The potential role of Kv4.3 K⁺ channel in heart hypertrophy

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Transient outward K⁺ current (Iₒ) plays a crucial role in the early phase of cardiac action potential repolarization. Kv4.3 K⁺ channel is an important component of Iₒ. The function and expression of Kv4.3 K⁺ channel decrease in variety of heart diseases, especially in heart hypertrophy/heart failure. In this review, we summarized the changes of cardiac Kv4.3 K⁺ channel in heart diseases and discussed the potential role of Kv4.3 K⁺ channel in heart hypertrophy/heart failure. In heart hypertrophy/heart failure of mice and rats, downregulation of Kv4.3 K⁺ channel leads to prolongation of action potential duration (APD), which is associated with increased [Ca²⁺], activation of calcineurin and heart hypertrophy/heart failure. However, in canine and human, Kv4.3 K⁺ channel does not play a major role in setting cardiac APD. So, in addition to Kv4.3 K⁺ channel/APD/[Ca²⁺] pathway, there exits another mechanism of Kv4.3 K⁺ channel in heart hypertrophy and heart failure: downregulation of Kv4.3 K⁺ channels leads to CaMKII dissociation from Kv4.3–CaMKII complex and subsequent activation of the dissociated CaMKII, which induces heart hypertrophy/heart failure. Upregulation of Kv4.3 K⁺ channel inhibits CaMKII activation and its related harmful consequences. We put forward a new point-of-view that Kv4.3 K⁺ channel is involved in heart hypertrophy/heart failure independently of its electric function, and drugs inhibiting or upregulating Kv4.3 K⁺ channel might be potentially harmful or beneficial to hearts through CaMKII.

Introduction

Since transient outward K⁺ current (Iₒ) was first described as an early outward current in sheep Purkinje fibers, there has been significant progress in the structure, regulator, electrophysiology of Iₒ and Iₒ related Kv K⁺ channels. The channels responsible for cardiac Iₒ are composed of Kv4.2 (KCND2), Kv4.3 (KCND3) and Kv1.4 (KCNA4) subunits. There is now consensus that Iₒ slows phase 1 repolarization, decreases phase 1 notch depth and affects all of the currents activated later in the action potential. Kv4.3 K⁺ channel is an important component of Iₒ. Lots of studies have shown that the function and expression of Kv4.3 K⁺ channel decrease in variety of heart diseases, such as hypertrophy, heart failure, myocardial infarction, heart value disease, atrial fibrillation, and diabetic cardiomyopathy et al. Here, we summarized the progresses on the function and expression of Kv4.3 K⁺ channel in heart diseases, especially in heart hypertrophy and heart failure, and discussed the potential role of downregulation of Kv4.3 K⁺ channel in heart hypertrophy/heart failure.

Kv4.3 K⁺ Channel and Its Auxiliary Protein Subunits

Kv4.3 belongs to voltage activated (Kv) K⁺ channel, mammalian Shal-related family. It is encoded by KCND3 gene and expressed in heart, brain and smooth muscle. The pharmacological and electrophysiological properties of Kv4.3 K⁺ channel have been well reviewed by Gutman et al. Although the currents carried by Kv4.3 α-subunits show similar biophysical properties to native Iₒ, there are some differences between them. The native Kv4.3 K⁺ channel needs auxiliary protein subunits (β-subunits) to modulate its biophysical properties and trafficking. Several Kv auxiliary protein subunits have been identified. Kv-channel interacting proteins 2 (KChIP2) is a functional modifier of Kv4.3 K⁺ channel and particularly abundant in the heart. KChIP2 is required for the generation of native Iₒ. It increases Kv4.3 K⁺ channel expression, enhances Iₒ current amplitude and slows inactivation of Iₒ. KChIP2/mice lack the Iₒ current and are highly susceptible to ventricular tachycardia. Dipetidyl peptidase-like proteins (DPPs) are other kinds of auxiliary subunits. DPP6/10 accelerates the inactivation kinetics and recovery from inactivation of both Kv4.3 K⁺ channel/A-type currents. DPP6/10 regulates Kv4.3 gating through a mechanism distinct from that of the KChIPs. Co-expression of DPP6 in addition to Kv4.3 and KChIP2a produces Iₒ current with similar kinetics as in human ventricular myocytes. Synapse-associated protein 97 (SAP97), a member of the membrane-associated guanylate kinases (MAGUK) family, influences the trafficking and anchoring of cardiac Kv4.2/3 channels. Suppression of SAP97 inhibits Iₒ in cardiac myocytes. SAP97 forms a tripartite complex with Kv4.3 K⁺ channel and CaMKII in cardiac myocytes and is necessary for CaMKII-dependent phosphorylation of Kv4.3. Other accessory subunits show varying effects on Kv4.3 K⁺ channel

