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Review

Role of voltage-gated potassium channel α subunits in cardiovascular system

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Abstract: Voltage-gated ion channels (VGICs) are central to cellular excitation, orchestrating skeletal and cardiac muscle contractions and enabling neural signal transduction. Among these, voltage-gated potassium (Kv) channels are particularly significant in cardiac electrophysiology, especially during the repolarization phase of the cardiac action potential. In cardiac myocytes, Kv channels are integral to a multitude of sophisticated functions, including electrical conduction. Despite their importance, research on Kv channels in the context of cardiovascular diseases is limited. This review offers a comprehensive summary of the structural complexities of Kv channels, delineating the regulatory mechanisms involved in channel gating, expression, and membrane localization. Additionally, we examine the role of different Kv α-subunits in modulating Kv channels and their impact on cardiac remodeling, and assess the potential of targeting Kv channels for the development of anti-arrhythmic therapies.

Key words: cardiovascular disease; voltage-gated potassium channels; arrhythmia; cardiac remodeling

电压门控钾离子通道α亚基在心血管系统中的作用

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摘 要：电压门控离子通道(voltage-gated ion channels, VGICs)与细胞的兴奋过程息息相关，参与骨骼肌和心肌的收缩和神经信号转导。电压门控钾离子(voltage-gated potassium, Kv)通道在心脏信号转导中发挥着重要的作用，直接影响着心脏动作电位的复极化过程，心肌细胞中的钾离子通道调节电传导等许多复杂的心脏功能。目前Kv通道对心血管疾病的相关研究有限，因此本文总结了Kv通道的复杂结构，通道门控性、表达和膜定位的调节机制，以及不同α亚基在调控Kv通道中的作用及其对心脏重构的影响，并探讨Kv通道作为抗心律失常药物潜在靶点的可能性。

关键词：心血管疾病；电压门控钾离子通道；心律失常；心肌重塑

Cardiovascular disease consistently ranks as the foremost cause of mortality globally, representing a critical challenge in contemporary medical research [1]. Amidst the myriad factors contributing to cardiovascular pathology, potassium channels have emerged as key elements in the intricate landscape of cardiac health. A substantial body of research underscores the profound association between potassium channels and cardiovascular diseases, particularly noting their pivotal role in the modulation of cardiac electrical signaling [2, 3]. Recent advancements in this field have highlighted a notable aberration in the expression of voltage-gated potassium (Kv) channels in cardiac pathologies. This revelation marks a paradigm shift, suggesting that these channels may serve as potential therapeutic targets in the management and treatment of cardiovascular

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diseases [4]. Intriguingly, some subunits of these channels, characterized by their highly tissue-specific expression, present as promising pharmacological targets. Their unique expression patterns and functional roles in cardiac physiology and pathology endow them with the potential to herald a new era in the targeted treatment of cardiovascular diseases [5]. Researches underscore the critical and evolving role of potassium channels in cardiovascular health, setting the stage for a deeper exploration into their potential as novel therapeutic targets. The focus on Kv channel α subunits reflects a growing trend towards more precise and personalized approaches in cardiovascular medicine.

1 Overview of Kv channels

Potassium ion channels are divided into four categories: Kv channels with a 6S transmembrane structure, calcium-activated channels (K_{Ca} channels) with a 6S or 7S transmembrane structure, inward rectifier channels (K_{ir} and K_{ATP} channels) with a 2S transmembrane structure, and two-pore potassium ion channels (K_{2P} channel family) with a 4S transmembrane structure [6–8]. Among these, Kv channels are a subtype of potassium ion channels regulated by changes in membrane voltage. They play a role in various physiological activities such as cell excitation, contraction, metabolism, and the cell cycle [9–11]. These channels regulate their activity through changes in membrane potential and the duration of potential changes, maintaining the action potential in excitable cells [12, 13]. In mammalian cardiac muscle cells, the duration and amplitude of the action potential also largely depend on Kv channels [14, 15].

1.1 Classification of Kv channels

Kv channels are a type of transmembrane glycoprotein complex, where the α subunit within the complex determines the channel's type and function. In 2005, the International Union of Pharmacology (IUPHAR) classified potassium ion channels into 12 subtypes based on amino acid sequences [16]. When considering the Kv channel family, its primary components include the electrically active α-subunits, electrically silent α-subunits (KvS), and auxiliary β-subunits [10]. These three subunit types play crucial roles in regulating cell membrane potential, maintaining resting membrane potential, and influencing cellular physiological activities.

1.1.1 Electrically active and silent α subunits

According to ion permeability, α subunits can be categorized into electrically active α subunits and electrically KvS [17].The electrically active α subunits are core members of the Kv channel family (Table 1). They possess specific conductive properties and, by forming homotetramers consisting of four homologous transmembrane domains, directly participate in regulating cellular excitability and the generation of action potentials. These electrically active α subunits maintain resting membrane potential in excitable cells, modulate action potential formation, and participate in cell proliferation and protein transport in non-excitable cells [18–22]. The conductive subunits of potassium ion channels, encompassing the Kv1, Kv2, Kv3, Kv4, Kv7, Kv10, Kv11, and Kv12 families, are fundamental to ion permeability processes. These subunits form the core architecture of the channels, facilitating the selective passage of potassium ions across the cell membrane, a crucial aspect in maintaining cellular electrochemical gradients. Each of these families exhibits unique biophysical properties and tissue-specific expression patterns, contributing to the functional diversity observed in potassium channels.

