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Atrial fibrillation: Therapeutic potential of atrial K^+ channel blockers

Ursula Ravens [a,b,c,*], Katja E. Odening [a,b]

[a] Institute of Experimental Cardiovascular Medicine, University Heart Center Freiburg-Bad Krozingen, Freiburg, Germany
[b] Department of Cardiology and Angiology I, University Heart Center Freiburg-Bad Krozingen, Freiburg, Germany
[c] Department of Physiology, Medical Faculty Carl-Gustav-Carus, TU Dresden, Dresden, Germany

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ABSTRACT

Despite the epidemiological scale of atrial fibrillation, current treatment strategies are of limited efficacy and safety. Ideally, novel drugs should specifically correct the pathophysiological mechanisms responsible for atrial fibrillation with no other cardiac or extracardiac actions. Atrial-selective drugs are directed toward cellular targets with sufficiently different characteristics in atria and ventricles to modify only atrial function. Several potassium (K^+) channels with either predominant expression in atria or distinct electrophysiological properties in atria and ventricles can serve as atrial-selective drug targets. These channels include the ultra-rapidly activating, delayed outward-rectifying Kv1.5 channel conducting I_{Kur}, the acetylcholine-activated inward-rectifying Kir3.1/Kir3.4 channel conducting $I_{K,ACh}$, the Ca^{2+}-activated K^+ channels of small conductance (SK) conducting I_{SK}, and the two pore domain K^+ (K2P) channels TWIK-1, TASK-1 and TASK-3 that are responsible for voltage-independent background currents I_{TWIK-1}, I_{TASK-1}, and I_{TASK-3}. Here, we briefly review the characteristics of these K^+ channels and their roles in atrial fibrillation. The antiarrhythmic potential of drugs targeting the described channels is discussed as well as their putative value in treatment of atrial fibrillation.

Contents

1. Introduction

Atrial fibrillation (AF) is a serious cardiovascular health problem associated with an increased risk for stroke and heart failure. Clinical symptoms associated with this arrhythmia comprise palpitations, rapid and irregular pulse, weakness, reduced exercise capacity, fatigue, dizziness, shortness of breath and even chest pain, all of which may substantially reduce quality of life. One hallmark of atrial fibrillation is its progressive nature due to electrical and structural remodelling of the tissue at the cellular and subcellular levels. The irregular, high-frequency excitations of the atria cause characteristic abbreviation of atrial effective refractory period, hypocontractility, abnormal cellular Ca^{2+} handling and structural remodelling [for expert reviews of these topics see (Schotten et al., 2011; Heijman et al., 2014)].

The therapeutic strategy for atrial fibrillation pursues two aims, i.e. prevention of stroke with oral anticoagulants in combination with antiarrhythmic treatment (Camm et al., 2012). The latter consist of restoration of sinus rhythm using electrical or pharmacological conversion, drugs to control ventricular rate, or interventional ablation procedures. In the early stages of the disease, either restoration of sinus rhythm is attempted by electrical or pharmacological conversion, or alternatively,

Abbreviations: ACh, acetylcholine; AF, atrial fibrillation; AP, action potential; APD, action potential duration; $cI_{K,ACh}$, consitutively active $I_{K,ACh}$; GIRK, G protein-coupled inwardly-rectifying potassium channel; hERG, human ether-a-go-go related gene channels; IC_{50}, concentration of half-maximum inhibition; K2P, two pore domain K^+ channels; $rI_{K,ACh}$, receptor-activated $I_{K,ACh}$; SK channels, Ca^{2+}-activated K^+ channels of small conductance; SR, sinus rhythm; TASK, TWIK-related acid-sensitive K^+ channels; TWIK, tandem of P domains, weak inward-rectifying K^+ channels.

* Corresponding author at: Institute of Experimental Cardiovascular Medicine, Heart Center University of Freiburg, Elsässer Str. 2Q, 79110 Freiburg, Germany.
E-mail addresses: Ursula.Ravens@tu-dresden.de, ursula.ravens@universitaets-herzzentrum.de (U. Ravens).

