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Chapter

Potassium Channels in the Vascular Diseases

Yan-Rong Zhu, Xiao-Xin Jiang, Peng Ye, Shao-liang Chen and Dai-Min Zhang

Abstract

The vessel wall is an intricate structure composed of three layers: the intima (consisting of endothelial cells), media (consisting of smooth muscle cells and elastic fibers), and externa (consisting of the extracellular matrix scaffold). The homeostasis of the vasculature depends on the consistent function of each layer. In the vascular system, potassium channels are well known to regulate vascular function. The interactions between vascular conditions and membrane potential are complicated. In this chapter, we will focus on the functional regulation of KCa channel, K_{ATP} channel, and K_V channel in the vascular system. Researchers may continuously obtain insights into the functions of these channels and identify new therapeutic targets for vascular diseases.

Keywords: potassium channel, vascular diseases, BK channel, Kv channel, K_{ATP} channel

1. Introduction

The vascular system, which includes an extensive network of arteries, capillaries, and veins, exhibits specific biochemical, cellular, and transport functions. The absorption of essential nutrients and removal of cellular metabolic products both depend on the vasculature [1]. The vessel wall is an intricate structure composed of three layers: the intima, media, and externa. The homeostasis of the vascular system depends on the consistent function of each layer. The thinnest constituent layer is the intima, which consists of a single layer of endothelial cells (ECs) on a basement membrane. Although ECs are typically flat, they are plump or cuboidal in venules composed of numerous endothelial cells [2]. Endothelial cells perform critical functions in all aspects of tissue homeostasis; in addition, they regulate vascular tone by interacting with components of the peripheral nervous system and are related to inflammatory and immunological processes [3, 4]. The media mainly contains smooth muscle cells (SMCs) and elastic fibers. Elastic fibers are mainly a source of structural support, while SMCs play a vital role in maintaining the vascular structure, vascular repair, remodeling, and disease. VSMCs exhibit extraordinary plasticity and undergo remodeling in response to local hemodynamic changes, mechanical forces, hormones, and cytokines [5, 6]. The most remarkable functions of VSMCs are to regulate vascular tone and vessel diameter, which determines blood pressure and tissue perfusion. Some components of vascular contractility, such as the actin cytoskeleton, are required for VSMC proliferation and migration. Circular

RNA, microRNA, and some other transcription factors jointly regulate the expression of smooth muscle α-actin (α-SMA) and the contraction of VSMCs [7, 8]. The outer most layer of the vessel wall is the adventitia. In vertebrates, the adventitia is important because the fibroelastic connective tissue stroma is an important structural component of all tissues. The adventitial stroma contains an extracellular matrix scaffold including fibroblasts, blood and lymphatic vessels, nerve endings, progenitor cells, and immune cells. In one sense, the adventitia is the most complex and heterogeneous compartment of the vessel wall [9].

Ion channels play an important role in the mechanism of action of vasodilators and vasoconstrictors that modulate vascular tone and the effects of disease states, such as hypertension, obesity, and diabetes, which depend on ion channel expression and function. We focus on the basic properties, physiological functions, regulation, and pathological alterations in major classes of K^+ channels that have been detected in VSMCs and/or ECs, including Ca^{2+}-activated K^+ channels, ATP-sensitive K^+ channels, and voltage-gated K^+ channels.

2. Vascular function

In the vascular system, transmembrane voltage regulates vascular function. The interactions between vascular conditions and membrane potential are complicated [10]. The hyperpolarization of the smooth muscle cell membrane potential is evoked by the activation of ion channels, which contributes to vasodilation. A decrease in Ca^{2+} influx resulting from a decrease in the open probability of voltage-dependent calcium channels (Ca_V) and the Ca_V-dependent activation of the sarcoplasmic reticulum are crucial factors contributing to this process [11]. The depolarization of vascular smooth muscle cells causes contraction by opening Ca_V and inducing calcium release. The Ca^{2+}-activated K^+ channels (K_{Ca}) are considered key elements that control vascular tone and blood pressure by modulating membrane hyperpolarization and relaxation. Ca^{2+}-activated K^+ channels, including large conductance Ca^{2+}- and voltage-activated K^+ (BK) channels, intermediate conductance Ca^{2+}-activated K^+ channels (IK), and small-conductance Ca^{2+}-activated K^+ (SK) channels, are widely expressed in the vascular system. Intercellular conduction of electric signals underlies the spread of vasodilation to resistance arteries [10, 12].