Whereas the KvS constitute another essential subunit type, primarily involved in interacting with electrically active α subunits to form heterotetramers, thereby modulating the functional activity of Kv channels [22]. Kv5, Kv6, Kv8, and Kv9 subunits are categorized as KvS. They lack the ability to form functional homotetrameric channels independently but play a significant role in modulating the activity of electrically active α subunits when co-assembled. This modulation is achieved through alterations in channel gating, ion selectivity, and pharmacological sensitivity, thus providing an additional layer of regulation to potassium channel functionality. Recent investigations have revealed the presence of a variety of silent α subunits, including Kv5.1, Kv6.1, Kv6.2, Kv6.3, Kv8.2, Kv9.1, and Kv9.2, within pulmonary artery vascular smooth muscle [40].

1.1.2 Auxiliary β-subunits

Auxiliary β-subunits also play a critical role in the assembly and regulation of Kv channels (Table 2). Through interaction with electrically active α subunits, they regulate the gating of S6 within the tetramer, controlling the channel's activity. These β-subunits modulate the gating properties of the S6 segment within the tetrameric channel structure, thereby influencing the overall activity and kinetics of the ion channels. This regulatory mechanism is essential for the precise con-

Table1. Electrically active α subunits of voltage-gated potassium (Kv) channels

Electrically active α-subunit	Subtypes	Gene	Current (function)	Cardiovascular diseases
Kv1	Kv1.1	KCNA1	-	Atrial fibrillation [23]
	Kv1.2	KCNA2	Delayed rectifier, slow (activate AP phase 3 by voltage and depolarization) [24]	Ventricular arrhythmias [25]
	Kv1.3	KCNA3	-	Hypertension [26]
	Kv1.4	KCNA4	Transient outward current, slow (activate AP phase 1 by voltage and depolarization)	Heart failure [27]
	Kv1.5	KCNA5	Delayed rectifier, ultrarapid (activate AP phase 1 by voltage and depolarization)	Atrial fibrillation [28]
	Kv1.6	KCNA6	-	-
	Kv1.7	KCNA7	Delayed rectifier, ultrarapid (activate AP phase 1 by voltage and depolarization)	Progressive familial heart block [29]
Kv2	Kv2.1	KCNB1	Delayed rectifier, fast (activate AP phase 3 by voltage and depolarization)	Pulmonary artery hypertension [30]
	Kv2.2	KCNB2	-	-
Kv3	Kv3.1	KCNC1	-	-
	Kv3.2	KCNC2	-	-
	Kv3.3	KCNC3	-	-
	Kv3.4	KCNC4	-	Congestive heart failure [31]
Kv4	Kv4.1	KCND1	-	-
	Kv4.2	KCND2	Transient outward current, fast (activate AP phase 1 by voltage and depolarization)	Ventricular tachycardia [32]
	Kv4.3	KCND3	Transient outward current, fast (activate AP phase 1 by voltage and depolarization)	Atrial fibrillation [33]; congestive heart failure [31]
Kv7	Kv7.1	KCNQ1	Delayed rectifier, slow (activate AP phase 3 by voltage and depolarization)	Long QT syndrome [34]; Atrial fibrillation [35]
	Kv7.2	KCNQ2	-	Hypertension [36]
	Kv7.3	KCNQ3	-	Hypertension [36]
	Kv7.4	KCNQ4	-	Hypotension [37]
	Kv7.5	KCNQ5	-	Hypotension [37]
Kv10	Kv10.1	KCNH1	-	Coronary artery ectasia [38]
	Kv10.2	KCNH5	-	-
Kv11	Kv11.1	KCNH2	Delayed rectifier, fast (activate AP phase 3 by voltage and depolarization)	Long QT syndrome [39]
	Kv11.2	KCNH6	-	-
	Kv11.3	KCNH7	-	-
Kv12	Kv12.1	KCNH8	-	-
	Kv12.2	KCNH3	-	-
	Kv12.3	KCNH4	-	-

AP, action potential. -, no report.

trol of ion flow, impacting cellular excitability and signaling.

The presence of these subunits allows electrically active α subunits to form complex tetrameric structures, thereby increasing the diversity of Kv channels [22]. This classification underscores the intricate interplay between different subunits and highlights the complexity of potassium channel regulation in cardiovascular diseases. Among these three subunit types, the conductive properties of electrically active α subunits, the combination patterns of KvS, and the regulatory mechanisms of auxiliary β-subunits interact to provide the foundation for the multifunctionality and high specificity of Kv channels.

