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REVIEW

CaMKII in Vascular Signalling: "Friend or Foe"?

Obialunanma V. Ebenebe, Alison Heather, Jeffrey R. Erickson *

Department of Physiology, School of Medical Sciences and HeartOtago, University of Otago, Dunedin, Otago, New Zealand

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Signalling mechanisms within and between cells of the vasculature enable function and maintain homeostasis. However, a number of these mechanisms also contribute to the pathophysiology of vascular disease states. The multifunctional signalling molecule calcium/calmodulin-dependent kinase II (CaMKII) has been shown to have critical functional effects in many tissue types. For example, CaMKII is known to have a dual role in cardiac physiology and pathology. The function of CaMKII within the vasculature is incompletely understood, but emerging evidence points to potential physiological and pathological roles. This review discusses the evidence for CaMKII signalling within the vasculature, with the aim to better understand both positive and potentially deleterious effects of CaMKII activation in vascular tissue.

Keywords CaMKII • Vascular disease • Atherosclerosis • Endothelial cells

Introduction

Calcium-mediated signalling is essential for maintaining homeostasis and function within the cardiovascular system (CVS). The multifunctional enzyme calcium/calmodulin-dependent kinase II (CaMKII) has been shown to contribute to both physiological and pathological signalling in cardiac tissue. Basal activity of the kinase contributes to excitation-contraction coupling in the heart [1], while chronic activation of CaMKII underlies pro-arrhythmic signalling and heart failure [2]. Interestingly, CaMKII is also expressed abundantly in vascular tissue, though its role there is less defined. This review presents evidence for a similar dual action of CaMKII within cells of the vasculature while highlighting potential avenues of research. The aim is to build on the current understanding of CaMKII signalling in cardiovascular health and disease.

CaMKII Structure, Activation and Function

CaMKII is a multifunctional serine/threonine kinase comprised of 6–12 monomers that form a dodecameric holoenzyme. Each monomer consists of three domains, a catalytic domain that incorporates the kinase activity of the enzyme, a regulatory domain that mediates the function of the catalytic domain, and an association domain that drives multimeric assembly (Figure 1).

At rest, the kinase is maintained in an inactive state due to interaction between the regulatory and catalytic domains. In the presence of calcium, where calcium/calmodulin complex (Ca^{2+}/CaM) is formed, Ca^{2+}/CaM binds to the regulatory domain causing its dissociation from the catalytic domain (Figure 1). This frees the kinase to act on a variety of target proteins, itself included. The intersubunit phosphorylation of the regulatory domain at Threonine-286/287 (isoform dependent), a process known as auto-phosphorylation, occurs during sustained calcium transients. Otherwise, the dissociation of Ca^{2+}/CaM allows the re-association of the regulatory domain and auto-inhibits the catalytic activity. The process of auto-phosphorylation results in a constitutively active, Ca^{2+}/CaM–independent enzyme, a key feature of the CaMKII structure/function relationship. In addition to auto-phosphorylation, other post-translational modifications of the regulatory domain result in Ca^{2+}/CaM-independence. In hyperglycaemic conditions, CaMKII is O-GlcNAcylated at

*Corresponding author at: Department of Physiology, School of Biomedical Sciences, University of Otago, P.O. Box 913, Dunedin, New Zealand. Tel.: +64 3 4703414, Fax: +64 3 4797323., Email: jeff.erickson@otago.ac.nz