3. Ca^{2+}-activated K^+ channel

3.1 The structure of BK channel

BK channels (also known as MaxiK) are widely expressed in vascular smooth muscle cells. Vascular BK channels comprise four pore-forming subunits (BK-α) and four auxiliary subunits: β_1 subunits (BK-β_1) and/or γ_1 subunits (BK-γ_1). BK α, which is encoded by the KCNMA1 gene, has seven transmembrane domains (S0–S6). BK-α has an extra transmembrane segment, S0, and thus its N-terminus is located in the extracellular space. S1–S4 form the voltage-sensor domain (VSD), and S5 and S6 form the ion permeation domain that encompasses the conserved K^+ filter (TVGYG) in the pore loop. The C-terminus of BK channels modulates the voltage sensor and affects the pore, thus influencing channel opening. The ability of specific BK channels to open as a function of Ca^{2+} concentration or as a function of voltage sensors is due to the use of alternative splice sites [13–15]. The C-terminus contains two homologous structural units termed "regulators of conductance for K^+": the proximal portion RCK domain (RCK1) and the distal portion RCK domain (RCK2).

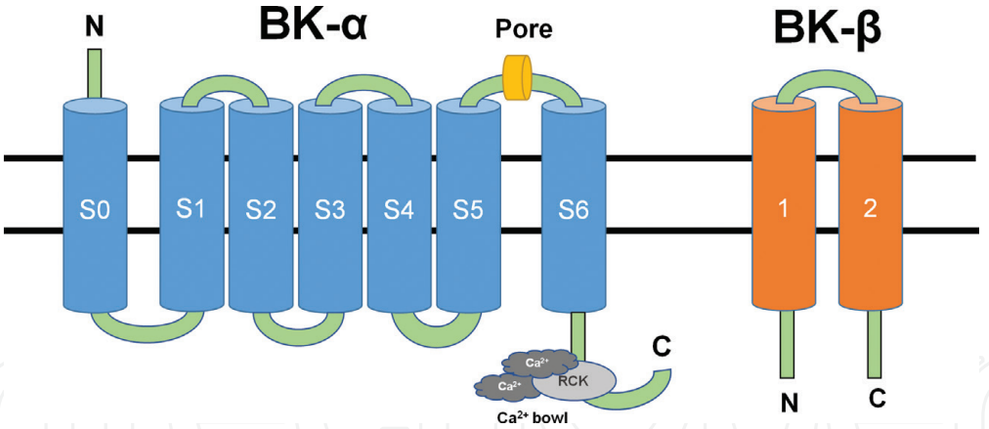

Figure 1.
Schematic structure of one BKα-subunit consisting of 7 transmembrane domains (S0–S6). S1–S4 constitute the voltage-sensing unit, and the S5-P loop-S6 form the ion permeation domain. The Ca^{2+} bowl is a high-affinity divalent cation-binding domain, and the RCK domain (regulator of conductance for K^+) in the C-terminal region is responsible for Ca^{2+} sensitivity. The presence of the β1 subunit increases Ca^{2+} sensitivity and thus channels activity.

The RCK1 domain is related to the formation of the Ca^{2+}-binding site, and the RCK2 contains a "high-affinity" Ca^{2+} bowl domain. The "gating ring" is a Ca^{2+}-sensing apparatus composed of four pairs of RCK1 and RCK2 domains, and the function of gating ring is responsible for allosteric activation of BK channel by Ca^{2+} binding [15–19] (**Figure 1**). Four types of β subunits (BK-β) and four types of γ subunits (BK-γ) modulate almost all aspects of the pharmacological actions and physiological processes mediated by BK channels. The functional mechanism of BK channels regulated by β and γ auxiliary subunits is extremely complicated but is crucial to our understanding of its implications in vascular diseases. In the vasculature, BK-β_1, which is encoded by KCNMB1, is the dominant isoform in VSMCs, and the dysfunction of the β_1 is associated with diabetes, hypertension, and other vascular diseases. Knockout of the BK-β_1 gene produces a remarkable decrease in the Ca^{2+} sensitivity of the channel. In addition, coexpression of the BK-β_1 subunit with the BK-α subunit dramatically alters the calcium sensitivity, similar to the results observed in native VSMCs [15, 20, 21]. As an auxiliary subunit of the BK channels, BK-γ also affects BK channel activity by modulating the voltage and Ca^{2+} sensitivity. The BK-γ subunit has the ability to regulate vascular tone, and knockdown of BK-γ subunits contributes to pressure-induced vasoconstriction and a decrease in the activity of functional BK channels [15, 22, 23].

3.2 The physiological function of BK channel

Hundreds of proteins (such as β-catenin and caveolins) are reported to interact with BK channels in various systems *in vitro* and/or *in vivo*. The mutual effect between BK channel and these proteins regulates the BK channel functions and influences the biological pathways mediated by BK channels [24–26]. However, a key characteristic of BK channels is their ability to couple with calcium channels that mediate the increase of intracellular Ca^{2+}. BK channels can prevent Ca^{2+} channels from further activation and limit Ca^{2+} influx. In smooth muscle cells, ryanodine receptors cause local, transient calcium release events from the endoplasmic reticulum. These spontaneous calcium release events lead to the activation of nearby BK channels, which induce membrane hyperpolarization. This kind of potassium current is called the spontaneous transient outward current (STOC), and by blocking, STOC contributes to the increased vascular muscle tone [24, 27, 28]. Accordingly, BK channel is a key regulator to induce vasodilatation.

