Available online at www.sciencedirect.com
ScienceDirect
Progress in Biophysics and Molecular Biology 96 (2008) 281–293
Progress in Biophysics & Molecular Biology
www.elsevier.com/locate/pbiomolbio

Review

Changes in action potentials and intracellular ionic homeostasis in a ventricular cell model related to a persistent sodium current in SCN5A mutations underlying LQT3

G. Christé[a,*], M. Chahine[b], P. Chevalier[c], M. Pásek[d,e]

[a]*INSERM, ADR Lyon, Lyon, France*
[b]*Le Centre de Recherche Université Laval Robert-Giffard and Department of Medicine, Laval University, Québec, Canada*
[c]*Unité de Cardiologie et Soins Intensifs, Hôpital Cardiovasculaire et Pneumologique L. Pradel, Lyon, France*
[d]*Institute of Thermomechanics, Czech Academy of Sciences, Brno, Czech Republic*
[e]*Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic*

Available online 11 August 2007

Abstract

In LQT3 patients, SCN5A mutations induce ultraslow inactivation of a small fraction of the hNav1.5 current, i.e. persistent Na^+ current (I_{pNa}). We explored the time course of effects of such a change on the intracellular ionic homeostasis in a model of guinea-pig cardiac ventricular cell [Pasek, M., Simurda, J., Orchard, C.H., Christé, G., 2007b. A model of the guinea-pig ventricular cardiomyocyte incorporating a transverse–axial tubular system. Prog. Biophys. Mol. Biol., this issue]. Sudden addition of I_{pNa} prevented action potential (AP) repolarization when its conductance (g_{pNa}) exceeded 0.12% of the maximal conductance of fast I_{Na} (g_{Na}). With g_{pNa} at 0.1% g_{Na}, the AP duration at 90% repolarization (APD_{90}) was initially lengthened to 2.6-fold that in control. Under regular stimulation at 1 Hz it shortened progressively to 1.37-fold control APD_{90}, and intracellular $[Na^+]_i$ increased by 6% with a time constant of 106 s. Further increasing g_{pNa} to 0.2% g_{Na} caused an immediate increase in APD_{90} to 5.7-fold that in control, which decreased to 2.2-fold that in control in 30 s stimulation at 1 Hz. At this time diastolic $[Na^+]_i$ and $[Ca^{2+}]_i$ were, respectively, 34% and 52% higher than in control and spontaneous erratic SR Ca release occurred.

In the presence of I_{pNa} causing 46% lengthening of APD_{90}, the model cell displayed arrhythmogenic behaviour when external $[K^+]$ was lowered to 5 mM from an initial value at 5.4 mM. By contrast, when K^+ currents I_{Kr} and I_{Ks} were lowered in the model cell to produce the same lengthening of APD_{90}, no proarrhythmic behaviour was observed, even when external $[K^+]$ was lowered to 2.5 mM.

Keywords: Sudden death; Mutation; SCN5A; Long QT syndrome; Model

*Corresponding author. Present address: Bât. R. Dubois, 2° étage, Univ. Claude Bernard-Lyon1, F 69622 Villeurbanne Cedex, France. Tel.: +33 4 78 40 00 57; fax: +33 4 72 44 79 37.
E-mail address: christe@lyon.inserm.fr (G. Christé).

0079-6107/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pbiomolbio.2007.07.023

Contents

1. Introduction

Mechanisms by which mutation-induced alterations of the hNav1.5 current predispose LQT3 patients to arrhythmias have been explored from an electrical point of view (Bennett et al., 1995; Clancy and Rudy, 1999; Clancy et al., 2003; Tian et al., 2004; Henry and Rappel, 2004; Berecki et al., 2006). However, only few works have addressed possible changes in ionic homeostasis related to increased persistent or late Na^+ current (Priori et al., 1996; Bito et al., 2006; Noble and Noble, 2006). In particular, the presence of a persistent Na^+ current (I_{pNa}) during the action potential (AP) might cause elevation of intracellular [Na^+], a condition that predisposes to calcium overload and arrhythmogenesis (Levi et al., 1997; Noble and Noble, 2006; see also Maltsev and Undrovinas, 2007, this issue). We explored whether this effect would be quantitatively important in a computer model of cardiac ventricular myocyte. We also compared the immediate and delayed effects of introducing a persistent Na^+ current. Finally, we compared the alterations of ionic homeostasis in two modifications of the model producing equivalent AP prolongation as in symptomatic LQT (addition of a persistent Na^+ current or decreased K^+ currents) and their response to manoeuvres likely to aggravate sodium overload: tachycardia and hypokalaemia. We discussed the relevance of the effects produced by the model to clinical situations. Part of this work was reported in abstract form (Christé et al., 2005, 2006).

2. Methods

A ventricular cell model that includes ionic currents, intracellular ionic homeostasis and a single compartment tubular system (Pasek et al., 2003) was modified to closely match the properties of guinea-pig ventricular cells at 37 °C as described in Pasek et al. (2007b), a companion paper in this issue. This model was written and integrated under the MATLAB environment (The MathWorks). A persistent Na^+ current (termed I_{pNa} in the rest of the text) was formulated according to the description of Sakmann et al. (2000), see Eqs. (A7)–(A10) in Appendix A to the paper by Pasek et al. (2007b) in this issue (note that the persistent sodium current was designated I_{Naps} in that paper). The conductance of this current in control conditions was 0.0053 mS/cm^2.

In the first series of modelling attempts (Figs. 1–3), the model was implemented with a transient outward (I_{to}) current (as in Pasek et al., 2003) to approach the ion current conditions of a human myocyte. The immediate and long-term effects of introducing a persistent I_{pNa} were explored in these conditions.

In the second series of model challenges (Figs. 4 and 5), three versions of our model (Pasek et al., 2007b, this issue) were used. The unmodified version of the model is named the *Cont* model. In the first modification (named $+I_{pNa}$ model) of the model *Cont*, the maximal conductance of I_{pNa} (g_{pNa}) was set to 0.02 mS/cm^2 to simulate a LQT3 condition. In a second modification (named $-I_K$ model) of model *Cont*, the maximal conductance for both I_{Kr} and I_{Ks} was reduced by 67%, to simulate a LQT1/LQT2 condition. Both modified models and the control model were run for at least 600 s cell lifetime to ensure that all variables had reached