Table 2. Ancillary β-subunits of voltage-gated potassium (Kv) channels

Ancillary β-subunits	Subtype	Gene	Current (function)
Kvβ	Kvβ1	KCNAB1	Delayed rectifier, ultrarapid (activate AP phase 1 by voltage and depolarization)
	Kvβ2	KCNAB2	
	Kvβ3	KCNAB3	
KChIP	KChIP1	KCNIP1	Transient outward current, fast (activate AP phase 1 by voltage and depolarization)
	KChIP2	KCNIP2	
	KChIP3	KCNIP3	
	KChIP4.2	CSEN	
	KChIP4.3	KCNIP4	
KChAP	KChAP	PIAS3	Transient outward current, fast (activate AP phase 1 by voltage and depolarization)
KCNE	MinK	KCNE1	Delayed rectifier, slow; Transient outward current, fast; Delayed rectifier, fast (activate AP phase 1&3 by voltage and depolarization)
	Mink-like	KCNE1L	
	MIRP1	KCNE2	Transient outward current, fast; Delayed rectifier, fast (activate AP phase 1&3 by voltage and depolarization)
	MIRP2	KCNE3	
	MIRP3	KCNE4	
	MIRP4	KCNE5.1	Delayed rectifier, slow (activate AP phase 3 by voltage and depolarization)
DPLP	DPLP10	DPP10	-
NCS	NCS-1	FREQ	Transient outward current, fast (activate AP phase 1 by voltage and depolarization)

AP, action potential. -, no report.

2 Structure and function of Kv channels

2.1 Structure of Kv channels

Kv channels, as tetrameric transmembrane proteins, exhibit a dynamic ability to open or close in response to alterations in membrane potential. These channels, integral components of the transmembrane glycoprotein complex family, primarily consist of four α-subunits. These α-subunits are pivotal in dictating the specific type and function of Kv channels. In their architecture, each electrically active α subunits can independently form a functional homotetramer, comprising four homologous transmembrane domains (see Fig. 1). This homotetrameric structure is fundamental to the channel's ability to conduct potassium ions across the cell membrane, playing a critical role in cellular excitability and signaling. In addition to the electrically active α subunits, KvS cannot form active channels on their own. Instead, they interact with electrically active α subunits to create heterotetrameric structures, thereby exerting regulatory control over the channel's functional activity. These interactions introduce a layer of complexity in channel behavior, modulating aspects such as ion selectivity, gating kinetics, and pharmacological properties [22]. In mammals, the heterotetrameric configurations often involve combinations of KvS subunits with Kv2.1, typically in ratios of 1:3 or 2:2 [41]. This structural diversity allows for a vast array of potassium channel isoforms, each with unique electrophysiological characteristics. Moreover, the regulatory landscape of Kv channels extends beyond the α-subunits. Various β-subunits also play a crucial role in modulating the activity of these channels. These β-subunits can associate with the α-subunit tetrameric structure, further influencing the channel's functionality [42].

Each α subunit of Kv channel possesses structurally distinct intracellular N-terminal and C-terminal domains, integral to the assembly and functional regulation of the heterotetrameric potassium channel and each monomer consists of six transmembrane segments (S1–S6) with the S5–S6 region forming the domain swapped pore and non-domain swapped pore (Fig. 2) [43]. The C-terminus of silent subunits (KvS), such as KCNS, is characteristically shorter. In contrast, conductive α-subunits like Kv2.1 feature an elongated C-terminus, which harbors specific signals pivotal for protein transport and cellular localization [44]. These structural variations in the C-terminal regions confer distinct functional roles when forming either homotetrameric or heterotetrameric channels. This modulation is indicative of the intricate regulatory mechanisms governing the electrophysiological properties of Kv

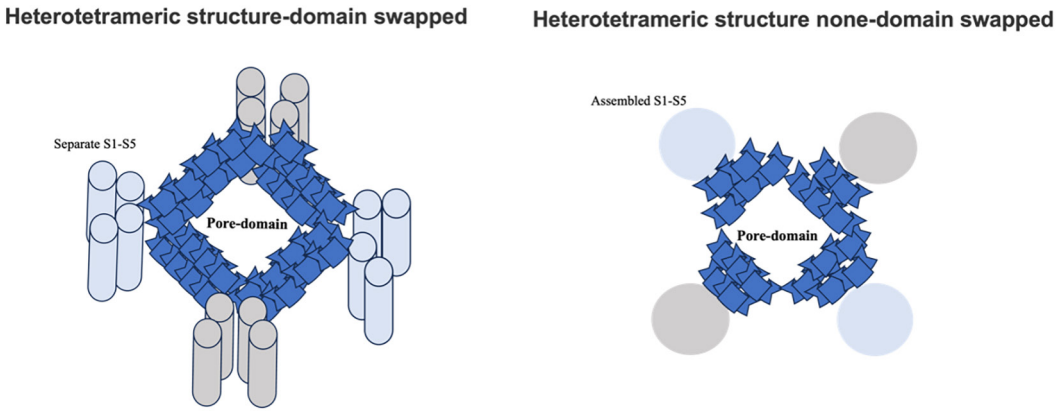

Fig. 1. Comparison of non-domain-swapped and domain-swapped architectures of voltage-gated potassium (Kv) channels. Left, non-domain swapped structure; Right, domain-swapped structure. The transmembrane core domains are depicted viewed from the cytoplasmic side.