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pharmacological strategies to control ventricular rate are employed. As atrial fibrillation progresses to more persistent or permanent forms, these strategies fail and even ablation procedures have limited chances of success.

Although intuitively, rhythm control would appear to be a more physiological therapeutic goal in comparison with rate control because it actually resolves atrial fibrillation while the latter does not, clinical trials have failed to demonstrate a superior outcome of rhythm control even in patient populations at high risk for atrial fibrillation-related mortality (Talajic et al., 2010). One reason for the lack of superiority of rhythm over rate control could lie in the modest efficacy of the current antiarrhythmic drugs in concert with their high propensity for ventricular proarrhythmic effects. Interestingly, one of the most effective antiarrhythmic drugs, amiodarone, does not promote ventricular tachyarrhythmias but is burdened with severe extracardiac side effects related to multiple organ systems.

Despite the epidemiological scale of the arrhythmia, current treatment options are far from being satisfactory, mainly because of their limited efficacy and unwanted side effects. Ablation techniques consist of irreversible tissue destruction by using radiofrequency or cryoablation in order to remove ectopic foci or to abolish conduction of triggered activity from the pulmonary veins to atrial tissue and/or to disrupt conduction within re-entry circuits. Pharmacological approaches allow targeting therapy to the specific patho-electrophysiological mechanisms (Heijman et al., 2016), e.g. suppression of ectopic and triggered activity with Na^+ channel blockers, disruption of re-entry by prolongation of action potential duration (APD) and effective refractory period with K^+ channel blockers, and restoration of compromised cellular Ca^{2+} handling with several experimental drugs [for reviews see (Burashnikov & Antzelevitch, 2009; Ravens, 2010; Heijman et al., 2014; Heijman & Dobrev, 2015)]. Reversing AF-induced APD shortening has also been attempted by gene transfer, and proof-of-principle of this concept was provided in a pig model of burst pacing-induced AF: by introducing a dominant-negative mutant of the hERG channel by means of adenovirus, the onset of persistent AF was suppressed or delayed due to prolongation of atrial effective refractory period (Soucek et al., 2012).

Despite their recognized antiarrhythmic activity, class I (Na^+ channel blockers) and class III antiarrhythmic drugs (K^+ channel blockers prolonging APD) are not dependably effective. Ideally, drugs should only affect atrial targets without any influence on the ventricles. For instance, excessive prolongation in ventricular APD by conventional class III antiarrhythmic drugs (mainly hERG channel blockers) is associated with a high risk of life-threatening torsades de pointes arrhythmias that may exacerbate into ventricular fibrillation (Sanguinetti & Mitcheson, 2005). To circumvent this problem the concept of "atrial-selective" drug development (Ehrlich et al., 2007) has attracted enormous scientific and pharmaceutical interest in identifying novel targets for drugs to treat atrial fibrillation [for reviews see (Ravens et al., 2013; El-Haou et al., 2015; Hancox et al., 2016)]. The present review provides an update of the recent developments in the search for new atria-targeting antiarrhythmic drugs that are directed at various K^+ channels.

