Journal of Molecular and Cellular Cardiology 61 (2013) 11–19

Contents lists available at SciVerse ScienceDirect

Journal of Molecular and Cellular Cardiology

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

Review article

Cardiac sodium transport and excitation–contraction coupling

J.M. Aronsen [a,b,c], F. Swift [a,b], O.M. Sejersted [a,b,*]

[a] Institute for Experimental Medical Research, Oslo University Hospital Ullevål and University of Oslo, Oslo, Norway
[b] KG Jebsen Cardiac Research Center and Center for Heart Failure Research, University of Oslo, Oslo, Norway
[c] Bjørknes College, Oslo, Norway

ARTICLE INFO

Article history:
Received 17 April 2013
Received in revised form 17 May 2013
Accepted 5 June 2013
Available online 14 June 2013

Keywords:
EC-coupling
Sodium
Microdomains
Calcium

ABSTRACT

The excitation–contraction coupling (EC-coupling) links membrane depolarization with contraction in cardiomyocytes. Ca^{2+} induced opening of ryanodine receptors (RyRs) leads to Ca^{2+} induced Ca^{2+} release (CICR) from the sarcoplasmic reticulum (SR) into the dyadic cleft between the t-tubules and SR. Ca^{2+} is removed from the cytosol by the SR Ca^{2+} ATPase (SERCA2) and the Na,Ca-exchanger (NCX). The NCX connects cardiac Ca^{2+} and Na^+-transport, leading to Na^+-dependent regulation of EC-coupling by several mechanisms of which some still lack firm experimental evidence. Firstly, NCX might contribute to CICR during an action potential (AP) as Na^+-accumulation at the intracellular site together with depolarization will trigger reverse mode exchange bringing Ca^{2+} into the dyadic cleft. The controversial issue is the nature of the compartment in which Na^+ accumulates. It seems not to be the bulk cytosol, but is it part of a widespread subsarcolemmal space, a localized microdomain ("fuzzy space"), or as we propose, a more localized "spot" to which only a few membrane proteins have shared access (nanodomains)? Also, there seems to be spots where the Na,K-pump (NKA) will cause local Na^+ depletion. Secondly, Na^+ determines the rate of cytosolic Ca^{2+} removal and SR Ca^{2+} load by regulating the SERCA2/NCX-balance during the decay of the Ca^{2+} transient. The aim of this review is to describe available data and current concepts of Na^+-mediated regulation of cardiac EC-coupling, with special focus on subcellular microdomains and the potential roles of Na^+ transport proteins in regulating CICR and Ca^{2+} extrusion in cardiomyocytes. We propose that voltage gated Na^+ channels, NCX and the NKA α2-isoform all regulate cardiac EC-coupling through control of the "Na^+ concentration in specific subcellular nanodomains in cardiomyocytes. This article is part of a Special Issue entitled "Na^+ Regulation in Cardiac Myocytes."

Contents

* Corresponding author at: Institute for Experimental Medical Research, Oslo University Hospital Ullevål and University of Oslo, Kirkeveien 166, 0407 Oslo, Norway. Tel.: +47 93401058.
E-mail address: o.m.sejersted@medisin.uio.no (O.M. Sejersted).

0022-2828/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.yjmcc.2013.06.003

1. Introduction — "The digitalis paradigm"

The clinical effects of digitalis were described over 200 years ago [1], but it was not until the early 1950s that it was found that this drug inhibits transport of Na^+ and K^+ [2]. Some years later the Na,K-pump (NKA) was discovered, and eventually it became clear that this membrane protein was a high affinity receptor for digitalis [3,4]. However, the effect of digitalis on cardiac contractility remained a mystery until the link between intracellular Na^+ and Ca^{2+} was described [5–7]. Eventually, this led to the cloning of the Na,Ca-exchanger (NCX) [8], and finally it was shown that digitalis has no effect on cardiac contractility in NCX-deficient mice [9]. Together, the membrane proteins NKA and NCX form an electroneutral, ATP-driven system, which pumps one Ca^{2+} ion out of the cell in exchange for two K^+ ions at the same time as three Na^+ ions are cycled across the membrane. The link to Na^+ transport introduces a voltage sensitivity, which is most pronounced for NCX. Also, the two transporters are functionally coupled through intracellular Na^+, and the concentration of Na^+ at the intracellular sites is an important determinant of transport rate of both proteins. Inhibiting NKA with digitalis will thus cause the heart to lose K^+, intracellular Na^+ concentration to increase and SR Ca^{2+} load to increase [10,11]. This simple scheme explaining the effect of digitalis on cardiac contractility with two tightly linked key players – NKA and NCX – could be coined the digitalis paradigm implying that the concentrations of Na^+ and Ca^{2+} are linked in the bulk cytosol. Later, it has become apparent that the picture is more complicated, especially since digitalis can increase contractility without a change in global cytosolic Na^+ concentration [12,13]. We can probably no longer regard intracellular Na^+ as one single pool. The purpose of this review is to describe the regulatory role of Na^+ on the excitation–contraction coupling (EC-coupling) in cardiomyocytes in light of the current knowledge about Na^+ and Ca^{2+} transporters and their localization. We will first describe Na^+ fluxes and the proteins that carry Na^+. Then we will discuss the concept of ionic microdomains, the existence of which so far is mainly based on indirect evidence. Finally follows a perusal of the evidence that Na^+ regulates the EC-coupling and the extrusion of Ca^{2+} from the cell.

