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Calmodulin kinase signaling in heart: an intriguing candidate target for therapy of myocardial dysfunction and arrhythmias

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Abstract

The multifunctional Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII) has emerged as a proarrhythmic and procardiomyopathic signal in a wide range of structural heart diseases. This review discusses CaMKII structure and function and recent evidence implicating CaMKII inhibition as a potential strategy for treating myocardial dysfunction and arrhythmias in the setting of structural heart disease.

Keywords: Calmodulin kinase; Arrhythmia; Sudden death; Cellular calcium; Structural heart disease; Electrophysiology

Abbreviations: CaMKII, Ca^{2+}/calmodulin (CaM)-dependent protein kinase II; CREB, cyclic AMP response element (CRE)-binding protein; DAD, delayed afterdepolarization; EAD, early afterdepolarization; MEF2, myocyte enhancer factor 2; PKA, protein kinase A; RAAS, renin-angiotensin-aldosterone signaling; SERCA2a, sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum; VF, ventricular fibrillation; VT, ventricular tachycardia.

Contents

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1. Introduction

Cardiac arrhythmias with sudden death constitute the largest single cause of mortality in the western world. Antiarrhythmic drugs that are ion channel antagonists have been unsuccessful in reducing mortality in patients at high risk for sudden death and, in some cases, have actually increased mortality (Echt et al., 1991). On the other hand, β adrenergic receptor antagonist drugs have been successful in reducing sudden death in high-risk populations (Effect of metoprolol CR/XL in chronic heart failure, 2001). β "blockers" impede generation of a downstream protein kinase, protein kinase A (PKA), that is proarrhythmic and procardiomyopathic. PKA phosphorylation of key Ca^{2+} homeostatic proteins increases cellular Ca^{2+} flux (Ginsburg & Bers, 2004) and "recruits" activity of the Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII; Talosi et al., 1993). CaMKII shares multiple protein targets with PKA, as well as acting at separate proteins, and CaMKII activity and expression are up-regulated in arrhythmia-prone, structurally diseased hearts (Zhang & Brown, 2004). Furthermore, cardiac CaMKII overexpression causes cardiac hypertrophy, chamber dilation, dysfunction (Zhang et al., 2003), and potentially proarrhythmic electrical remodeling changes (Maier et al., 2003a), whereas CaMKII inhibition reduces cellular arrhythmia triggers (Anderson et al., 1998; Wu et al., 1999a, 1999b, 2002a) and suppresses arrhythmias (Mazur et al., 1999; Wu et al., 2002a; Gbadebo et al., 2002; Kirchhof et al., 2004). Based upon these findings, CaMKII inhibition is an intriguing drug target for preventing arrhythmias and for improving cardiac function.

2. The multifunctional Ca^{2+}/calmodulin-dependent protein kinase II

2.1. Structure

The multifunctional CaMKII is an intracellular protein that is present at the cell membrane, in the cytoplasm, and in the nucleus of many cells including cardiac myocytes. CaMKII plays important functional roles in all of these locations and has the capability of linking cellular responses to changes in cytoplasmic Ca^{2+} (Ca_i^{2+}) levels throughout the cardiac myocyte (e.g., see Maier & Bers, 2002). The CaMKII holoenzyme is an assembly of 8–12 monomers (Fig. 1; Kolodziej et al., 2000). Each monomer contains an N terminus catalytic domain and a C terminus association domain that flank a regulatory domain. The regulatory