3.3 The function of BK channel in diabetes and hypertension

Diabetes is an independent risk factor for vascular diseases and is associated with increased risks of vascular complications, such as coronary artery disease, stroke, nephropathy, neuropathy, and retinopathy [29]. Vascular BK channel dysfunction is mainly due to a significant downregulation of BK-β_1 subunit expression in vessels from subjects with T1DM and T2DM. The activity of BK channels is regulated by many factors, such as angiotensin II, reactive oxygen species (ROS), nitric oxide (NO), carbon monoxide (CO), and protein kinase A- and protein kinase C-mediated signaling pathways.

According to Lu et al., the ROS signaling cascade facilitates Forkhead box O subfamily transcription factor-3a (FOXO-3a)-dependent F-box-only protein (FBXO)-mediated BK-β_1 degradation and leads to the dysfunction of diabetic BK channels. In diabetic mouse aortas and in high glucose-cultured human coronary arterial smooth muscle cells, p-Akt (S473) levels are decreased, and the level of protein kinase C (PKC) β, which stimulates ROS generation and contributes to diabetic cardiovascular complications in diabetic rats, is distinctly increased [29, 30]. This group also revealed that the nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway plays a significant role in regulating coronary BK channel function and vasodilation in mice with high-fat diet (HFD)-induced obesity/diabetes [31].

Hypertension, which is characterized by increased arterial tone, is another risk factor for cardiovascular diseases. Substantial evidence shows decreased expression of the BK-β_1 subunit that is considered to contribute to the development of vascular dysfunction during hypertension. Loss-of-function mutations in BK-β_1 decrease the prevalence of diastolic hypertension in humans [32]. Recently, the regulated trafficking of BK channel subunits (including α subunit and auxiliary β_1 and γ subunits) has been accepted as a functional mechanism to modulate arterial contractility. Endothelin-1 (ET-1) is a vasoconstrictor that activates protein kinase C (PKC) and stimulates PKC-mediated phosphorylation of Rab11A at serine 177. Subsequently, surface β_1 trafficking is reduced, resulting in a decrease in BK channel currents and vasoconstriction [33, 34].

3.4 BK channel in ECs

BK channels are expressed in both VSMCs and endothelial cells [35, 36]. In the majority of the systemic vasculature, endothelial BK channels are electrically quiescent, but may be disinhibited under pathophysiological conditions [37]. Hydrogen sulfide (H_2S) is an important, endogenously generated gaseous signaling molecule. H_2S-mediated vasodilation involves the activation of endothelial BK channels, which depends on Ca^{2+} influx through endothelial transient receptor potential vanilloid-4 (TRPV4) channels [38].

Using the whole-cell recording technique, Dong et al. examined the effect of CO on the activity of BK channels. The application of exogenous CO-activated BK channels in endothelial cells and the stimulation of endogenous CO production increased BK channel activity in human umbilical vein endothelial cells (HUVECs). Stimulation of soluble guanylate cyclase (sGC) production is responsible for the early stage, but not the latter stage, of this process. The CO-induced activation of BK channels plays an essential role in modulating vascular function. In endothelial cells, BK channels are activated by CO and induce the hyperpolarization of the membrane potential. Afterwards, the driving force for Ca^{2+} influx increases, and the increase in the intracellular Ca^{2+} concentration stimulates NO generation, which diffuses into the smooth muscle cells to activate BK channels [35].

Another key factor that interacts with BK channels and likely exerts a negative regulatory effect on channel activity is caveolin-1 (Cav-1). Under normal conditions, Cav-1 limits the contribution of the BK channels to EDHF-mediated arteriolar dilation. In obesity, the decreased expression of Cav-1 increases the contribution of the BK channels to EDHF-mediated arteriolar dilation, which seems essential for maintaining vascular homeostasis [39]. Chronic hypoxia (CH) enhances the activity of BK channels in ECs and alters vasoreactivity via the loss of an inhibitory effect of Cav-1. Under this condition, BK channels in ECs display a similar unitary conductance but greater Ca^{2+} sensitivity than BK channels from vascular smooth muscle cells [40].

Anandamide is an endogenous ligand for specific G-protein-coupled cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors. In the cardiovascular system, anandamide acts as a direct BK_{Ca} opener, and vasodilatory responses to cannabinoids are thought to require a G-protein-coupled receptor (GPCR) located on endothelial cells, the activation of which results in the direct modification of BK_{Ca} channel activity and BK_{Ca}-dependent vasodilation. BK_{Ca} channels act as cellular sensors for cannabinoids in *in vitro* and *in situ* endothelial cells [40]. The mechanism of action of anandamide on endothelial cells was not previously believed to require CB1, CB_2, or non-CB_1/CB_2 receptors, but was related to direct modulation of the BK_{Ca} channel gating without modification of unitary conductance [41]. However, the roles of BK_{ca} in endothelial cells observed in response to *in vitro* and *in situ* cannabinoid-induced vasodilation are undisputed.

