Towards the Development of AgoKirs: New Pharmacological Activators to Study Kir2.x Channel and Target Cardiac Disease

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Abstract: Inward rectifier potassium ion channels (Iκ1-channels) of the Kir2.x family are responsible for maintaining a stable negative resting membrane potential in excitable cells, but also play a role in processes of non-excitable tissues, such as bone development. Iκ1-channel loss-of-function, either congenital or acquired, has been associated with cardiac disease. Currently, basic research and specific treatment are hindered by the absence of specific and efficient Kir2.x channel activators. However, twelve different compounds, including approved drugs, show off-target Iκ1 activation. Therefore, these compounds contain valuable information towards the development of agonists of Kir channels, AgoKirs. We reviewed the mechanism of Iκ1 channel activation of these compounds, which can be classified as direct or indirect activators. Subsequently, we examined the most viable starting points for rationalized drug development and possible safety concerns with emphasis on cardiac and skeletal muscle adverse effects of AgoKirs. Finally, the potential value of AgoKirs is discussed in view of the current clinical applications of potentiators and activators in cystic fibrosis therapy.

Keywords: inward rectifier channel; Kir2; agonist; Iκ1; Andersen syndrome; heart failure

1. Kir2.x Expression, Structure and Rectification

Kir2.x potassium channels are part of the inward rectifier K⁺ (Iκ1) channels family, which are of major importance for stabilizing the resting membrane potential of excitable cells and contribute to final action potential repolarization in cardiomyocytes [1,2]. Additionally, Iκ1 has an important role in non-excitable cells, for example, in osteoblasts, in which Iκ1 channels are involved in chondrogenesis and osteoblastogenesis [3].

Kir2.x channels are expressed in several excitable tissues, such as skeletal muscle (Kir2.1, Kir2.2, and Kir2.6), brain (Kir2.1, Kir2.2, and Kir2.3), and heart (Kir2.1, Kir2.2, and Kir2.3) [4]. Within tissues, isoform expression can vary. For example, Kir2.3 is dominantly expressed in the atria, whereas Kir2.1 is mainly present in the ventricles and has a higher channel density [5]. An intermediate level of expression of Kir2.x channels is present in smooth muscle tissue and the retina [4].

Iκ1 channels are homo- or heterotetrameric assemblies of Kir2.x monomeric subunits [6,7]. An individual subunit consists of a transmembrane and a cytoplasmic region. The transmembrane
region of the channel controls ion selectivity and channel gating, and the cytoplasmic domain functions as a gating regulator [1].

Depending on the membrane potential ($V_m$) relative to the potassium equilibrium potential ($E_K$), $I_{K_1}$ channels conduct either inward or outward current. The outward currents are smaller due to rectification properties. Inward rectification is based on binding of polyamines and $\text{Mg}^{2+}$ in the conducting pore region, at $V_m$ more positive than $E_K$ and inhibiting outward current [8]. Polyamine and $\text{Mg}^{2+}$ dependent blocks are absent at more negative $V_m$ than $E_K$, which results in inward current [9]. Each $K_{ir.2.x}$ isoform displays its own characteristic rectification profile [5].

Whereas much knowledge on $K_{ir.2.x}$ function has been derived from experimental in vitro studies and transgenic mice, insights on the physiological contributions of $I_{K_1}$ in larger organisms can only be deduced from a few experimental large animal studies using specific inhibitors [10,11] and patients with gain- or loss-of-function mutations [5]. For example, specific $I_{K_1}$ inhibition in awake dogs induced adverse effects like premature ventricular contractions, respiratory distress, and mild generalized muscle weakness [11]. On the contrary, the effects of specific $I_{K_1}$ activation have not been investigated in large animals. Therefore, as argued before [12], specific $I_{K_1}$ modifying compounds, i.e., inhibitors and activators, would benefit experimental studies on the role of $I_{K_1}$ in muscle contraction, cardiac function, neuronal excitation, and bone development.

