Gene Associated with Episodic Ataxia Type-1 Syndrome Impair Heteromeric Voltage-Gated K(+) Channel Function. *FASEB J.* **1999**, *13*, 1335–1345.
39. Lu, Q.; Peevey, J.; Jow, F.; et al. Disruption of Kv1.1 N-Type Inactivation by Novel Small Molecule Inhibitors (Disinactivators). *Bioorganic Med. Chem.* **2008**, *16*, 3067–3075.
40. Stühmer, W.; Ruppersberg, J. P.; Schröter, K. H.; et al. Molecular Basis of Functional Diversity of Voltage-Gated Potassium Channels in Mammalian Brain. *EMBO J.* **1989**, *8*, 3235–3244.
41. Rudy, B.; McBain, C. J. Kv3 Channels: Voltage-Gated K⁺ Channels Designed for High-Frequency Repetitive Firing. *Trends Neurosci.* **2001**, *24*, 517–526.
42. Waters, M. F.; Minassian, N. A.; Stevanin, G.; et al. Mutations in Voltage-Gated Potassium Channel KCNC3 Cause Degenerative and Developmental Central Nervous System Phenotypes. *Nat. Genet.* **2006**, *38*, 447–451.
43. Zhao, J.; Zhu, J.; Thornhill, W. B. Spinocerebellar Ataxia-13 Kv3.3 Potassium Channels: Arginine-to-Histidine Mutations Affect Both Functional and Protein Expression on the Cell Surface. *Biochem. J.* **2013**, *454*, 259–265.
44. Jerng, H. H.; Pfaffinger, P. J.; Covarrubias, M. Molecular Physiology and Modulation of Somatodendritic A-Type Potassium Channels. *Mol. Cell. Neurosci.* **2004**, *27*, 343–369.
45. Häusser, M.; Spruston, N.; Stuart, G. J. Diversity and Dynamics of Dendritic Signaling. *Science* **2000**, *290*, 739–744.
46. Singh, B.; Ogiwara, I.; Kaneda, M.; et al. A Kv4.2 Truncation Mutation in a Patient with Temporal Lobe Epilepsy. *Neurobiol. Dis.* **2006**, *24*, 245–253.
47. Smith, S. E. P.; Xu, L.; Kasten, M. R.; et al. Mutant LGII Inhibits Seizure-Induced Trafficking of Kv4.2 Potassium Channels. *J. Neurochem.* **2012**, *120*, 611–621.
48. Escoubas, P.; Diochot, S.; Célérier, M.-L.; et al. Novel Tarantula Toxins for Subtypes of Voltage-Dependent Potassium Channels in the Kv2 and Kv4 Subfamilies. *Mol. Pharmacol.* **2002**, *62*, 48–57.
49. Lundby, A.; Jespersen, T.; Schmitt, N.; et al. Effect of the Ito Activator NS5806 on Cloned K v4 Channels Depends on the Accessory Protein KChIP2. *Br. J. Pharmacol.* **2010**, *160*, 2028–2044.
50. Brown, D. A.; Adams, P. R. Muscarinic Suppression of a Novel Voltage-Sensitive K⁺ Current in a Vertebrate Neurone. *Nature* **1980**, *283*, 673–676.
51. Brown, D. A.; Passmore, G. M. Neural KCNQ (Kv7) Channels. *Br. J. Pharmacol.* **2009**, *156*, 1185–1195.
52. Singh, N. A.; Westenskow, P.; Charlier, C.; et al. KCNQ2 and KCNQ3 Potassium Channel Genes in Benign Familial Neonatal Convulsions: Expansion of the Functional and Mutation Spectrum. *Brain* **2003**, *126*, 2726–2737.
53. Singh, N. A.; Charlier, C.; Stauffer, D.; et al. A Novel Potassium Channel Gene, KCNQ2, Is Mutated in an Inherited Epilepsy of Newborns. *Nat. Genet.* **1998**, *18*, 25–29.
54. Charlier, C.; Singh, N.; Ryan, S. G.; et al. A Pore Mutation in a Novel KQT-Like Potassium Channel Gene in an Idiopathic Epilepsy Family. *Nat. Genet.* **1998**, *18*, 53–55.
55. Gillling, M.; Rasmussen, H. B.; Calloe, K.; et al. Dysfunction of the Heteromeric KV7.3/KV7.5 Potassium Channel Is Associated with Autism Spectrum Disorders. *Front. Genet.* **2013**, *4*, 54.
56. Hu, H.; Vervaeke, K.; Storm, J. F. Two Forms of Electrical Resonance at Theta Frequencies, Generated by M-Current, H-Current and Persistent Na⁺ Current in Rat Hippocampal Pyramidal Cells. *J. Physiol.* **2002**, *545*, 783–805.