3.5 Structures of SK and IK channel

SK and IK channels are two distinct types of voltage-independent K_{Ca} channels; these channels exhibit a close association between their calcium sensitivity and calmodulin [42]. In contrast to intestinal smooth muscle, little evidence is available suggesting a functional role for SK channels in vascular smooth muscle cells, although an unidentified apamin (a specific blocker of SK channel channels)-sensitive and voltage-dependent conductance has been reported [43]. In healthy and freshly isolated vascular smooth muscle cells, IK channels are expressed at very low levels. In contrast, the expression of IK channels increases when the vascular system is impaired, and this phenomenon also appears in proliferating smooth muscle cells [44].

The family of SK channels consists of three members: SK1 (also known as KCa2.1), which is encoded by the KCNN1 gene; SK2 (also known as KCa2.2), which is encoded by the KCNN2 gene; and SK3 (also known as KCa2.3), which is encoded by the KCNN3 gene. SK channels consist of six transmembrane regions (TMs) and a single pore loop, with four subunits located around a central pore. Both the N-terminus and C-terminus are oriented toward the cytoplasm. SK channels have no charged amino acids in the fourth TM domain, which is usually an important component of a voltage sensor. SK channels are activated and deactivated solely as a consequence of Ca^{2+} binding or release [45]. SK channels are heteromeric complexes that comprise pore-forming α subunits and the Ca^{2+}-binding protein calmodulin (CaM) (**Figure 2**). CaM is not only necessary for Ca^{2+} sensitivity but also critical for the trafficking of SK channels. CaM binds to and activates its target proteins in both Ca^{2+}-replete and Ca^{2+}-depleted forms. CaM mutants affect the interaction of CaM with its target proteins [45, 46]. CaM binds to a highly conserved CaM-binding domain (CaMBD) residing within the C-terminus of the SK channels that is located immediately distal to the sixth transmembrane segment [47, 48]. Maria A. Schumacher et al. explored the structure of the CaMBD/Ca^{2+}/CaM complex, and in this complex, CaM binds three α-helices instead of one, and the N-lobe and C-lobe of each CaM molecule contact different CaMBD monomers. The structure of the CaMBD/Ca^{2+}/CaM complex provides detailed information about both Ca^{2+}-dependent and Ca^{2+}-independent CaM interactions in a single complex [48].

