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

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Transient outward K^+ current (I_{to}) plays a crucial role in the early phase of cardiac action potential repolarization. Kv4.3 K^+ channel is an important component of I_{to}. 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 $[Ca^{2+}]_i$, 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/$[Ca^{2+}]_i$ 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 (I_{to}) was first described as an early outward current in sheep Purkinje fibers, there has been significant progress in the structure, regulator, electrophysiology of I_{to} and I_{to} related Kv K^+ channels. The channels responsible for cardiac I_{to} are composed of Kv4.2 (KCND2), Kv4.3 (KCND3) and Kv1.4 (KCNA4) subunits. There is now consensus that I_{to} plays a crucial role in the early phase of cardiac action potential repolarization and prominent phase 1 notch in cardiomycoytes. The reduction of I_{to} 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 I_{to}. 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,[1] myocardial infarction,[2] heart value disease,[3] atrial fibrillation,[4,5] and diabetic cardiomyopathy[6] 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.

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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.[7] Although the currents carried by Kv4.3 α-subunits show similar biophysical properties to native $I_{to,}$ 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[8] and particularly abundant in the heart.[9] KChIP2 is required for the generation of native I_{to}.[9,10] It increases Kv4.3 K^+ channel expression, enhances I_{to} current amplitude and slows inactivation of $I_{to.}$[9] KChIP2-/- mice lack the I_{to} current and are highly susceptible to ventricular tachycardia.[11,12] Dipeptidyl peptidase-like proteins (DPPs) are other kinds of auxiliary subunits. DPP6/10 accelerates the inactivation kinetics and recovery from inactivation of both Kv4.2 and Kv4.3/KChIP A-type currents.[13-15] DPP6/10 regulates Kv4.3 gating through a mechanism distinct from that of the KChIPs.[14,15] Co-expression of DPP6 in addition to Kv4.3 and KChIP2a produces I_{to} current with similar kinetics as in human ventricular myocytes.[15] 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 I_{to} 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.[16,17] Other accessory subunits show varying effects on Kv4.3 K^+ channel

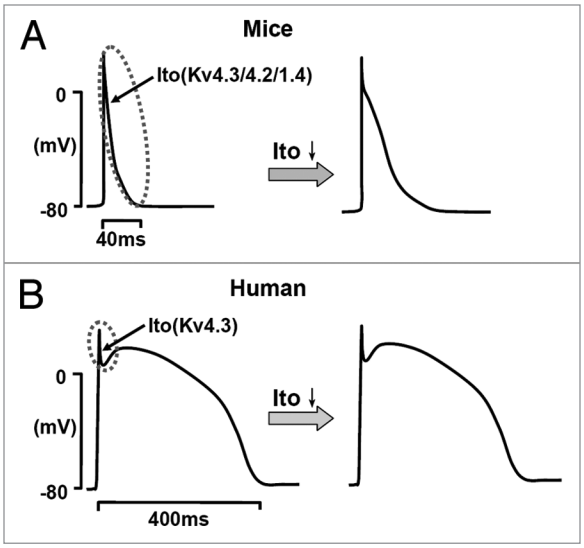

Figure 1. Role of Kv4.3 K^+ channel in determining cardiac action potential duration (APD). (**A**) Inhibition of Kv4.3 K^+ channel prolongs cardiac APD in mice. (**B**) Inhibition of Kv4.3 K^+ channel is not necessarily related to APD prolongation in human.

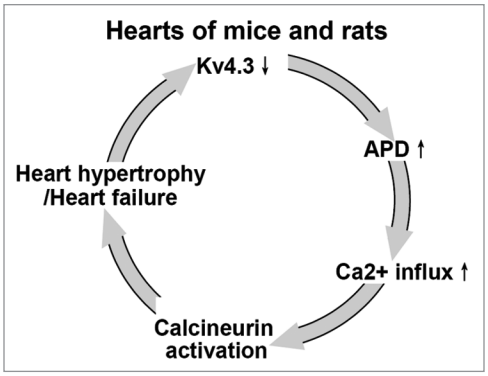

Figure 2. Role of Kv4.3 K^+ channel in heart hypertrophy/heart failure in mice and rats. For heart hypertrophy/heart failure in mice and rats, the molecular mechanism is that downregulation of Kv4.3 K^+ channels leads to prolongation of action potential duration (APD), which is associated with increased $[Ca^{2+}]_i$, activation of calcineurin and heart hypertrophy/heart failure.

expression and kinetics. Co-expression of Kvβ1, Kvβ2 or Kvβ3 increases Kv4.3-encoded Kv current densities without changing kinetics.[18-21] K^+ channel accessory protein (KChAP), a chaperone for Kv4.3, increases Kv4.3 K^+ channel expression without altering kinetics.[22,23] Mink and Mink-related peptide 2 (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,[1] myocardial infarction,[2] heart value disease,[3] atrial fibrillation[4,5,25] and diabetic cardiomyopathy.[6] 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[26,27] 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.[28] In male rats with aldosterone chronic treatment, the cardiac Kv4.3 mRNA expression decreases.[29] 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 Kv1.5 and 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.[30]

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.[31] 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.[32] 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.[33] 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,[9] 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

(DPP6) causes familial idiopathic ventricular fibrillation. Xiao et al. reported that DPP6 expression with Kv4.3 and neuronal calcium sensor-1 greatly enhanced purkinje fibers I_{to} and that its overexpression might contribute to idiopathic ventricular fibrillation through altering purkinje fibers I_{to} properties.[39] Other two individual groups showed that mutations in the pore forming subunit Kv4.3 led to I_{to} increase which was associated with the brugada syndrome,[40] and early-onset lone atrial fibrillation.[41] KCND3 mutations (p.Val392Ile and p.Gly600Arg mutations) significantly increased I_{to} currents and served as a rare genetic substrate in the pathogenesis of autopsy-negative sudden unexplained death.[42]