2. Genetic alterations in familial forms of atrial fibrillation — clues for novel drug targets

Although atrial fibrillation is often associated with other cardiovascular diseases there is also an early-onset, familial form of AF that develops in young individuals without any cardiovascular disease. Such "lone AF" appears to have a genetic cause (Ellinor et al., 2005). Investigation of genetic variants in ion channels associated with atrial fibrillation provides a better understanding of the pathophysiological mechanisms of AF. In addition, the changes in channel function caused by these AF-associated genetic variants may also serve as a valuable source of inspiration, which drug targets could be worth pursuing in the search for novel therapeutic approaches of AF. Mutations and rare variants in genes encoding cardiac ion channels have been linked to familial and lone atrial fibrillation [reviewed in (Andreasen et al., 2015; Christophersen & Ellinor, 2016)]. It is noteworthy that gain-of-function mutations in potassium channels abbreviate the atrial action potential by enhancing repolarization and therefore may contribute to maintenance of AF via enhancing re-entry circuits. In contrast, loss-of-function mutations in potassium channels prolong APD and atrial effective refractory period. In spite of being an accepted antiarrhythmic mechanism, APD prolongation also bears an arrhythmogenic potential, because excessive prolongation in the late plateau phase may reactivate depolarizing Na^+ and Ca^{2+} inward currents causing early afterdepolarization (Bers, 2008). Indeed, Nielsen et al. reported a J-shaped relationship between proarrhythmic risk and QTc duration (Nielsen et al., 2013). It should be noted that although the QT interval reflects the duration of the ventricular action potential, it is also a surrogate of atrial APD. Similarly as known in the ventricles, where both ADP shortening and APD prolongation can be pro-arrhythmic (e.g., in short and long QT-syndromes), APD shortening and prolongation may similarly facilitate arrhythmia in the atria."

Typical cardiac potassium channels expressed in atrial *and* ventricular cells are KvLQT1/I_{Ks} and hERG/I_{Kr} encoded by *KCNQ1* and *KCNH2* genes, respectively (see also Fig. 1A). Mutations in these two genes are clinically associated with a combination of atrial and ventricular arrhythmia in the setting of short-QT or long-QT syndrome (Harrell et al., 2015; Hayashi et al., 2015; Steffensen et al., 2015).

Several ion channels are predominantly expressed in the atria. Mutations in the genes encoding for these channels confer an arrhythmogenic phenotype that is limited to atrial arrhythmia (Olson et al., 2006; Calloe et al., 2007; Yang et al., 2009; Christophersen et al., 2013; Macri et al., 2014; Hayashi et al., 2015). Atrial fibrillation has been linked to mutations in the *KCNA5* gene that encodes for Kv1.5 channels (Fig. 1A), and was associated both with variants that enhance I_{Kur} (Olson et al., 2006; Yang et al., 2009; Hayashi et al., 2015) as well as variants that decrease I_{Kur} (Christophersen et al., 2013; Hayashi et al., 2015). This seemingly paradoxical effect of pro-arrhythmic effects conferred by gain- and loss-of-function mutations was also observed in patients with hereditary short- and long-QT syndromes, in whom the association between duration of QT interval and prevalence of AF was highest at both extremes [J-shaped; (Nielsen et al., 2013)]. A loss of function mutation in the *KCNJ5* gene encoding Kir3.4 channels (Fig. 1B) was found in a patient with a single episode of AF (Calloe et al., 2007). When co-expressed with M_2 acetylcholine receptors in Xenopus oocytes, the mutated channel showed reduced acetylcholine-activated inward rectifier current, but the pathophysiological link of this finding to AF is unclear – particularly since activation of Kir3.1/3.4 channels (rather than reduction) by vagal stimulation can trigger AF (Stavrakis et al., 2015). Genetic variations in the *KCNN3* gene for Ca^{2+}-activated channels of small conductance (SK3; Fig. 1A) (Ellinor et al., 2010) or in the *KCNK3* gene for two-pore domain K^+ channels (Fig. 1C; TASK-1) (Liang et al., 2014) may similarly contribute to an atrial substrate for arrhythmogenesis. In addition, trafficking deficient mutations in *HCN4* have been linked to atrial fibrillation and sinus bradycardia (Macri et al., 2014). Taken together, these observations support the notion that "atrial" potassium channels may be targets for treatment of atrial fibrillation.

3. Atrial-selective drug targets

Many of the channels discussed below are widely distributed and functionally active not only in atria but also in the central nervous system, requiring drugs that do not pass the blood brain barrier for atrial-selective action. However, this problem should be possible to cope with pharmaceutically.