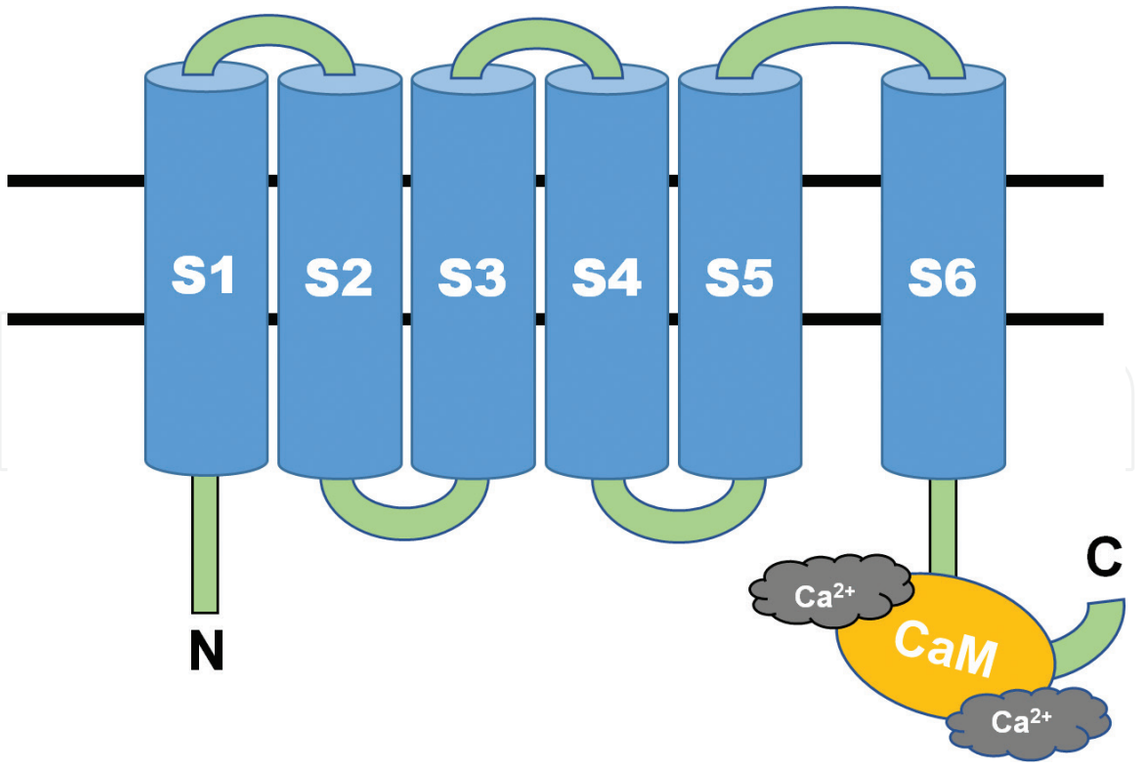

Figure 2.
Schematic of IK and three subtypes of SK (SK1, SK2, and SK3). SK3 and IK are thought to be the predominant KCa channels expressed in systemic vascular endothelia. The basic structure consisting of six transmembrane domains (S1–S6). The constitutively bound calmodulin (CaM), at the C-terminus. The founding member of Ca^{2+} binding proteins is CaM, a small, acidic, modular protein endowed with gymnastic-like flexibility that chelate Ca^{2+} ions.

IK channel (also known as KCa 3.1) is widely expressed in cells of the immune system and red and white blood cells, where it plays an important role in cellular activation, migration, and cytokine production [49–51]. Moreover, KCa3.1 is also expressed in dedifferentiated vascular smooth muscle cells, fibroblasts, and the vascular endothelium, where the channel is involved in the EDH response [52, 53]. The KCa3.1 channel is a tetrameric membrane protein with each subunit (comprising 427 amino acids) organized in six transmembrane segments, S1–S6, with a pore motif between segments 5 (S5) and 6 (S6). The channel assembly and trafficking are regulated by the constitutively bound calmodulin (CaM) molecule, which also confers Ca^{2+} sensitivity [54, 55]. Ca^{2+} binds to the CaM-KCa3.1 complex in the C-terminus of KCa3.1. As the CaM-binding domain of KCa3.1 is directly connected to the S6 transmembrane helix, activation of the channel gate at the level of the selectivity filter might depend upon the coupling between each of the channel pore helices and the associated S6 transmembrane segment. The interactions of the KCa3.1 pore helix with the S5 and S6 transmembrane segments also contribute to setting POmax, which is one of the distinguishing features of the Ca^{2+}-dependence of the KCa3.1 channel [55].

3.6 SK and IK channel and EDH responses

In small arterial and arteriolar ECs, KCa channels are activated by intrinsic spontaneous or receptor-mediated Ca^{2+} events, which contribute to the hyperpolarization of SMCs and vasodilation through a NO-independent process. This response is known as endothelium-dependent hyperpolarization (EDH), and it is the predominant mechanism in ECs [56]. SK and IK channels operate in parallel to generate EDH; they contribute to smooth muscle hyperpolarization and

vasorelaxation, and the hyperpolarization of the endothelial cells in turn increases calcium influx by increasing the driving force for this ion, but the channels can be activated independently. SK channels are distributed throughout the endothelial cell membrane, but cluster in the proximity of the large gap junctions between endothelial cells. In contrast, IK channels are only present in detectable amounts at endothelial cell projections toward adjacent smooth muscle cells, where they can form myoendothelial gap junctions [57]. EDHF-mediated responses play a physiological role in regulating vascular resistance. In rats, the hypotensive response to endothelium-dependent agonists, such as acetylcholine and bradykinin, is rapidly compensated within 1 day after treatment with the NOS inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME). The compensatory relaxation is mediated by the activation of SK and IK channels. Endothelial dysfunction, measured as a reduced endothelium-dependent hypotensive response, does not develop after the inhibition of NOS activity [58].

Over the past two decades, studies examining the physiological role of hydrogen sulfide (H_2S) have received increasing attention. Cystathionine γ-lyase (CSE) generates H_2S under physiological conditions, and a CSE deletion in mice reduces H_2S levels in some tissues, including the aorta. These mice lacking the CSE gene display pronounced hypertension, indicating that H_2S is a physiological vasodilator and regulator of blood pressure [59]. In many ways, either H_2S itself is an EDHF or H_2S releases EDHF from the endothelium [60, 61]. The resting membrane potential of SMCs is increased in CSE knockout mice, and methacholine (a cholinergic-muscarinic agonist)-induced endothelium-dependent relaxation of mesenteric arteries was abolished. Methacholine hyperpolarizes SMCs in endothelium-intact mesenteric arteries from wild-type mice. The application of atropine (a muscarinic antagonist) or charybdotoxin and apamin, which block SK/IK channels, or knockout of the CSE gene in mice inhibited this effect. Simultaneously, the expression of SK2.3, but not the IK3.1 channel, in vascular tissues was increased by H_2S and decreased by a CSE inhibitor or CSE gene knockout [51]. Moreover, insufficient H_2S levels impair EDHF-induced vascular relaxation by increasing oxidative stress and IK inactivation in mice with type 2 diabetes mellitus (T2DM)/hyperhomocysteinemia (HHcy) [62].