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

As discussed above, in the hearts, I_{to} is responsible for the initial phase of repolarization and for setting the plateau voltage of the action potential. Kv4.3 K^+ channel expression in the hearts is species-specific. Kv4.3 K^+ channel underlies a significant fraction of the I_{to} in canine and human cardiomyocytes, Kv4.3, Kv4.2 and Kv1.4 contribute to I_{to} in mice, rat cardiomyocytes.[43] However, Kv4.3 K^+ channel is believed to be absent in the guinea pig.[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 K^+ currents of I_{to}. Canine and human cardiomyocytes have a "spike-and-dome" shape action potential, in which the rapid repolarizing phase 1 is attributed to I_{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^+ 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^+ channels would have different physiological or pathological role in the heart of different species. Indeed, inhibition of I_{to} prolongs the APD of cardiomyocytes in mice (**Fig. 1A**), however, the relationship between I_{to} inhibition and APD prolongation is not a simple monotonic correlation in cardiomyocytes in human (**Fig. 1B**). Therefore, the role of Kv4.3 K^+ channels cannot be simply explained in aspect of electrophysiology.

Kv4.3 K^+ Channel and Heart Hypertrophy/Heart Failure

Kv4.3 K^+ channel and heart hypertrophy/heart failure in mice and rat

We have previously reviewed the role of I_{to} in the electrical remodeling of pathological cardiac hypertrophy in mice and rats.[45] Here, we summarized the changes of Kv4.3 K^+ channel in hypertrophy/heart failure. In left ventricle hypertrophy rats treated with mineralocorticoid and subjected to abdominal aortic stenosis, Kv4.3 mRNA was downregulated.[46] Downregulation of Kv4.3 was also reported in rats with monocrotaline-induced right ventricular hypertrophy.[47] Angiotensin 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.[48] In rabbits exposed to long-term tachycardia, Kv4.3 was downregulated at both transcription and protein levels.[49] Huang B et al. reported that myocardial infarction downregulated Kv4.3 mRNA and protein expression in rat ventricular myocytes.[50] In rat model of type I diabetes, Kv4.3 protein density of left ventricular myocytes decreased.[51] Inversely, the decrease of Kv4.3 expression led to certain consequences. Reduction of Kv4.2/Kv4.3-based I_{to} prolonged APD, resulting in cardiac myocyte hypertrophy.[52] The downregulation of Kv4.3 K^+ currents and channel expression enhanced sympathoexcitation in hypertrophic or failing rat hearts.[53] Lebeche et al. found that in vivo gene transfer of Kv4.3 restored the downregulation of I_{to} and abrogated the hypertrophic response.[54] Infection of adenovirus carrying the Kv4.3 gene reversed hypertrophy induced by Ang II in cultured neonatal rat ventricular myocytes.[55] Also, in vivo infection of Ad Kv4.3 abrogated the hypertrophy induced by aortic stenosis in rats.[54]

The molecular mechanism of I_{to} downregulation contributing to hypertrophy/heart failure is considered to be mediated by prolonged APD related Ca^{2+} signal. Kv4.3 channel contributes significantly to I_{to} in rat, canine, and human cardiac myocytes.[43] Diminished Kv4.3 levels reduce the cardiac transient outward K^+ current. In rodents, I_{to} is a major repolarizing current throughout the comparatively short cardiac action potential necessary to maintain extremely high heart rates. Reduction of I_{to} prolongs APD and increases Ca^{2+} influx through voltage dependent L-type Ca^{2+} channels, thereby elevating $[Ca^{2+}]_i$.[56] Ca^{2+} is an essential cofactor for several hypertrophy signaling pathways, including calcineurin, a Ca^{2+}-dependent protein phosphatase. Its activity is increased in pathological conditions, including hypertrophy and myocardial infarction.[57] The downregulation of I_{to} is observed with overexpression of calcineurin and is partly reversed by the calcineurin inhibitor CsA.[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 calcineruin and NFAT3 have also been shown to mediate the hypertrophic response in the heart, such as the protein kinase C pathway[59] or the mitogen-activated protein kinase (MAPK) pathway.[60] The major mechanism between Kv4.3 K^+ channel and heart hypertrophy/heart failure in mice and rats was summarized in **Figure 2**.

Kv4.3 K^+ 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.[61] Downregulation of Kv4.3 was also reported in cultured adult canine left ventricular cardiomyocytes subjected to pacing.[62] In dogs with ventricular tachypacing-induced chronic heart failure (CHF), Kv4.3 protein expression in purkinje fibers decreased.[63] In a dog model of atrial pacing-induced atrial fibrillation, Kv4.3 decreased at both mRNA and

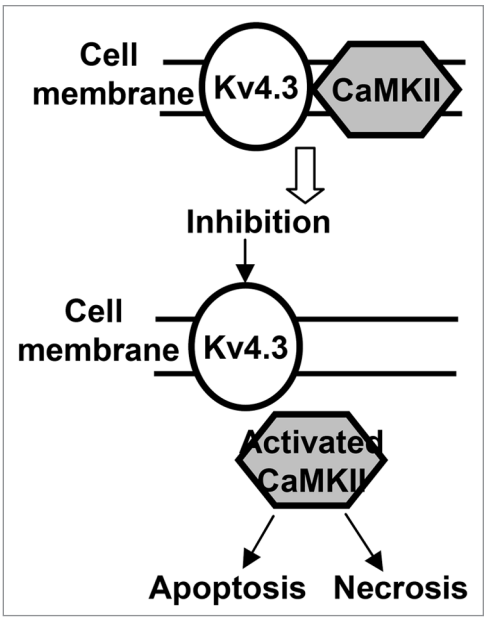

Figure 3. The schematic diagram showing that inhibition of Kv4.3 K^+ channel induces cell apoptosis and necrosis through activating CaMKII. (Reproduced with permission, from Li et al., 2012, Biochem J, 441,859–67. © The Biochemical Society.)