57. Morgado-Bernal, I. Learning and Memory Consolidation: Linking Molecular and Behavioral Data. *Neuroscience* **2011**, *176*, 12–19.
58. Wang, X. Neurophysiological and Computational Principles of Cortical Rhythms in Cognition. *Physiol. Rev.* **2010**, *90*, 1195–1268.
59. Kennedy, D. P.; Adolphs, R. The Social Brain in Psychiatric and Neurological Disorders. *Trends Cogn. Sci.* **2012**, *16*, 559–572.
60. Kubisch, C.; Schroeder, B. C.; Friedrich, T.; et al. KCNQ4, a Novel Potassium Channel Expressed in Sensory Outer Hair Cells, Is Mutated in Dominant Deafness. *Cell* **1999**, *96*, 437–446.
61. Coucke, P. J.; Van Hauwe, P.; Kelley, P. M.; et al. Mutations in the KCNQ4 Gene Are Responsible for Autosomal Dominant Deafness in Four DFNA2 Families. *Hum. Mol. Genet.* **1999**, *8*, 1321–1328.
62. Hübner, C. A.; Jentsch, T. J. Ion Channel Diseases. *Hum. Mol. Genet.* **2002**, *11*, 2435–2445.
63. Kharkovets, T.; Hardelin, J. P.; Safieddine, S.; et al. KCNQ4, a K⁺ Channel Mutated in a Form of Dominant Deafness, Is Expressed in the Inner Ear and the Central Auditory Pathway. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 4333–4338.
64. Jentsch, T. J. Neuronal KCNQ Potassium Channels: Physiology and Role in Disease. *Nat. Rev. Neurosci.* **2000**, *1*, 21–30.
65. French, J. A.; Abou-Khalil, B. W.; Leroy, R. F.; et al. Randomized, Double-Blind, Placebo-Controlled Trial of Ezogabine (Retigabine) in Partial Epilepsy. *Neurology* **2011**, *76*, 1555–1563.

66. Brodie, M. J.; Lerche, H.; Gil-Nagel, A.; et al. Efficacy and Safety of Adjunctive Ezogabine (Retigabine) in Refractory Partial Epilepsy. *Neurology* **2010**, *75*, 1817–1824.
67. Lowry, F. Epilepsy Drug Ezogabine Gets Green Light from FDA Advisory Panel <http://www.medscape.com/viewarticle/726809> (accessed Feb 4, 2015).
68. Kapetanovic, I. M.; Yonekawa, W. D.; Kupferberg, H. J. The Effects of D-23129, a New Experimental Anticonvulsant Drug, on Neurotransmitter Amino Acids in the Rat Hippocampus In Vitro. *Epilepsy Res.* **1995**, *22*, 167–173.
69. Rode, F.; Svalø, J.; Sheykhzade, M.; et al. Functional Effects of the KCNQ Modulators Retigabine and XE991 in the Rat Urinary Bladder. *Eur. J. Pharmacol.* **2010**, *638*, 121–127.
70. GlaxoSmithKline. *Starting Trobalt (Retigabine): Points to Discuss with Patients*; **2013**. GlaxoSmithKline, Brentford, UK.
71. Splinter, M. Y. Efficacy of Retigabine in Adjunctive Treatment of Partial Onset Seizures in Adults. *J. Cent. Nerv. Syst. Dis.* **2013**, *5*, 31–41.
72. Gil-Nagel, A.; Brodie, M. J.; Leroy, R.; et al. Safety and Efficacy of Ezogabine (Retigabine) in Adults with Refractory Partial-Onset Seizures: Interim Results from Two Ongoing Open-Label Studies. *Epilepsy Res.* **2012**, *102*, 117–121.
73. Wehner, T.; Chinmasami, S.; Novy, J.; et al. Long Term Retention of Retigabine in a Cohort of People with Drug Resistant Epilepsy. *Seizure* **2014**, *23*, 878–881.
74. Padilla, K.; Wickenden, A. D.; Gerlach, A. C.; et al. The KCNQ2/3 Selective Channel Opener ICA-27243 Binds to a Novel Voltage-Sensor Domain Site. *Neurosci. Lett.* **2009**, *465*, 138–142.
75. Knaus, H. G.; Schwarzer, C.; Koch, R. O.; et al. Distribution of High-Conductance Ca²⁺-Activated K⁺ Channels in Rat Brain: Targeting to Axons and Nerve Terminals. *J. Neurosci.* **1996**, *16*, 955–963.
76. Grunnet, M.; Kaufmann, W. A. Coassembly of Big Conductance Ca²⁺-Activated K⁺ Channels and L-Type Voltage-Gated Ca²⁺ Channels in Rat Brain. *J. Biol. Chem.* **2004**, *279*, 36445–36453.
