Journal of Molecular and Cellular Cardiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Nitric oxide synthase regulation of cardiac excitation–contraction coupling in health and disease

Jillian N. Simon [1], Drew Duglan [1], Barbara Casadei, Ricardo Carnicer *

Radcliffe Department of Medicine, Division of Cardiovascular Medicine, University of Oxford, Oxford, UK

ARTICLE INFO

Article history:
Received 2 December 2013
Received in revised form 4 March 2014
Accepted 5 March 2014
Available online xxxx

Keywords:
Myocardial function
Microdomain
Heart failure
Arrhythmia
Ischemia/reperfusion
Preconditioning

ABSTRACT

Significant advances in our understanding of the ability of nitric oxide synthases (NOS) to modulate cardiac function have provided key insights into the role NOS play in the regulation of excitation–contraction (EC) coupling in health and disease. Through both cGMP-dependent and cGMP-independent (*e.g. S*-nitrosylation) mechanisms, NOS have the ability to alter intracellular Ca^{2+} handling and the myofilament response to Ca^{2+}, thereby impacting the systolic and diastolic performance of the myocardium. Findings from experiments using nitric oxide (NO) donors and NOS inhibition or gene deletion clearly implicate dysfunctional NOS as a critical contributor to many cardiovascular disease states. However, studies to date have only partially addressed NOS isoform-specific effects and, more importantly, how subcellular localization of NOS influences ion channels involved in myocardial EC coupling and excitability. In this review, we focus on the contribution of each NOS isoform to cardiac dysfunction and on the role of uncoupled NOS activity in common cardiac disease states, including heart failure, diabetic cardiomyopathy, ischemia/reperfusion injury and atrial fibrillation. We also review evidence that clearly indicates the importance of NO in cardioprotection. This article is part of a Special Issue entitled 'Redox Signalling in Heart'.

Contents

1. Introduction

Long recognised as a key signalling molecule in the nervous system and the vasculature, nitric oxide (NO) is now also known to

* Corresponding author at: L6, West Wing, Division of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK. Tel.: +44 1865 234647.
E-mail address: Ricardo.carnicer@cardiov.ox.ac.uk (R. Carnicer).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.yjmcc.2014.03.004
0022-2828/

play an important regulatory role in cardiac function. The 'endothelial' and 'neuronal' isoforms of nitric oxide synthase (eNOS and nNOS, respectively) are the enzymes responsible for the constitutive production of NO within the cardiomyocyte [1,2], whereas the inducible NOS isoform (iNOS) is only expressed in the presence of acute injury and inflammation [3]. Several cofactors are essential for the conversion of arginine and oxygen into citrulline and NO by NOS: tetrahydrobiopterin (BH_4) and heme at the N-terminal catalytic oxygenase domain, along with flavins and nicotinamide adenine dinucleotide phosphate (NADPH) at the C-terminal reductase domain. In healthy hearts, the expression of eNOS and nNOS in left ventricular (LV) myocytes is subject to distinct subcellular localization. eNOS is bound to invaginations of the sarcolemmal membrane called caveolae, where it associates with caveolin-3 in an inactive state [4] and can also be bound to the nuclear membrane [5]. nNOS is localized to the sarcoplasmic reticulum (SR), where it associates with the ryanodine receptor (RyR) and xanthine oxidoreductase (XOR) [6], and, to a lesser extent, to the sarcolemmal membrane [7] (Fig. 1). Yet this compartmentalisation of NOS remains dynamic; indeed, as a cause or consequence of disease states, such as heart failure and ischemia–reperfusion (I/R) injury, NOS can translocate to different subcellular domains [8,9]. Moreover, as will be considered in this review, NOS can deviate from normal function in the presence of heart disease. In particular, in the presence of reduced availability of L-arginine [10] or BH_4 [11–13], an altered phosphorylation state [14–16], or *S*-glutathionylation [15,17], the electron flow through the enzyme results in a reduction of molecular oxygen at the prosthetic heme site or reductase domain [17], rather than formation of NO, a phenomenon often referred to as NOS uncoupling.

2. NOS in heart failure

Heart failure (HF) defines the clinical syndrome arising from a multitude of cardiac pathologies, including myocardial infarction (MI), hypertension, diabetes and genetically-linked cardiac disorders (*i.e.* hypertrophic cardiomyopathy, dilated cardiomyopathy associated with Duchenne muscular dystrophy (DMD), *etc.*), in which heart disease causes progressive structural remodelling and deterioration of pump function. In the early stages of HF, the heart can initially compensate for the dysfunction through hypertrophy and neurohumoral activation to preserve left ventricular (LV) ejection fraction. However, as HF progresses, further impairment of myocardial contraction and relaxation and loss of intrinsic regulatory mechanisms, such as the force–frequency response, exacerbate pump dysfunction.

