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Review Article

A Little Too Much: Cardiac Electrophysiological Effects of Elevated Inward Rectifying Current Carried by the $K_{IR}2.1$ Ion Channel Protein

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Inward rectifier currents carried by $K_{IR}2.1$ proteins have an important role in cardiac electrophysiology. Animal knock-outs and human loss-of-function mutation carriers experience cardiac pro-arrhythmia, but phenotypes are not confined to the heart since these channels are prominently expressed in many other organs and tissues. We here review the other end of the spectrum, in which gain-of-function of the $K_{IR}2.1$ carried I_{K1} results in action potential shortening in isolated cardiomyocytes, and QT shortening in animals and humans. Gain-of-function mutations in patients often result in short QT syndrome accompanied with atrial fibrillation. Remarkable, skeletal muscle, neurological and developmental abnormalities are less prominent in these patients compared to their loss-of-function counterparts. Finally, the most common pathological arrhythmia, atrial fibrillation, is associated with $K_{IR}2.1$ upregulation at the mRNA and protein level, and concomitant enhanced I_{K1} density in atrial tissues.

Key Words: atrial fibrillation, drugs, I_{K1}, $K_{IR}2.1$, short QT syndrome

Introduction

Action potential (AP) formation stands at the basis of cardiac contraction. The uneven distribution of sodium, potassium and calcium ions between the intra- and extra-cellular compartment in concert with the presence of voltage sensitive and ion selective channels on the sarcolemma enables the cardiac myocyte to rapidly change its membrane potential and hence creating an AP. Between subsequent APs, potassium conductance resulting from inward rectifier channels formed by $K_{IR}2.x$ proteins, maintain a stable resting membrane potential (RMP) that lies close to the potassium reversal potential. Many basic science insights in the function of these $K_{IR}2.x$ channels have been obtained from experimental models and human disease in which $K_{IR}2.x$ carried inward rectifier current (I_{K1}) is reduced. Very informative are the numerous studies on *KCNJ2* mutations that result in $K_{IR}2.1$ loss-of-function causing Andersen-Tawil syndrome in men. Patients show a variety of clinical signs like periodic paralysis, cardiac arrhythmias and developmental abnormalities. Recently, this interesting field has been comprehensively reviewed (24). On the other side of the coin, we find gain-of-function studies that contribute necessary additional information on the role of this intriguing ion current on cardiac electrophysiology. As recently it was identified that particular drugs are able to cause increases in $K_{IR}2.1$, whereas a very common cardiac arrhythmia, *i.e.* atrial fibrillation (AF), has been associated with enhanced I_{K1} function. This review therefore aims to overview the electrophysiological effects of increased I_{K1} in experimental models and by gain-of-function mutations leading to human disease.

K_{IR} Channel Properties

I_{K1} has a pronounced influence on cardiac excitability and arrhythmogenesis (7). Potassium inward rectifier channels have a unique characteristic whereby they generate large K^+ current at potentials negative to the equilibrium potential of K^+ (E_K) (16). However at potentials positive to the E_K there is less current flow. This inward rectification of K^+ is due to intracellular Mg^{2+} and polyamines. They are able to physically block K^+ leaving the cell, by binding deep in the channel (27) interacting with the trans-membrane and cytoplasmic regions (16). K_{IR} channels have a mutual structure consisting of two membrane-spanning domains (TM1 and TM2) linked together by a pore-forming region (H5), which protrudes back into the cell membrane (16). The amino and carboxyl-terminals are located in the intracellular region, the general structure is shown, with the $K_{IR}2.1$ channel, in Fig. 1. Currently there are 15 known K_{IR} subunits; they have been classified in to seven subfamilies, $K_{IR}1.x$ to $K_{IR}7.x$ (16). Sequence homology, between subfamily is 40%, increasing to approximately 60% within subfamilies (5). In the heart numerous K_{IR} channels have been identified, such as

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Table 1. Drugs with I_{K1} increasing properties as off target effects

