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Cardiac ion channel trafficking defects and drugs

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ABSTRACT

Fine control over the functional expression of cardiac ion channels is required to maintain normal action potential (AP) duration and QTc times. A growing number of drugs interfere with normal trafficking of ion channels to and from the plasma membrane, thereby altering the number of channels on the cell surface. Most drugs do this at clinically relevant concentrations, which may lead to potentially life-threatening cardiac arrhythmias. Recently, major progress has been made in the understanding of the subcellular mechanisms by which drugs affect the trafficking of ion channels, which is of great benefit for the development of ways to counteract these adverse drug effects. Pharmacological correction seems to be a promising approach to address the trafficking defects induced by several drugs. However, as pharmacological correction is hampered by concomitant direct channel block or unspecific effects, further studies are needed to improve its potential as a clinical therapy.

Contents

1. Introduction

Each heart contraction is triggered by the cardiac action potential (AP), which results from the balance between depolarizing and repolarizing ion currents. The AP shape is determined by the function of cardiac ion channels and differs between several regions of the heart (Fig. 1). Changes in either expression, subcellular localization and/or conduction in any of these ion channels will alter AP properties, potentially predisposing the heart to life-threatening arrhythmias (Nerbonne & Kass, 2005; Balijepalli et al., 2010; Harkcom & Abbott, 2010). A decrease in repolarizing currents or an increase in depolarizing currents will prolong AP duration, which is reflected by a prolonged QT interval on the surface electrocardiogram (ECG), known as Long QT Syndrome (LQTS), and enhances the susceptibility for Torsade de Pointes arrhythmias. Opposite changes will result in a shortened QT interval that is associated with atrial fibrillation (Harkcom & Abbott, 2010).

Drugs can pose a pro-arrhythmic threat by inhibiting the function of cardiac ion channels via two fundamentally different mechanisms (van der Heyden et al., 2008): 1) the well-known direct block of channel conductance, and 2) the more recently discovered mechanism of disrupted ion channel trafficking to and from the cell surface membrane (Fig. 2). Whereas some drugs induce adverse effects via only one of these mechanisms, others act via a combination of both.

The aim of this article is to provide an overview of (potential) pro-arrhythmic drugs affecting the trafficking of cardiac ion channels, which takes the clinical dosing and therefore relevance of these trafficking defects into consideration. It is imperative to characterize drug effects at the cellular level in order to avoid or correct drug-induced cardiotoxicity. Therefore, the subcellular mechanisms by which drugs interfere with normal ion channel trafficking will be discussed. Finally,

Abbreviations: 17-AAG, 17-allylamino-17-demethoxygeldanamycin; AP, action potential; AV block, atrioventricular block; ECG, electrocardiogram; ER, endoplasmic reticulum; hERG, human ether-à-go-go-related gene; HPCD, 2-hydroxypropyl-β-cyclodextrin; Hsp, heat shock protein; I_{Kr}, rapid component of the delayed rectifier current; K_{IR}, inward rectifying channel; K_v, voltage-gated potassium channel; LQTS, Long QT Syndrome; Na_v, voltage-gated sodium channel; QTc, corrected QT interval; TCA, tricyclic antidepressant.

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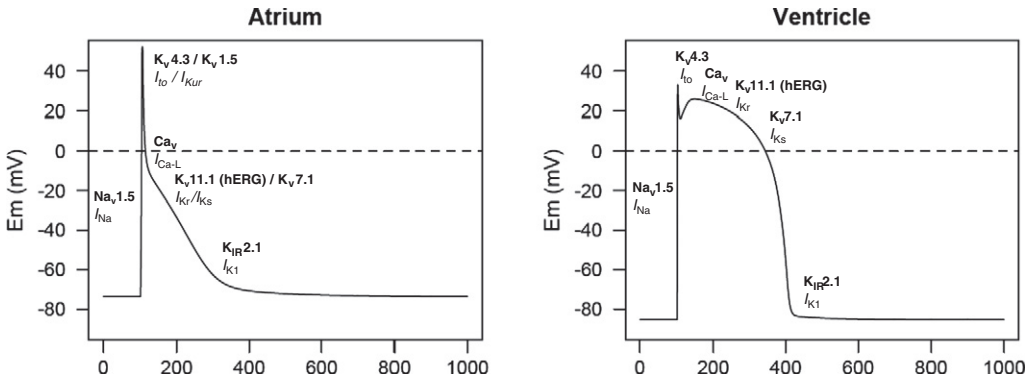

Fig. 1. The atrial and ventricular action potential (AP). In the working myocardium, the AP can be subdivided into five phases. The initial depolarization (phase 0) results from rapid activation of voltage-gated sodium (Na_v) channels, most importantly $Na_v1.5$. This is followed by transient repolarization (phase 1) due to the activation of voltage-gated potassium (K_v) channels, such as $K_v4.3$ (and $K_v1.5$ in the atria), and inactivation of Na_v channels. Subsequently, voltage-gated calcium (Ca_v) channels open, resulting in calcium influx. During the plateau phase (phase 2), there is a balance between calcium influx and potassium efflux. The slowly increasing potassium currents in this phase are conducted by $K_v11.1$ (hERG) and $K_v7.1$ channels. When the Ca_v channels inactivate, the repolarizing potassium currents predominate and the plateau phase proceeds into final repolarization (phase 3). During this phase, the inward rectifying channels (K_{IR}), such as $K_{IR}2.1$, also open and contribute to return the membrane potential to the resting membrane potential (phase 4) (Nerbonne & Kass, 2005; Harkcom & Abbott, 2010).

focus shifts to pharmacological correction that might be a promising approach to counteract these adverse drug effects.

