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CaMKII as a target for arrhythmia suppression

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ABSTRACT

Calcium/calmodulin-dependent protein kinase II (CaMKII) has emerged as key enzyme in many cardiac pathologies, especially heart failure (HF), myocardial infarction and cardiomyopathies, thus leading to contractile dysfunction and malignant arrhythmias. While many pathways leading to CaMKII activation have been elucidated in recent years, hardly any clinically viable compounds affecting CaMKII activity have progressed from basic in vitro science to in vivo studies.

This review focuses on recent advances in anti-arrhythmic strategies involving CaMKII.

Specifically, both inhibition of CaMKII itself to prevent arrhythmias, as well as anti-arrhythmic approaches affecting CaMKII activity via alterations in signaling cascades upstream and downstream of CaMKII will be discussed.

Contents

1. Introduction

Disturbed intracellular ion handling is a hallmark of CaMKII dysfunction in cardiac pathologies, such as heart failure (HF), leading to contractile dysfunction and arrhythmias (Luo & Anderson, 2013). Affecting expression or activity of CaMKII could therefore be a promising strategy, not only for the prevention of arrhythmias, but also as a therapeutic option in systolic (Sossalla et al., 2010a) and diastolic ventricular dysfunction.

While CaMKII-mediated arrhythmias are of great concern in chronic disease (e.g. HF or atrial fibrillation; AF) and in genetic syndromes (e.g. long QT syndrome), acute conditions involving CaMKII-dysfunction, such as reperfusion injury, also lead to malignant arrhythmias and

Abbreviations: AF, atrial fibrillation; Ang-II, angiotensin-II; AP, action potential; CaM, calmodulin; CaMKII, calcium/calmodulin-dependent kinase II; DAD, delayed afterdepolarization; DOX, doxorubicin; EAD, early afterdepolarization; HF, heart failure; LTCC, L-type Ca^{2+}-channel; MI, myocardial infarction; MMVV, CaMKII Met281/282Val mutation (resistant to oxidation); NCX, Na^{+}/Ca^{2+}-exchanger; NKA, Na^{+}/K^{+}-ATPase; PLN, phospholamban; ROS, reactive oxygen species; RYR2, ryanodine receptor; SERCA, sarcoplasmic-endoplasmic reticulum Ca^{2+}-ATPase; S2814A, RYR2 Ser2814Ala mutation (resistant to CaMKII phosphorylation); SR, sarcoplasmic reticulum; TG, transgenic; VT, ventricular tachycardia.

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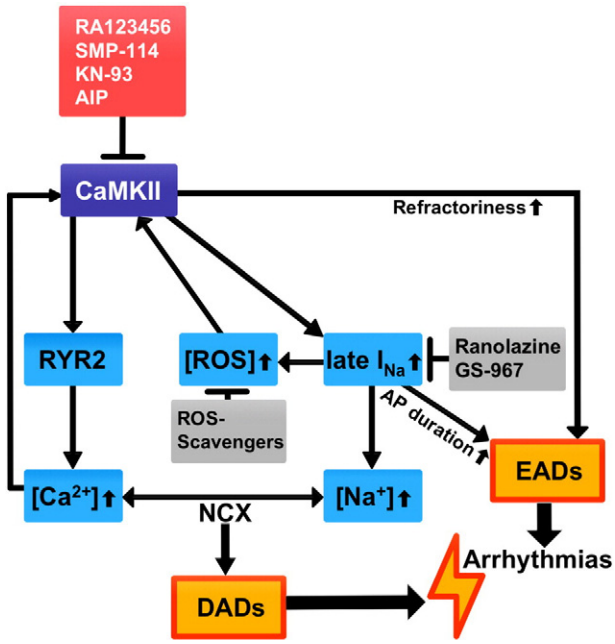

Fig. 1. Illustration of the most important pathways of CaMKII-mediated arrhythmogenesis as well as their feedback on CaMKII activity and the compounds that interfere with these mechanisms (Fig. 1).

subsequently mortality (Manning & Hearse, 1984; Wit & Janse, 2001; Rajtik et al., 2016).

Arrhythmias in conditions of acute versus chronic CaMKII activation will be discussed separately, since in many cardiac pathologies, CaMKII expression and expression of CaMKII target proteins are also altered (e.g. HF; Luo & Anderson, 2013), thus affecting strategies of arrhythmia suppression.

Where in vivo models are available, they will be discussed preferentially. In addition, since in vivo data is still scarce for many pathologies known to exhibit severe arrhythmias, cellular and molecular data will be discussed as well.

2. Brief overview of calcium/calmodulin-dependent kinase II structure and activation

CaMKII is a multifunctional serine/threonine protein kinase that is expressed in many tissues (Solà et al., 1999; Maier & Bers, 2007; Kubokawa et al., 2011; Ozcan et al., 2012). Four major isoforms (α, β,γ, and δ) and 20+ splice variants of CaMKII exist (Bayer & Schulman, 2001). CaMKIIδ is the most prevalent and relevant cardiac isoform (Maier, 2003; Backs et al., 2009), with the splice variant δ_B, which can traffic into the nucleus due to its nuclear localization-sequence, and δ_C, the cytosolic isoform (Zhang & Brown, 2004).