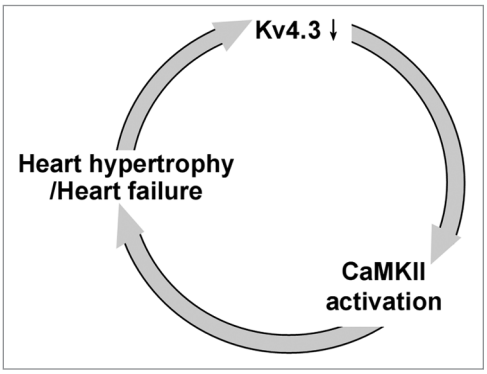

Figure 4. Kv4.3-CaMKII pathway in heart hypertrophy/heart failure. Downregulation of Kv4.3 K^+ channel leads to CaMKII dissociation from Kv4.3–CaMKII complex and subsequent activation of the dissociated CaMKII, which induces heart hypertrophy/heart failure. The molecular mechanism may present in mice, rat, canine, and human.

protein levels.[64] CHF downregulated Kv4.3 mRNA and protein expression in canine cardiac tissues and cardiomyocytes, as well as in terminally failing human heart tissue samples.[65] In human failing heart tissues and isolated ventricular myocytes, Kv4.3 K^+ currents and channel expression decreased.[1] Borlak et al. observed significant reduction of the gene expression of Kv4.3 at transcript level in patients suffered from ischemic or dilatative cardiomyopathy.[66] Kv4.3 was significantly reduced in patients with paroxysmal and persistent atrial fibrillation.[3]

The native cardiac I_{to} 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 I_{to} (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.[67] 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.[68] And, Dong et al. found that in animals such as dogs that had a broad cardiac action potential, I_{to} did not play a major role in setting the APD.[69]

It has been established that downregulation of Kv4.3 K^+ channel leads to prolongation of APD, which is associated with increased $[Ca^{2+}]_i$, activation of calcineurin and heart hypertrophy/heart failure in mice or rats. However, it is unclear whether the molecular mechanism of I_{to}-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[70,71] 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 Ca^{2+}/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,[72] cardiac infarction,[73] and atrial fibrillation.[74] Kv4.3 K^+ channel forms a tripartite complex with the anchoring protein SAP97 and CaMKII in cardiac myocytes.[75] Keskanokwong et al.[70] reported that Kv4.3 K^+ channel, by binding to the CaM binding sites on the inactive CaMKII, prevented Ca^{2+}-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. In our recent work by using the HEK293 and HEK293T cells models, we found that inhibition of Kv4.3 K^+ channel with 4-AP or Kv4.3 small interfering RNA induced cell apoptosis and necrosis, which were completely rescued by specific CaMKII inhibitor KN-93 but not the negative control KN-92, suggesting that Kv4.3 K^+ channel contributed to cell apoptosis and necrosis through CaMKII activation **(Fig. 3)**.[71] Excessive

activation of CaMKII plays an essential role in the development of cardiac hypertrophy and failure.[72,76] Activation of membrane-localized CaMKII directly phosphorylates several membrane ion channels, such as L-type Ca^{2+} channels,[77] potassium channel, and fast sodium channel,[78] which in turn amplifies CaMKII activity and exacerbates the cardiac pathological progression. Moreover, CaMKII-dependent phosphorylation changes the gating of Ca^{2+} channels and Na^{+} channels, which favors arrhythmogenesis.[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^{+} channel is the upstream factor of CaMKII and directly regulates CaMKII activation. Upregulation of Kv4.3 K^{+} 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,[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^{+} channels would be protective against cardiac arrhythmias through inhibiting excessive CaMKII activation. Thus, upregulation of Kv4.3 K^{+} 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 for human are more significance clinically. As discussed in the above parts, downregulation of cardiac Kv4.3 K^{+} 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^{+} channel inhibits CaMKII activation and the CaMKII activation related harmful consequences. This opinion clearly explains the role of Kv4.3 K^{+} 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–$[Ca^{2+}]_i$–heart hypertrophy/heart failure pathway.

Kv4.3 K^{+} 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^{+} channel.[83-85] It was very interesting that celecoxib, diltiazem and nicotine were reported to be related to increased cardiovascular risk or sudden cardiac death.[86-87] On the other hand, tamoxifen, the mixed agonist/antagonist of estrogen receptor, upregulated cardiac Kv4.3 K^{+} channel[88] and also exhibited powerful cardioprotective effects.[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.

