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Review

Pharmacological exploration of the resting membrane potential reserve: Impact on atrial fibrillation

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ABSTRACT

The cardiac action potential arises and spreads throughout the myocardium as a consequence of highly organized spatial and temporal expression of ion channels conducting Na^+, Ca^{2+} or K^+ currents. The cardiac Na^+ current is responsible for the initiation and progression of the action potential. Altered Na^+ current has been found implicated in a number of different arrhythmias, including atrial fibrillation. In the atrium, the resting membrane potential is more depolarized than in the ventricles, and as cardiac Na^+ channels undergo voltage-dependent inactivation close to this potential, minor changes in the membrane potential have a relatively large impact on the atrial Na^+ current. The atrial resting membrane potential is established following ionic currents through the inwardly rectifying K^+ currents I_{K1}, $I_{K,ACh}$ and $I_{K,Ca}$ and to a lesser extent by other ion channels as well as by exchangers and pumps. This review will focus on the relative and regulated contribution of I_{K1}, $I_{K,ACh}$ and $I_{K,Ca}$, and on pharmacological modification of the channels underlying these currents in respect to the resting membrane potential, Na^+ channel availability and atrial electrophysiology in health and disease.

Contents

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1. Introduction

Atrial arrhythmia, and in particular atrial fibrillation (AF), is an increasing health problem with the aging population (Lloyd-Jones et al., 2004; Krijthe et al., 2013). While the mainstay of current treatment of AF is rate and rhythm control pharmacotherapy, ablation of the atrial conduction pathway and anti-coagulation therapy (Camm et al., 2012), the present treatment regimes often are inadequate (Gillis et al., 2013). Therefore, development of novel pharmacological strategies based on mechanistic modulation of atrial excitability is of an imperative necessity as potential novel therapeutic options. The resting membrane potential (RMP), defined as the relatively stable potential between action potentials, also termed diastolic potential, plays a central role in controlling a number of electrophysiological parameters in the atrium and changes in this potential may prove pivotal in controlling excitability of the atrium and thereby define whether the atrium is prone to arrhythmia. Pharmacological modification of the ion channels underlying the RMP may therefore present new treatment options in AF. However, in cases with overlap in expression between atrium and ventricle it is possible that modulation of such a basic property as RMP may induce severe adverse effects in ventricular tissue. On the other hand, the RMP is generated due to activity of a series of ion channels and transporters, which may compensate each other their functions.

The cardiac Na^+ current, conducted through $Na_v1.5$ voltage-gated channels, undergoes voltage-dependent inactivation, a so-called state-dependent inactivation, at depolarizing potentials (Schneider et al., 1994; Petitprez et al., 2008). In non-diseased human atrium, RMP has been found to be approximately −75 mV, while the potential in atrial tissue from patients with chronic AF is around −79 mV (Christ et al., 2008). As these values are very close to the half inactivation of the cardiac $Na_v1.5$ channel, and as it is the Na^+ current that is strongly associated with the progression of action potentials, a minor change in RMP will have a large impact on the electrical impulse of the atrium (Schneider et al., 1994). Reduced Na^+ current will both slow the conduction velocity of the action potential and prolong the refractory period between action potentials (Schneider et al., 1994).

2. RMP reserve

Three different non-voltage-gated cardiac K^+ currents-I_{K1}, $I_{K,ACh}$, and $I_{K,Ca}$-are important in controlling RMP (Fig. 1.). These currents partly overlap in temporal expression both during the later part of the action potential and during diastolic repolarization and do therefore constitute a RMP reserve, i.e. a decrease in one of the currents will have minor effect on the potential due to a buffering, or even increased activity, of the others. Still, an increased current from any of these three K^+ channels will, modestly, hyperpolarize the RMP and thereby increase conduction velocity and decrease refractoriness, while a reduction will have the opposite effect. As the half-inactivation of cardiac Na^+ channels is close to atrial RMP (Schneider et al., 1994; Petitprez et al., 2008), small changes in the atrial RMP will have a relatively profound effect on the Na^+ channel availability and thereby be closely coupled to the genesis of AF.