2. $K_{ir.2.x}$ Disease Relationships

$I_{K_1}$ function and disease have a bidirectional relationship. On the one hand, mutations can affect $K_{ir.2.x}$ function, while, on the other hand, diseased states influence $K_{ir.2.x}$ function. Both congenital and acquired loss-of-function may result from impaired functional $K_{ir.2.x}$ expression at the plasma membrane, for example, due to aberrant transcription, trafficking, or gating kinetics.

Gain-of-function mutations in the $KCNJ2$ gene encoding $K_{ir.2.1}$ are associated with ventricular arrhythmia like short QT syndrome type 3 [13] or atrial arrhythmia such as congenital atrial fibrillation (AF) [14,15]. Loss-of-function mutations in $KCNJ2$ are associated with autosomal dominant Andersen syndrome (AS) [16]. This disease is characterized by symptoms like ventricular arrhythmias, periodic muscle paralysis, and dysmorphologies such as a broad forehead, a cleft palate, and small hands and feet [17].

AF results in increased $I_{K_1}$ densities in atrial tissue [18–20], which thereafter causes a shortening of the atrial effective refractory period that ultimately promotes and stabilizes atrial re-entry. Chronic heart failure (HF) induces loss-of-function of $I_{K_1}$. In experimental models of HF, $I_{K_1}$ is reduced in canine and rabbit ventricles [21–23]. More recently, heart failure following myocardial infarction (MI) in a porcine model shows significantly decreased $I_{K_1}$ density [24]. Also, declined density of whole-cell $I_{K_1}$ was also found in terminal HF patients [25].

Inward rectifier current inhibition has been suggested as a potential avenue in AF therapy [26]. Indeed, in preclinical and clinical settings, pharmacological $I_{K_1}$ inhibition is an effective method of AF reduction [10,27]. Moreover, pharmacological activators have been developed for several ion channels and successfully implemented in clinical therapy to treat cystic fibrosis, hypertension, and alopecia, to name a few applications [28–30]. Currently, no drugs are available that specifically target impaired $I_{K_1}$, whereas such a treatment may be effective in AS and HF. However, twelve drugs and compounds exert $I_{K_1}$ activating capacity (Figure 1, Table 1). We will review these drugs for indirect and direct properties to activate the different $K_{ir.2.x}$ channels, focusing on $K_{ir.2.1}$, $K_{ir.2.2}$, and $K_{ir.2.3}$.
**Table 1. Compounds with **$I_{K1}$** activating properties.**

| Compound | Readout | Test System | Dose-Effect Relation | Mechanism of Action | Ref. |
|----------|---------|-------------|----------------------|---------------------|------|
| **Direct activators** | | | | | |
| Flecainide | C | CHO cells | $I_{Kir2.1}$ EC$_{50}$/Emax ($-50$ mV) = $0.4 \pm 0.01$ µM/53.9 ± 3.6% | Interaction with Cys311 | [31] |
| PREGS | C | guinea pig ventricular cmc | $I_{Kir2.1}$ 1 µM: 19.5 ± 3.2% ($-120$ mV); 30.0 ± 9.5% ($-40$ mV) | Interaction with Cys311 | [31] |
| Propafenone | C | CHO cells | $I_{Kir2.1}$ EC$_{50}$ ($-70$ mV) = 15.6 ± 0.9 µM | Binding extracellular site | [32] |
| Timolol | C | CHO cells | $I_{Kir2.1}$ EC$_{50}$ ($-50$ mV) = 3.2 ± 0.3 µM | Interaction with Cys311 | [33] |
| **Indirect activators** | | | | | |
| Aldosterone | C | rabbit ventricular cmc | $I_{K1}$ 10 nM: 1.6-fold increase NPo of 30 pS current | MR-independent activation | [34] |
| Isoproterenol | C | Xenopus oocytes | $I_{Kir2.1}$ EC$_{50}$ = 27.4 nM * | Unknown | [35] |
| Valsartan | R,P | rat ventricle | 10 mg/kg/day for 7 days prevented $K_{ir2.1}$ downregulation | Casein Kinase 2 inhibition and/or Th1 immune response inhibition and/or NF-$x$B-miR-16 pathway | [37–39] |
| Zacopride | C | rat ventricular cMC, H9c2 cells | 20 µM (48 h) prevented $K_{ir2.1}$ downregulation | Th1 immune response inhibition | [38] |
| LPS | P,C | mouse pulmonary micro-vascular endothelial cells | 10 ng/mL (up to 24 h): 1.5-fold increase $K_{ir2.1}$ | PKA dependent | [40] |
| Morphine | C | rabbit ventricular cMC | $I_{K1}$ (−60 mV) = 25 ± 9% (0.1 µM); 32 ± 11% (1 µM) | Opioid-receptor pathway independent | [41] |
| Polydatin | C | rat ventricular cMC | $I_{K1}$ 10 µM: approx. 40% (−100 mV) | Unknown | [42] |
| Tenidap | C | CHO cells | $I_{Kir2.2}$ EC$_{50}$ = 1.3 µM * | Extracellularly, unaffected by pA2, PKC, and AA secondary pathways | [43] |