Acknowledgments

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References

1. Kääb S, Dixon J, Duc J, Ashen D, Näbauer M, Beuckelmann DJ, Steinbeck G, McKinnon D, Tomaselli GF. Molecular basis of transient outward potassium current downregulation in human heart failure: a decrease in Kv4.3 mRNA correlates with a reduction in current density. Circulation 1998; 98:1383-93; PMID:9760292; http://dx.doi.org/10.1161/01.CIR.98.14.1383
2. Rossow CF, Minami E, Chase EG, Murry CE, Santana LF. NFATc3-induced reductions in voltage-gated K+ currents after myocardial infarction. Circ Res 2004; 94:1340-50; PMID:15087419; http://dx.doi.org/10.1161/01.RES.0000128406.08418.34
3. Gaborit N, Steenman M, Lamirault G, Le Meur N, Le Bouter S, Lande G, Léger J, Charpentier F, Christ T, Dobrev D, et al. Human atrial ion channel and transporter subunit gene-expression remodeling associated with valvular heart disease and atrial fibrillation. Circulation 2005; 112:471-81; PMID:16027256; http://dx.doi.org/10.1161/CIRCULATIONAHA.104.506857
4. Ji Q, Liu H, Mei Y, Wang X, Feng J, Ding W. Expression changes of ionic channels in early phase of cultured rat atrial myocytes induced by rapid pacing. J Cardiothorac Surg 2013; 8:194; PMID:24074263; http://dx.doi.org/10.1186/1749-8090-8-194
5. Brundel BJ, Van Gelder IC, Henning RH, Tuinenburg AE, Wietses M, Grandjean JG, Wilde AA, Van Gilst WH, Crijns HJ. Alterations in potassium channel gene expression in atria of patients with persistent and paroxysmal atrial fibrillation: differential regulation of protein and mRNA levels for K+ channels. J Am Coll Cardiol 2001; 37:926-32; PMID:11693772; http://dx.doi.org/10.1016/S0735-1097(00)01195-5
6. Qin D, Huang B, Deng L, El-Adawi H, Ganguly K, Sowers JR, El-Sherif N. Downregulation of K(+) channel genes expression in type I diabetic cardiomyopathy. Biochem Biophys Res Commun 2001; 283:549-53; PMID:11341759; http://dx.doi.org/10.1006/bbrc.2001.4825
7. Gutman GA, Chandy KG, Grissmer S, Lazdunski M, McKinnon D, Pardo LA, Robertson GA, Rudy B, Sanguinetti MC, Stühmer W, et al. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. Pharmacol Rev 2005; 57:473-508; PMID:16382104; http://dx.doi.org/10.1124/pr.57.4.10
8. Decher N, Uyguner O, Scherer CR, Karaman B, Yüksel-Apak M, Busch AE, Steinmeyer K, Wollnik B. hKChIP2 is a functional modifier of hKv4.3 potassium channels: cloning and expression of a short hKChIP2 splice variant. Cardiovasc Res 2001; 52:255-64; PMID:11684073; http://dx.doi.org/10.1016/S0008-6363(01)00374-1
9. An WF, Bowlby MR, Betty M, Cao J, Ling HP, Mendoza G, Hinson JW, Mattsson KI, Strassle BW, Trimmer JS, et al. Modulation of A-type potassium channels by a family of calcium sensors. Nature 2000; 403:553-6; PMID:10676964; http://dx.doi.org/10.1038/35000592
10. Foeger NC, Wang W, Mellor RL, Nerbonne JM. Stabilization of Kv4 protein by the accessory K+ channel interacting protein 2 (KChIP2) subunit is required for the generation of native myocardial fast transient outward K+ currents. J Physiol 2013; 591:4149-66; PMID:23713033
11. Kuo HC, Cheng CF, Clark RB, Lin JJ, Lin JL, Hoshijima M, Nguyên-Trân VT, Gu Y, Ikeda Y, Chu PH, et al. A defect in the Kv channel-interacting protein 2 (KChIP2) gene leads to a complete loss of I(to) and confers susceptibility to ventricular tachycardia. Cell 2001; 107:801-13; PMID:11747815; http://dx.doi.org/10.1016/S0092-8674(01)00588-8
12. Thomsen MB, Sosunov EA, Anyukhovsky EP, Özgen N, Boyden PA, Rosen MR. Deleting the accessory subunit KChIP2 results in loss of I(to,f) and increased I(K,slow) that maintains normal action potential configuration. Heart Rhythm 2009; 6:370-7; PMID:19251214; http://dx.doi.org/10.1016/j.hrthm.2008.11.023