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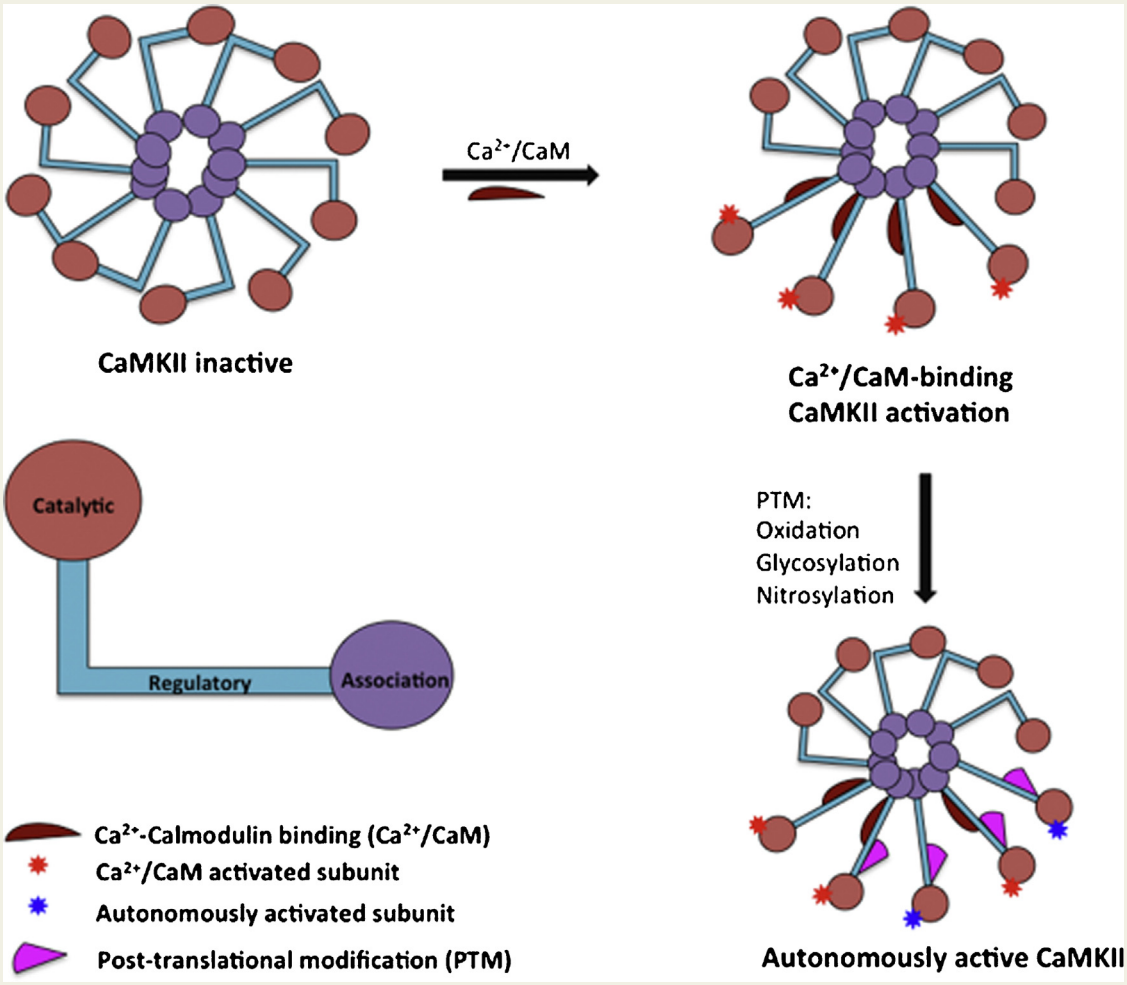

Q1 **Figure 1** Schematic representation of CaMKII structure/function relationship in CaM-dependent and autonomous activation. Binding of calcium/calmodulin complex (Ca^{2+}/CaM) to the regulatory domain activates the kinase. Post-translational modification can occur via oxidation, glycosylation or nitrosylation, after Ca^{2+}/CaM-dependent activation, which results in an autonomous Ca^{2+}/CaM-independent activity.

Serine-279, a covalent modification that contributes to cardiac pathology in diabetes [3]. In elevated oxidative stress, CaMKII is oxidised at a pair of methionine residues (281/282; isoform dependent) [4]. More recently, modification by S-nitrosylation has been shown in the neuronal and cardiac isoforms of CaMKII [5,6]. CaMKII inhibition was observed after S-nitrosylation of the inactive kinase at Cysteine-273, through reduction in Ca^{2+}/CaM binding affinity. Following activation by Ca^{2+}/CaM, S-nitrosylation at Cysteine-290 stabilises its activity, in a Ca^{2+}/CaM- independent manner. Autonomous activation of CaMKII, coupled with numerous downstream targets of CaMKII, contributes to both physiological and pathological signalling mechanisms (Figure 2).

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Several isoforms of CaMKII have been identified; the α and β isoforms are expressed predominantly in the nervous system [7] while the γ and δ isoforms are expressed in the cardiovascular system and other tissues. The diversity in these tissue-specific isoforms and their splice variants (13 CaMKIIγ variants and 15 CaMKIIδ) [8], allows a large degree of functional variety. For example, overexpression of cytosolic CaMKII δ_C enhances sarcoplasmic reticulum (SR) Ca^{2+} spark frequency in cardiomyocytes, which is unchanged in the expression of nuclear-targeted CaMKII δ_B [9]. Since most tissues express at least two isoforms of the kinase, CaMKII will almost always be expressed as a heterogeneous multimer. Ubiquitous deletion of a subunit, e.g. in CaMKII$\delta_C^{-/-}$ mice, elucidates the influence that particular isoform has on multimerisation. Vascular signalling of CaMKII is associated with various mechanisms that can have either physiological and/or pathological outcomes. The isoform-specific distribution of the kinase in vascular cells and their corresponding phenotypes is yet to be fully established. Gray and Heller-Brown extensively reviewed the different phenotypes exhibited in the heart of transgenic mice with specific delta subtype knockouts [10]. They conclude that the ratio between subtypes determines the overall function of the kinase. Applying this principle to the different isoforms in the vasculature could explain the possible duplicity of the kinase.

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