Atrial-Selective Potassium Channel Blockers

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KEYWORDS

• $I_{K,ACh}$ • I_{Kur} • K2P channels • SK channels • Kv1.1 channels • Atrial fibrillation

KEY POINTS

- Atrial selective K^+ channels largely contribute to differences in the shape of the atrial versus ventricular action potential.
- Acetylcholine-activated inward-rectifier K^+ current ($I_{K,ACh}$) and ultrarapid delayed-rectifier K^+ current (I_{Kur}) represent classical atrial-selective K^+ currents, which are absent in ventricular myocytes.
- None of the "pure" blockers of I_{Kur} or $I_{K,ACh}$ passed phase II clinical trials yet.
- K2P channels, SK channels, and Kv1.1 channels have been shown recently to contribute to atrial repolarization and may represent novel atrial-selective drug targets.
- Because multichannel blockers are established compounds for treatment of atrial fibrillation, specific combinations of ion channel blockade may be an additional promising approach.

INTRODUCTION

Atrial fibrillation (AF), the most frequent cardiac arrhythmia, is associated with increased morbidity and mortality.[1] Currently available pharmacologic interventions for AF have major limitations, including limited efficacy and risk of life-threatening ventricular proarrhythmic side effects.[2–4] Amiodarone, a classical K^+ channel blocker that affects also a wide range of other ion channels and receptors, is currently the most frequently prescribed antiarrhythmic compound for AF therapy, suggesting that blocking of K^+ channels may be a promising therapeutic principle for AF.

The shape of a cardiac action potential (AP) is determined by the fine-tuned balance between depolarizing inward currents ($I_{Ca,L}$ and I_{Na}) and repolarizing outward currents (K^+ currents; Fig. 1). In patients with long-standing persistent and permanent (chronic) AF (cAF), the predominance of K^+ currents is supposed to lead to AP shortening, a major hallmark of electrical remodeling.[5,6] Because AP shortening promotes the maintenance of reentry excitations, it is assumed that inhibition of repolarizing K^+ currents may prevent the maintenance of AF.[2–4] Conversely, inhibition of ventricular K^+ channels may lead to extensive AP prolongation in the ventricle, which may promote the occurrence of "torsades de pointes" ventricular arrhythmias.[7] Therefore, atrial-selective inhibition of cardiac K^+ channels is a major goal in development of novel anti-AF K^+ channel blockers.

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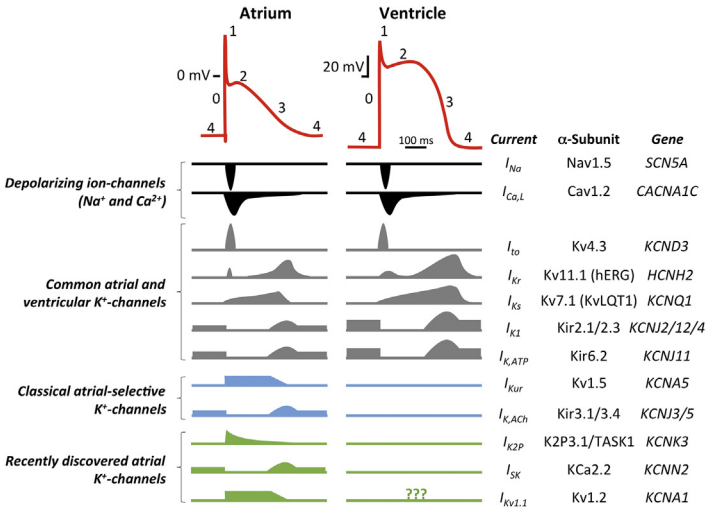