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expression and kinetics. Co-expression of Kvβ1, Kvβ2 or Kvβ3 increases Kv4.3-encoded Kv current densities without changing kinetics. K+ channel accessory protein (KChAP), a chaperone for Kv4.3, increases Kv4.3 K+ channel expression without altering kinetics. K+ channel accessory protein (KChAP), a chaperone for Kv4.3, increases Kv4.3 K+ channel expression without altering kinetics.18-21 KChAP increases Kv4.3 K+ channel expression without altering kinetics.22,23 MiRP2 has been reported to decrease Kv4.3 encoded current densities.24 Downregulation of Kv4.3 K+ Channel in Heart Diseases

The downregulation of Kv4.3 protein and mRNA levels has been observed in many heart diseases, such as cardiac hypertrophy, heart failure, myocardial infarction, heart value disease, atrial fibrillation and diabetic cardiomyopathy. In addition to the downregulation of Kv4.3 K+ channel in heart hypertrophy/heart failure which will be discussed in the later part of the article, downregulation of Kv4.3 K+ channel is also observed in both in vivo and in vitro tachypaced models and the hormone-related heart diseases. In experimental hypothyroidism, cardiac Kv4.3 protein expression in both epicardium of the left ventricle and right ventricle decreases. In male rats with aldosterone chronic treatment, the cardiac Kv4.3 mRNA expression decreases. In addition to cardiomyocytes, Kv4.3 K+ channel is also involved in fibroblast function. Cardiac fibroblasts are crucial for regulating cardiac extracellular matrix and are the main source of cardiac fibrosis. Recently, Wu et al. reported that the mRNA expression of Kv4.3 was smaller in CHF fibroblast than control fibroblast. Suppressing Kv current with TEA enhanced fibroblast proliferation. These results suggest that reduced Kv channel expression in CHF may contribute to cardiac fibrosis.20 Presently, several mechanisms involving downregulation of cardiac Kv4.3 K+ channel have been reported. Rossow et al. reported that increased β-adrenergic signaling and activated calcineurin/NFATc3 were essential in reduction of mRNA and protein level of Kv4.3 after myocardial infarction (MI).2 Zhang et al. reported that both phenylephrine (PE) and angiotensin II directly downregulated Kv4.3 mRNA and protein in neonatal rat myocytes, but through different mechanisms. PE inhibited transcription of the Kv4.3 gene whereas Ang II was more likely involved in destabilization of channel mRNA.3 Indeed, Zhou et al. reported that Ang II and stretch specifically destabilized cardiac Kv4.3 channel mRNA and decreased the mRNA stability via activating NADPH oxidase.3 Our group also found that bone morphogenetic protein-4 contributed to the downregulation of Kv4.3 channel in pathological cardiac hypertrophy via NADPH-Ros signal pathways.35 High-mobility group box 1 (HMGB1), a proinflammatory cytokine, has been reported to increase in the serum of patients with myocardial infarction, Liu et al. reported that HMGB1 decreased the mRNA and protein levels of the Kv4.3 channel through HMGB1-RAGE (the receptor for advanced glycation end products) interaction.34 The auxiliary protein subunits of Kv channels are also changed in the pathological state and may contribute to the downregulation of Kv4.3 K+ channels. For example, as an auxiliary protein subunit known to increase Kv4.3 channels expression, KChIP2 mRNA and protein expressions were reported to be decreased by hypertrophy-inducing stimuli both in vivo and in vitro, and the mechanism was through activation of JNKs.35 In addition, the downregulation of KChIP2 mRNA and/or protein expressions has also been shown in heart failure mice models.36-37 Grubb et al. reported that, compared with the wild type mice with heart failure, KChIP2-/- heart failure mice showed a larger reduction of K+-current density.38 These results suggest that the reduction of KChIP2 may contribute to the downregulation of Kv4.3 K+ channels in heart diseases.