2. Drugs affect the trafficking of cardiac ion channels

Ion channel trafficking involves both forward (towards the plasma membrane) and backward (internalization from the plasma membrane) transport (Fig. 2). Each ion channel may have its own specific processing steps, but there is no complete trafficking pathway known for any cardiac ion channel (Eckhardt et al., 2005; Steele et al., 2007; Nalos et al., 2011). In general, ion channels are synthesized, folded, and core-glycosylated (in the case of $K_v11.1$ and $K_v1.5$) in the endoplasmic reticulum (ER) and then subjected to ER-resident quality control mechanisms, such as heat shock protein (Hsp) 70 and 90 interactions with $K_v11.1$ (Ficker et al., 2003; Steele et al., 2007; Staudacher et al., 2010). When correctly folded, channels are transported to Golgi, where further processing like complex glycosylation occurs, and then forwarded to the plasma membrane, all by vesicular transport along microtubuli and/or actin filaments. From the cell surface, channels become internalized and can either be recycled or degraded in proteasomes or lysosomes (Schumacher et al., 2009; Harkcom & Abbott, 2010; Smyth & Shaw, 2010; Nalos et al., 2011).

Initially, studies investigating drug-affected ion channel trafficking focused on drugs that reduce the number of sarcolemmal $K_v11.1$ ion channels (Dennis et al., 2007; van der Heyden et al., 2008; Staudacher et al., 2010). However, drugs may also interfere with normal trafficking of other channels, like $Na_v1.5$, $K_v1.5$, $K_{IR}2.1$ or Kv7.1 (Jansen et al., 2008;

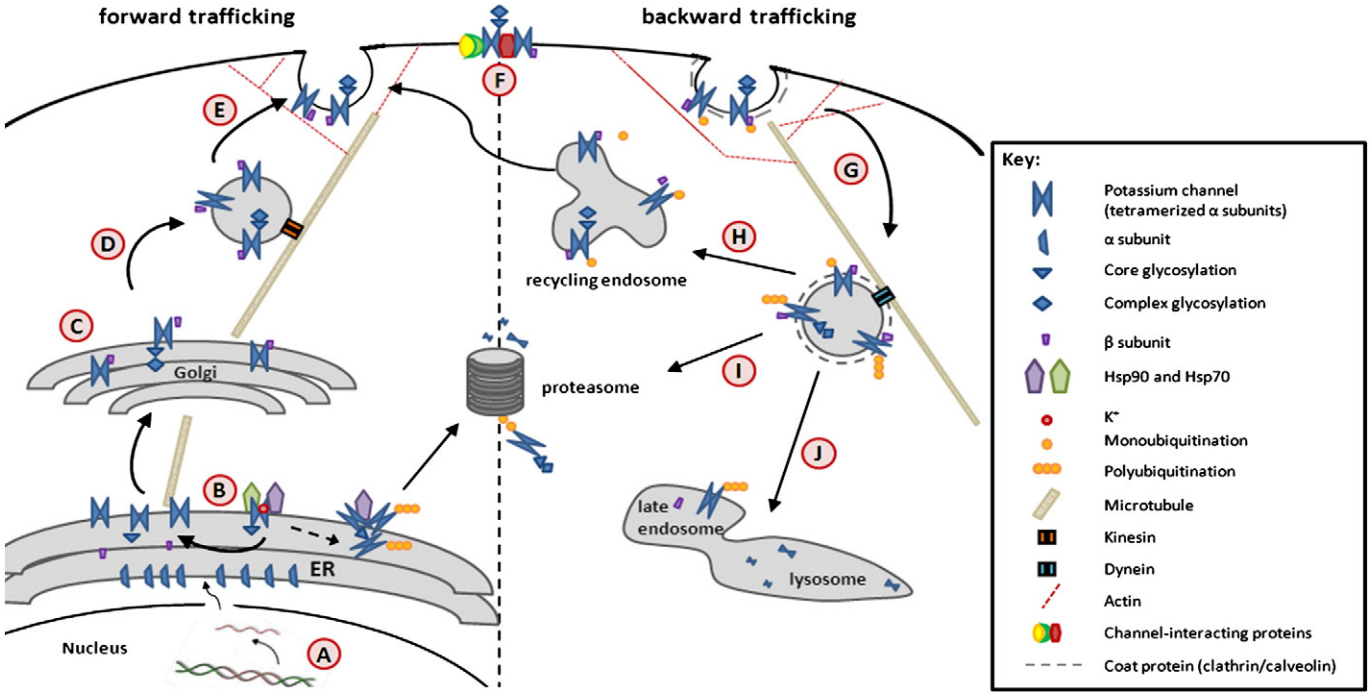

Fig. 2. Regulatory steps in the trafficking of potassium channels. (A) Gene transcription; (B) protein folding + core glycosylation of $K_v11.1$ and $K_v1.5$ channels (aggregation and degradation of misfolded channels); (C) post-translational modifications, including complex glycosylation; (D) anterograde vesicular trafficking along microtubuli; (E) membrane insertion; (F) interactions with ancillary proteins; (G) internalization (retrograde vesicular trafficking along microtubuli); (H) recycling; (I) proteasomal degradation; (J) lysosomal degradation. ER, endoplasmic reticulum.