13. Dougherty K, Tu L, Deutsch C, Covarrubias M. The dipeptidyl-aminopeptidase-like protein 6 is an integral voltage sensor-interacting β-subunit of neuronal K(V)4.2 channels. Channels (Austin) 2009; 3:122-8; PMID:19372736; http://dx.doi.org/10.4161/chan.3.2.8333
14. Li H-L, Qu Y-J, Lu YC, Bondarenko VE, Wang S, Skerrett IM, Morales MJ. DPP10 is an inactivation modulatory protein of Kv4.3 and Kv1.4. Am J Physiol Cell Physiol 2006; 291:C966-76; PMID:16738002; http://dx.doi.org/10.1152/ajpcell.00571.2005
15. Radicke S, Cotella D, Graf EM, Ravens U, Wettwer E. Expression and function of dipeptidyl-aminopeptidase-like protein 6 as a putative β-subunit of human cardiac transient outward current encoded by Kv4.3. J Physiol 2005; 565:751-6; PMID:15890703; http://dx.doi.org/10.1113/jphysiol.2005.087312
16. El-Haou S, Balse E, Neyroud N, Dilanian G, Gavillet B, Abriel H, Coulombe A, Jeromin A, Hatem SN. Kv4 potassium channels form a tripartite complex with the anchoring protein SAP97 and CaMKII in cardiac myocytes. Circ Res 2009; 104:758-69; PMID:19213956; http://dx.doi.org/10.1161/CIRCRESAHA.108.191007
17. Godreau D, Vranckx R, Maguy A, Rücker-Martin C, Goyenvalle C, Abdelshafy S, Tessier S, Couétil JP, Hatem SN. Expression, regulation and role of the MAGUK protein SAP-97 in human atrial myocardium. Cardiovasc Res 2002; 56:433-42; PMID:12445884; http://dx.doi.org/10.1016/S0008-6363(02)00602-8
18. Yang E-K, Alvira MR, Levitan ES, Takimoto K. Kvbeta subunits increase expression of Kv4.3 channels by interacting with their C termini. J Biol Chem 2001; 276:4839-44; PMID:11087728; http://dx.doi.org/10.1074/jbc.M004768200
19. Deschênes I, Tomaselli GF. Modulation of Kv4.3 current by accessory subunits. FEBS Lett 2002; 528:183-8; PMID:12297301; http://dx.doi.org/10.1016/S0014-5793(02)03296-9
20. Yang EK, Alvira MR, Levitan ES, Takimoto K. Kvbeta subunits increase expression of Kv4.3 channels by interacting with their C termini. J Biol Chem 2001; 276:4839-44; PMID:11087728; http://dx.doi.org/10.1074/jbc.M004768200
21. Wang L, Takimoto K, Levitan ES. Differential association of the auxiliary subunit Kvbeta2 with Kv1.4 and Kv4.3 K+ channels. FEBS Lett 2003; 547:162-4; PMID:12860406; http://dx.doi.org/10.1016/S0014-5793(03)00705-1
22. Kuryshev YA, Gudz TI, Brown AM, Wible BA. KChAP as a chaperone for specific K(+) channels. Am J Physiol Cell Physiol 2000; 278:C931-41; PMID:10794667
23. Wible BA, Yang Q, Kuryshev YA, Accili EA, Brown AM. Cloning and expression of a novel K+ channel regulatory protein, KChAP. J Biol Chem 1998; 273:11745-51; PMID:9565597; http://dx.doi.org/10.1074/jbc.273.19.11745
24. Lundby A, Olesen S-P. KCNE3 is an inhibitory subunit of the Kv4.3 potassium channel. Biochem Biophys Res Commun 2006; 346:958-67; PMID:16782062; http://dx.doi.org/10.1016/j.bbrc.2006.06.004
25. Grammer JB, Bosch RF, Kühlkamp V, Seipel L. Molecular remodeling of Kv4.3 potassium channels in human atrial fibrillation. J Cardiovasc Electrophysiol 2000; 11:626-33; PMID:10868735; http://dx.doi.org/10.1111/j.1540-8167.2000.tb00024.x
26. Xiao L, Coutu P, Villeneuve LR, Tadevosyan A, Maguy A, Le Bouter S, Allen BG, Nattel S. Mechanisms underlying rate-dependent remodeling of transient outward potassium current in canine ventricular myocytes. Circ Res 2008; 103:733-42; PMID:18723449; http://dx.doi.org/10.1161/CIRCRESAHA.108.171157
27. Akar FG, Wu RC, Juang GJ, Tian Y, Burysek M, Disilvestre D, Xiong W, Armoundas AA, Tomaselli GF. Molecular mechanisms underlying K+ current downregulation in canine tachycardia-induced heart failure. Am J Physiol Heart Circ Physiol 2005; 288:H2887-96; PMID:15681701; http://dx.doi.org/10.1152/ajpheart.00320.2004
28. Ferrer T, Arín RM, Casis E, Torres-Jacome J, Sanchez-Chapula JA, Casis O. Mechanisms responsible for the altered cardiac repolarization dispersion in experimental hypothyroidism. Acta Physiol (Oxf) 2012; 204:502-12; PMID:21933354; http://dx.doi.org/10.1111/j.1748-1716.2011.02364.x
29. Dartsch T, Fischer R, Gapelyuk A, Weiergraeber M, Ladage D, Schneider T, Schirdewan A, Reuter H, Mueller-Ehmsen J, Zobel C. Aldosterone induces electrical remodeling independent of hypertension. Int J Cardiol 2013; 164:170-8; PMID:21764470; http://dx.doi.org/10.1016/j.ijcard.2011.06.100
30. Wu C-T, Qi X-Y, Huang H, Naud P, Dawson K, Yeh Y-H, Harada M, Kuo C-T, Nattel S. Disease and region-related cardiac fibroblast potassium current variations and potential functional significance. Cardiovasc Res 2014; PMID:24596399; http://dx.doi.org/10.1093/cvr/cvu055
31. Zhang T-T, Takimoto K, Stewart AF, Zhu C, Levitan ES. Independent regulation of cardiac Kv4.3 potassium channel expression by angiotensin II and phenylephrine. Circ Res 2001; 88:476-82; PMID:11249870; http://dx.doi.org/10.1161/01.RES.88.5.476