Although the downregulation of Kv4.3 K+ channel is observed in variety of heart diseases, it is noteworthy that recent works show that enhancement of Kv4.3 K+ channel leads to some severe cardiac arrhythmias. A chromosomal haplotype producing cardiac overexpression of dipeptidyl peptidase-like protein-6
The relationship between I\textsubscript{to} inhibition and APD prolongation is species-specific. Kv4.3 K\textsuperscript{+} channel underlies a significant fraction of the I\textsubscript{to} currents and served as a rare genetic substrate in the pathogenesis of autopsy-negative sudden unexplained death.\textsuperscript{42}

**Kv4.3 Downregulation and Cardiac Action Potential Duration (APD)**

As discussed above, in the hearts, I\textsubscript{to} is responsible for the initial phase of repolarization and for setting the plateau voltage of the action potential. Kv4.3 K\textsuperscript{+} channel expression in the hearts is species-specific. Kv4.3 K\textsuperscript{+} channel underlies a significant fraction of the I\textsubscript{to} in canine and human cardiomyocytes, Kv4.3, Kv4.2 and Kv4.1 contribute to I\textsubscript{to} in mice, rat cardiomyocytes.\textsuperscript{43} However, Kv4.3 K\textsuperscript{+} channel is believed to be absent in the guinea pig.\textsuperscript{44} The action potential waveforms of cardiomyocytes are markedly different in different species. Mice and rat cardiomyocytes have a relatively brief action potential with a "triangular" shape. This abbreviated waveform is mainly attributed to the large repolarizing currents of I\textsubscript{to}. Canine and human cardiomyocytes have a "spike-and-dome" shape action potential, in which the rapid repolarizing phase 1 is attributed to I\textsubscript{to} (mainly encoded by Kv4.3) and the later repolarizing phase is the net result of varieties of activated inward and outward currents. Since the contribution of Kv4.3 K\textsuperscript{+} channel to cardiac action potential is different in different species, such as in mice, rat, canine, and human, it is reasonable to speculate that Kv4.3 K\textsuperscript{+} channels would have different physiological or pathological role in the heart of different species. Indeed, inhibition of I\textsubscript{to} prolongs the APD of cardiomyocytes in mice (Fig. 1A), however, the relationship between I\textsubscript{to} inhibition and APD prolongation is not a simple monotonic correlation in cardiomyocytes in human (Fig. 1B). Therefore, the role of Kv4.3 K\textsuperscript{+} channels cannot be simply explained in aspect of electrophysiology.