77. Marrion, N. V.; Tavalin, S. J. Selective Activation of Ca²⁺-Activated K⁺ Channels by Co-Localized Ca²⁺ Channels in Hippocampal Neurons. *Nature* **1998**, *395*, 900–905.
78. Müller, A.; Kukley, M.; Uebachs, M.; et al. Nanodomains of Single Ca²⁺ Channels Contribute to Action Potential Repolarization in Cortical Neurons. *J. Neurosci.* **2007**, *27*, 483–495.
79. Du, W.; Bautista, J. F.; Yang, H.; et al. Calcium-Sensitive Potassium Channelopathy in Human Epilepsy and Paroxysmal Movement Disorder. *Nat. Genet.* **2005**, *37*, 733–738.
80. Gu, N.; Vervaeke, K.; Storm, J. F. BK Potassium Channels Facilitate High-Frequency Firing and Cause Early Spike Frequency Adaptation in Rat CA1 Hippocampal Pyramidal Cells. *J. Physiol.* **2007**, *580*, 859–882.
81. Bentzen, B. H.; Olesen, S.; Rønn, L. C. B.; et al. BK Channel Activators and Their Therapeutic Perspectives. *Front. Physiol.* **2014**, *5*, 1–12.
82. Nardi, A.; Olesen, S.-P. BK Channel Modulators: A Comprehensive Overview. *Curr. Med. Chem.* **2008**, *15*, 1126–1146.
83. Bagal, S. K.; Brown, A. D.; Cox, P. J.; et al. Ion Channels as Therapeutic Targets: A Drug Discovery Perspective. *J. Med. Chem.* **2013**, *56*, 593–624.
84. Park, W. S.; Kang, S. H.; Son, Y. K.; et al. The Mitochondrial Ca²⁺-Activated K⁺ Channel Activator, NS 1619 Inhibits L-Type Ca²⁺ Channels in Rat Ventricular Myocytes. *Biochem. Biophys. Res. Commun.* **2007**, *362*, 31–36.
85. Jensen, B. S. BMS-204352: A Potassium Channel Opener Developed for the Treatment of Stroke. *CNS Drug Rev.* **2002**, *8*, 353–360.
86. Takumi, T.; Ishii, T.; Horio, Y.; et al. A Novel ATP-Dependent Inward Rectifier Potassium Channel Expressed Predominantly in Glial Cells. *J. Biol. Chem.* **1995**, *270*, 16339–16346.
87. Higashi, K.; Fujita, A.; Inanobe, A.; et al. An Inwardly Rectifying K⁽⁺⁾ Channel, Kir4.1, Expressed in Astrocytes Surrounds Synapses and Blood Vessels in Brain. *Am. J. Physiol. Cell Physiol.* **2001**, *281*, C922–C931.
88. Kofuji, P.; Newman, E. A. Potassium Buffering in the Central Nervous System. *Neuroscience* **2004**, *129*, 1045–1056.
89. Olsen, M. L.; Sontheimer, H. Functional Implications for Kir4.1 Channels in Glial Biology: From K⁺ Buffering to Cell Differentiation. *J. Neurochem.* **2008**, *107*, 589–601.
90. Ransom, C. B.; Ransom, B. R.; Sontheimer, H. Activity-Dependent Extracellular K⁺ Accumulation in Rat Optic Nerve: The Role of Glial and Axonal Na⁺ Pumps. *J. Physiol.* **2000**, *522*, 427–442.
91. Butt, A. M.; Kalsi, A. Inwardly Rectifying Potassium Channels (Kir) in Central Nervous System Glia: A Special Role for Kir4.1 in Glial Functions. *J. Cell. Mol. Med.* **2006**, *10*, 33–44.
92. Bordey, A.; Sontheimer, H. Properties of Human Glial Cells Associated with Epileptic Seizure Foci. *Epilepsy Res.* **1998**, *32*, 286–303.
93. Scholl, U. I.; Choi, M.; Liu, T.; et al. Seizures, Sensorineural Deafness, Ataxia, Mental Retardation, and Electrolyte Imbalance (SeSAME Syndrome) Caused by Mutations in KCNJ10. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 5842–5847.
94. Freudenthal, B.; Kulaveerasingam, D.; Lingappa, L.; et al. KCNJ10 Mutations Disrupt Function in Patients with East Syndrome. *Nephron Physiol.* **2011**, *119*, 40–48.
95. Bockenhauer, D.; Feather, S.; Stancescu, H. C.; et al. Epilepsy, Ataxia, Sensorineural Deafness, Tubulopathy, and KCNJ10 Mutations. *N. Engl. J. Med.* **2009**, *360*, 1960–1970.