C, current; cMC, cardiomyocyte; P, protein; R, mRNA. * Voltages unknown.
Figure 1. Chemical structures of $I_{K1}$ activating compounds, obtained from the Royal Society of Chemistry-owned ChemSpider website (accessed on 12 June 2020). Structure name and ChemSpider ID is given. Full records can be retrieved at http://www.chemspider.com/Chemical-Structure.ID.html, in which ID should be substituted by the ID number provided above the structure.

3. AgoKirs, Agonists of $K_{ir}$ Function

3.1. Indirect Activators

3.1.1. Aldosterone

Aldosterone is part of the renin-angiotensin-aldosterone-system (RAAS) and is essential in $Na^+$ homeostasis. Activation of aldosterone and the mineralocorticoïd receptor (MR) play an important role in the pathophysiology of cardiovascular disease.

In vitro studies using isolated rabbit ventricular cardiomyocytes demonstrated that 10 nmol/L of aldosterone caused a rapid activation (within minutes to days) of a 30 pS $K^+$-selective current. This current had pharmacological and biophysical properties that are consistent with those of the $I_{K1}$-current. By use of RU28318, a specific MR-antagonist, and potassium canrenoate, a non-specific MR-antagonist, the underlying mechanism was determined as independent of the MR pathway [34].

Furthermore, cardiac tissue of rats implanted with osmotic minipumps showed a dose-dependent aldosterone effect on $K_{ir}$ expression after four weeks. At a dose of 0.5 $\mu$g/h, a moderate increase of $K_{ir}$2.1 and $K_{ir}$2.3 was observed [35], whereas, in another study, decreased expression levels of $K_{ir}$2.1 surprisingly was shown at 1 $\mu$g/h aldosterone [45].

3.1.2. Isoproterenol

Isoproterenol, or isoprenaline (ISO), is a synthetic $\beta$-adrenoceptor ($\beta$-AR) agonist that has a cardiac muscle stimulating and bronchodilating effect. $\beta_3$-AR stimulation leads to intracellular signal transduction pathways, including protein kinase A and C (PKA and PKC) [46]. In Xenopus oocytes, 10 $\mu$M ISO activated $K_{ir}$2.2 currents via a PKA-dependent pathway [36], consistent with findings on the role of PKA in $K_{ir}$2.2 activation [47]. Furthermore, ISO also activated $K_{ir}$2.1 currents via a PKC-dependent pathway [36].
3.1.3. Tenidap

Tenidap is a non-steroidal cyclooxygenase and lipoxygenase inhibitor [48] but also a potent Kir2.3 opener. By use of $^{86}$Rb$^+$ cell efflux and patch clamp electrophysiology, it was found that tenidap increased Kir2.3 carried inward and outward current in Chinese hamster ovary (CHO) cells [44]. Tenidap showed some channel specificity as it did not enhance Kir2.1 and Kv1.5 channel activity [44]; however, it did activate IKATP channels [49].