**Kv4.3 K\textsuperscript{+} Channel and Heart Hypertrophy/Heart Failure**

Kv4.3 K\textsuperscript{+} channel and heart hypertrophy/heart failure in mice and rat

We have previously reviewed the role of I\textsubscript{to} in the electrical remodeling of pathological cardiac hypertrophy in mice and rats.\textsuperscript{55} Here, we summarized the changes of Kv4.3 K\textsuperscript{+} channel in hypertrophy/heart failure. In left ventricle hypertrophy rats treated with mineralocorticoid and subjected to abdominal aortic stenosis, Kv4.3 mRNA was downregulated.\textsuperscript{46} Downregulation of Kv4.3 was also reported in rats with monocrotaline-induced right ventricular hypertrophy.\textsuperscript{47} Angiotsin II (Ang II) and phenylephrine (PE), the known stimulators of cardiac myocyte hypertrophy, downregulated Kv4.3 mRNA and protein levels in neonatal rat cardiac myocytes.\textsuperscript{48} In rabbits exposed to long-term tachycardia, Kv4.3 was downregulated at both transcription and protein levels.\textsuperscript{49} Huang et al. reported that myocardial infarction downregulated Kv4.3 mRNA and protein expression in rat ventricular myocytes.\textsuperscript{50} In rat model of type I diabetes, Kv4.3 protein density of left ventricular myocytes decreased.\textsuperscript{51} Interestingly, the decrease of Kv4.3 expression led to certain consequences. Reduction of Kv4.2/Kv4.3-based I\textsubscript{to} prolonged APD, resulting in cardiac myocyte hypertrophy.\textsuperscript{52} The downregulation of Kv4.3 K\textsuperscript{+} currents and channel expression enhanced sympathoexcitation in hypertrophic or failing rat hearts.\textsuperscript{53} Lebeche et al. found that in vivo gene transfer of Kv4.3 restored the downregulation of I\textsubscript{to} and abrogated the hypertrophic response.\textsuperscript{54} Injection of adenovirus carrying the Kv4.3 gene reversed hypertrophy induced by Ang II in cultured neonatal rat ventricular myocytes.\textsuperscript{55} Also, in vivo infection of Ad Kv4.3 abrogated the hypertrophy induced by aortic stenosis in rats.\textsuperscript{54}

The molecular mechanism of I\textsubscript{to} downregulation contributing to hypertrophy/heart failure is considered to be mediated by prolonged APD related Ca\textsuperscript{2+} signal. Kv4.3 channel contributes significantly to I\textsubscript{to} in rat, canine, and human cardiac myocytes.\textsuperscript{45} Diminished Kv4.3 levels reduce the cardiac transient outward K\textsuperscript{+} current. In rodents, I\textsubscript{to} is a major repolarizing current throughout the comparatively short cardiac action potential necessary to maintain extremely high heart rates. Reduction of I\textsubscript{to} prolongs APD and increases Ca\textsuperscript{2+} influx through voltage dependent L-type Ca\textsuperscript{2+} channels, thereby elevating [Ca\textsuperscript{2+}]\textsubscript{i}.\textsuperscript{56} Ca\textsuperscript{2+} is an essential cofactor for several hypertrophy signaling pathways, including calcineurin, a Ca\textsuperscript{2+}-dependent protein phosphatase. Its activity is increased in pathological conditions, including hypertrophy and myocardial infarction.\textsuperscript{57} The downregulation of I\textsubscript{to} is observed with overexpression of calcineurin and is partly reversed by the calcineurin inhibitor CsA.\textsuperscript{58} NFAT3 is normally phosphorylated in the cytoplasm. When NFAT3 is dephosphorylated by calcineurin, it translocates into the nucleus where it can interact with GATA4 to activate transcription of hypertrophic response genes. Other signaling pathways other than calcineurin and NFAT3 have also been shown to mediate the hypertrophic response in the heart, such as the protein kinase C pathway\textsuperscript{59} or the mitogen-activated protein kinase (MAPK) pathway.\textsuperscript{60} The major mechanism between Kv4.3 K\textsuperscript{+} channel and heart hypertrophy/heart failure in mice and rats was summarized in Figure 2.