The activation of SK/IK channels may regulate electrical conduction along the endothelium of intact vessels, and some factors limit this process, such as myoendothelial coupling to SMCs, perivascular nerve activity, and circulating vasoactive agents. Using intact EC tubes produced after the dissociation of SMCs with mild enzymatic digestion, Behringer and his colleagues found that activation of SK/IK channels impairs the transmission between axial signals. This effect results from a decrease in membrane resistance (r_m) that dissipates charge as current flows from cell to cell along the endothelium [63]. Another group verified these results and further assessed impairments in electric conduction along the endothelium of resistance arteries through the enhanced activation of SK/IK channels. Fresh EC tubes were isolated from resistance arteries in skeletal muscle from different groups of mice. Group 1 included young mice (approximately 4–6 month old), group 2 included middle-aged mice (approximately 12–14 month old), and group 3 included old mice (approximately 24–46 month old). The ability of the endothelium of skeletal muscle resistance arteries to conduct electric signals is impaired with aging. The dual function of SK/IK channels in initiating and modulating electric signaling along the endothelium is altered with aging. By increasing the activation of SK/IK channels (particularly the IK channel), aging promotes hyperpolarization of the endothelium while decreasing its ability to conduct electrical signals. Oxidative stress activates SK/IK channels in the resistance artery endothelium via the action of hydrogen peroxide (H_2O_2) [64].

4. ATP-sensitive potassium channel in the vascular system

Functional K_{ATP} channels are hetero-octameric membrane protein complexes that comprise four inward-rectifier potassium channel 6 (Kir6, either Kir6.1 or Kir6.2) subunits and four ABCC (ATP-binding cassette, subfamily C) family member sulfonylurea receptor (SUR) subunits, including SUR1, SUR2A, or SUR2B. The Kir6 subunit (Kir6.1 or Kir6.2) has two membrane-spanning regions (M1 and M2) with intracellular N- and C-termini. The latter two are alternative splice variants, differing from each other only in the C-terminal 42 amino acids. The SURx subunit has 17 transmembrane regions, arranged in three domains: TMD0, TMD1, and TMD2. A conserved intracellular nucleotide binding fold (NBF1), with Walker A and Walker B domains, exists between TMD1 and TMD2. A second intracellular nucleotide binding fold (NBF2) exists in the C-terminus region of the protein. It is thought that NBF1 binds (and hydrolyzes) MgATP, whereas MgADP binds primarily to NBF2 to stimulate channel activity (**Figure 3**). KATP channels are expressed in a variety of cell types, including cardiac, smooth, and skeletal muscles, with tissue-specific diversity in the receptor subtypes. While pancreatic K_{ATP} channels are associated with SUR1, cardiovascular channels interact with SUR2 subtypes. In VSMC, SUR2B interacts with Kir6.1 to form K_{ATP}, and more rarely, Kir6.2 may be the ion pore-forming subunit. The Kir6 channel pore-forming subunits are the ATP sensor, and their activity is regulated by PIP2. K_{ATP} channels are inhibited by elevated intracellular ATP and stimulated by ADP under physiological conditions [46, 65–67].

In blood vessels, K_{ATP} channels remain closed under normal physiological conditions; however, they are activated when the cell metabolism is disturbed by hypoxia or ischemia, resulting in an efflux of potassium ions and membrane hyperpolarization. The decreased membrane excitability leads to a shortened cardiac action potential, inhibition of neurotransmitter release, and relaxation of vascular smooth muscles, which play key roles in limiting cellular damage or regulating blood pressure [68, 69]. In skeletal muscle arteries and arteries, alterations in metabolic activity induce changes in local oxygen tension and are an important mediator of