3.1.4. Valsartan

Valsartan is a highly selective angiotensin type 1 receptor antagonist and is widely used in the treatment of mild to moderate essential hypertension [50]. In rats with MI, induced by coronary artery ligation, Kir2.1 mRNA, protein, and the resulting IK1 became downregulated, which was associated with ventricular arrhythmias [51]. Such downregulation of Kir2.1/IK1 was prevented by Valsartan [37–39], possibly involving multiple mechanisms.

Firstly, casein kinase 2 dependent Kir2.1 downregulation after MI was prevented by valsartan. Secondly, valsartan treatment after MI decreased T-helper cell levels and thereby ameliorated IK1/Kir2.1 downregulation. Thirdly, valsartan reduced miRNA-16 levels by the prevention of NF-κB upregulation and thereby prevented downregulation of Kir2.1/KCNJ2/IK1 in infarcted hearts. Currently, it is unknown to what extent the working mechanism of valsartan on each individual signaling pathway contributed to restoring normal Kir2.1 expression in MI rat hearts. Nevertheless, the authors stated that a direct interaction of valsartan with the Kir2.1 ion channel, resulting in its activation, appeared improbable.

3.1.5. Zacopride

Zacopride (ZAC) is an antiemetic, gastroprokinetic, and anxiolytic drug. It is a selective antagonist of the 5-hydroxytryptamine (5-HT)3 receptor and agonist of 5-HT4 receptor. In the adrenal glands, ZAC is known to stimulate the secretion of aldosterone [52].

Rats treated with ZAC showed elevated levels of Kir2.1 protein in left ventricular tissue [53]. Furthermore, ZAC treatment prevented ischemia-mediated downregulation of left ventricular Kir2.1 protein [54] (note [55]). Additionally, ZAC enhanced both the inward and outward IK1 current in rat ventricular myocytes [56,57] but not in atrial cardiac myocytes [40]. ZAC-induced Kir2.1 channel activation appeared to be mediated by PKA-dependent phosphorylation of Ser425 in the Kir2.1 C-terminus [40]. In human embryonic kidney 293 cells and CHO cells, ZAC increased IK1 carried by ectopic homotetrameric Kir2.1 channels but not current carried by homotetrameric Kir2.2 or Kir2.3 channels or heterotetrameric channels containing Kir2.1, Kir2.2, or Kir2.3 [40,57].

3.2. Direct Activators

Within the class of direct activators, interactions with the extracellular domain and cytoplasmic domain have been indicated. The direct activators currently described display isoform specificity and may open the way towards tissue-specific activation of IK1.

3.2.1. Flecainide

Flecainide, a class Ic antiarrhythmic drug, is known to block Na$^+$ channels and voltage-dependent K$^+$ (Kv) channels. Thereby, flecainide effectively prolongs action potential duration (APD) in the atria but not in the ventricles [58]. On the other hand, flecainide increases IK1 selectively in the ventricles, offering a possible explanation for a difference in effect on atrial and ventricular APD [31].

Flecainide specifically activated Kir2.1 channels by a mechanism involving Cysteine311 (Cys311) and had no effect on Kir2.2 or Kir2.3 channels that contain an alanine instead of a cysteine residue on their equivalent positions (312 and 303, respectively) [31].

Flecainide’s mode of action likely involved antagonizing spermine-mediated rectification, resulting in increased outward current. Spermine was shown to inhibit IK1 in a concentration-dependent
manner. The presence of flecainide decreased spermine’s inhibiting effect, as a rightward shift in the concentration-effect curve was observed [31]. The fact that the E\text{max} of spermine was saturated at 82.1 ± 5.5% in the presence of flecainide suggests that spermine block was decreased in a noncompetitive manner by flecainide through allosteric changes to the binding site for polyamines [31].