Fig. 1. Contribution of depolarizing inward and repolarizing outward currents to the atrial and ventricular action potential (AP). Activity of inward currents ($I_{Ca,L}$, L-type Ca^{2+}-current; I_{Na}, sodium current) and outward currents during the cardiac AP is displayed together with underlying channel α-subunit and corresponding gene. Outward currents are mediated by potassium (K^+) channels, which are expressed in both atrium and ventricle ($I_{K,ATP}$, adenosine triphosphate-sensitive inward-rectifier K^+ current; I_{K1}, inward-rectifier K^+ current; I_{Kr} and I_{Ks}, rapidly and slowly activating delayed-rectifier current; I_{to}, transient outward), and by K^+ currents, which are predominantly expressed in the atria ($I_{K,ACh}$, acetylcholine-activated inward-rectifier K^+ current; I_{K2P}, 2-pore domain channel mediated K^+ current; I_{Kur}, ultrarapidly delayed-rectifier K^+ current; $I_{Kv1.1}$, Kv1.1 channel mediated K^+ current; I_{SK}, SK2-channel mediated K^+ current). The contribution of I_{K2P}, I_{SK}, and $I_{Kv1.1}$ has been estimated based on recent publications.[10,13,89] (*Adapted from* The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation 1991;84(4):1831–51 and Ravens U and Cerbai E. Role of potassium currents in cardiac arrhythmias. Europace 2008;10(10):1133–7; with permission.)

The differences in AP shape between atria and ventricles are mainly owing to the atrial-selective occurrence of K^+ channels, which provide a potential target for atrial-selective antiarrhythmic therapy.[8] The best validated atrial-specific ion currents are the acetylcholine-activated inward-rectifier K^+ current ($I_{K,ACh}$) and ultrarapid delayed-rectifier K^+ current (I_{Kur}), which are absent in ventricular myocytes. Recent publications show that 2-pore domain K^+ channels (K2P channels),[9,10] small-conductance Ca^{2+}-activated K^+ channels (SK channels),[11,12] and Kv1.1 channels[13] may also contribute to the atrial repolarization, potentially representing atrial-specific drug targets (Fig. 2).

Herein we review the molecular and electrophysiologic characteristics of atrial-selective K^+ channels and their potential pathophysiologic role in AF. We summarize the currently available K^+ channel blockers focusing on the most important compounds that highlight general principles or that have been evaluated in clinical studies (Fig. 3). For a detailed overview we refer the interested readers to a recent excellent review by El-Haou and colleagues.[14]

CLASSICAL ATRIAL-SELECTIVE K^+ CHANNELS

Acetylcholine-Activated Inward-Rectifier K^+ Current

The hallmark of inward-rectifier K^+ channels is the high conductance of K^+ ions into the cell, whereas the physiologically more relevant outward conductance is relatively low (see Fig. 2B).[15] Despite this relatively small outward conductance at physiologic potentials, inward-rectifier K^+ channels are major contributors to the late AP repolarization and play a major role in stabilizing the resting membrane potential.[8,16] Increased inward-rectifier K^+ currents have been shown to contribute to APD shortening in cAF patients and to stabilization of reentrant excitations.[3,5] In addition to basal inward-rectifier K^+ current I_{K1}, atrial, but not ventricular myocytes express $I_{K,ACh}$ channels, which are physiologically activated by the vagal neurotransmitter acetylcholine in a muscarinic (M)-receptor-dependent manner.[15,17–19] The $I_{K,ACh}$ channel is a heterotetramer composed of 2 Kir3.1- and 2 Kir3.4 subunits[20] and binding of G-protein βγ-subunits to the N- and C-terminus leads to a stronger interaction of phosphatidylinositol 4,5-bisphosphate with the channel, resulting in channel activation.[21,22] In cAF, $I_{K,ACh}$ develops agonist-independent (constitutive) activity, which has been suggested to contribute to the increased total inward-rectifier K^+ current.[23,24] Because $I_{K,ACh}$ is atrial selective, constitutively active $I_{K,ACh}$ currents represent a potential atrial- and pathology-specific drug target of AF.[2,25]

Blockers

Several antiarrhythmic drugs like amiodarone, flecainide, quinidine, chloroquine, and verapamil possess $I_{K,ACh}$-blocking effects that may