32. Zhou C, Ziegler C, Birder LA, Stewart AF, Levitan ES. Angiotensin II and stretch activate NADPH oxidase to destabilize cardiac Kv4.3 channel mRNA. Circ Res 2006; 98:1040-7; PMID:16556864; http://dx.doi.org/10.1161/01.RES.0000218989.52072.e7
33. Sun B, Sheng Y, Huo R, Hu CW, Lu J, Li SL, Liu X, Wang YC, Dong DL. Bone morphogenetic protein-4 contributes to the down-regulation of Kv4.3 K+ channels in pathological cardiac hypertrophy. Biochem Biophys Res Commun 2013; 436:591-4; PMID:23747723; http://dx.doi.org/10.1016/j.bbrc.2013.05.113
34. Liu W, Deng J, Xu J, Wang H, Yuan M, Liu N, Jiang Y, Liu J. High-mobility group box 1 (HMGB1) downregulates cardiac transient outward potassium current (I_{to}) through downregulation of Kv4.2 and Kv4.3 channel transcripts and proteins. J Mol Cell Cardiol 2010; 49:438-48; PMID:20483361; http://dx.doi.org/10.1016/j.yjmcc.2010.05.004
35. Jia Y, Takimoto K. Mitogen-activated protein kinases control cardiac KChIP2 gene expression. Circ Res 2006; 98:386-93; PMID:16385079; http://dx.doi.org/10.1161/01.RES.0000201956.86258.e1
36. Wang Y, Cheng J, Chen G, Rob F, Naseem RH, Nguyen L, Johnstone JL, Hill JA. Remodeling of outward K+ currents in pressure-overload heart failure. J Cardiovasc Electrophysiol 2007; 18:869-75; PMID:17537202; http://dx.doi.org/10.1111/j.1540-8167.2007.00864.x
37. Suzuki T, Shioya T, Murayama T, Sugihara M, Odagiri F, Nakazato Y, Nishizawa H, Chugun A, Sakurai T, Daida H, et al. Multistep ion channel remodeling and lethal arrhythmia precede heart failure in a mouse model of inherited dilated cardiomyopathy. PLoS One 2012; 7:e35353; PMID:22514734; http://dx.doi.org/10.1371/journal.pone.0035353
38. Grubb S, Speerschneider T, Occhipinti D, Fiset C. OLESEN SP, THOMSEN MB, CALLOE K. Loss of K+ Currents in Heart Failure Is Accentuated in KChIP2 Deficient Mice. J Cardiovasc Electrophysiol 2014; http://dx.doi.org/10.1111/jce.12422
39. Xiao L, Koopmann TT, Ördög B, Postema PG, Verkerk AO, Iyer V, Sampson KJ, Boink GJJ, Mamarbachi MA, Varro A, et al. Unique cardiac Purkinje fiber transient outward current β-subunit composition: a potential molecular link to idiopathic ventricular fibrillation. Circ Res 2013; 112:1310-22; PMID:23532596; http://dx.doi.org/10.1161/CIRCRESAHA.112.300227
40. Giudicessi JR, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, Albertson RM, Antzelevitch C, Schwartz PJ, Ackerman MJ. Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. Heart Rhythm 2011; 8:1024-32; PMID:21349352; http://dx.doi.org/10.1016/j.hrthm.2011.02.021
41. Olesen MS, Refsgaard L, Holst AG, Larsen AP, Grubb S, Haunsø S, Svendsen JH, Olesen S-P, Schmitt N, Calloe K. A novel KCND3 gain-of-function mutation associated with early-onset of persistent lone atrial fibrillation. Cardiovasc Res 2013; 98:488-95; PMID:23400760; http://dx.doi.org/10.1093/cvr/cvt028
42. Giudicessi JR, Ye D, Kritzberger CJ, Nesterenko VV, Tester DJ, Antzelevitch C, Ackerman MJ. Novel mutations in the KCND3-encoded Kv4.3 K+ channel associated with autopsy-negative sudden unexplained death. Hum Mutat 2012; 33:989-97; PMID:22457051; http://dx.doi.org/10.1002/humu.22058
43. Dixon JE, Shi W, Wang H-S, McDonald C, Yu H, Wymore RS, Cohen IS, McKinnon D. Role of the Kv4.3 K+ channel in ventricular muscle. A molecular correlate for the transient outward current. Circ Res 1996; 79:659-68; PMID:8831489; http://dx.doi.org/10.1161/01.RES.79.4.659
44. Varró A, Lathrop DA, Hester SB, Nánási PP, Papp JG. Ionic currents and action potentials in rabbit, rat, and guinea pig ventricular myocytes. Basic Res Cardiol 1993; 88:93-102; PMID:8389123
45. Liu HB, Yang BF, Dong DL. Calcineurin and electrical remodeling in pathologic cardiac hypertrophy. Trends Cardiovasc Med 2010; 20:148-53; PMID:21742270; http://dx.doi.org/10.1016/j.tcm.2010.12.003
46. Capuano V, Ruchon Y, Antoine S, Sant MC, Renaud JF. Ventricular hypertrophy induced by mineralocorticoid treatment or aortic stenosis differentially regulates the expression of cardiac K+ channels in the rat. Mol Cell Biochem 2002; 237:1-10; PMID:12236575; http://dx.doi.org/10.1023/A:1016518920693
47. Lee J-K, Nishiyama A, Kambe F, Seo H, Takeuchi S, Kamiya K, Kodama I, Toyama J. Downregulation of voltage-gated K(+) channels in rat heart with right ventricular hypertrophy. Am J Physiol 1999; 277:H1725-31; PMID:10564125
48. Zhang TT, Takimoto K, Stewart AF, Zhu C, Levitan ES. Independent regulation of cardiac Kv4.3 potassium channel expression by angiotensin II and phenylephrine. Circ Res 2001; 88:476-82; PMID:11249870; http://dx.doi.org/10.1161/01.RES.88.5.476
49. Tsuji Y, Zicha S, Qi XY, Kodama I, Nattel S. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation 2006; 113:345-55; PMID:16432066; http://dx.doi.org/10.1161/CIRCULATIONAHA.105.552968
50. Huang B, Qin D, El-Sherif N. Early down-regulation of K+ channel genes and currents in the postinfarction heart. J Cardiovasc Electrophysiol 2000; 11:1252-61; PMID:11083246; http://dx.doi.org/10.1046/j.1540-8167.2000.01252.x