96. Nichols, C. G. KATP Channels as Molecular Sensors of Cellular Metabolism. *Nature* **2006**, *440*, 470–476.
97. Gloyn, A. L.; Diatloff-Zito, C.; Edghill, E. L.; et al. KCNJ11 Activating Mutations Are Associated with Developmental Delay, Epilepsy and Neonatal Diabetes Syndrome and Other Neurological Features. *Eur. J. Hum. Genet.* **2006**, *14*, 824–830.
98. Ashcroft, F. M.; Gribble, F. M. ATP-Sensitive K⁺ Channels and Insulin Secretion: Their Role in Health and Disease. *Diabetologia* **1999**, *42*, 903–919.
99. Zawar, C.; Plant, T. D.; Schirra, C.; et al. Cell-Type Specific Expression of ATP-Sensitive Potassium Channels in the Rat Hippocampus. *J. Physiol.* **1999**, *514*, 327–341.

100. Griesemer, D.; Zawar, C.; Neumcke, B. Cell-Type Specific Depression of Neuronal Excitability in Rat Hippocampus by Activation of ATP-Sensitive Potassium Channels. *Eur. Biophys. J.* **2002**, *31*, 467–477.
101. Judge, S. I. V.; Smith, P. J. Patents Related to Therapeutic Activation of K(ATP) and K(2P) Potassium Channels for Neuroprotection: Ischemic/hypoxic/anoxic Injury and General Anesthetics. *Expert Opin. Ther. Pat.* **2009**, *19*, 433–460.
102. Patel, C.; Yan, G. X.; Antzelevitch, C. Short QT Syndrome: From Bench to Bedside. *Circ. Arrhythmia Electrophysiol.* **2010**, *3*, 401–408.
103. Delisle, B. P.; Anson, B. D.; Rajamani, S.; et al. Biology of Cardiac Arrhythmias: Ion Channel Protein Trafficking. *Circ. Res.* **2004**, *94*, 1418–1428.
104. Wang, Q.; Curran, M. E.; Splawski, I.; et al. Positional Cloning of a Novel Potassium Channel Gene: KVLQT1 Mutations Cause Cardiac Arrhythmias. *Nat. Genet.* **1996**, *12*, 17–23.
105. Schwartz, P. J.; Spazzolini, C.; Crotti, L.; et al. The Jervell and Lange-Nielsen Syndrome: Natural History, Molecular Basis, and Clinical Outcome. *Circulation* **2006**, *113*, 783–790.
106. Splawski, I.; Tristani-Firouzi, M.; Lehmann, M. H.; et al. Mutations in the hminK Gene Cause Long QT Syndrome and Suppress Iks Function. *Nat. Genet.* **1997**, *17*, 338–340.
107. Olesen, M. S.; Bentzen, B. H.; Nielsen, J. B.; et al. Mutations in the Potassium Channel Subunit KCNE1 Are Associated with Early-Onset Familial Atrial Fibrillation. *BMC Med. Genet.* **2012**, *13*, 24.
108. Bellocq, C.; Van Ginneken, A. C. G.; Bezzina, C. R.; et al. Mutation in the KCNQ1 Gene Leading to the Short QT-Interval Syndrome. *Circulation* **2004**, *109*, 2394–2397.
109. Chen, Y.; Xu, S.-J.; Bendahhou, S.; et al. KCNQ1 Gain-of-Function Mutation in Familial Atrial Fibrillation. *Science* **2003**, *299*, 251–254.
110. Lai, L.-P.; Su, M.-J.; Tseng, Y.-Z.; et al. Sensitivity of the Slow Component of the Delayed Rectifier Potassium Current (IKs) to Potassium Channel Blockers: Implications for Clinical Reverse Use-Dependent Effects. *J. Biomed. Sci.* **1999**, *6*, 251–259.
111. Schenzer, A.; Friedrich, T.; Pusch, M.; et al. Molecular Determinants of KCNQ (Kv7) K⁺ Channel Sensitivity to the Anticonvulsant Retigabine. *J. Neurosci.* **2005**, *25*, 5051–5060.
112. Seeböhm, G.; Pusch, M.; Chen, J.; et al. Pharmacological Activation of Normal and Arrhythmia-Associated Mutant KCNQ1 Potassium Channels. *Circ. Res.* **2003**, *93*, 941–947.
113. Towart, R.; Linders, J. T. M.; Hermans, A. N.; et al. Blockade of the I(Ks) Potassium Channel: An Overlooked Cardiovascular Liability in Drug Safety Screening? *J. Pharmacol. Toxicol. Methods* **2009**, *60*, 1–10.
114. London, B.; Trudeau, M.; Newton, K.; et al. Two Isoforms of the Mouse Ether-a-Go-go-Related Gene Coassemble to Form Channels With Properties Similar to the Rapidly Activating Component of the Cardiac Delayed Rectifier K⁺ Current. *Circ. Res.* **1997**, *81*, 870–878.