All CaMKII isoforms feature an N-terminal catalytic subunit with ATP- and substrate binding-sites, an autoinhibitory domain with a calmodulin-binding site, and, at the C-terminus, an association domain, which mediates the assembly of larger CaMKII holoenzymes (Rellos et al., 2010).

The holoenzyme in vivo is comprised of a stacked double six-ring of CaMKII monomers (dodecameric assembly), however, a dimer structure has been described as well and may function as a storage pool of inactive CaMKII-units (Rellos et al., 2010).

Importantly, CaMKII activity can be acutely or chronically increased under pathologic conditions such as HF where both expression and activity of CaMKII have been found to be increased (Hoch et al., 1999; Zhang, 2003).

2.1. Calcium/calmodulin-dependent kinase II activation

In its native state, CaMKII is inhibited by its autoregulatory domain, which functions as pseudo-substrate, thus blocking the catalytic domain (Rellos et al., 2010).

Canonically, CaMKII is activated by calmodulin (CaM) binding to its CaMKII binding site (T206/T207), which occurs when CaM affinity for CaMKII is increased by Ca^{2+}-binding to CaM which is a prerequisite for CaMKII activity (Hudmon & Schulman, 2002; Wagner et al., 2011). The affinity (K_D) of CaM for CaMKII is only sufficiently low to allow CaM–CaMKII-binding in the presence of ATP (Hudmon & Schulman, 2002). CaM-binding to a CaMKII monomer increases the affinity of other associated CaMKII monomers in the dodecamer for CaM-binding (*cooperativity*; Johnson et al., 2014). CaM consequently functions as allosteric activator of CaMKII that lowers the inhibitory potency of the autoregulatory domain, thus enabling substrate access to the catalytic domain (Hudmon & Schulman, 2002). When ATP (and Mg^{2+}) are present, these conformational changes "stretch" CaMKII, and allow a so-called intersubunit-phosphorylation, during which the kinase domain of one monomer catalyzes phosphorylation of T287 in the autoregulatory domain of an adjacent CaMKII monomer (Rellos et al., 2010). The T287 phosphorylation increases the affinity of the enzyme for CaM by a factor of 1000 (Hudmon & Schulman, 2002). Also, this "auto-"phosphorylation prevents re-association of the catalytic and autoinhibitory domain even after CaM-dissociation (Colbran et al., 1989), thus rendering the enzyme *autonomous* from Ca^{2+}/CaM (as long as T287 remains phosphorylated; Maier & Bers, 2002, 2007).

When T287 is phosphorylated during CaMKII activation, T305/T306 in the autoregulatory domain are also phosphorylated and prevent re-binding of CaM to the enzyme after it has dissociated ("CaM-capping"; Rellos et al., 2010). This appears to be an autoregulatory process, preventing excessive CaMKII activation (Rellos et al., 2010). CaMKII can thus be activated by sudden changes in cellular $[Ca^{2+}]$, e.g. increases of the frequency of the systolic Ca^{2+}-transient, and can even remain active after the stimulation frequency has receded (Eshete & Fields, 2001). Both frequency and amplitude of the Ca^{2+}-transient appear to exert an influence on the duration of the autonomous activity of CaMKII and may be important for cardiac excitation–contraction coupling, specifically for the force–frequency relationship (De Koninck & Schulman, 1998). It is believed that this activation of CaMKII due to higher frequency of Ca^{2+}-signals as well as higher amplitude of the individual Ca^{2+}-transients contributes to CaMKII activation downstream of β-adrenergic signaling due to the resulting increase of heart rate and higher systolic Ca^{2+}-transients. However, also another mechanism of CaMKII activation upon β-adrenergic stimulation has been described, that is via EPAC (exchange-protein activated by cAMP, for review see (Ruiz-Hurtado et al., 2013). CaMKII is also rendered autonomous from CaM-binding by o-glycosylation at S279 (Erickson et al., 2013), and, importantly, by oxidation at M281/282 (Erickson et al., 2008).

These mechanisms of CaMKII activation should be considered with respect to therapeutic CaMKII inhibition in the context of certain pathophysiological conditions, for example high blood glucose (such as diabetes) or conditions of oxidative stress (with high cytosolic concentrations of reactive oxygen species (ROS)), because CaMKII inhibitors preventing autophosphorylation at T287 may show reduced or even no efficacy in these conditions, whereas ATP-competitive inhibitors should still be effective.

2.2. Cardiac excitation-contraction coupling and the role of calcium/calmodulin-dependent kinase II

Upon electrical stimulation of a cardiomyocyte, activation of sarcolemmal voltage-gated sodium channels ($Na_v1.5$) results in an inward sodium current (I_{Na}) that rapidly depolarizes the cell membrane