Mechanism of Proarrhythmic Effects of Potassium Channel Blockers

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KEYWORDS

• Cardiac action potentials • K^+ channels blockers • Antiarrhythmic drugs • Proarrhythmic effects • Mechanism of arrhythmia

KEY POINTS

- Prolongation of the cardiac action potential by K^+ channel blockers is well recognized as an antiarrhythmic mechanism, but can exacerbate to life-threatening arrhythmia.
- The risk for drug-induced torsades de pointes arrhythmia and subsequent ventricular fibrillation is best documented for Kv11.1 (hERG) and Kv7.1 (KvLQT1) channel blockers.
- Potassium channels with predominant expression in the atrial myocardium may be beneficial in supraventricular arrhythmias without proarrhythmic risk in the ventricles.
- Many compounds target K^+ channels that were only recently discovered to also be expressed in the heart (eg, K2P and SK channels). The antiarrhythmic and proarrhythmic potential of such compounds is discussed.

INTRODUCTION

Excitability of the Heart: Basic Cardiac Electrophysiology

To accomplish its life-supporting function of pumping oxygenated blood around the body, the heart contracts and relaxes in a regulated fashion. This contraction process is preceded by electrical excitation that is initiated in the sinoatrial node and spreads throughout the heart in an orderly manner via the specialized cardiac conduction system. The action potential (AP) of the working myocardium lasts for several hundreds of milliseconds, with the delayed repolarization securing a refractory state for new excitations throughout the entire contraction phase. The sequence of ventricular excitation ensures that the cardiac contraction wave travels from the apex to the base and from endocardial to epicardial layers, whereas repolarization and relaxation take the reverse direction. Thus, the AP duration is shorter in epicardial than endocardial muscle and also shorter in the basal than the apical region. This heterogeneity of AP duration safeguards against bulging of the ventricles during a pumping cycle.

Action potentials and repolarization reserve

The shape of the cardiac AP is governed by voltage-dependent and time-dependent changes in ion movements across the cell membrane via selective ion channels, transporters, exchangers, and pumps.[1] Ion channels are hydrophobic protein complexes that span across the cell membrane and contain a hydrophilic pore that can open and close as the channel passes through an activated, inactivated, or deactivated stage in a voltage-dependent and time-dependent fashion.

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The driving force for current flow through an open channel is determined by the transmembrane concentration gradients for a particular ion species as well as by the membrane potential. Inward and outward flow of cations causes depolarization and repolarization, respectively. AP initiation of the cardiomyocyte happens as a response to the activation of voltage-gated Na^+ channels causing a fast depolarizing upstroke. The initial repolarization is caused by inactivating Na^+ current and the rapidly activating transient outward current. During the long plateau phase of the cardiac AP inward current mainly via L-type Ca^{2+} channels and outward current via a large variety of K^+ channels will temporarily be in balance until eventually K^+ currents prevail causing final repolarization. Delayed repolarization in human myocardium relies mainly on the large diversity of cardiac K^+ channels (Fig. 1), but also on a particular redundancy in the heart known as the "repolarization reserve," in which one current is taking over if another one should fail.[2]

Potassium channels

Potassium channels form a large family of ion channel proteins (see Nerbonne JM: Molecular Basis of Functional Myocardial Potassium Channel Diversity, in this issue) that are involved in controlling both resting membrane potential and AP shape and duration. The K^+ currents that play a role in the heart are listed in Fig. 1, which also contains the nomenclature of the gene encoding the pore-forming α-subunit of a particular K^+ channel.