Compound	Main Effect	Dose-Effect Relation	Reference
Flecainide	$Na_v1.5$ Antagonist	$K_{IR}2.1$ EC_{50} (-50 mV) = 0.4 ± 0.01 μM	(3)
		$K_{IR}2.1$ EC_{50} (-120 mV) = 0.8 ± 0.01 μM	
		$K_{IR}2.1$ E_{max} (-50 mV) = 53.9 ± 3.6%	
		$K_{IR}2.1$ E_{max} (-120 mV) = 22 ± 1.9%	
Propafenone	Na^+ Channel Antagonist	$K_{IR}2.1$ EC_{50} (-50 mV) = 12.0 ± 3.0 nM	(14)
		$K_{IR}2.1$ E_{max} (-50 mV) = 42.0 ± 2.6%	
Timolol	Non-Selective β-Antagonist	$K_{IR}2.1$ EC_{50} (-50 mV) = 3.2 ± 0.3 nM	(14)
Zacopride[#]	5-HT3 Antagonist	$K_{IR}2.1$ EC_{50} (-50 mV) = 30.7 μM	(20, 37)
	5-HT4 Agonist	$K_{IR}2.1$ E_{max} (-50 mV) = 40.7 ± 9.7%	
		$K_{IR}2.1$ E_{max} (-110 mV) = 9.6% ± 4.2%	

[#]a study of Zacopride mediated activation of I_{K1} in attenuating ventricular remodeling following myocardial infarction by the same group contained data irregularities in Fig. 1 and Fig. 2, and has been retracted by the authors.

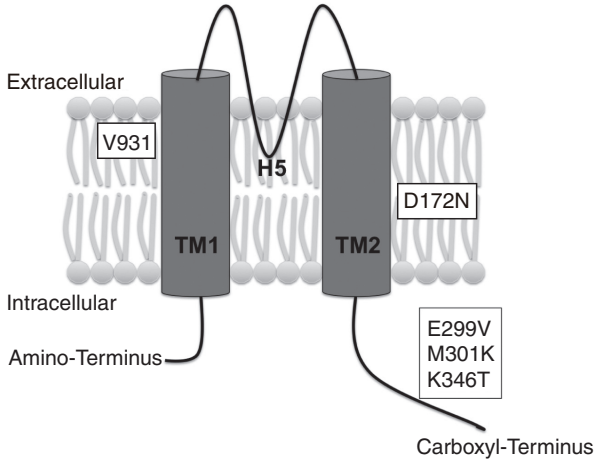

Fig. 1. Schematic representation of the $K_{IR}2.1$ channel protein structure with the transmembrane regions 1 and 2 (TM1,2) and the pore-loop (H5) domain illustrated. Currently known gain-of-function mutations are depicted by single letter coding.

$K_{IR}2.1$, $K_{IR}2.2$, $K_{IR}2.3$, $K_{IR}3.1$, $K_{IR}3.4$, $K_{IR}6.2$. These channels have varying rectifying strengths and locations where they are expressed (5). I_{K1} is crucial for shaping the cardiac AP for the following reasons. By adding to a negative RMP, it supports sodium channel availability in AP upstroke formation. Furthermore, its outward current component contributes significantly to the final phase of repolarization.

I_{K1} density, properties and expression of the underlying protein subunits differs between the atria and ventricle. In general, ventricular I_{K1} density is much higher (6-10 fold) than that of the atria (7). Ventricular I_{K1} channels are dominated by the presence of $K_{IR}2.1$ subunits, whereas atrial I_{K1} results from more equal expression of $K_{IR}2.1$, $K_{IR}2.2$ and $K_{IR}2.3$ subunits (11). Here, we will focus on $K_{IR}2.1$ channels, the highest expressed and best studied isoform in the heart. $K_{IR}2.1$ becomes also expressed in many other tissues (5) and this is likely the basis for the pleiotropic phenotype as seen in patients with *KCNJ2* loss-of-function mutations.