115. Curran, M. E.; Splawski, I.; Timothy, K. W.; et al. A Molecular Basis for Cardiac Arrhythmia: HERG Mutations Cause Long QT Syndrome. *Cell* **1995**, *80*, 795–803.
116. Perrin, M. J.; Subbiah, R. N.; Vandenberg, J. I.; et al. Human Ether-a-Go-Go Related Gene (hERG) K⁺ Channels: Function and Dysfunction. *Prog. Biophys. Mol. Biol.* **2008**, *98*, 137–148.
117. Brugada, R.; Hong, K.; Dumaine, R.; et al. Sudden Death Associated with Short-QT Syndrome Linked to Mutations in HERG. *Circulation* **2004**, *109*, 30–35.
118. Itoh, H.; Sakaguchi, T.; Ashihara, T.; et al. A Novel KCNH2 Mutation as a Modifier for Short QT Interval. *Int. J. Cardiol.* **2009**, *137*, 83–85.
119. Abbott, G. W.; Sesti, F.; Splawski, I.; et al. MiRP1 Forms IKr Potassium Channels with HERG and Is Associated with Cardiac Arrhythmia. *Cell* **1999**, *97*, 175–187.
120. Jiang, M.; Zhang, M.; Tang, D. G.; et al. KCNE2 Protein Is Expressed in Ventricles of Different Species, and Changes in Its Expression Contribute to Electrical Remodeling in Diseased Hearts. *Circulation* **2004**, *109*, 1783–1788.
121. Gaborit, N.; Le Bouter, S.; Szuts, V.; et al. Regional and Tissue Specific Transcript Signatures of Ion Channel Genes in the Non-Diseased Human Heart. *J. Physiol.* **2007**, *582*, 675–693.
122. Yang, Y.; Xia, M.; Jin, Q.; et al. Identification of a KCNE2 Gain-of-Function Mutation in Patients with Familial Atrial Fibrillation. *Am. J. Hum. Genet.* **2004**, *75*, 899–905.
123. Zhou, P.; Babcock, J.; Liu, L.; et al. Activation of Human Ether-a-Go-Go Related Gene (hERG) Potassium Channels by Small Molecules. *Acta Pharmacol. Sin.* **2011**, *32*, 781–788.
124. Bentzen, B. H.; Bahrke, S.; Wu, K.; et al. Pharmacological Activation of Kv11.1 in Transgenic Long QT-1 Rabbits. *J. Cardiovasc. Pharmacol.* **2011**, *57*, 223–230.
125. Kaufman, E. S.; Ficker, E. Is Restoration of Intracellular Trafficking Clinically Feasible in the Long QT Syndrome? The Example of HERG Mutations. *J. Cardiovasc. Electrophysiol.* **2003**, *14*, 320–322.
126. Niwa, N.; Nerbonne, J. M. Molecular Determinants of Cardiac Transient Outward Potassium Current (Ito) Expression and Regulation. *J. Mol. Cell. Cardiol.* **2010**, *48*, 12.
127. Workman, A. J.; Marshall, G. E.; Rankin, A. C.; et al. Transient Outward K⁺ Current (ITO) Reduction Prolongs Action Potentials and Promotes Afterdepolarisations: A Dynamic-Clamp Study in Human and Rabbit Cardiac Atrial Myocytes. *J. Physiol.* **2012**, *17*, 4289–4305.
128. Giudicessi, J. R.; Ye, D.; Tester, D. J.; et al. Transient Outward Current (Ito) Gain-of-Function Mutations in the KCND3-Encoded Kv4.3 Potassium Channel and Brugada Syndrome. *Heart Rhythm* **2011**, *8*, 1024–1032.
129. Olesen, M. S.; Refsgaard, L.; Holst, A. G.; et al. A Novel KCND3 Gain-of-Function Mutation Associated with Early-Onset of Persistent Lone Atrial Fibrillation. *Cardiovasc. Res.* **2013**, *98*, 488–495.
130. Lundby, A.; Ravn, L. S.; Svendsen, J. H.; et al. KCNE3 Mutation V17M Identified in a Patient with Lone Atrial Fibrillation. *Cell. Physiol. Biochem.* **2008**, *21*, 47–54.
131. Delpón, E.; Cordeiro, J. M.; Núñez, L.; et al. Functional Effects of KCNE3 Mutation and Its Role in the Development

- of Brugada Syndrome. *Circ. Arrhythm. Electrophysiol.* **2008**, *1*, 209–218.
132. Calloe, K.; Cordeiro, J. M.; Di Diego, J. M.; et al. A Transient Outward Potassium Current Activator Recapitulates the Electrocardiographic Manifestations of Brugada Syndrome. *Cardiovasc. Res.* **2009**, *81*, 686–694.