**Kv4.3 K\textsuperscript{+} channel and heart hypertrophy/heart failure in canine and human**

In a canine model of tachycardia-induced heart failure, Kv4.3 was downregulated at both transcription and protein levels in epicardial, midmyocardial and endocardial layers of left ventricle.\textsuperscript{61} Downregulation of Kv4.3 was also reported in cultured adult canine left ventricular cardiomyocytes subjected to pacing.\textsuperscript{62} In dogs with ventricular tachypacing-induced chronic heart failure (CHF), Kv4.3 protein expression in purkinje fibers decreased.\textsuperscript{63} In a dog model of atrial pacing-induced atrial fibrillation, Kv4.3 decreased at both mRNA and
protein levels. CHF downregulated Kv4.3 mRNA and protein expression in canine cardiac tissues and cardiomyocytes, as well as in terminally failing human heart tissue samples. In human failing heart tissues and isolated ventricular myocytes, Kv4.3 K+ currents and channel expression decreased. Borlak et al. observed significant reduction of the gene expression of Kv4.3 at transcript level in patients suffered from ischemic or dilatative cardiomyopathy. Kv4.3 was significantly reduced in patients with paroxysmal and persistent atrial fibrillation.

The native cardiac Ito, encoded by Kv4.3 in canine or humans is responsible for the initial rapid phase of action potential repolarization, discernible as a notch preceding the plateau phase. In contrast to the role of Ito (Kv4.3) in determining the shape of action potential in mice or rats, there is no inevitable relationship between Kv4.3 and action potential duration in canine and humans. By using a model of canine ventricular myocyte model, Greenstein et al. evidenced that increasing Kv4.3 density shortened APD at high baseline Kv4.3 K+ current densities, whereas at lower levels, increasing Kv4.3 density produced modest prolongation of APD. Thus, the relationship between APD and Kv4.3 K+ current was not a simple monotonic correlation. Indeed, a clinic study showed that mutations in KCND2 and KCND3 gene responsible for Kv4.2 and Kv4.3 were not a frequent cause of long QT syndrome in human. And, Dong et al. found that in animals such as dogs that had a broad cardiac action potential, Ito did not play a major role in setting the APD.

It has been established that downregulation of Kv4.3 K+ channel leads to prolongation of APD, which is associated with increased [Ca2+], activation of calcineurin and heart hypertrophy/heart failure in mice or rats. However, it is unclear whether the molecular mechanism of Ito-induced hypertrophic response in mice and rats can be extrapolated to the diseased human heart. What is the role of downregulation of Kv4.3 K+ channel in human and canine hypertrophic hearts?

Kv4.3 and CaMKII

Downregulation of Kv4.3 K+ currents occurs in hypertrophic or failing canine and human hearts, but it is not clear that the downregulation of Kv4.3 K+ channels is only a consequence of diseases or it can be an initiator to promote the disease process. The recent works and our study showed that downregulation of Kv4.3 K+ channels contributed to heart hypertrophy and heart failure through activating CaMKII and the new role of Kv4.3 K+ channel was independent of its electric function. Upregulation of Kv4.3 K+ channels would be protective through coupling more reserved Ca2+/calmodulin-dependent protein kinases II (CaMKII) and inhibiting CaMKII activation.