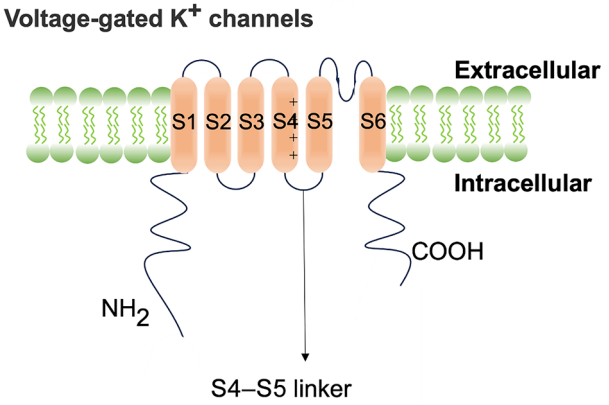

Fig. 2. Structure scheme of α subunit of voltage-gated potassium (Kv) channel. Each α subunit of Kv channel contains six transmembrane segments, C-terminus and N-terminus. The S1 segment links to N-terminus and the S6 segment links to C-terminus. Among all the segments, S4 is the only electronical segment which modulates the gate of Kv channel.

channels, highlighting the complexity of channel assembly and function at the molecular level [45].

The intricate interplay between electrically active and silent subunits in the formation of heterotetramers represents a complex regulatory mechanism within Kv channels. While substantial progress has been made in elucidating the functional impacts of these interactions, the exact biochemical and biophysical mechanisms through which heterotetramers influence cellular processes remain an active area of research.

2.2 The physiological function of Kv channels

Kv channels comprise the largest and most diverse class of ion channels. These channels establish the resting membrane potential and modulate the frequency and duration of action potentials in nerve and muscle, as well as being the targets of several antiarrhythmic drugs in the heart [24]. Kv channels consist of principal α-subunits and multiple β-subunits. The major subfamilies of α-subunits are important in generating outward current in the heart. Electrically active α-subunits are present in excitable and nonexcitable cells. In excitable cells, they maintain resting membrane potential, repolarize action potential, and determine firing frequency. In nonexcitable cells, they also maintain resting membrane potential and regulate cell proliferation, protein traffic, and interactions with subcellular structures.

The electrically active α-subunits can generate voltage dependent K^+ current when expressed in homogonous systems. Table 1 summarized different types of electrically active α-subunits of K^+ channels and their role in action potential. K^+ channels are also highly regulated and are the basis for the change in action potential configuration in response to variation in heart rate. Voltage-gated cardiac K^+ currents generally fall into 4 categories: transient outward current (I_{to}) and delayed rectifier which including slow (I_{Ks}), rapid (I_{Kr}) and ultrarapid currents (I_{Kur})[46]. Different subunit can regulate the same current and action potential phase, and most of electrically active α subunits can also form various K^+ currents that activate the action potential at a certain phase. The electrically silent α subunits and β subunits that co-assemble to form the various types of K^+ channels, and their role in the generation of the action potential are summarized in Table 3 and 2 [24].

2.2.1 The physiological function of subunits in transient outward current

There are two functionally distinct I_{to} phenotypes across the free wall of the left ventricle [29]. Based upon their voltage-dependent kinetics of recovery from inactivation, two kinetically and pharmacologically distinct transient outward K^+ currents, referred to as $I_{to,fast}$ (recovery time constants on the order of tens of milliseconds) and $I_{to,slow}$ (recovery time constants on the order of thousands of milliseconds) have been distinguished in mouse left ventricular myocytes [47]. Among all subunits, Kv1.4 and Kv4 have been proven to be related to I_{to} [48]. Ni *et al*. explored the changes in the recovery or restitution of the AP duration (APD) and/or its dynamic stability (alternans) can be modulated by I_{to}. They also found the functional consequences of this by deletion of 50% of native I_{to} (Kv4.3) and its replacement with Kv1.4. Interestingly, significant changes in the short-term stability of the human atrial AP waveform were revealed [49]. $I_{to,fast}$ predominates in the mid- and epicardium, whereas the slowly recovering $I_{to,slow}$ dominates in the endocardium. $I_{to,slow}$ has been ascribed to Kv1.4, but Kv1.5 may also contribute, as Kv1.5 mRNA has consistently been found in human and canine ventricles, and in many species the molecular identity of $I_{to,slow}$ remains poorly defined [50]. $I_{to,fast}$ channels consist of a tetramer of pore-forming Kv4 α subunits [51]. In human and canine hearts Kv4.3 is the predominant α subunit of $I_{to,fast}$, but Kv4.2 mRNA has been reported in human ventricle [52]. Recently, a mutation in the gene encoding Kv4.2 have been reported in a patient with a J-wave syndrome, further supporting a functional role for Kv4.2 in the human ventricle [49].

Several members of the promiscuous KCNE β subunit family modulates Kv4 currents in heterologous systems and mutations in KCNE subunits affecting Kv4.3 current density and/or kinetics have been implicated in cardiac arrhythmias in humans. KCNE2 has been reported to induce an "overshoot" in Kv4.3 peak currents during recovery from inactivation; the overshoot implying that the peak amplitude of the recovered current is transiently larger than that of the current activated by the reference pulse [53].