3.2.2. Propafenone

Propafenone, just like flecainide, is a class Ic antiarrhythmic drug, mainly used in the treatment of ventricular tachycardias. Supra-therapeutic concentrations (>1 µM) of propafenone inhibited K\text{ir}2.x current [59]. Propafenone interacted with the cytoplasmic domain of the channel, which decreased the negative charge of the pore and the channel affinity for PIP2, a lipid critical for channel activation [59].

Given its structural similarities with flecainide, the effect of propafenone on K\text{ir}2.1 carried current was tested at lower concentrations. At 0.5 µM, propafenone enlarged inward and outward K\text{ir}2.1 current [33]. Propafenone significantly decreased spermine-induced block and thus relieved inward rectification, similarly as observed for flecainide [33]. However, propafenone failed to enhance both inward and outward K\text{ir}2.2 and K\text{ir}2.3 carried current [33]. In cells expressing K\text{ir}2.1/2.2, K\text{ir}2.1/2.3, and K\text{ir}2.2/2.3 heterotetrameric channels, propafenone also failed to increase inward and outward current [33]. Propafenone also did not modify I\text{K1} recorded in human right atrial myocytes [33].

The molecular structure of propafenone can be described as an L-like shape, in which a long and short arm are joined by an aromatic ring [33]. Molecular dynamics simulations predicted interaction with K\text{ir}2.1, in which the hydrophobic long arm of propafenone embeds in a hydrophobic pocket formed by subunit A of the channel. The short arm, on the other hand, contains a group that formed a hydrogen bond with cysteine residue Cys311, which is part of the G-loop [33,60]. This critical hydrogen bond between Cys311 and propafenone was promoted due to the binding orientation of the alkylamino tail, which enabled propafenone’s hydroxyl group to be in close proximity to Cys311 [33].

To determine a potential role of Cys311 and propafenone interaction, mutations creating a cysteine were made in K\text{ir}2.2 (A312C) and K\text{ir}2.3 (A303C). These mutations made the channels responsive to activation with 0.5 µM propafenone. With respect to channel kinetics, it was found that opening frequency and mean open probability were increased at all tested voltages [33].

3.2.3. Timolol

Structural similarities and the common Cys311 binding site of flecainide and propafenone have led to the development of a pharmacophore model for binding to this particular site. The model predicted that a drug must have the following molecular properties that enable interaction with Cys311: (1) an “L-like” configuration with a short and long arm, joined by an aromatic ring at an angle of approximately 100 degrees; (2) a hydrogen bond acceptor/donor group in the short arm that interacts with Cys311; (3) a hydrophobic group in the long arm that interacts with a hydrophobic pocket in subunit A of K\text{ir}2.1; (4) a hydrogen bond between Arg67 or Glu63 and the drug for stabilization. By screening drugs for these properties, timolol was found as a potential activator of K\text{ir}2.1 [33]. Timolol, a non-selective β-receptor antagonist, selectively activated K\text{ir}2.1 by directly binding to Cys311 and thereby increased I\text{K1} in the ventricles [33].

3.2.4. Pregnenolone Sulfate

Pregnenolone sulfate (PREGS) is an endogenous neurosteroid. PREGS modulates the function of multiple neurotransmitter receptors and channels, among which were voltage-gated K+ channels [61]. PREGS-enhanced K\text{ir}2.3 carried current in Xenopus oocytes when applied extracellularly only, whereas no current response in K\text{ir}1.1, K\text{ir}2.1, K\text{ir}2.2, or K\text{ir}3.1/K\text{ir}3.2 channels was observed [32].
3.3. Unknown Mechanism of Activation

3.3.1. LPS (lipopolysaccharides)

Lipopolysaccharides (LPS) are an important constituent of the cell wall of gram-negative bacteria. LPS can injure pulmonary microvascular walls. In those vessels, K\textsubscript{ir}2.1 plays a role in vasodilation by modulating the membrane potential and intracellular Ca\textsuperscript{2+} concentration. Treatment of mouse pulmonary microvascular endothelial cells with LPS enhanced K\textsubscript{ir}2.1 channel expression and Ba\textsuperscript{2+} sensitive I\textsubscript{K1} current [41].

