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Two candidates at the heart of dysfunction: The ryanodine receptor and calcium/calmodulin protein kinase II as potential targets for therapeutic intervention—An in vivo perspective

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ABSTRACT

At the start of a new decade (2011), heart failure and sudden cardiac death are still leading causes of mortality worldwide. There is a very obvious need for improved treatment strategies. Research over the past decade has focused on understanding and realising the therapeutic potential of molecular mechanisms that underlie the pathophysiology of cardiac dysfunction. There is now recognition that cell- and gene-based therapies could prove beneficial if aimed at the appropriate molecular targets. Two cardiac proteins that have received considerable attention over the last decade, have been identified as possible therapeutic targets. The cardiac sarcoplasmic reticulum Ca^{2+} release channel (ryanodine receptor) and calcium/calmodulin dependent kinase II (CaMKIIδ) can act independently and in partnership, to regulate cardiac Ca^{2+} handling. CaMKIIδ, by the very nature of its core function as a kinase, also modulates cardiac function globally, promoting effects on gene transcription and modulating inflammatory and proliferative responses, all events that are associated with both the functional and dysfunctional heart. In vivo approaches using genetic and pharmacologic strategies have revealed the prominent role of both proteins in cardiac dysfunction. More excitingly, they have also shown the potential for cardioprotection that modulation at the level of each protein can have. Translating these effects to the human heart is in its infancy. Whether intervention at these targets could result in clinical application is unknown at present, however current in vivo research has proved invaluable in revealing the potential that targeting of RyR and CaMKIIδ could have in limiting cardiac dysfunction.

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Abbreviations: ACE, angiotensin converting enzyme; APD, action potential duration; RyR2, Ryanodine receptor, type 2; CaMKII, Calcium/calmodulin dependent protein kinase II; CaT, calcium transient; LTCC, L-type Ca^{2+} channel; SERCA, sarco/endoplasmic reticulum Ca^{2+}ATPase; NCX, Na^{+}/Ca^{2+} exchanger; CaT, Ca^{2+} transient; SR, sarcoplasmic reticulum; CPVT, catecholaminergic polymorphic ventricular tachycardia; FKBP12.6, FK506 binding protein 12.6; HDAC, histone deacetylase.

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1. Introduction

Heart failure is a significant health problem and is the leading cause of death worldwide (Lopez et al., 2001). Cardiac dysfunction is a broad term that covers the progressive functional changes that occur from the initial compensatory hypertrophic response of the heart to a stress or insult to the final stage of heart failure. As the heart adapts and remodels in response to the initial insult, arrhythmias and ischaemic heart disease can occur, increasing the risk of sudden death. Cardiac dysfunction is therefore a dynamic process and the approach to therapeutic intervention has to reflect that.

Pharmacological therapy has been the mainstay of treatment for cardiac dysfunction for the last century however although mortality is improving, it remains high (Stewart et al., 2001). The potential lack of selectivity and range of side effects in current therapies is only exacerbated by the need for multiple therapies or 'polypharmacy' in many patients (McMurray & Pfeffer, 2002a,b). There has been a shift from using digitalis and diuretics in the 1960's, inotropes and vasodilators in the 1970's to a focus on drugs that block targets in the renin-angiotensin system and sympathetic nervous system (Miller, 2003). The current guidelines of the European Society of Cardiology for chronic heart failure treatment include a combination of ACE inhibitor, β-blocker and diuretic. Additional pharmaceutical approaches include positive inotropic therapy. In spite of anticipated promising effects, long-term treatment with these groups of drugs has led to adverse events (Packer, 1993; Coats, 1999; McMurray & Pfeffer, 2002b). There is an obvious need for an improved pharmacological approach.

With the disappointingly slow evolution of drug-based therapies, alternative approaches for treating dysfunction are emerging. These include gene and cell based therapies and improved cardioversion therapy. Myocardial gene transfer has been achieved using recombinant viruses as vectors (Melo et al., 2004) however, although promising results have been achieved in cellular and animal studies, improvements in delivery are required for safety in humans. Cardiac regeneration following disease using embryonic stem cell therapy has great potential. It has been shown that differentiated stem cells delivered to infarcted rat hearts, can improve cardiac function if they are delivered with specific pro-survival ingredients (Laflamme, 2007). However, this approach is not without obstacles and the possibility of immunological rejection as well as the susceptibility of embryonic stem cells to form teratomas after injection, present limitations for progression of this area at the moment (Segers & Lee, 2008). The use of implantable cardioverter defibrillators has proved successful in anti-arrhythmic therapy for patients at risk of sudden cardiac death. The advent of a subcutaneous device that does not require a lead should further improve their use (Bardy et al., 2010) however these devices, as well as being very expensive, are only suitable for a certain group of patients and do not target the underlying mechanism of dysfunction.