51. Qin D, Huang B, Deng L, El-Adawi H, Ganguly K, Sowers JR, El-Sherif N. Downregulation of K(+) channel genes expression in type I diabetic cardiomyopathy. Biochem Biophys Res Commun 2001; 283:549-53; PMID:11341759; http://dx.doi.org/10.1006/bbrc.2001.4825
52. Kassiri Z, Zobel C, Nguyen TT, Molkentin JD, Backx PH. Reduction of I(to) causes hypertrophy in neonatal rat ventricular myocytes. Circ Res 2002; 90:578-85; PMID:11909822; http://dx.doi.org/10.1161/01.RES.0000012223.86441.A1
53. Gao L, Li Y, Schultz HD, Wang W-Z, Wang W, Finch M, Smith LM, Zucker IH. Downregulated Kv4.3 expression in the RVLM as a potential mechanism for sympathoexcitation in rats with chronic heart failure. Am J Physiol Heart Circ Physiol 2010; 298:H945-55; PMID:20044444; http://dx.doi.org/10.1152/ajpheart.00145.2009
54. Lebeche D, Kaprielian R, del Monte F, Tomaselli G, Gwathmey JK, Schwartz A, Hajjar RJ. In vivo cardiac gene transfer of Kv4.3 abrogates the hypertrophic response in rats after aortic stenosis. Circulation 2004; 110:3435-43; PMID:15557376; http://dx.doi.org/10.1161/01.CIR.0000148176.33730.3F
55. Lebeche D, Kaprielian R, Hajjar R. Modulation of action potential duration on myocyte hypertrophic pathways. J Mol Cell Cardiol 2006; 40:725-35; PMID:16600293; http://dx.doi.org/10.1016/j.yjmcc.2006.01.018
56. Kaprielian R, Wickenden AD, Kassiri Z, Parker TG, Liu PP, Backx PH. Relationship between K+ channel down-regulation and [Ca2+]i in rat ventricular myocytes following myocardial infarction. J Physiol 1999; 517:229-45; PMID:10226162; http://dx.doi.org/10.1111/j.1469-7793.1999.0229z.x
57. Molkentin JD, Lu JR, Antos CL, Markham B, Richardson J, Robbins J, Grant SR, Olson EN. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell 1998; 93:215-28; PMID:9568714; http://dx.doi.org/10.1016/S0092-8674(00)81573-1
58. Dong D, Duan Y, Guo J, Roach DE, Swirp SL, Wang L, Lees-Miller JP, Sheldon RS, Molkentin JD, Duff HJ. Overexpression of calcineurin in mouse causes sudden cardiac death associated with decreased density of K+ channels. Cardiovasc Res 2003; 57:320-32; PMID:12566105; http://dx.doi.org/10.1016/S0008-6363(02)00661-2
59. Vega RB, Harrison BC, Meadows E, Roberts CR, Papst PJ, Olson EN, McKinsey TA. Protein kinases C and D mediate agonist-dependent cardiac hypertrophy through nuclear export of histone deacetylase 5. Mol Cell Biol 2004; 24:8374-85; PMID:15367659; http://dx.doi.org/10.1128/MCB.24.19.8374-8385.2004
60. Dolmetsch RE, Lewis RS, Goodnow CC, Healy JI. Differential activation of transcription factors induced by Ca2+ response amplitude and duration. Nature 1997; 386:855-8; PMID:9126747; http://dx.doi.org/10.1038/386855a0
61. Akar FG, Wu RC, Juang GJ, Tian Y, Burysek M, Disilvestre D, Xiong W, Armoundas AA, Tomaselli GF. Molecular mechanisms underlying K+ current downregulation in canine tachycardia-induced heart failure. Am J Physiol Heart Circ Physiol 2005; 288:H2887-96; PMID:15681701; http://dx.doi.org/10.1152/ajpheart.00320.2004
62. Xiao L, Coutu P, Villeneuve LR, Tadevosyan A, Maguy A, Le Bouter S, Allen BG, Nattel S. Mechanisms underlying rate-dependent remodeling of transient outward potassium current in canine ventricular myocytes. Circ Res 2008; 103:733-42; PMID:18723449; http://dx.doi.org/10.1161/CIRCRESAHA.108.171157
63. Maguy A, Le Bouter S, Comtois P, Chartier D, Villeneuve L, Wakili R, Nishida K, Nattel S. Ion channel subunit expression changes in cardiac Purkinje fibers: a potential role in conduction abnormalities associated with congestive heart failure. Circ Res 2009; 104:1113-22; PMID:19359601; http://dx.doi.org/10.1161/CIRCRESAHA.108.191809
64. Yue L, Melnyk P, Gaspo R, Wang Z, Nattel S. Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation. Circ Res 1999; 84:776-84; PMID:10205145; http://dx.doi.org/10.1161/01.RES.84.7.776
65. Zicha S, Xiao L, Stafford S, Cha TJ, Han W, Varro A, Nattel S. Transmural expression of transient outward potassium current subunits in normal and failing canine and human hearts. J Physiol 2004; 561:735-48; PMID:15498806; http://dx.doi.org/10.1113/jphysiol.2004.075861
66. Borlak J, Thum T. Hallmarks of ion channel gene expression in end-stage heart failure. FASEB J 2003; 17:1592-608; PMID:12958166; http://dx.doi.org/10.1096/fj.02-0889com
67. Greenstein JL, Wu R, Po S, Tomaselli GF, Winslow RL. Role of the calcium-independent transient outward current I(to1) in shaping action potential morphology and duration. Circ Res 2000; 87:1026-33; PMID:11090548; http://dx.doi.org/10.1161/01.RES.87.11.1026
68. Frank-Hansen R, Larsen LA, Andersen P, Jespersgaard C, Christiansen M. Mutations in the genes KCND2 and KCND3 encoding the ion channels Kv4.2 and Kv4.3, conducting the cardiac fast transient outward current (ITO,f), are not a frequent cause of long QT syndrome. Clin Chim Acta 2005; 351:95-100; PMID:15563876; http://dx.doi.org/10.1016/j.cccn.2004.08.017
69. Dong M, Sun X, Prinz AA, Wang HS. Effect of simulated I(to) on guinea pig and canine ventricular action potential morphology. Am J Physiol Heart Circ Physiol 2006; 291:H631-7; PMID:16565319; http://dx.doi.org/10.1152/ajpheart.00084.2006