2.2.2 The physiological function of α subunits in delayed rectifier

The delayed rectifier K^+ current (I_K) can be separated into three components (I_{Kr}, I_{Ks} and I_{Kur}) based on the differences in the kinetics and pharmacological properties of cardiac myocytes in mammalian species. I_{Kr} and I_{Ks} play essential roles in providing outward currents to initiate the repolarization of the atrial and ventricular action potentials in mammalian animals. Blockage of the I_{Kr} and I_{Ks} currents by their selective blockers delays the repolarization process and markedly reduces the pacemaker activity in sinoatrial node cells of guinea pigs, suggesting that both I_{Kr} and I_{Ks} currents contribute to the regulation of the sinoatrial node function [54]. In the presence of β- adrenergic stimulation, the dominance contribution involved in the action potentials of ventricular cells is reversed from I_{Kr} to I_{Ks} [55]. Besides, some studies have shown that β-adrenergic stimulation preferentially enhances I_{Ks} in guinea pig ventricular myocytes and sinoatrial node cells [56, 57]. In addition, activation of the β-adrenergic receptor pathway enhances Ca^{2+} entry into cardiac myocytes through the Ca^{2+} channel, which modulates the positive inotropic effect of β-adrenergic receptor activation [58]. Outwardly recti-

Table 3. Electrically silent α subunits of voltage-gated potassium (Kv) channel

Electrically silent α-subunit	Subtype	Gene	Current (Function)	Cardiovascular diseases
Kv5	Kv5.1	KCNF1	Regulate Kv2 current	-
Kv6	Kv6.1	KCNG1	Regulate Kv2 current	-
	Kv6.2	KCNG2	Regulate Kv2 current	Familial sick sinus syndrome [67]
	Kv6.3	KCNG3	Regulate Kv2 current	-
	Kv6.4	KCNG4	Regulate Kv2 current	-
Kv8	Kv8.1	KCNV1	Regulate Kv2 current	-
	Kv8.2	KCNV2	Regulate Kv2 current	-
Kv9	Kv9.1	KCNS1	Regulate Kv2 current	-
	Kv9.2	KCNS2	Regulate Kv2 current	-
	Kv9.3	KCNS3	Regulate Kv2 current	Pulmonary hypertension [72]

-, no report.

fying K^+ currents with rapid activation kinetics and little or no inactivation were identified in atrial myocytes from several species [59]. These kinetics were reflected in the early current nomenclature, such as I_{Kur}.

Kv2.1 and Kv11.1 are two main subunits regulating I_{Kr} [60]. O'Connell *et al*. found that clustered Kv2.1 channels did not efficiently conduct K^+, whereas the nonclustered channels were responsible for the high threshold delayed rectifier K^+ current typical of Kv2.1. Comparison of gating and ionic currents indicated only 2% of the surface channels conduct, suggesting that the clustered channels still responded to membrane potential changes [61]. The Kv2.1 voltage-activated potassium channel is a prominent delayed-rectifier Kv channel in the mammalian central nervous system, where its mechanisms of activation and inactivation are critical for regulating action potentials in excitable cells [44, 62]. Research conducted by David *et al*. has brought to light that the current density of heterotetramers formed by Kv2.1 and Kv6.4 is markedly reduced in comparison to Kv2.1 homotetramers [63]. This observation underscores the capacity of Kv6.4 to significantly impact the electrophysiological properties of the channel, potentially affecting a range of cellular functions. The human ether-a-go-go related gene (hERG) encodes the pore-forming subunit of the rapid component of the delayed rectifier K^+ channel, Kv11.1, which is expressed in the heart and involved in chromosome 7-associated long QT syndrome, an inherited disorder associated with a markedly increased risk of ventricular arrhythmias and sudden cardiac death [64].

Both Kv1 and Kv7 are related to I_{Ks}. The I_{Ks} is the slow component of cardiac delayed rectifier current which is critical for the late phase repolarization of cardiac action potential. This current is also an important target to regulate the cardiac electivity to accommodate to heart rate alterations in response to exercise or emotional stress and can be up-regulated by β-adrenergic or other signal molecules. I_K usually originated by the co-assembly of pore-forming KCNQ1 α-subunit and accessory KCNE1 β-subunit. Mutations in any subunit can bring about severe long QT syndrome as characterized by deliquium, seizures and sudden death [65]. At present, Kv1.1 has been proposed as a novel and promising target for the treatment of brain disorders characterized by hyperexcitability [66]. Meanwhile Trosclair *et al*. found an important functional role for Kv1.1 in ventricles that related to myocardial repolarization and contractility [67].