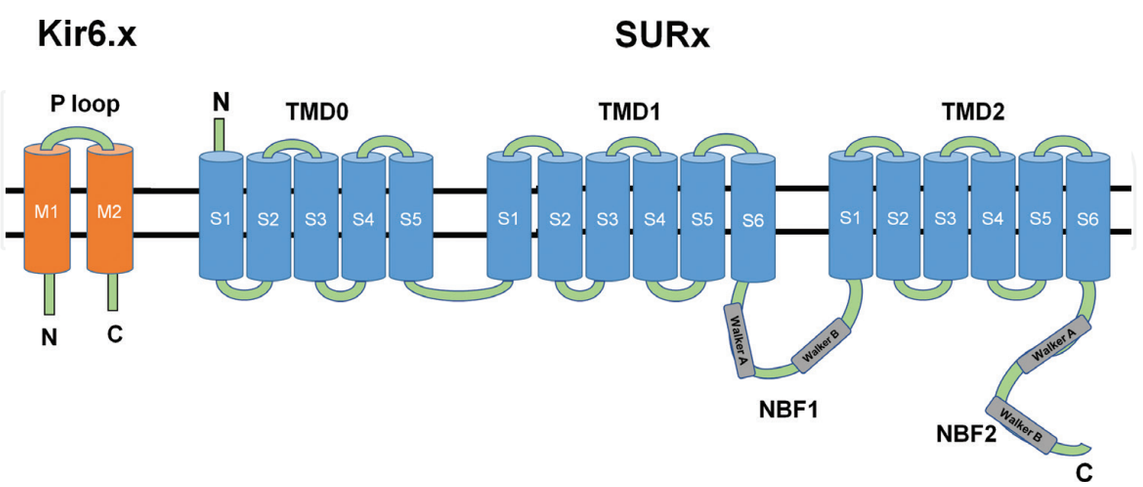

Figure 3.
K_{ATP} channels are hetero-octameric membrane protein complexes that are composed of four inward-rectifier potassium channel 6 (Kir6.x) subunits and sulfonylurea receptor (SURx) subunits. The Kir6.x subunit (Kir6.1 or Kir6.2) has two membrane-spanning regions (M1 and M2) with intracellular N- and C-termini. Two SURx subunits have been described: SUR1 and SUR2 (SUR2A or SUR2B). The latter two are alternative splice variants, differing from each other only in the C-terminal 42 amino acids. The SURx subunit has 17 transmembrane regions, arranged in three domains: TMD0, TMD1, and TMD2. A conserved intracellular nucleotide binding fold (NBF1), with Walker A and Walker B domains, exists between TMD1 and TMD2. A second intracellular nucleotide binding fold (NBF2) exists in the C-terminus region of the protein. It is thought that NBF1 binds (and hydrolyzes) MgATP, whereas MgADP binds primarily to NBF2 to stimulate channel activity.

vasomotor responses. Vasodilation (hypoxic vasodilation) is caused by decreased oxygen tension, and vasoconstriction (hyperoxic vasoconstriction) is caused by the increased oxygen tension [70, 71]. K_{ATP} channels are known to link cell metabolism and cell membrane potential, and decreased oxygen tension results in a depletion of intracellular ATP levels, which contributes to the opening of K_{ATP} channels and the subsequent hyperpolarization and relaxation of the VSMCs [71].

Renal hyperfiltration is a main characteristic of the early stage of type 1 diabetes mellitus (DM), and altered renal hemodynamics promote the eventual development of diabetic nephropathy. The hyperfiltration state is ascribed to the dilation of afferent arterioles and diminished responsiveness of this vascular segment to various vasoconstrictors, while the diameters of efferent arterioles and vasoconstrictor responsiveness are typically unaltered [72–74]. The membrane potential (E_m) and afferent arteriolar dilation are closely related in subjects with DM. K_{ATP} channels are quiescent in normal rats but exert a vasodilatory effect on afferent arteriolar tone during the hyperfiltration stage of diabetes. Increases in both the functional availability and basal activation of K_{ATP} channels promote afferent arteriolar vasodilation during the early stage of DM, changes that likely contribute to the etiology of diabetic hyperfiltration [73]. However, the involvement of K_{ATP} channels in the renal afferent arteriolar dilation during the early stage of DM is still controversial. Additional studies are needed to completely elucidate the potential roles of renal vascular K_{ATP} channels in early diabetic hyperfiltration [74].

5. K_V channel in VSMCs

K_V channels comprise a large family of channels that are expressed in both excitable and nonexcitable cells. In excitable cells, such as neurons or cardiac myocytes, the control of the resting membrane potential (resting E_m) and frequency and duration of action potentials depend on K_V channels. In nonexcitable tissues, these channels are involved in various processes ranging from secretion to cell proliferation [75]. In humans, K_V channels are encoded by 40 genes, and each Kv channel gene encodes a single protein; functional Kv channels are divided into 12 subfamilies (K_V1–K_V12). All mammalian K_V channels consist of four α-subunits and six transmembrane α-helical segments (S1–S6), and a membrane-reentering P-loop forms each α-subunit. This ion conduction pore is lined by four S5–P–S6 sequences. The four S1–S4 segments, each containing four positively charged arginine residues in the S4 helix, act as voltage sensor domains and "gate" the pore by "pulling" on the S4–S5 linker [76, 77]. The large number of K_V channel genes combined with the possibility of heterotetramerization creates a large functional diversity of K_V currents. This diversity is increased by the interactions of these channels with accessory proteins that are capable of modulating the gating properties and assist in trafficking and multimerization [75]. Since the K_V channel subunits form homo and heterotetramers, the biophysical properties, physiological regulatory mechanisms, and pharmacological properties of these channels vary. Although the $K_V1.1$–1.6 mRNAs have been detected in rat cerebral arteries, only the $K_V1.2$ and 1.5 proteins were detected, suggesting that in the cerebral vasculature, the functional K_V channel is a $K_V1.2/1.5$ heterotetramer. Members of the K_V1 and K_V2 family are postulated to be the predominant Kv channels that regulate arterial tone (**Table 1**) [78, 79].