Drugs that Increase I_{K1}

As there has been a lack of pharmacological tools to specifically enhance I_{K1} it has been hard to decipher the role of I_{K1} up-regulation in cardiac excitability. However in recent years a number of drugs have been identified that increase $K_{IR}2.1$ carried currents, albeit not specific for I_{K1}, listed in Table 1. Drugs such as timolol and zacopride did show a decrease in action potential duration (APD) (20, 31), which would be expected with a $K_{IR}2.1$ increase. Yet its source whether due to a primary mechanism of action or secondary effect, has not been deciphered yet. Caballero *et al*. (3) disscusses the potential role that $K_{IR}2.1$, could have when flecainide is administered. Flecainide increases the effective refractory period (ERP) and prolongs the APD, which is more evident in the atrial cells compared to ventricular cells. Interestingly flecainide is shown to increase I_{K1} in ventricular myocytes and not in the atria. The authors suggest that the increase in I_{K1} can account for the differences seen in APD in ventricle versus atria (3). They speculate that the I_{K1} increase can overcome the effects of I_{Kr} blockade on APD prolongation in ventricles. Additionally in the atrial cells, APD prolongation is evident due to blockade of I_{Kr} without interference of increased I_{K1}. Finally, whether I_{K1} increase in ventricular myocytes could be a contributing factor to the ventricular pro-

Table 2. Electrophysiological parameters in experimental models with increased I_{K1}

Model	Phenotype	Electrophysiological Parameters	Remark	Reference
$K_{IR}2.1$ Transgenic Mice (line 1)	Normal Life Span	↓ QT_c ≈ 42% Anesthetized; ↓ QT_c ≈ 60% Isolated Heart	↑ I_{K1} Conductance by 9-Fold	(19)
	Stable Heart Rhythm	↔ PR; ↔ QRS	9-Fold at Reversal Potential	
	↓ HR	↓ MAP_{90} ≈ 77%; ↓ MAP_{75} ≈ 71%; ↔ MAP_{50}		
	↑ Heart Hypertrophy[#]	↓ APD_{90} ≈ 64%; ↓ ADP_{75} ≈ 29%[#]; ↔ APD_{50}		
	PVC	↓ ERP ≈ 31%		
$K_{IR}2.1$ Transgenic Mice (line 2)	↑ Mortality	↓ QT_c ≈ 44% Anesthetized; ↓ QT_c ≈ 58% Isolated Heart	↑ I_{K1} Conductance by 10-Fold at Reversal Potential	(19)
	↓ HR	↑ PR = 29%; ↑ QRS = 10%		
	↑ Right Atrium Size	↓ MAP_{90} = 82%; ↓MAP_{75} = 76%; ↔ MAP_{50}		
	↑ Ventricular Size	↓ APD_{90} ≈ 64%; ↓ ADP_{75} ≈ 25%[#]; ↔ APD_{50}		
	AV Block	↓ ERP ≈ 43%		
	Atrial Fibrillation			
	PVC			
Adeno-Human $K_{IR}2.1$ Guinea Pigs	↔ Cell Size	↓ QT_c ≈ 8%	↑ Ba^{2+} Sensitive Outward I_{K1} by 107.1%	(23)
	no Arrhythmias Observed	↓ APD_{90} ≈ 44%; ↓ APD_{50} ≈ 47%	Effect on APD and RMP is I_{K1} Density Dependent	
		Hyperpolarized RMP		
		↔ Reversal Potential		
Lentiviral Mouse $K_{IR}2.1$-GFP NRVM	↔ Cellular Composition	↓ ADP_{80} ≈ 59%*		(29)
	↔ Apoptosis, Necrosis or Nuclear Cell Damage	↑ CV ≈ 51%*		

↓ QT_c ≈ 42% to be read as "a decrease in QT_c by approximately 42%". [#]non-significant. *compared with empty lentiviral vector. *Abbreviations*: HR, heart rate; PVC, premature ventricular contraction; AV, atrial-ventricular; QT_c, rate corrected activation-repolarization time on electrocardiogram; PR, atrial-ventricular conduction time; QRS, ventricular activation time; APDx, action potential duration at x% of maximal repolarization; MAPx, monophasic action potential duration at x% of maximal repolarization; ERP, effective refractory period; CV, conduction velocity.

arrhythmic effects that are, although rarely, seen in flecainide remains to be studied further.