Kv1.5 channels are the molecular correlate of I_{Kur} in human cardiomyocytes. The channel protein complex for the ultrarapidly activating outward current is made up of four α-subunits encoded by *KCNA5*, various ancillary subunits, and additional anchoring and/or scaffolding proteins [59]. Interaction of Kvβ subunits with Kv1.5 controls channel trafficking and integration into the plasma membrane and modulates activation and inactivation kinetics of the current [68]. The major group of ancillary subunits that associate with Kv1.5 channels are Kvβ subunits, but KChIP2 also modifies channel properties. In the heart, Kvβ1.2, Kvβ1.3, and Kvβ2.1 are most abundantly expressed [69]. When co-expressed with Kv1.5, they shift the steady-state activation and inactivation curves to more negative potentials. Though the Kv1.5 current can be regarded as a 'sustained' current at room temperature, inactivation proceeds much faster at more physiological temperature [70]. Moreover, the time course of recovery from inactivation is also faster at higher temperature.

3 The relationship between Kv channels and cardiovascular diseases

In cardiac myocytes, voltage-gated Na^+ (Nav), K^+ (Kv), and Ca^{2+} (Cav) channels are responsible for the activation and maintenance of action potentials (Fig. 3) [71]. Numerous potassium ion channels play a crucial role in regulating repolarization and action potentials in neurons and cardiac cells [72]. Kv channels directly influence cardiac repolarization and serve as primary modulators of membrane electrical activity in excitable cells. Recent findings also established a close association between Kv channels and congenital heart diseases [73]. As early as 1995, Barry *et al*. identified the expression of many Kv channels in cardiac tissues [74]. Subsequent studies by Brahmajothi *et al*. further confirmed the differential expression levels of these ion channels in various locations within the heart [75]. This series of studies collectively provides compelling evidence for the crucial importance of Kv channels in cardiac function.

3.1 The relationship between electrically active α-subunits and cardiovascular diseases

Extensive animal experiments have consistently demonstrated that alterations in conductive subunits with electrical conduction properties can directly lead to pathological changes in the heart. Glasscock *et al*.,

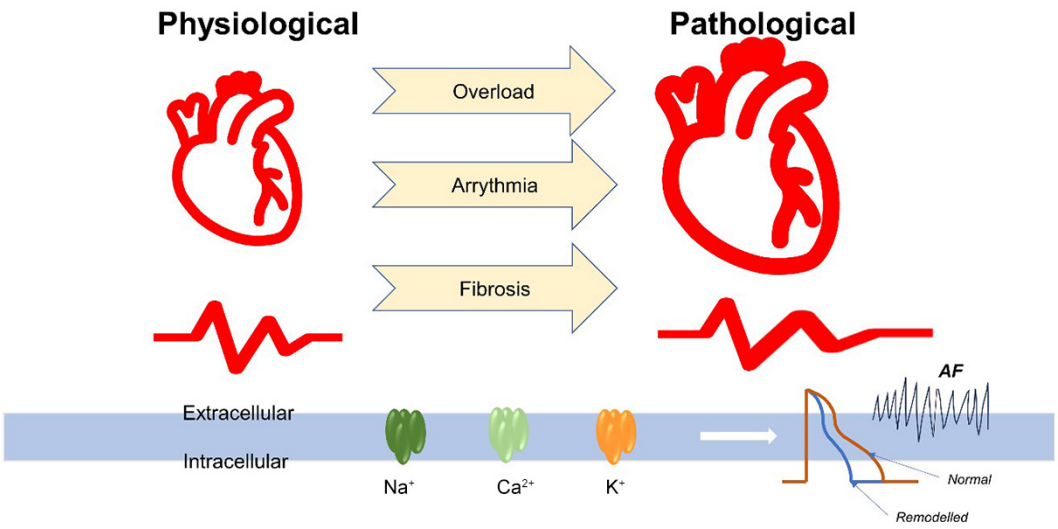

Fig. 3. Relationship of voltage-gated channels and cardiovascular diseases. Normal cardiac structure and electrophysiological signals undergo pathological transformation with increasing cardiac load, cardiac fibrosis, and arrhythmia. The current formed by ion channels on the cell membrane can affect the electrical signals of the heart, accompanied by changes in cardiac electrophysiological signals, manifested as atrial fibrillation (AF).

through animal experiments, observed atrial remodeling and fibrosis in the absence of Kv1.1 [23], and Glasscock's subsequent animal studies reiterated the pathological changes associated with gene deletion, with an increased propensity for atrial fibrillation. In cases of pathological myocardial hypertrophy combined with ventricular arrhythmias [76], changes in the mRNA expression of other subtypes of the Kv1 α subunit, specifically Kv1.5 and Kv1.4, resulted in a significant prolongation of the action potential plateau, suggesting that α subunits regulate changes in potassium ion channels and may be associated with the occurrence of ventricular arrhythmias induced by myocardial hypertrophy [77]. McCauly *et al*.'s animal experiments also indicated changes such as increased Kv1.5 and atrial fibrosis in obesity-induced atrial fibrillation [28].

Alterations in cardiac electrical signals can lead to common hereditary arrhythmias, such as long QT syndrome, which is closely linked to Kv7 and Kv11 [78]. Research suggests that reduced expression of Kv7.1 prolongs the action potential duration in ventricular myocardial cells, and mutations leading to Kv7.1 gene loss result in long QT syndrome [2]. Similarly, within the Kv channel family, Kv11.1, as an important gene associated with long QT syndrome, is found to be linked to ventricular arrhythmias and sudden death [64].

