

Review

Ca²⁺ currents in cardiac myocytes: Old story, new insights[☆]

Fabien Brette^{a,*}, Jérôme Leroy^b, Jean-Yves Le Guennec^c, Laurent Sallé^d^a*School of Biomedical Sciences, University of Leeds, Worsley Building Leeds, LS2 9NQ, UK*^b*Department of Pharmacology, University College London, London WC1E 6BT, UK*^c*Emi-U 0211 Nutrition, Croissance, Cancer, Université de Tours, 37000 Tours, France*^d*EA3212 Laboratoire de Physiologie Cellulaire, Université de Caen, 14032 Caen, France*

Available online 25 February 2005

Abstract

Calcium is a ubiquitous second messenger which plays key roles in numerous physiological functions. In cardiac myocytes, Ca²⁺ crosses the plasma membrane via specialized voltage-gated Ca²⁺ channels which have two main functions: (i) carrying depolarizing current by allowing positively charged Ca²⁺ ions to move into the cell; (ii) triggering Ca²⁺ release from the sarcoplasmic reticulum. Recently, it has been suggested that Ca²⁺ channels also participate in excitation–transcription coupling. The purpose of this review is to discuss the physiological roles of Ca²⁺ currents in cardiac myocytes. Next, we describe local regulation of Ca²⁺ channels by cyclic nucleotides. We also provide an overview of recent studies investigating the structure–function relationship of Ca²⁺ channels in cardiac myocytes using heterologous system expression and transgenic mice, with descriptions of the recently discovered Ca²⁺ channels α_{1D} and α_{1E} . We finally discuss the potential involvement of Ca²⁺ currents in cardiac pathologies, such as diseases with autoimmune components, and cardiac remodeling.

© 2005 Elsevier Ltd. All rights reserved.

Keywords: Cardiac; Myocytes; Calcium current; L-type calcium channel; T-type calcium channel; Modulation; Autoimmune; Remodeling

[☆]Since the acceptance of this manuscript, a study showing a mutation in human Ca_v1.2 has appeared in Cell (Splawski et al., 2004). In this paper, the authors demonstrated that Timothy syndrome is linked to a missense mutation in Ca_v1.2 (G406R, at the end of S6 in the first domain, see Fig. 6). Interestingly, functional expression reveals that this mutation induces a gain of function by dramatically reducing the voltage dependent inactivation of the channel. Therefore, this mutation might explain the long QT observed in patient with this disorder.

*Corresponding author. Department of Physiology, University of Bristol, Medical Sciences Building, Bristol BS8 1TD, UK.

E-mail address: f.brette@bristol.ac.uk (F. Brette).

Contents

1. Introduction	2
2. Physiological function of cardiac Ca^{2+} channels.	4
2.1. Depolarizing current.	5
2.1.1. Working cells (ventricular, atrial)	5
2.1.2. Nodal cells	8
2.1.3. Conducting tissue.	10
2.2. Excitation–contraction coupling.	10
2.2.1. Triggering sarcoplasmic reticulum Ca release	10
2.2.2. Direct activation of contraction.	13
2.2.3. Loading of the sarcoplasmic reticulum.	14
2.3. Excitation–transcription coupling.	14
3. Modulation of cardiac Ca^{2+} channels	16
3.1. Regulation by voltage.	17
3.1.1. Activation	17
3.1.2. Inactivation	17
3.1.3. Facilitation	17
3.2. Regulation by calcium	18
3.2.1. Inactivation	19
3.2.2. Facilitation	20
3.3. Regulation by cyclic nucleotides	21
3.3.1. cAMP.	22
3.3.2. cGMP.	24
4. Biophysical structure-function of cardiac Ca^{2+} channels	31
4.1. Molecular Structure of the predominant L-type Ca^{2+} channel	32
4.1.1. Structure-function of α_{1C}	32
4.1.2. Structure-function of β subunit	37
4.1.3. Structure-function of $\alpha_2\delta$	40
4.1.4. Structure-function of γ	41
4.2. T-type Ca^{2+} channels.	41
4.3. Molecular structure of others Ca^{2+} channels (α_{1D} , α_{1E})	44
5. Cardiac Ca^{2+} channels and physio-pathological conditions	46
5.1. Diseases with autoimmune components	46
5.1.1. Congenital heart block	46
5.1.2. Cardiomyopathies	47
5.2. Cardiac remodeling	49
5.2.1. Cardiac memory	49
5.2.2. Heart failure	49
5.2.3. Atrial fibrillation	52
6. Conclusions and futures directions	53
Acknowledgements.	54
References	54

1. Introduction

The importance of extracellular Ca^{2+} in cardiac contraction has been known since the classical experiments of Ringer at the end of the XIXth century, which demonstrated that frog cardiac muscle cannot contract in Ca^{2+} free solutions (Ringer, 1883). More than half a century

Download English Version:

<https://daneshyari.com/en/article/2070656>

Download Persian Version:

<https://daneshyari.com/article/2070656>

[Daneshyari.com](https://daneshyari.com)