133. Olson, T. M.; Alekseev, A. E.; Liu, X. K.; et al. Kv1.5 Channelopathy due to KCNA5 Loss-of-Function Mutation Causes Human Atrial Fibrillation. *Hum. Mol. Genet.* **2006**, *15*, 2185–2191.
134. Yang, Y.; Li, J.; Lin, X.; et al. Novel KCNA5 Loss-of-Function Mutations Responsible for Atrial Fibrillation. *J. Hum. Genet.* **2009**, *54*, 277–283.
135. Van Wagoner, D. R.; Pond, A. L.; McCarthy, P. M.; et al. Outward K⁺ Current Densities and Kv1.5 Expression Are Reduced in Chronic Human Atrial Fibrillation. *Circ. Res.* **1997**, *80*, 772–781.
136. Tian, D.; Frishman, W. H. Vernakalant: A New Drug to Treat Patients with Acute Onset Atrial Fibrillation. *Cardiol. Rev.* **2011**, *19*, 41–44.
137. Dobrev, D.; Friedrich, A.; Voigt, N.; et al. The G Protein-Gated Potassium Current IK_{ACh} Is Constitutively Active in Patients with Chronic Atrial Fibrillation. *Circulation* **2005**, *112*, 3697–3706.
138. Machida, T.; Hashimoto, N.; Kuwahara, I.; et al. Effects of a Highly Selective Acetylcholine-Activated K⁺ Channel Blocker on Experimental Atrial Fibrillation. *Circ. Arrhythmia Electrophysiol.* **2011**, *4*, 94–102.
139. Hashimoto, N.; Yamashita, T.; Tsuruzoe, N. Characterization of In Vivo and In Vitro Electrophysiological and Antiarrhythmic Effects of a Novel IK_{ACh} Blocker, NIP-151: A Comparison with an IK_r-Blocker Dofetilide. *J. Cardiovasc. Pharmacol.* **2008**, *51*, 162–169.
140. Yang, Y.; Yang, Y.; Liang, B.; et al. Identification of a Kir3.4 Mutation in Congenital Long QT Syndrome. *Am. J. Hum. Genet.* **2010**, *86*, 872–880.
141. Beckmann, C.; Rinne, A.; Littwitz, C.; et al. G Protein-Activated (GIRK) Current in Rat Ventricular Myocytes Is Masked by Constitutive Inward Rectifier Current (IK₁). *Cell. Physiol. Biochem.* **2008**, *21*, 259–268.
142. Skibsbjerg, L.; Poulet, C.; Diness, J. G.; et al. Small-Conductance Calcium-Activated Potassium (SK) Channels Contribute to Action Potential Repolarization in Human Atria. *Cardiovasc. Res.* **2014**, *103*, 156–167.
143. Diness, J. G.; Bentzen, B. H.; Sørensen, U. S.; et al. Role of Calcium Activated Potassium Channels in AF Pathophysiology and Therapy. *J. Cardiovasc. Pharmacol.* **In press**.
144. Diness, J. G.; Sørensen, U. S.; Nissen, J. D.; et al. Inhibition of Small-Conductance Ca²⁺-Activated K⁺ Channels Terminates and Protects against Atrial Fibrillation. *Circ. Arrhythmia Electrophysiol.* **2010**, *3*, 380–390.
145. Jackson, W. F. Ion Channels and Vascular Tone. *Hypertension* **2000**, *35*, 173–178.
146. Ng, F. L.; Davis, A. J.; Jepps, T. A.; et al. Expression and Function of the K⁺ Channel KCNQ Genes in Human Arteries. *Br. J. Pharmacol.* **2011**, *162*, 42–53.
147. Miguel-Velado, E.; Moreno-Domínguez, A.; Colinas, O.; et al. Contribution of Kv Channels to Phenotypic Remodeling of Human Uterine Artery Smooth Muscle Cells. *Circ. Res.* **2005**, *97*, 1280–1287.
148. Yuan, J. X.; Aldinger, A. M.; Juhaszova, M.; et al. Dysfunctional Voltage-Gated K⁺ Channels in Pulmonary Artery Smooth Muscle Cells of Patients with Primary Pulmonary Hypertension. *Circulation* **1998**, *98*, 1400–1406.
149. Yuan, X. J.; Wang, J.; Juhaszova, M.; et al. Attenuated K⁺ Channel Gene Transcription in Primary Pulmonary Hypertension. *Lancet* **1998**, *351*, 726–727.
150. Pozeg, Z. I.; Michelakis, E. D.; McMurtry, S.; et al. In Vivo Gene Transfer of the O₂-Sensitive Potassium Channel Kv1.5 Reduces Pulmonary Hypertension and Restores Hypoxic Pulmonary Vasoconstriction in Chronically Hypoxic Rats. *Circulation* **2003**, *107*, 2037–2044.