3.3.2. Morphine

Morphine is the main element of opium and is used as an anesthetic or sedative as agonist of the \(\mu\), \(\delta\), and \(\kappa\) opioid receptors [62]. In rabbit ventricular myocytes, morphine significantly increased I\textsubscript{K1}, independent of the opioid-receptor pathway [42]. In human atrial myocytes, morphine was unable to enlarge I\textsubscript{K1} [63].

3.3.3. Polydatin

Polydatin (PD), also known as piceid (3,4\textprime;5-trihydroxystilbene-3-\(\beta\)-D-glucoside), is a monocrystalline compound found, for example, in Polygonum cuspidatum Sieb. et Zucc. (Polygonaceae), peanuts, and grapes. PD has a therapeutic effect on hypertension, arrhythmia, hypertrophy, cardiac ischemia, and heart failure by means of manipulation of Ca\textsuperscript{2+} mobilization [64]. In rat ventricular myocytes, PD increased I\textsubscript{K1} in a concentration-independent manner [43].

4. Lead Compounds and Clinical Perspective

Due to their similar chemical structure, the drugs flecainide, propafenone, and timolol are able to directly activate K\textsubscript{ir}2.1 channels by means of their interaction with cysteine residue Cys311. This off-target effect can be exploited for rationalized drug development towards specific I\textsubscript{K1} activators. This provides a promising perspective in the search for a suitable AgoKir.

As mentioned above, timolol has been found to be an activator of K\textsubscript{ir}2.1 after being selected based on the criteria proposed by a pharmacophore model developed by [33]. This opens the possibility to develop a new drug with a higher specificity for K\textsubscript{ir}2.1 channels that meets the requirements of the model. Medicinal chemistry approaches involving modifications to the long and short arm of one of these three existing drugs might be an important step to explore properties that increase specificity for the K\textsubscript{ir}2.1 channel. For example, flecainide’s principal mechanism of action is the inhibition of cardiac Na\textsubscript{v}1.5 sodium channels [65]. It might be possible to modify parts of the flecainide molecule that, as per the pharmacophore model, are not essential for binding to K\textsubscript{ir}2.1, but are important for interaction with Na\textsubscript{v}1.5 to steer specificity.

Out of all the drugs reviewed in this article, the ones directly activating K\textsubscript{ir}2.1 by binding to Cys311 provide the most viable basis for the development of AgoKirs. As discussed earlier, I\textsubscript{K1} channels are homo- or heterotetrameric assemblies of K\textsubscript{ir}2.x monomeric subunits. Only the K\textsubscript{ir}2.1 subunit has the cysteine residue Cys311 as part of its G-loop. K\textsubscript{ir}2.2 and K\textsubscript{ir}2.3 subunits contain an alanine instead of a cysteine residue on their equivalent positions (312 and 303, respectively) [31]. Propafenone and flecainide both cannot activate homo- or heterotramers of K\textsubscript{ir}2.2 and K\textsubscript{ir}2.3 channels. These observations indicate the potential for isoform-specific K\textsubscript{ir}2.x activating compound development by targeting this channel domain but also indicate that other regions of the channel protein should be targeted for the development of multi-isoform activators. Furthermore, high throughput screening methods, such as automated patch-clamp, optical membrane potential detection, and ion-flux measurements, are being developed that will further aid the generation of AgoKirs [66].