Since an increase in $K_{IR}2.1$ can have both anti- and pro-arrhythmic properties dependent on the underlying disease mechanism, it shows the importance of considering I_{K1} effects in drug development. However, the listed drugs do not further help with deciphering the role of $K_{IR}2.1$ up-regulation on the cardiac electrophysiological properties. This is due to the vast amount of primary and secondary targets and, yet unknown side-effects, that these compounds have. Thus more specificity is needed, which can be established by molecular tools in experimental animal models.

Molecular Tools to Upregulate I_{K1}

To date there are three successful methods in which $K_{IR}2.1$ has been up-regulated in animal models/cells, highlighted in Table 2. Transgenic mice (line 1 and 2), adenovirus with human $K_{IR}2.1$ in guinea pig and lentivirus cardiomyocyte model with mice $K_{IR}2.1$-eGFP all display enhanced I_{K1} function. The data obtained from these animal and cell models gives a clear indication of the effect of $K_{IR}2.1$ up-regulation on its electrophysiological parameters without many additional confounding variables. In all conditions there was a decrease in APD. Additionally there was a general decrease in QT interval, monophasic action potential duration (MAPD), and ERP. This is expected; as an overexpression of $K_{IR}2.1$ would allow more of the positively charged potassium ions to exit the cell, thus decrease the APD. There was some variation between effects on APD_{50} as in transgenic mice there was no change and in guinea pigs injected with adenovirus there was a 47% decrease. As the I_{K1} densities between the two are comparable, it is believed this is due to the difference in AP morphology and the level of expression of the underlying ion channels between guinea pigs and mice. Hyperpolarization of the RMP was seen in adenovirus human-$K_{IR}2.1$ treated guinea pigs, which reflects findings with gain-of-function patients (6, 18, 26). An increase of conduction velocity (CV) was observed in the $K_{IR}2.1$-GFP neonatal rat ventricular cardiomyocytes, however it was not measured elsewhere and varies to that seen in gain-of-function patients (18). There were other ECG differences observed in the line 2 transgenic mice, *i.e.* increased PR and QRS intervals, that were not observed in line 1 mice which had a lower level of I_{K1} transgenic expression compared to line 2 mice. It is important to mention that Sekar *et al*. (29) found that eGFP had significant effects on neonatal rat ventricular myocytes showing a decrease in APD and CV, conflicting the belief that eGFP is physiologically inert. Thus for the transgenic mouse model that fused the GFP to the wild-

Table 3. *KCNJ2* gain-of-function mutations associated with human disease

Mutation	Phenotype	Electrophysiological Parameters	Remark	Reference
V93I	Atrial Fibrillation	↓ APD_{90} 26% Het; ↓ APD_{90} 55% Hom	↓ CV Due to Hyperpolarized RMP	(18, 35)
	Normal QT	↓ ERP		
	no Syncope	Hyperpolarized RMP		
	no Frequent PVC	↓ CV = 8% Het; ↓ CV = 12% Hom		
	no Frequent Ventricular Tachycardia	↓ $I_{Ca\text{-}L}$ during the AP Plateau Phase		
	Normokalemic, no Muscle Weakness	↔ I_{Kur}, I_{Kr} and I_{Ks}		
	no Developmental Abnormalities	↔ Intercellular Electrical Coupling		
D172N	Short QT	↓ QT (315-320 ms)		(26)
	Presyncopal Events	Narrow and Peaked T-Wave		
	Palpitations	↓ APD ≈ 15% Hom		
	Rare Seizure Like Activities	Hyperpolarized RMP		
	Lamenting Tachycardia	↑ Vmax		
	no Developmental Abnormalities	↔ CV		
	no Muscle Disease			
E299V	Atrial Fibrillation	↓ QT (200 ms)		(6)
	Short QT	Peaked T-Wave		
	Mild Left Ventricular Dysfunction	no Distinctive ST Segments		
	Reduced EF (EF ≈ 40%)	↓ APD_{80} 56% Het; ↓ APD_{80} 67% Hom		
	no Ventricular Arrhythmias	Hyperpolarized RMP		
		↑ Vmax		
		↔ CV		
M301K	Atrial Fibrillation	↓ QT (172 ms), ↓ QT_c (194 ms)		(15)
	Syncope	↓ APD_{90} ≈ 67% Het		
	Sudden Death Due to Ventricular Tachyarrhythmia			
	no Structural Cardiac Abnormalities			
	Mental Retardation			
	Abnormal Oesophagal Blood Vessels			
	Epilepsy			
	Kawasaki Disease			
K346T	Short QT	↓ QT (275 ms); ↓ QT_c (331 ms)	In cis with a Gain-of-Function *KCNJ10* Mutation, Encoding the $K_{IR}4.1$ Channel	(1, 30)
	Intellectual Disabilities	Narrow and Peaked T-Wave		
	Autism Spectrum Disorder			
	Infantile Spasm			
	Normokalemic			