Kv2.1, an electrically active α-subunit within the Kv channel family, has garnered considerable attention in recent research. Its critical role in forming ion pores and determining action potentials in excitatory cells underpins its physiological importance. Particularly in the cardiovascular system, the expression of Kv2.1 is intricately linked to stress-overload states, suggesting a potential role in cardiac adaptability and pathophysiology [79]. Emerging studies have begun to unravel the complex dynamics of Kv2.1 in cardiovascular diseases. For instance, in pulmonary hypertension, a significant down-regulation of Kv2.1 mRNA expression has been observed in pulmonary artery smooth muscle cells [80, 81]. This alteration in expression levels may reflect an adaptive or maladaptive response to the altered hemodynamic environment characteristic of this disease. Furthermore, the expression of Kv channels, including Kv2.1, undergoes significant modulation in hypertensive conditions induced by pregnancy. This modulation not only impacts the electrical activity of the maternal heart, but also influences the timing of cardiac repolarization, a critical factor in maintaining effective cardiac function during pregnancy [82]. Intriguingly, a contrasting response is evident in the left ventricle of mice subjected to stress-overload-induced left ventricular hypertrophy, as modeled by transverse aortic constriction (TAC). In this model, an up-regulation of Kv2.1 expression has been observed, suggesting an adaptive response to the increased workload and stress on the heart. This up-regulation potentially contributes to the

alterations in potassium channel currents associated with cardiac repolarization. These changes are not merely a consequence of altered gene expression; they also arise from modifications in cardiomyocyte size and the density of channels within the myocardial tissue [83]. These findings underscore the multifaceted role of Kv2.1 in the cardiovascular system, particularly in the context of disease states. The differential expression and regulatory patterns of Kv2.1 in various cardiac pathologies offer insights into the channel's role in cardiac adaptation and provide avenues for targeted therapeutic interventions.

Recent investigations into the regulatory mechanisms of potassium ion channels, particularly those mediated by Kv2.1, have revealed a complex network of modulation involving multiple subunits [44]. A striking aspect of this regulation is the apparent gender-specific differences in Kv2.1 expression and function. Research by O'Dwyer *et al*. has uncovered that the expression level and functional dynamics of Kv2.1 vary distinctly between genders. Notably, the expression of Kv2.1 protein is significantly higher in female mouse cardiomyocytes compared to their male counterparts. This disparity extends to functional implications: in male cardiomyocytes, Kv2.1 predominantly regulates membrane potential, while in female rat cardiomyocytes, it not only modulates membrane potential, but also facilitates the aggregation of Ca^{2+} current, a key calcium channel subunit [4]. The expression patterns of Kv2.1 in myocardial and vascular smooth muscle cells further exemplify its diverse roles. In arterial muscle cells, Kv2.1 tends to aggregate within the whole cell, whereas in ventricular muscle cells, it is more dispersed, primarily localizing to the transverse tubules and sarcolemma [61]. This spatial distribution suggests a nuanced role of Kv2.1 in different cardiac and vascular tissues. The channel's function is further modulated by its association with various silent subunits in myocardial or vascular smooth muscle, subtly influencing the electrical signal conduction of cardiomyocytes. Kv2.1 is capable of forming homotetramers, creating potassium ion channels in the sarcolemma of arterial smooth muscle and regulating the critical current of action potential repolarization in cardiomyocytes – I_{Kr} [61]. The interaction of Kv2.1 with KvS or auxiliary β subunits to form heterotetramers tailors its electrophysiological effects across different tissues [44, 71], impacting the excitability and contractility of excitatory contractile cells [61]. The modulation of Kv2.1 activity extends to its interaction with other Kv channels. For instance, studies by McCrossan *et al*. have demonstrated that two β subunits, KCNE1 and KCNE2, can be complex with Kv2.1 in the heart, reducing channel current density and accelerating the inactivation rate [83]. This interaction plays a pivotal role in mediating arrhythmic conditions. The opening of Kv2.1 channels induces hyperpolarization of the cell membrane, thereby diminishing the activity of L-type Ca^{2+} channels and promoting smooth muscle relaxation [4, 84]. This mechanism holds significant potential in antiarrhythmic therapies and in the prevention of arrhythmias. Consequently, genes regulating this type of current have emerged as potential targets for numerous antiarrhythmic drugs [85–87].

In conclusion, the activity of the Kv2.1 channel may play a pivotal role in myocardial remodeling, a key process in cardiac pathology and adaptation. The modulation of Kv2.1 by both silent α subunits and auxiliary β subunits is of particular interest, given their potential to finely tune channel activity. Notably, the tissue-specific differential expression of these subunits underscores a sophisticated regulatory mechanism, suggesting a tailored influence of Kv2.1 channel activity in diverse cardiac environments.