In the following molecular identity, electrophysiology and pharmacology of these three inwardly rectifying, non-voltage-gated K^+ currents will be described. This will be followed by discussion of the extent to which pharmacological inhibition of

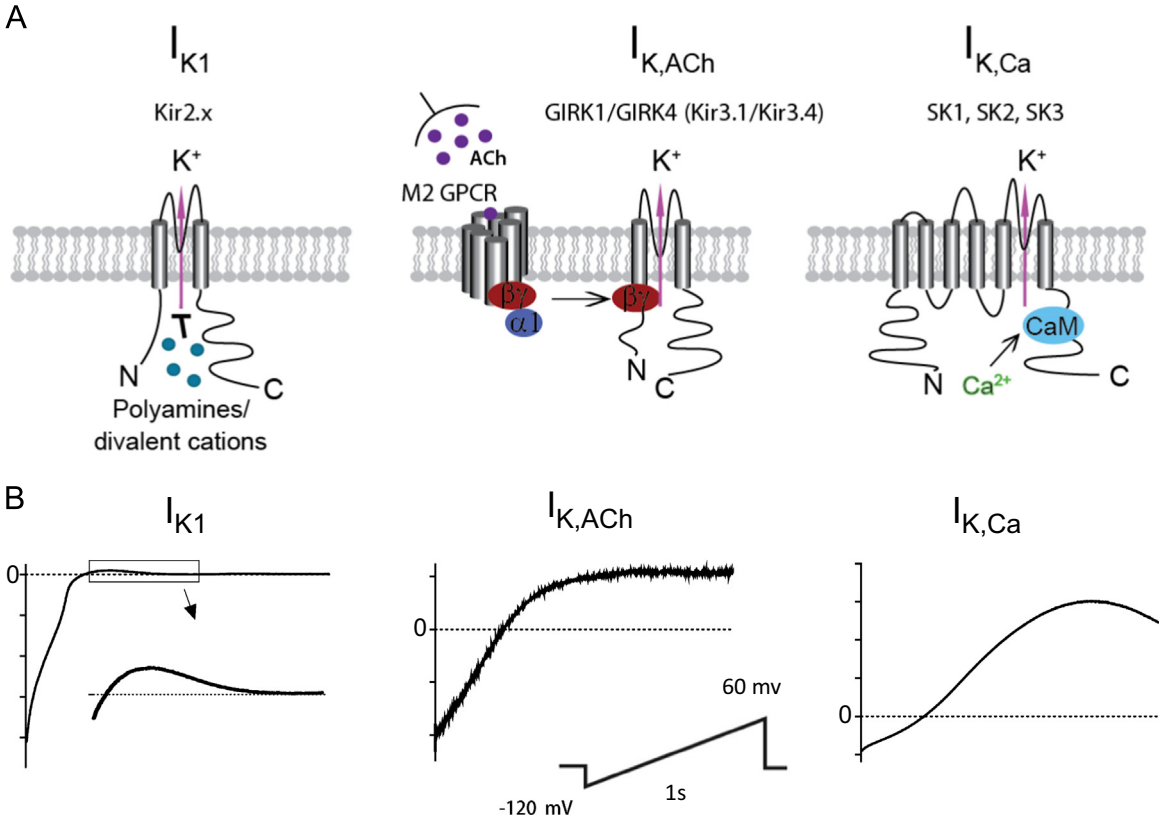

Fig. 1. Topology of single protein subunits constituting I_{K1}, $I_{K,ACh}$ and $I_{K,Ca}$ currents. $K_{ir}2.x$ and $K_{ir}3.x$ proteins contain 2 transmembrane regions, an extracellular pore-loop and intracellularly located N- and C-termini. SK proteins cross the membrane six times and carry an extracellular pore loop between transmembrane region 5 and 6. Calmodulin binding occurs at the C-terminus. Strong rectification of I_{K1} is achieved by polyamine/Mg^{2+} pore block upon depolarisation, whereas less stringent rectification is observed for $I_{K,ACh}$ and $I_{K,Ca}$ channels (B).