Abbreviations: PVC, premature ventricular contraction; QT(c), (rate corrected) activation-repolarization time on electrocardiogram; APDx, action potential duration at x% of maximal repolarization; ERP, effective refractory period; CV, conduction velocity; RMP, resting membrane potential; Het, heterozygous; Hom, homozygous; Vmax, maximal action potential upstroke velocity; EF, ejection fraction.

type $K_{IR}2.1$ cDNA for both animal lines, it may have some influence on the observed APD decrease.

The up-regulation of the $K_{IR}2.1$ channel in rodent animal models showed a general decrease in QT, APD, MAPD and ERP. Since the expression levels of the individual ion channel proteins that form the AP are different between rodents and humans, and hence result in a different AP morphologies between species, emphasis should be given on the role of I_{K1} channels in human cardiac electrophysiology. Very informative in this respect are the small number of human gain-of-function mutations in the $K_{IR}2.1$ coding gene that has been identified and described together with the associated clinical phenotype.

Human Gain-of-Function *KCNJ2* Mutations Enhancing I_{K1}

In general, human *KCNJ2* autosomal dominant gain-of-function mutations are associated with the short QT syndrome Type 3 and AF (Table 3). These gain-of-function mutations are rare but can cause severe heart complications early on in life. The gain-of-function mutations can weaken the inward rectification, meaning more $I_{KIR2.1}$ can be found at potentials positive to the E_K as seen in the D172N, E299V and M301K mutations (6, 15, 26). Studies in cell lines demonstrated that inhibition of normal $K_{IR}2.1$ channel internalization and degradation results in increased levels of $K_{IR}2.1$ protein expression and functional I_{K1} (17, 33). Interestingly, the K346T mutation exhibited an increased I_{K1} amplitude of both the inward and outward component, and an impaired channel protein degradation may be at the basis of this finding (1). Remarkably, the V93I mutation can increase the activity of the $K_{IR}2.1$ channel

however does not display a decrease in QT interval (35).

Many of the gain-of-function mutations are associated with AF and brain disorders such as epilepsy and mental retardation. As $K_{IR}2.1$ is also localized and involved in cell excitability in the brain, it is likely to account for the latter phenotype. There are many common electrophysiological parameters between the mutations, such as a decreased QT, APD and a hyperpolarized RMP. Conduction velocity seems to be unaffected, or slightly decreased due to the hyperpolarized RMP. This overlaps with the data obtained from the overexpressed $K_{IR}2.1$ in rodent animal models. Interestingly, in many of the patients a narrowed and peaked, asymmetric T wave was observed in ECG recordings. Simulation studies provided evidence that this morphology may be due to a sudden acceleration of the final phase of repolarization which is caused by an increased contribution of outward potassium current by the mutant channels (26). While the V93I mutation did not associate with altered conduction in other potassium currents (I_{Kur}, I_{Kr} and I_{Ks}), there was a decreased L-type calcium current. This reduction can facilitate the shortening of the AP and the ERP (32).