Classification of K^+ channels is based on their rectifier properties describing how the channel is passing current better in one direction than the other, and on their kinetic function, although auxiliary subunits (β-subunits) also modify channel behavior. The outward rectifier K^+ channels (Kv channels) are formed by 4 α-subunits, each consisting of 6 transmembrane segments.[1] The inwardly rectifying K^+ channels (Kir family) are composed of 4 α-subunits that contain only 2 transmembrane segments.[3] In addition, weak inward rectifier channels have been detected and

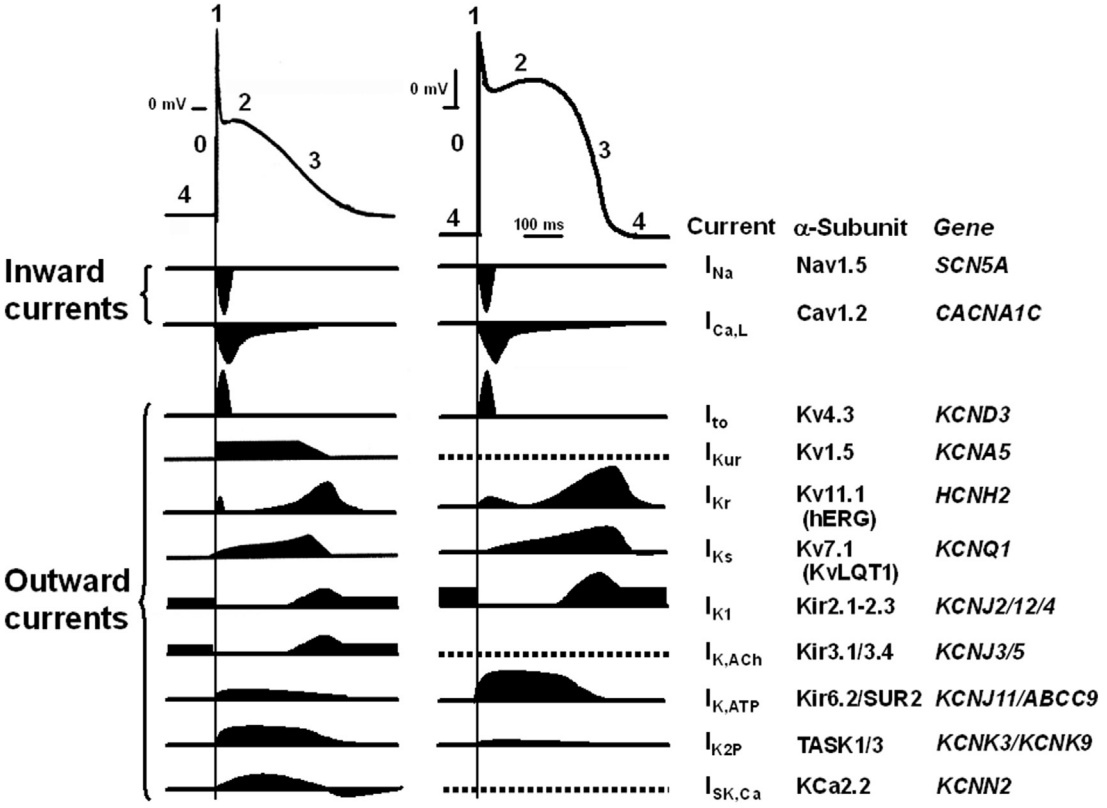

Fig. 1. Inward, depolarizing and outward, repolarizing currents that underlie the atrial and ventricular AP. Inward currents: I_{Na}, sodium current; $I_{Ca,L}$, L-type calcium current; I_{to}, transient outward current; I_{Kur}, ultra rapidly activating delayed rectifier current; I_{Kr} and I_{Ks}, rapidly and slowly activating delayed rectifier current; I_{K1}, inward rectifier current; $I_{K,ACh}$, acetylcholine-activated potassium current. Note, that I_{Kur} is present in atria only. Phase 0, rapid depolarization; phase 1, rapid early repolarization phase; phase 2, slow repolarization phase ("plateau" phase); phase 3, rapid late repolarization phase; phase 4, resting membrane potential. (*Adapted from* Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. Europace 2008;10(10):1134; with permission.)