K_V channels regulate membrane potential. Numerous studies have been conducted to explore the mechanisms by which these channels affect vascular tone in subjects with hypertension. Under Ca^{2+}-replete conditions, K_V currents in arterial SMCs from hypertensive animals are altered. $K_V1.2$ is expressed at higher levels, whereas $K_V1.5$ is expressed at the same levels in SMCs from hypertensive animals

Family	Subtype in vascular	Gene name	Inhibitor
Ca^{2+}-activated K^+ channels (Kca)	KCa1(BKCa)	KCNMA1 KCNMB1-4	Iberiotoxin (IBTX) Charybdotoxin Paxilline
	KCa2(SKCa)	KCNN1-3	Apamin UCL1684 TRAM-34 Psora-4
	KCa3(IKCa)	KCNN4	Charybdotoxin Clotrimazole TRAM-34 NS6180 Psora-4
ATP-sensitive K^+ channels (K_{ATP})	Kir6.1	KCNJ8	Glibenclamide Tolbutamide
	Kir6.2	KCNJ11	Tolbutamide Glibenclamide ML133
Voltage-gated K^+ channels (K_V)	Kv1	KCNA	4-Aminopyridine(4-AP) Tetraethylammonium (TEA) Correolide α-Dendrotoxin
	Kv2	KCNB	4-Aminopyridine(4-AP) Tetraethylammonium (TEA) Ba^{2+} SsmTx-1
	Kv7	KCNQ	TEA Linopirdine XE991 Chromanol 293B

Table 1.
The three family members of K^+ channels.

than in cells from normal animals [80]. Li et al. confirmed the effect of exercise training on alterations in K_V expression in thoracic aorta smooth muscle cells from spontaneously hypertensive rats (SHR). Rats were divided into three groups, a sedentary spontaneously hypertensive group (SHR-SED) and an exercise training spontaneously hypertensive group (SHR-EX), along with age-matched Wistar-Kyoto rats (WKYs) as the control group. Significantly, lower levels of the $K_V1.2$ and $K_V1.5$ channels were detected in the SHR-SED group than in the WKY group, while this decrease was inhibited in the SHR-EX group. Exercise training reverses the pathological expression of the $K_V1.2$ and $K_V1.5$ channels in aortic myocytes from SHRs, and thus is one of the favorable effects of exercise training on large conduit arteries [81].

The $K_V1.5$ protein is present in the vascular smooth muscle layer of both porcine and human coronary arteries, including microvessels [82]. The mean arterial pressure (MAP), myocardial blood flow (MBF), and ejection fraction (EF) have been measured in wild-type (WT) mice, mice null for $K_V1.5$ channels ($K_V1.5^{-/-}$), and mice with inducible, smooth muscle-specific expression of $K_V1.5$ channels

(on $K_V1.5^{-/-}$ and wild type backgrounds). During a norepinephrine (NE) infusion, significantly lower values for EF and MSF were observed in $K_V1.5^{-/-}$ mice than in WT mice. The expression of $K_V1.5$ channels in smooth muscle in mice on the null background rescued this phenotype of impaired metabolic dilation, indicating that Kv1.5 channels in vascular smooth muscle play a critical role in coupling myocardial blood flow to cardiac metabolism. The absence of these channels disassociates metabolism from flow, resulting in cardiac pump dysfunction and tissue hypoxia [83].

In addition to the K_V1 family, the K_V7 ($K_V7.4$ and $K_V7.5$) family has recently been shown to be a major determinant of vascular tone. K_V7 is expressed at similar levels in the murine aorta, carotid, femoral, and mesenteric artery, whereas the expression of $K_V7.4$ and $K_V7.5$ is greater than or equal to $K_V7.1$ [84]. By activating $K_V7.4$ channels, the application of 4-aminopyridine (4-AP) to noradrenaline-preconstricted rat mesenteric arteries contributes to the relaxation of the vessel [85]. The interaction between microRNAs (miRs) and $K_V7.4$ is also important in the vasculature. The expression of miR153 is increased in mesenteric, renal, and thoracic aortic arteries from SHRs compared to NT rats. In SHRs, the expression of $K_V7.4$ is decreased, whereas this change is not consistently associated with a change in transcript level because a difference in mRNA levels was not observed in renal and mesenteric arteries between SHRs and normotensive (NT) rats. In a study using synthetic RNA molecules, miR153 repressed the translation of $K_V7.4$ mRNA rather than degrading the transcript. Thus, miRs regulate the expression of Kv7.4 in the vasculature, and this post-transcriptional regulatory pathway might contribute to vascular dysfunction [86].

6. Conclusions and further perspective

Studies performed over several decades have substantially improved our knowledge of the expression of K^+ channels in the vascular system and their roles in regulating vascular tone and tissue perfusion. Dysfunctional K^+ channels can alter vascular homeostasis through heterogeneous and complex mechanisms. K^+ channels are targets for gene therapy for hypertension. The BK β_1 subunit, K_V 1.5, K_V 7.4, and some other genes should be studied as gene therapy targets. However, some remaining questions still deserve to study. How these K^+ channels work in microvasculature? How can we design better drugs to target these channels with some degree of specificity?

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Conflicts of interest

The authors have no conflict of interest to declare.

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