2. Overview of EC-coupling and Na^+-fluxes in cardiomyocytes

2.1. Cardiac EC-coupling

The EC-coupling in cardiomyocytes links electrical depolarization to contraction. Membrane depolarization is initiated by opening of voltage gated Na^+ channels, leading to Na^+-influx (I_{Na}) which in a feed-forward manner further depolarizes the membrane. Voltage gated L-type Ca^{2+} channels (LTCCs) subsequently open to allow Ca^{2+} influx from the cell exterior. Ca^{2+} ions entering the cytosol bind to and open ryanodine receptors (RyRs) in the membrane of the SR, leading to rapid release of Ca^{2+} into the cytosol. Thus, a small Ca^{2+} influx via LTCCs initiates a large Ca^{2+} release from the SR through a feed-forward amplification mechanism called Ca^{2+} induced Ca^{2+} release (CICR) [14]. Contraction of the cardiomyocytes is initiated by binding of Ca^{2+} to Troponin C of the myofilaments, inducing a conformational change which allows cross-bridges to form between myosin and actin. Since the peak of the intracellular Ca^{2+} concentration is at a steep part of the force–pCa curve, a larger Ca^{2+} transient will activate more cross-bridges and therefore induce a stronger contraction and vice versa. In order for the muscle to relax, Ca^{2+} must be removed from the cytosol. Ca^{2+} reuptake into the SR is mediated by SERCA2 and Ca^{2+} is also extruded out of the cell mainly via NCX.

2.2. Na^+ fluxes in cardiomyocytes

Intracellular Na^+-concentration in cardiomyocytes is a primary determinant of cardiac contractility, and even minor changes in intracellular global Na^+-concentration have a large impact on contractility [15,16]. Cardiomyocytes have a large electrochemical transmembrane Na^+-gradient, which is the basis for secondary active transport of a variety of molecules including Ca^{2+} and H^+, connecting Na^+-fluxes in cardiomyocytes to EC-coupling and pH-regulation. The intracellular Na^+-level in cardiomyocytes is 4–16 mM, and is determined by the balance between Na^+ influx ("leak" rate) and efflux ("pump" rate) [17], as illustrated in Fig. 1. As the Na,K-pump (NKA) is the only Na^+ efflux mechanism using ATP to pump Na^+ against its electrochemical gradient, the properties and transport kinetics of NKA will be one determinant of the intracellular Na^+ concentration and thereby regulate

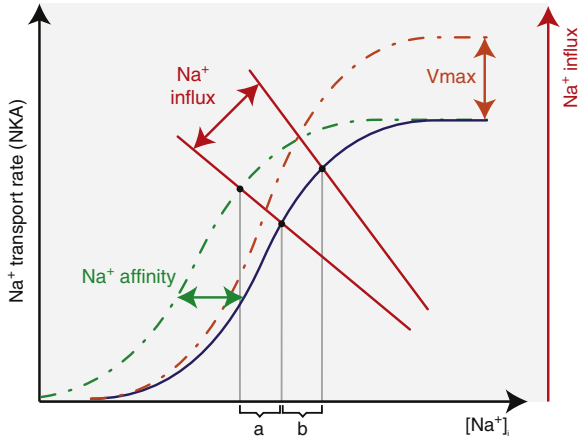

Fig. 1. Intracellular levels of Na^+ are determined by the balance between Na^+ influx and efflux. Na^+ influx through voltage gated Na^+-channels, NCX and other transport proteins is balanced by Na^+ efflux through the NKA. NKA-mediated efflux of Na^+ is dependent on the Na^+ concentration, the Na^+ affinity of NKA and the maximal transport rate (V_{max}) for NKA. By this scheme, the Na^+-concentration could be altered by either altered NKA kinetics (at a given Na^+-influx) as suggested by a), or alterations in Na^+-influx at a given NKA transport rate as suggested by b).