3.2 The relationship between silent α subunits and cardiovascular diseases

The expression patterns of silent α subunits are notably more specific and restricted compared to the ubiquitous presence of Kv2.1, leading to a unique functional diversity in the heterotetramers formed by Kv2/KvS combinations. These heterotetramers exhibit distinct characteristics and functions in different tissues, particularly influenced by the type of silent subunits involved. In the realm of current research, there is growing evidence that heterotetramers formed by Kv2 and various silent subunits play a critical role in modulating the functionality of Kv2 channels in specific tissues. For instance, in the nervous system, these heterotetramers contribute to signal transmission, as highlighted in the study [88]. Similarly, in the cardiovascular system, the interaction between Kv2 and silent subunits is crucial for regulating cardiac electrophysiology, impacting the heart's response to various physiological and pathological stimuli [89]. The heart, as a complex organ with various cell types, exhibits a particularly intriguing expression pattern of these subunits. Multiple silent α subunits are expressed in cardiac cells, and their assembly with Kv2

in heterotetramers is hypothesized to be instrumental in precisely regulating the ionic currents across different cardiac cell types. This regulation is vital for maintaining the heart's rhythm and contractility.

The diversity in function observed across different tissues may be attributed to the expression of distinct KvS subunits. Moreover, variations in the levels of KvS subunits within a given tissue could serve as a marker for functional changes, suggesting a dynamic interplay between subunit composition and tissue-specific physiological processes. Kv6, akin to other silent KvS subunits, is incapable of forming functional Kv channels in a homotetrameric configuration. Only through co-expression with Kv2.1 and thus forming a heterotetrameric structure, voltage-activated I_{Kr} can be effectively regulated [17]. Michael and his colleagues embarked on a series of intricate co-expression experiments in HEK cells to unravel the dynamic interplay between Kv2.1 and Kv6.4 subunits [90]. By maintaining a constant amount of Kv2.1 plasmids and varying the dose of Kv6.4, they observed a significant reduction in current amplitude with increasing Kv6.4 concentration, thereby illustrating the regulatory impact of Kv6.4 on Kv2.1 channel function. Multiple KvS subunits, including Kv6, are known to be expressed in the heart, where they form heterotetramers with Kv2. This complex formation is thought to be integral in fine-tuning ionic currents across different cardiomyocytes [61]. Kv6.2, in particular, is highly expressed in the cardiac tissue, underscoring its potential significance in cardiac electrophysiology [91]. A study by Fantozzi *et al*. demonstrated that pulmonary artery smooth muscle hypertrophy under pressure overload conditions leads to a down-regulation of Kv6.2 [92]. This finding highlights the sensitivity of Kv6.2 expression to pathophysiological stress. Further emphasizing the importance of Kv6.2 in cardiac function, Rathjens *et al*. [93] revealed a cardioprotective effect following specific TBX5 knockout in a mouse model of heart failure and arrhythmia, where Kv6.2 expression was increased. Moreover, genetic studies have established a strong association between Kv6.2 and cardiovascular diseases. Mutations or deletions in the Kv6.2 gene have been linked to sinus node dysfunction. During voltage-dependent K^+ channel inactivation, the amino terminal of Kv6.2 interacts specifically with the amino terminal of Kv2.1. This interaction is crucial for regulating Kv channel currents, which, in turn, influence Ca^{2+} influx during the repolarization phase [89]. Such modulation shortens the duration of action potential repolarization and subsequently affects cardiac contractility, illustrating the multifaceted role of Kv6.2 in cardiac physiology and pathology.

These above studies all suggest a close association between silent subunits and cardiovascular diseases. The understanding of KvS subunit expression and function holds significant potential for advancing our knowledge in cellular electrophysiology and pathophysiology.

4 Summary

The Kv channel family plays a pivotal role in cardiovascular physiology, comprising a diverse array of subunits each contributing to the fine-tuning of cardiac and vascular functions. Current research highlights the significance of homotetrameric complexes formed by electrically active α subunits, which orchestrate a variety of potassium ion currents essential for the initiation and regulation of action potentials. These currents, carried by different Kv channel subtypes (e.g., Kv1, Kv2, Kv4, Kv7, Kv10, Kv11), serve distinct roles in modulating cardiac electrophysiological properties and vascular tone.

In cardiovascular diseases, the dysregulation of Kv channel activity is a key factor in pathological cardiac electrophysiological remodeling, presenting potential targets for therapeutic intervention. Particularly, the exploration of "silent" subunits offers a novel avenue for drug development, aiming to modulate channel activity with enhanced specificity and safety. Yet, the intricate mechanisms by which these silent subunits influence the function of electrically active counterparts remain largely unexplored, underscoring the need for further research.

Understanding the comprehensive roles of Kv channels in cardiovascular health and disease holds the promise of uncovering new therapeutic strategies. Future investigations should focus on elucidating the molecular mechanisms governing Kv channel regulation, the interaction between different subunits, and their impact on cardiovascular pathophysiology. Moreover, integrating insights from genetic, pharmacological, and biophysical studies will be crucial in translating basic research into clinical applications. By advancing our knowledge in these areas, we aim to pave the way for novel interventions that can more effectively treat or prevent cardio-

vascular diseases, ultimately contributing to improved patient outcomes.

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