CaMKII, the serine/threonine-specific protein kinase, is involved in many heart diseases, such as heart hypertrophy/heart failure, cardiac infarction, and atrial fibrillation. Kv4.3 K+ channel forms a tripartite complex with the anchoring protein SAP97 and CaMKII in cardiac myocytes. Keskanokwong et al. reported that Kv4.3 K+ channel, by binding to the CaM binding sites on the inactive CaMKII, prevented Ca2+-induced excessive CaMKII activation; in addition, these effects were independent on Kv4.3 K+ channel activation and action potential. They also showed that blockade of Kv4.3 with 4-aminopyridine (4-AP) or Ad-Kv4.3 antisense induced CaMKII dissociation from Kv4.3-CaMKII complex and subsequent activation of the dissociated CaMKII, which induces heart hypertrophy/heart failure. The molecular mechanism may present in mice, rat, canine, and human.
activation of CaMKII plays an essential role in the development of cardiac hypertrophy and failure.\textsuperscript{7,27} Activation of membrane-localized CaMKII directly phosphorylates several membrane ion channels, such as L-type Ca\textsuperscript{2+} channels,\textsuperscript{77} potassium channel, and fast sodium channel,\textsuperscript{78} which in turn amplifies CaMKII activity and exacerbates the cardiac pathological progression. Moreover, CaMKII-dependent phosphorylation changes the gating of Ca\textsuperscript{2+} channels and Na\textsuperscript{+} channels, which favors arrhythmogenesis.\textsuperscript{79,80} Since the relationship between Kv4.3 and CaMKII and role of CaMKII in heart hypertrophy/heart failure have been proved, here, we put forward that Kv4.3 K\textsuperscript{+} channel is the upstream factor of CaMKII and directly regulates CaMKII activation. Upregulation of Kv4.3 K\textsuperscript{+} channel will be a strategy for treatment of heart hypertrophy/heart failure in canine and humans, the molecular mechanism in which is different from that currently observed in mice and rats. The mechanism is summarized in Figure 4. On the other hand, because CaMKII is a validated signal for cardiac arrhythmias,\textsuperscript{81,82} Kv4.3–CaMKII pathway is also of significance for cardiac arrhythmias. We have discussed that Kv4.3 channel is not necessarily related to APD changes in human hearts, however, Kv4.3 directly regulates CaMKII activation, indicating that upregulation of Kv4.3 K\textsuperscript{+} channels would be protective against cardiac arrhythmias through inhibiting excessive CaMKII activation. Thus, upregulation of Kv4.3 K\textsuperscript{+} channels is also a strategy for treatment of cardiac arrhythmias.

The Potential Role of Kv4.3 and CaMKII in Heart Diseases

Mice and rats are excellent experimental animals in biological studies, however, because of the species differences, the conclusion derived from mice or rats cannot be completely extrapolated to that in human, and the understandings are more significance clinically. As discussed in the above parts, downregulation of cardiac Kv4.3 K\textsuperscript{+} channel leads to CaMKII dissociation from Kv4.3–CaMKII complex and subsequent activation of the dissociated CaMKII, which induces heart hypertrophy/heart failure. Upregulation of cardiac Kv4.3 K\textsuperscript{+} channel inhibits CaMKII activation and the CaMKII activation related harmful consequences. This opinion clearly explains the role of Kv4.3 K\textsuperscript{+} channel in heart hypertrophy/heart failure in human. We do not exclude the possibility that the Kv4.3–CaMKII–heart hypertrophy/heart failure pathway occurs in mice and rats, but it is indeed different from the currently acknowledged pathway, Kv4.3–APD–[Ca\textsuperscript{2+}+]–heart hypertrophy/heart failure pathway.

Kv4.3 K\textsuperscript{+} channel is downregulated in many diseases like heart hypertrophy, heart failure, cardiac infarction, atrial fibrillation, nerve injury. Some drugs such as celecoxib, diltiazem and nicotine inhibit Kv4.3 K\textsuperscript{+} channel.\textsuperscript{83-85} It was very interesting that celecoxib, diltiazem and nicotine were reported to be related to increased cardiovascular risk or sudden cardiac death.\textsuperscript{86-87} On the other hand, tamoxifen, the mixed agonist/antagonist of estrogen receptor, upregulated cardiac Kv4.3 K\textsuperscript{+} channel\textsuperscript{88} and also exhibited powerful cardioprotective effects.\textsuperscript{89} The above information indicates that the Kv4.3-CaMKII signaling pathway might be involved in the pharmacological effects of these drugs. The Kv4.3-CaMKII-heart hypertrophy/heart failure pathway is an intriguing topic and still deserves extensive studies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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