151. Hill, M. A.; Zou, H.; Potocnik, S. J.; et al. Invited Review: Arteriolar Smooth Muscle Mechanotransduction: Ca(2+) Signaling Pathways Underlying Myogenic Reactivity. *J. Appl. Physiol.* **2001**, *91*, 973–983.
152. Jaggar, J. H.; Wellman, G. C.; Heppner, T. J.; et al. Ca²⁺ Channels, Ryanodine Receptors and Ca²⁺-Activated K⁺ Channels: A Functional Unit for Regulating Arterial Tone. *Acta Physiol. Scand.* **1998**, *164*, 577–587.
153. Nelson, M. T.; Cheng, H.; Rubart, M.; et al. Relaxation of Arterial Smooth Muscle by Calcium Sparks. *Science* **1995**, *270*, 633–637.
154. Yang, Y.; Li, P.-Y.; Cheng, J.; et al. Function of BKCa Channels Is Reduced in Human Vascular Smooth Muscle Cells from Han Chinese Patients With Hypertension. *Hypertension* **2012**, *61*, 519–525.
155. Amberg, G. C.; Bonev, A. D.; Rossow, C. F.; et al. Modulation of the Molecular Composition of Large Conductance, Ca(2+) Activated K(+) Channels in Vascular Smooth Muscle during Hypertension. *J. Clin. Invest.* **2003**, *112*, 717–724.
156. Tomás, M.; Vázquez, E.; Fernández-Fernández, J. M.; et al. Genetic Variation in the KCNMA1 Potassium Channel Alpha Subunit as Risk Factor for Severe Essential Hypertension and Myocardial Infarction. *J. Hypertens.* **2008**, *26*, 2147–2153.
157. Fernández-Fernández, J. M.; Tomás, M.; Vázquez, E.; et al. Gain-of-Function Mutation in the KCNMB1 Potassium Channel Subunit Is Associated with Low Prevalence of Diastolic Hypertension. *J. Clin. Invest.* **2004**, *113*, 1032–1039.
158. Edwards, G.; Félétou, M.; Weston, A. H. Endothelium-Derived Hyperpolarising Factors and Associated Pathways: A Synopsis. *Pflugers Arch. Eur. J. Physiol.* **2010**, *459*, 863–879.
159. Sandow, S. L.; Neylon, C. B.; Chen, M. X.; et al. Spatial Separation of Endothelial Small- and Intermediate-Conductance Calcium-Activated Potassium Channels (KCa) and Connexins: Possible Relationship to Vasodilator Function? *J. Anat.* **2006**, *209*, 689–698.
160. Sandow, S. L.; Tare, M.; Coleman, H. A.; et al. Involvement of Myoendothelial Gap Junctions in the Actions of Endothelium-Derived Hyperpolarizing Factor. *Circ. Res.* **2002**, *90*, 1108–1113.
161. Edwards, G.; Dora, K. A.; Gardener, M. J.; et al. K⁺ Is an Endothelium-Derived Hyperpolarizing Factor in Rat Arteries. *Nature* **1998**, *396*, 269–272.
162. Köhler, R. Single-Nucleotide Polymorphisms in Vascular Ca²⁺-Activated K⁺-Channel Genes and Cardiovascular Disease. *Pflugers Arch. Eur. J. Physiol.* **2010**, *460*, 343–351.

163. Yamaguchi, M.; Nakayama, T.; Fu, Z.; et al. Relationship between Haplotypes of KCNN4 Gene and Susceptibility to Human Vascular Diseases in Japanese. *Med. Sci. Monit.* **2009**, *15*, CR389–397.
164. Gurney, A.; Manoury, B. Two-Pore Potassium Channels in the Cardiovascular System. *Eur. Biophys. J.* **2009**, *38*, 305–318.
165. Ma, L.; Roman-Campos, D.; Austin, E. D.; et al. A Novel Channelopathy in Pulmonary Arterial Hypertension. *N. Engl. J. Med.* **2013**, *369*, 351–361.
166. Rowe, S. M.; Verkman, A. S. Cystic Fibrosis Transmembrane Regulator Correctors and Potentiators. *Cold Spring Harb. Perspect. Med.* **2013**, *3*, a009761.
167. Wainwright, C. E.; Elborn, J. S.; Ramsey, B. W.; et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N. Engl. J. Med.* **2015**, *373*, 220–231.
168. Duarri, A.; Jezierska, J.; Fokkens, M.; et al. Mutations in Potassium Channel KCND3 Cause Spinocerebellar Ataxia Type 19. *Ann. Neurol.* **2012**, *72*, 870–880.