Surgical transplantation of a donor heart is used for some patients with end stage heart failure and there is evidence now to suggest that this can be a long-lasting solution in certain cases. However, availability of donor hearts is a crucial limiting factor and, if available, transplantation is a major procedure and has a number of contraindications. There are obvious complications associated with transplant, such as organ rejection and/or infection. Ultimately if cardiac dysfunction can be successfully treated at an earlier stage, this extreme approach could be avoided.

Cardiac disease is a highly complex process but at the 'heart' of cardiac dysfunction lies impaired contractility of individual cardiac myocytes. Altered excitation-contraction coupling (Bers, 2002) in these cells results in associated Ca^{2+} handling abnormalities and ultimately defective Ca^{2+} transients (Hasenfuss & Pieske, 2002; Bers, 2006a,b). Tight regulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) within the cardiac myocyte is essential for maintaining homeostasis and normal contractile function. This is accomplished by a number of 'Ca^{2+} handling proteins' (Fig. 1). Briefly, Ca^{2+} enters the cell through L-type voltage-activated channels (LTCC's) and this allows a local increase in $[Ca^{2+}]_i$. This triggers a relatively larger release of Ca^{2+} from the sarcoplasmic reticulum (SR) via intracellular Ca^{2+} release channels (ryanodine receptors (RyRs)). The increase in $[Ca^{2+}]_i$ promotes cell contraction by Ca^{2+} binding to contractile proteins. In order for relaxation to occur, Ca^{2+} has to be removed from the cytosol. This is accomplished predominantly by the SR ATP-driven Ca^{2+} pump (SERCA) which pumps Ca^{2+} back in to the SR and by Ca^{2+} efflux from the cell via the Na^+/Ca^{2+} exchanger (NCX). All of these proteins exist as multi-protein complexes that are subject to regulation by other proteins and to biochemical modification e.g. phosphorylation. There is strong evidence to suggest that Calcium/calmodulin dependent protein kinase II (CaMKII) phosphorylates and modulates the function of all of these proteins in the heart. CaMKII can therefore link cardiac myocyte responses to altered Ca^{2+} handling locally and globally and is now recognised as an important modulator of cardiac function (Maier & Bers, 2002).

In addition to regulating Ca^{2+} handling events important in contractility, CaMKII is also emerging as a regulator of cardiac gene transcription as well as other events that are important in cardiac dysfunction, namely inflammation and fibrosis (Anderson, 2007). The possibility that CaMKII exists as a multifunctional signalling molecule in the heart, capable of affecting a wide range of 'dysfunctional' events could be important for future therapeutic strategies.

In cardiac disease, there is significant evidence for altered expression and importantly, altered function of Ca^{2+} handling proteins and Ca^{2+}/calmodulin dependent enzymes (Bers et al., 2003; Piacentino et al., 2003). Numerous studies using animal models have shown the value of targeting dysfunctional Ca^{2+}-handling proteins to improve cardiac function (Antoons & Sipido, 2008; Talukder et al., 2009). These studies have used both pharmacological and non-pharmacological approaches and have highlighted the potential strengths of selective targeting of Ca^{2+} handling in future drug development. In light of the limitations with current pharmacological approaches for treatment of cardiac disease, novel routes of targeting specific Ca^{2+} handling proteins may provide important insight into improved therapies.

In this review we will focus on the information provided by work examining effects of pharmacological and genetic intervention targeting RyR2 and/or CaMKII activity. Although both proteins can be termed Ca^{2+} handling proteins, RyR2 has a very specific role in intracellular Ca^{2+} release whereas CaMKII has much broader scope for cardiac regulation at a number of levels. This will be addressed in the review and specifically, the outcome of targeting these proteins on in vivo cardiac function will be discussed.

2. The role of RyR2 in regulation of cardiac function

RyRs are the main SR Ca^{2+} release channels in cardiac myocytes. They are functionally coupled to sarcolemmal LTCC's and the Ca^{2+}-induced Ca^{2+} release that results from this coupling is the trigger for cardiac myocyte contraction. There are three RyR isoforms with type 2 (RyR2) being the main form expressed in the heart. These channels exist as tetramers (with a molecular weight of ~2 MDa) and are complexed with a variety of other proteins either directly or indirectly (Bers, 2004). The role of RyR2 in cardiac contractility has already been reviewed extensively (Zalk et al., 2007; Eisner et al., 2009) however, the molecular mechanisms underlying how channel activity is controlled have yet to be fully elucidated. Two key elements crucial to RyR2 modulation of cardiac function are (i) the fact that the channel is complexed with, and modulated by other proteins, one of which (FKBP12.6) is important in stabilising RyR2 and (ii) the potential for RyR2 to be phosphorylated and functionally modulated. Both of these parameters could be exploited therapeutically for modulation of RyR2 function. Abnormal RyR2 function has been linked with cardiac arrhythmias (Jiang et al., 2005) and heart failure (Shannon et al., 2003) therefore targeting this channel therapeutically