Finally, whereas *KCNJ2* loss-of-function mutations are often associated with periodic muscle paralysis and developmental abnormalities too, gain-of-function mutations appear to be less associated with these phenotypes.

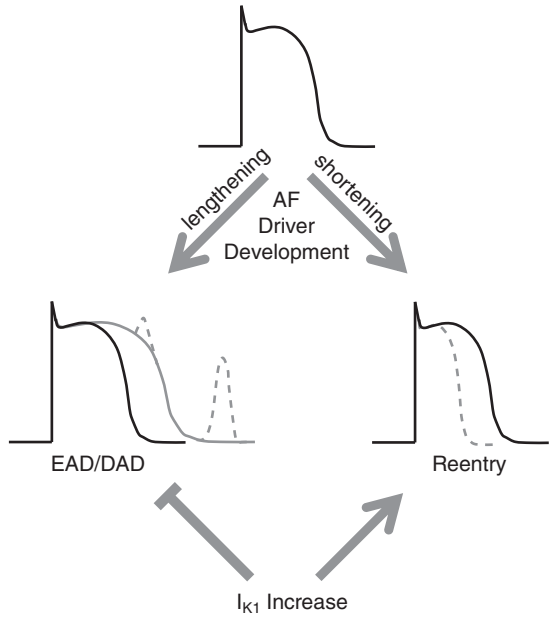

Fig. 2. Atrial AP lengthening promotes the occurrence of early and delayed afterpolarization (EAD/DAD) that may result in premature excitation. An increased I_{K1} density will inhibit this arrhythmic mechanism. AP shortening results in decreased effective refractory period of the atrial cell thereby promoting re-entry type arrhythmias. An increased I_{K1} density will promote this arrhythmic mechanism.

AF Associates with Increased Atrial I_{K1}

Approximately 23-26% of men and women above the age of 40 develop AF (21). Due to the irregular and uncoordinated, or even absence, of atrial contraction, clotting of the blood can occur and once released from within the diseased atria these cloths can cause stroke, lung embolization and myocardial infarction. Furthermore, the uncontrolled atrial activity results in non-regular ventricular activation and contraction, which on the long term can result in ventricular remodelling and heart failure. For these reasons, AF is strongly associated with stroke, heart failure, morbidity and increased mortality. The mechanisms underlying AF are multifactorial and can be classified into etiologic factors (heart disease, ageing, mutations) that cause atrial remodelling (structural, autonomic and electrical) which determines the electrophysiologic substrate enabling the two basic mechanisms driving AF initiation and perturbation (triggered activity and reentry) (28). In short, triggered activity arises from the occurrence of early and delayed after depolarizations (EADs, DADs) seen in the context of APD prolongation and aberrant sodium-calcium exchanger activity, respectively. Reentry mechanisms rely on ERP shortening (often concomitant with APD shortening), conduction slowing or both (Fig. 2). As seen in the previous sections, an increased I_{K1} density is associated with AP shortening in experimental models and patients, and it is therefore no surprise that *KCNJ2* gain-of-function mutations have been associated with AF as described in the previous section. Moreover, and from a general health perspective more relevant, a prominent and well documented feature of AF associated electrical remodelling is an increase in I_{K1}, along with increased expression of the underlying *KCNJ2* mRNA and $K_{IR}2.1$ protein (Table 4).