169. Schulze-Bahr, E.; Wang, Q.; Wedekind, H.; et al. KCNE1 Mutations Cause Jervell and Lange-Nielsen Syndrome. *Nat. Genet.* **1997**, *17*, 267–268.
170. Tyson, J.; Tranobjærg, L.; Bellman, S.; et al. IsK and KvLQT1: Mutation in Either of the Two Subunits of the Slow Component of the Delayed Rectifier Potassium Channel Can Cause Jervell and Lange-Nielsen Syndrome. *Hum. Mol. Genet.* **1997**, *6*, 2179–2185.
171. Neyroud, N.; Tesson, F.; Denjoy, I.; et al. A Novel Mutation in the Potassium Channel Gene KVLQT1 Causes the Jervell and Lange-Nielsen Cardioauditory Syndrome. *Nat. Genet.* **1997**, *15*, 186–189.
172. Jervell, A.; Lange-Nielsen, F. Congenital Deaf-Mutism, Functional Heart Disease with Prolongation of the Q-T Interval and Sudden Death. *Am. Heart J.* **1957**, *54*, 59–68.
173. Simons, C.; Rash, L. D.; Crawford, J.; et al. Mutations in the Voltage-Gated Potassium Channel Gene KCNH1 Cause Temple-Baraitser Syndrome and Epilepsy. *Nat. Genet.* **2015**, *47*, 73–77.
174. Laumonier, F.; Roger, S.; Guérin, P.; et al. Association of a Functional Deficit of the BKCa Channel, a Synaptic Regulator of Neuronal Excitability, with Autism and Mental Retardation. *Am. J. Psychiatry* **2006**, *163*, 1622–1629.
175. Barcia, G.; Fleming, M. R.; Deligniere, A.; et al. De Novo Gain of Function KCNT1 Channel Mutations Cause Malignant Migrating Partial Seizures of Infancy. *Nat. Genet.* **2013**, *44*, 1255–1259.
176. Zamorano-León, J. J.; Yañez, R.; Jaime, G.; et al. KCNH2 Gene Mutation: A Potential Link between Epilepsy and Long QT-2 Syndrome. *J. Neurogenet.* **2012**, *26*, 382–386.
177. Partemi, S.; Cestèle, S.; Pezzella, M.; et al. Loss-of-Function KCNH2 Mutation in a Family with Long QT Syndrome, Epilepsy, and Sudden Death. *Epilepsia* **2013**, *54*, 112–116.
178. Jespersen, T.; Grønnet, M.; Olesen, S.-P. The KCNQ1 Potassium Channel: From Gene to Physiological Function. *Physiology (Bethesda)* **2005**, *20*, 408–416.
179. Plaster, N. M.; Tawil, R.; Tristani-Firouzi, M.; et al. Mutations in Kir2.1 Cause the Developmental and Episodic Electrical Phenotypes of Andersen’s Syndrome. *Cell* **2001**, *105*, 511–519.
180. Piori, S. G.; Pandit, S. V.; Rivolta, I.; et al. A Novel Form of Short QT Syndrome (SQT3) Is Caused by a Mutation in the KCNJ2 Gene. *Circ. Res.* **2005**, *96*, 800–807.
181. Xia, M.; Jin, Q.; Bendahhou, S.; et al. A Kir2.1 Gain-of-Function Mutation Underlies Familial Atrial Fibrillation. *Biochem. Biophys. Res. Commun.* **2005**, *332*, 1012–1019.
182. Schulze-Bahr, E.; Neu, A.; Friederich, P.; et al. Pacemaker Channel Dysfunction in a Patient with Sinus Node Disease. *J. Clin. Invest.* **2003**, *111*, 1537–1545.
183. Calloe, K.; Ravn, L. S.; Schmitt, N.; et al. Characterizations of a Loss-of-Function Mutation in the Kir3.4 Channel Subunit. *Biochem. Biophys. Res. Commun.* **2007**, *364*, 889–895.
184. Ma, K.; Li, N.; Teng, S.; et al. Modulation of KCNQ1 Current by Atrial Fibrillation-Associated KCNE4 (145E/D) Gene Polymorphism. *Chin. Med. J. (Engl.)* **2007**, *120*, 150–154.
185. Ravn, L. S.; Aizawa, Y.; Pollevick, G. D.; et al. Gain of Function in IKs Secondary to a Mutation in KCNE5 Associated with Atrial Fibrillation. *Hear. Rhythm* **2008**, *5*, 427–435.
186. Olson, T. M.; Alekseev, A. E.; Moreau, C.; et al. K(ATP) Channel Mutation Confers Risk for Vein of Marshall Adrenergic Atrial Fibrillation. *Nat. Clin. Pract. Cardiovasc. Med.* **2007**, *4*, 110–116.