The reports on aldosterone and valsartan on K\textsubscript{ir}2.x/I\textsubscript{K1} regulation/activation are contradictory. Aldosterone production is part of RAAS, whereas valsartan is an antagonist of that system. Therefore, one would expect that these compounds have opposite effects on the activation and expression of the
Kir2.1 subunits. The findings, however, showed that valsartan was able to ameliorate MI-induced Kir2.1 downregulation. Unfortunately, the results for aldosterone were inconclusive. Two studies demonstrated upregulation, and only one study proved downregulation and therefore matched our expectations. This inconsistency between the outcomes of aldosterone and valsartan might indicate that both compounds use additional, RAAS independent pathways in order to activate IK1.

Specific AgoKirs may come with potential adverse effects. Gain-of-function mutations indicate the potential of developing reentry-based arrhythmias, either atrial, ventricular, or both. The underlying mechanism is likely AP shortening and reduction in the effective refractory period. Furthermore, due to the strong stabilization of the resting membrane potential, muscle and neuronal cells harboring IK1 may become less or even unexcitable. Therefore, it would be beneficial to develop (1) Kir2 isoform-specific AgoKirs and (2) AgoKirs with a wide therapeutic range.

Ion channel activators have been pursued in several other research fields, and, for some, they entered clinical practice. The research field advanced furthest with respect to channel activation is undoubtedly that of cystic fibrosis. This disease results mainly from insufficient cystic fibrosis transmembrane conductance regulator (CFTR) channel activity at the plasma membrane of glandular epithelial cells of, for example, the lungs, sweat glands, and gastrointestinal tract [29]. The CFTR channel research field developed both potentiators and correctors. Potentiators act on plasma membrane-localized channels and increase their open probability, whereas correctors address the impaired trafficking deficiencies and enhance forward trafficking of the channels by approaching several different steps of the trafficking machinery [29]. Clinically, a combination of potentiators and correctors appeared most effective (e.g., [67,68]). With respect to cardiac potassium channel activators, progress has been made for Kv11.1/IKr. Delayed rectifier IKr loss-of-function is associated with long QT syndrome type 2 and cardiac arrhythmia [69]. A number of compounds have been developed and tested in animal models for antiarrhythmic properties [70–73]. Currently, these activators mainly function to enhance channel kinetics resulting in increased potassium current. However, many of the forms of IKr loss-of-function are due to defective forward trafficking of the Kv11.1 proteins [74–76], and the development of compounds directly addressing this issue may be favorable. Unfortunately, existing enhancers of forward trafficking are also strong Kv11.1 inhibitors [77]. However, molecular insights in the rescue mechanism, including drug-channel interactions, may result in new rescuers of trafficking that do not display inhibition effects. In addition, activators alone might be sufficient in several conditions to increase current to sufficient levels to counteract arrhythmia [78]. With respect to inward rectifier currents, advances have been made in the application of drugs targeting IKATP channels. For example, minoxidil, an IKATP channel opener, is used as a vasodilator in the treatment of resistant hypertension [28] and to promote hair growth in androgenetic alopecia patients [30]. To our knowledge, specific AgoKirs have not been developed, but giving the new insights from the direct channel activators (flecainide, propafenone, timolol, PREGS) and the successes in other research fields, this development will be a valid way to counteract disease-associated loss-of-function of IK1 channels.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AF           | Atrial Fibrillation |
| AgoKir       | Agonist of Kir channel |
| AS           | Andersen Syndrome |
| CFTR         | Cystic Fibrosis Transmembrane Conductance Regulator |
| CHO          | Chinese Hamster Ovary |
| EK           | Potassium equilibrium potential |

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| EK           | Potassium equilibrium potential |
HEK Human Embryonal Kidney
HF Heart Failure
IK1 Inward rectifier current
IKATP ATP regulated inward rectifier current
ISO Isoproterenol/isoprenaline
K_{ir}2.x Isoform x of the inward rectifier protein K_{ir}2 family
LPS Lipopolysacharides
MI Myocardial Infarction
MR Mineral corticoid Receptor
PD Polydatin
PKA Protein Kinase A
PKC Protein Kinase C
PREGS Pregnenolone Sulfate
RAAS Renin-Angiotensin-Aldosterone-System
V_m Membrane potential
ZAC Zacopride

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