70. Keskanokwong T, Lim HJ, Zhang P, Cheng J, Xu L, Lai D, Wang Y. Dynamic Kv4.3-CaMKII unit in heart: an intrinsic negative regulator for CaMKII activation. Eur Heart J 2011; 32:305-15; PMID:21148163; http://dx.doi.org/10.1093/eurheartj/ehq469
71. Li Q, Zhang Y, Sheng Y, Huo R, Sun B, Teng X, Li N, Zhu JX, Yang BF, Dong DL. Large T-antigen up-regulates Kv4.3 K+ channels through Sp1, and Kv4.3 K+ channels contribute to cell apoptosis and necrosis through activation of calcium/calmodulin-dependent protein kinase II. Biochem J 2012; 441:859-67; PMID:22023388; http://dx.doi.org/10.1042/BJ20111604
72. Zhang T, Brown JH. Role of Ca2+/calmodulin-dependent protein kinase II in cardiac hypertrophy and heart failure. Cardiovasc Res 2004; 63:476-86; PMID:15276473; http://dx.doi.org/10.1016/j.cardiores.2004.04.026
73. Zhang R, Khoo MS, Wu Y, Yang Y, Grueter CE, Ni G, Price EE Jr., Thiel W, Guatimosim S, Song LS, et al. Calmodulin kinase II inhibition protects against structural heart disease. Nat Med 2005; 11:409-17; PMID:15793582; http://dx.doi.org/10.1038/nm1215
74. Dobrev D, Wehrens XH. Calmodulin kinase II, sarcoplasmic reticulum Ca2+ leak, and atrial fibrillation. Trends Cardiovasc Med 2010; 20:30-4; PMID:20685575; http://dx.doi.org/10.1016/j.tcm.2010.03.004
75. El-Haou S, Balse E, Neyroud N, Dilanian G, Gavillet B, Abriel H, Coulombe A, Jeromin A, Hatem SN. Kv4 potassium channels form a tripartite complex with the anchoring protein SAP97 and CaMKII in cardiac myocytes. Circ Res 2009; 104:758-69; PMID:19213956; http://dx.doi.org/10.1161/CIRCRESAHA.108.191007
76. Anderson ME, Brown JH, Bers DM. CaMKII in myocardial hypertrophy and heart failure. J Mol Cell Cardiol 2011; 51:468-73; PMID:21276796; http://dx.doi.org/10.1016/j.yjmcc.2011.01.012
77. Hudmon A, Schulman H, Kim J, Maltez JM, Tsien RW, Pitt GS. CaMKII tethers to L-type Ca2+ channels, establishing a local and dedicated integrator of Ca2+ signals for facilitation. J Cell Biol 2005; 171:537-47; PMID:16275756; http://dx.doi.org/10.1083/jcb.200505155
78. Bers DM, Grandi E. Calcium/calmodulin-dependent kinase II regulation of cardiac ion channels. J Cardiovasc Pharmacol 2009; 54:180-7; PMID:19333131; http://dx.doi.org/10.1097/FJC.0b013e3181a25078
79. Wang Y, Tandan S, Cheng J, Yang C, Nguyen L, Sugianto J, Johnstone JL, Sun Y, Hill JA. Ca2+/calmodulin-dependent protein kinase II-dependent remodeling of Ca2+ current in pressure overload heart failure. J Biol Chem 2008; 283:25524-32; PMID:18622016; http://dx.doi.org/10.1074/jbc.M803043200
80. Wagner S, Dybkova N, Rasenack EC, Jacobshagen C, Fabritz L, Kirchhof P, Maier SK, Zhang T, Hasenfuss G, Brown JH, et al. Ca2+/calmodulin-dependent protein kinase II regulates cardiac Na+ channels. J Clin Invest 2006; 116:3127-38; PMID:17124532; http://dx.doi.org/10.1172/JCI26620
81. Anderson ME. Pathways for CaMKII activation in disease. Heart Rhythm 2011; 8:1501-3; PMID:21699838; http://dx.doi.org/10.1016/j.hrthm.2011.04.027
82. Said M, Becerra R, Valverde CA, Kaetzel MA, Dedman JR, Mundiña-Weilenmann C, Wehrens XH, Vittone L, Mattiazzi A. Calcium-calmodulin dependent protein kinase II (CaMKII): a main signal responsible for early reperfusion arrhythmias. J Mol Cell Cardiol 2011; 51:936-44; PMID:21888910; http://dx.doi.org/10.1016/j.yjmcc.2011.08.010
83. Macías A, Moreno C, Moral-Sanz J, Cogolludo A, David M, Alemanni M, Pérez-Vizcaíno F, Zaza A, Valenzuela C, González T. Celecoxib blocks cardiac Kv1.5, Kv4.3 and Kv7.1 (KCNQ1) channels: effects on cardiac action potentials. J Mol Cell Cardiol 2010; 49:984-92; PMID:20858500; http://dx.doi.org/10.1016/j.yjmcc.2010.09.012
84. Wang H, Shi H, Zhang L, Pourrier M, Yang B, Nattel S, Wang Z. Nicotine is a potent blocker of the cardiac A-type K(+) channels. Effects on cloned Kv4.3 channels and native transient outward current. Circulation 2000; 102:1165-71; PMID:10973847; http://dx.doi.org/10.1161/01.CIR.102.10.1165
85. Caballero R, Gómez R, Núñez L, Moreno I, Tamargo J, Delpón E. Diltiazem inhibits hKv1.5 and Kv4.3 currents at therapeutic concentrations. Cardiovasc Res 2004; 64:457-66; PMID:15537499; http://dx.doi.org/10.1016/j.cardiores.2004.07.022
86. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352:1071-80; PMID:15713944; http://dx.doi.org/10.1056/NEJMoa050405
87. Ishikawa K, Nakai S, Takenaka T, Kanamasa K, Hama J, Ogawa I, Yamamoto T, Oyaizu M, Kimura A, Yamamoto K, et al.; Secondary Prevention Group. Short-acting nifedipine and diltiazem do not reduce the incidence of cardiac events in patients with healed myocardial infarction. Circulation 1997; 95:2368-73; PMID:9170398; http://dx.doi.org/10.1161/01.CIR.95.10.2368
88. El Gebeily G, Fiset C. Upregulation of ventricular potassium channels by chronic tamoxifen treatment. Cardiovasc Res 2011; 90:68-76; http://dx.doi.org/10.1093/cvr/cvq384; PMID:21131637
89. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. Circulation 2005; 112:3018-24; PMID:16275887