2.1. Changes in NOS expression and activity in the presence of HF

Although several studies have described changes in NOS expression and activity during HF, there remains a discrepancy in the directionality of the changes. In general there is strong evidence to support a reduction in NO production by the coronary endothelium in the presence of HF [18,19]. Such changes are likely to contribute to cardiac dysfunction through impaired myocardial perfusion and a reduced paracrine effect of endothelial-derived NO, although this is yet to be demonstrated. There is less agreement on the changes in the expression profile and activity of NOS in the myocardium. In both rodent and canine models of HF, an upregulation of constitutive NOS activity in the LV has been suggested [20,21], yet in HF patients both decreases [22] and increases [23,24] in

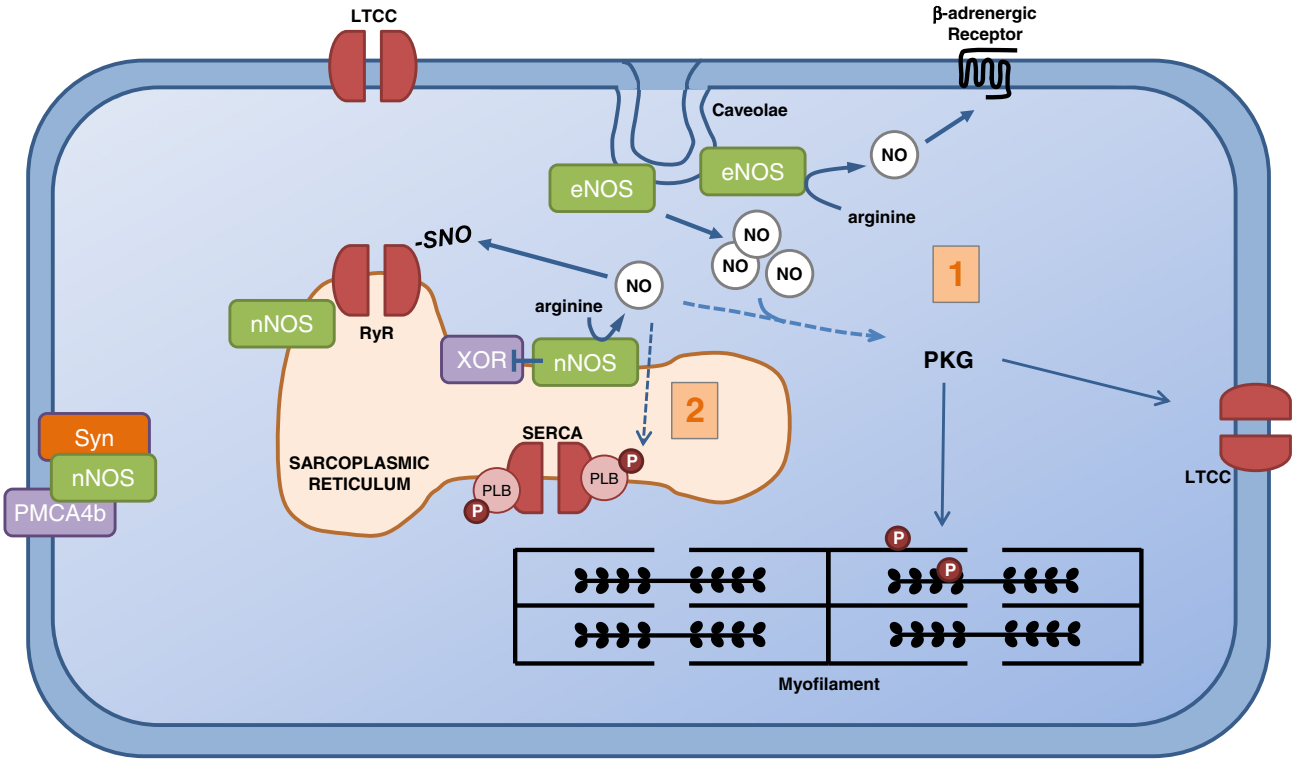

Fig. 1. NOS subcellular localization and regulation of physiological myocyte function. 1. NOS mediated generation of NO leads to the activation of PKG in a cGMP-dependent manner. Activation of PKG results in blunting of Ca^{2+} influx through the LTCC, as well as reduced myofilament Ca^{2+} sensitivity as a result of cTnI and cMyBP-C phosphorylation. NOS generated NO also interacts with β-adrenergic receptors (β-AR), likely exerting a blunting effect on inotropy by differential signalling through $\beta_{1/2}$ and β_3-AR. 2. Localization of nNOS within the SR dampens O_2^- produced by XOR, mediates PLB phosphorylation (in a cGMP-independent manner) and directly modifies the RyR through *S*-nitrosylation. Nitric oxide (NO), L-type Ca^{2+} channel (LTCC), NADPH oxidase (NADPHox), endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), xanthine oxidoreductase (XOR), protein kinase G (PKG), phosphorylation (P), phospholamban (PLB), sarcoplasmic reticulum ATPase (SERCA), ryanodine receptor (RyR).

Please cite this article as: Simon JN, et al, Nitric oxide synthase regulation of cardiac excitation–contraction coupling in health and disease, J Mol Cell Cardiol (2014), http://dx.doi.org/10.1016/j.yjmcc.2014.03.004