AF has been correlated with altered microRNA expression, which in turn may be one of the causative factors for structural and electrical remodelling observed in the arrhythmic atrium. In a study on the influence of AF on microRNA expression in atrial tissue from valvular heart disease patients, it was found that 15 microRNAs were up-regulated and 32 were down-regulated in the right atrial tissue from AF patients (4). Remarkably, no differences were found in left atrial tissue samples. Girmatsion (13) describes an inverse relation between microRNA-1 expression, an inhibitor of $K_{IR}2.1$ expression (36), and $K_{IR}2.1$ mRNA, protein and I_{K1} in left atrial tissue samples from AF patients. This inverse relationship could however not be confirmed by Luo *et al*. (22) in their study using right atrial appendage material from AF patients. Instead,

Table 4. Studies comparing human IK1 density and underlying proteins and transcripts in controls and AF

Number of subjects in study	Main findings in AF compared to controls	Reference
17 SR and 8 permanent AF	3.4-fold increase of outward I_{K1} (at -20 mV)	(2)
	2.0-fold increase of inward I_{K1} (at -90 mV)	
39 SR and 11 permanent AF	1.8-fold increase of inward I_{K1} (at -115 mV)	(34)
26 SR and 16 permanent AF	1.7-fold increase of inward I_{K1} (at -100 mV)	(9)
7 SR-VHD and 11 AF-VHD	1.9-fold increase of inward I_{K1} (at -100 mV)	
	1.8-fold increase in $K_{IR}2.1$ protein levels	(12)
46 SR and 33 permanent AF	1.9-fold increase of inward I_{K1} (at -100 mV)	(8)
	1.2-fold increase in I_{K1} open channel probability	
31 SR and 31 persistent AF	2.2-fold increase of inward I_{K1} (at -100 mV)	(13)
	1.5-fold increase in $K_{IR}2.1$ protein levels	
	0.9-fold decrease in $K_{IR}2.3$ protein levels[#]	
	3.0-fold increase in $K_{IR}2.1$ mRNA levels	
	0.2-fold decrease in $K_{IR}2.3$ mRNA levels	
10 SR and 12 AF	1.9-fold increase in $K_{IR}2.1$ protein levels	(22)
	1.8-fold increase in $K_{IR}2.1$ mRNA levels	

[#]non-significant. *Abbreviations*: SR, sinus rhythm; AF, atrial fibrillation; VHD, valvular heart disease

Luo *et al*. (22) found an inverse relationship between microRNA-26 and $K_{IR}2.1$ mRNA and protein expression, and showed by applying a variety of molecular tools the causative relation between microRNA-26 and $K_{IR}2.1$ expression. Important to note is the fact that both microRNA-1 and microRNA-26 were not detected among the 47 differentially regulated microRNAs described by Cooley (4). Apparently, $K_{IR}2.1$ regulation by microRNAs is complex and many additional studies are essential to shine light on these intriguing relationships.

Correcting Increased I_{K1} by Pharmacological Agents

Short QT and AF are the main symptoms of I_{K1} gain-of-function in patients. Although the number of patients with a monogenetic $K_{IR}2.1$ gain-of-function is rather small, they may benefit from specific I_{K1} inhibiting drugs. The largest group of patients that may benefit from I_{K1} inhibition can be found in those with persistent and longstanding persistent AF associated with I_{K1} upregulation as described above. Indeed, chloroquine that shows I_{K1}, I_{KAch} and I_{KATP} inhibiting capacity, is able to terminate both cholinergic AF and stretch induced AF in the isolated sheep heart (10, 25). For now, more specific I_{K1} inhibiting compounds are required to determine the contribution of enhanced I_{K1} in cardiac arrhythmias and to treat those that largely rely on enhanced I_{K1} as the underlying pathological cause.

Conclusion

Recently it was discovered that timolol, flecainide, propafenone and zacropride increase I_{K1}. Rodent animal studies and human monogenetic disease show high consensus and strongly demonstrate the role of $K_{IR}2.1$ carried I_{K1} in cardiac electrophysiology. In particular, APD and its derivatives MAPD and QT, are sensitive for I_{K1} increases. RMP values appear to be less affected by I_{K1} enhancement. Furthermore, spontaneous ventricular arrhythmias are rarely associated with increased I_{K1} density, whereas short QT syndrome and AF strongly correlate with $K_{IR}2.1$ gain-of-function. Acquired AF strongly associates with increased I_{K1}, although the underlying cause-effect relationships are still unclear. Partial reduction of I_{K1} in human disease like short QT syndrome and AF may be beneficial for patients.

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