Trends in Cardiovascular Medicine 26 (2016) 209–218

Available online at www.sciencedirect.com

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Mechanisms contributing to myocardial potassium channel diversity, regulation and remodeling

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ABSTRACT

In the mammalian heart, multiple types of K^+ channels contribute to the control of cardiac electrical and mechanical functioning through the regulation of resting membrane potentials, action potential waveforms and refractoriness. There are similarly vast arrays of K^+ channel pore-forming and accessory subunits that contribute to the generation of functional myocardial K^+ channel diversity. Maladaptive remodeling of K^+ channels associated with cardiac and systemic diseases results in impaired repolarization and increased propensity for arrhythmias. Here, we review the diverse transcriptional, post-transcriptional, post-translational, and epigenetic mechanisms contributing to regulating the expression, distribution, and remodeling of cardiac K^+ channels under physiological and pathological conditions.

Key words: Myocardial excitability, Arrhythmias, MicroRNAs, Transcription factors, Long non-coding RNAs, Cardiac hypertrophy, Heart failure, Diabetes.

Introduction

Cardiac action potentials are generated by the coordinated activation and inactivation of ion channels conducting depolarizing, inward (Na^+ and Ca^{2+}) and repolarizing, outward (K^+) currents (Fig. 1) [1]. While only a few Na^+ and Ca^{2+} channels account for cardiomyocyte depolarization, multiple types of voltage-gated (Kv) and non-voltage-gated inwardly rectifying (Kir) K^+ channels contribute to repolarization, determining action potential amplitudes, durations, and waveforms (Fig. 1; Table 1) [1]. Myocardial Kv and Kir channels are differentially expressed, resulting in regional- and cell type-specific differences in excitability and action potential waveforms (Fig. 1). The expression, distribution, and functioning of Kv and Kir channels are altered in a variety of cardiac and systemic diseases, leading to abnormal myocardial repolarization and increased propensity for life-threatening arrhythmias. A large number of Kv and Kir channel pore-forming α and accessory β subunits have been identified and the roles of many of these subunits in the generation of native myocardial Kv and Kir channels (Table 1) have been defined [1]. In addition, two pore domain (K2P) K^+ channels [2] and small conductance (SK) [3] Ca^{2+}-activated K^+ channels have been shown to be expressed and

This work was supported by US National Institutes of Health, United States (HL034161 and HL066388 to JMN), the Taiwan Ministry of Science and Technology (MOST103-2320-B-002-068-MY2 to KCY) and the Taiwan National Health Research Institute (Career Development Grant NHRI-EX104-10418SC to KCY).

The authors have indicated that there are no conflicts of interest.

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http://dx.doi.org/10.1016/j.tcm.2015.07.002
1050-1738/

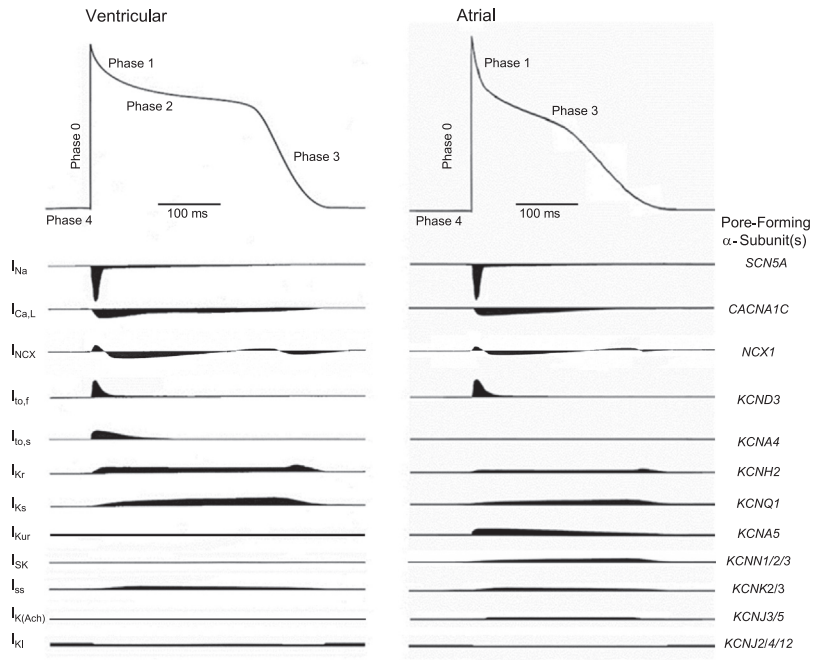

Fig. 1 – Schematics of action potential waveforms and underlying ionic currents in human ventricular (left) and atrial (right) myocytes. Note that relative inward (downward) and outward (upward) current densities and waveforms, estimated from voltage-clamp data and modeling studies, in non-diseased ventricular and atrial myocytes are shown. The voltage-gated inward Na^+ (Nav) and Ca^{2+} (Cav) currents in human atrial and ventricular myocytes are similar. In contrast, there are multiple types of outward K^+ currents, particularly Kv currents, contributing to atrial and ventricular action potential repolarization. In addition, the time- and voltage-dependent properties of the various Kv currents are distinct. Differences in the densities and in the detailed time- and voltage-dependent properties of the repolarizing Kv and Kir channels contribute to differences in the waveforms of atrial and ventricular action potentials. The genes encoding the pore-forming α subunits underlying the various cardiac ion channels are also indicated (on the right).

demonstrated to play roles in cardiac electrophysiological functioning. Here, the factors contributing to the diverse properties and functional roles of myocardial K^+ channels are reviewed, and the molecular mechanisms contributing to the physiological regulation and pathological remodeling of myocardial K^+ channels are discussed.

Molecular determinants of myocardial K^+ channel diversity

Although the hyperconserved (GYGD) sequence that underlies K^+ selectivity is a common feature of all K^+ channels, the activation, inactivation, and regulatory mechanisms vary markedly among different types of K^+ channels. The common ancestor of prokaryotic and eukaryotic K^+ channels formed a primitive channel structure with two transmembrane domains (TM) [4], which has evolved into over 100 different K^+ channel pore-forming α subunit genes (Fig. 2) through extensive gene duplication and divergence; more than 40 K^+ channel α subunit genes are expressed in the heart [1]. There are three types of K^+ channel α subunits: (1) the six transmembrane-domain (6-TM) family, which includes Kv and SK channels; (2) the two-transmembrane-domain (2-TM) Kir channels; and, (3) the four-transmembrane-domain (4-TM) K2P channels (Fig. 2). Some K^+ channel α subunit genes undergo alternative splicing [5] and different K^+ channel α subunits in the same subfamily can, in principle, heteromultimerize, thereby increasing the potential for functional K^+ channel diversity.

In addition to the pore-forming α subunits, multiple types of cytosolic and transmembrane K^+ channel accessory subunits, including Kvβ subunits, minK and minK-related proteins (MiRPs), K^+ channel interacting proteins (KChIPs), K^+ channel associated protein (KChAP), and the membrane-associated guanylate kinase homologs (MAGUK proteins), have been identified [1]. The various K^+ channel accessory subunits contribute to regulating trafficking, membrane anchoring, organization and biophysical properties of assembled, functional K^+ channel complexes.

Myocardial K^+ channel regulation

Multiple mechanisms contribute to the regulation of K^+ channel expression and functioning in cardiomyocytes (Fig. 3).

Transcriptional regulation of myocardial K^+ channels

Transcriptional mechanisms control the temporal and spatial expression of cardiac K^+ channels during development and in response to cardiac damage or disease. The fast component of the Kv4-encoded transient outward current, $I_{to,f}$, for