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ScienceDirect
Progress in Biophysics and Molecular Biology 96 (2008) 305–320
Progress in Biophysics & Molecular Biology
www.elsevier.com/locate/pbiomolbio

Review

Mechanisms underlying adaptation of action potential duration by pacing rate in rat myocytes

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Available online 10 August 2007

Abstract

Heart rate is an essential determinant of cardiac performance. In rat ventricular myocytes, a sudden increase in rate yields to a prolongation of the action potential duration (APD). The mechanism underlying this prolongation is controversial: it has been proposed that the longer APD is due to either: (1) a decrease in K^+ currents only or (2) an increase in Ca^{2+} current only. The aim of this study was to quantitatively investigate the contribution of Ca^{2+} and K^+ currents in the adaptation of APD to pacing rate. Simulation using a mathematical model of ventricular rat cardiac cell model [Pandit, S.V., Clark, R.B., Giles, W.R., Demir, S.S., 2001. A mathematical model of action potential heterogeneity in adult rat left ventricular myocytes. Biophys. J. 81, 3029–3051] predicted a role in the prolongation of APD for K^+ currents only. In patch clamp experiments, increasing the pacing rate leads to a significant increase in APD in both control and detubulated myocytes, although it was more marked in control than detubulated myocytes. Supporting the model prediction, we observed that increasing stimulation frequency leads to a decrease in K^+ currents in voltage clamped rat ventricular myocytes (square and action potential waveforms), and to a similar extent in both cell types. We have also observed that frequency-dependent facilitation of Ca^{2+} current occurred in control cells but not in detubulated cells (square and action potential waveforms). From these experiments, we calculated that the relative contribution of Ca^{2+} and K^+ currents to the longer APD following an increase in pacing rate is ~65% and ~35%, respectively. Therefore, in contrast to the model prediction, Ca^{2+} current has a significant role in the adaptation of APD to pacing rate. Finally, we have introduced a simplistic modification to the Pandit's model to account for the frequency-dependent facilitation of Ca^{2+} current.

Keywords: Cardiac; Myocyte; Action potential; Frequency; Calcium current; Facilitation; Potassium current

Contents

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doi:10.1016/j.pbiomolbio.2007.07.008

1. Introduction

Heart rate has long been known as an essential determinant of cardiac performance. In many species, an increase in cardiac frequency induces a positive inotropic effect known as the force–frequency relationship (the Bowditch staircase (Bowditch, 1871)). At the cellular level, modifications in Ca^{2+} and Na^+ homeostasis are responsible for the increase in contractile force (see Endoh (2004) for review). Concomitant to the change in contraction, action potential duration (APD) is modified by pacing rate; in most species, a sudden increase in rate yields an action potential with shorter duration (see Carmeliet (2004) for review). In contrast, in rat ventricular myocytes, a prolongation of the APD is observed (Fauconnier et al., 2003; Shigematsu et al., 1997; Shimoni et al., 1994, 1995; Watanabe et al., 1983). In rat myocytes, a similar increase in APD is observed when an extra stimulus is interpolated in a regular series of pacing, causing an extrasystole (e.g. Nanasi et al., 1996, see Carmeliet (2004) for review). Despite this unusual adaptation of APD to pacing rate, rat ventricular myocyte is the most widely used animal model in cardiac physiology. It is, therefore, of interest to investigate the mechanism underlying the prolongation of APD following an increase in pacing rate.

The mechanism underlying this prolongation is controversial: Shimoni et al. (1994) have proposed that frequency-dependent decrease in K^+ currents is the mechanism involved in the prolongation of APD (with no role for L-type Ca^{2+} current; I_{Ca}) in rat ventricular myocyte (Shimoni et al., 1994, 1995). More recently, Fauconnier et al. (2003) proposed that the increase in I_{Ca} following an increase in stimulation frequency (facilitation) contributes significantly to the prolongation of APD (with limiting role of K^+ currents). Facilitation of I_{Ca} has been extensively characterized using square depolarization from near physiological potentials to near the peak of the I_{Ca}–V curve ($\sim$0 mV) in several mammalian species including human (see Brette et al. (2006a) and Richard et al. (2006) for recent reviews). However, little is currently known about facilitation of I_{Ca} during a physiological stimulus (i.e. action potential). We have recently showed that facilitation of I_{Ca} is absent in rat ventricular myocytes where the t-tubules have been disrupted (Brette et al., 2004); detubulated myocytes are therefore a useful tool to test whether I_{Ca} participates in adaptation of APD to pacing rate. In addition, a recent mathematical model of rat ventricular cell reproduces the prolongation of APD when increasing the pacing rate (Pandit et al., 2001), even after modification of the model to account for change during type-1 diabetes (Pandit et al., 2003) or the presence of t-tubules (Pasek et al., 2006). However, in all cases, no investigation of the ionic currents underlying this adaptation of APD have been performed (Pandit et al., 2001, 2003; Pasek et al., 2006).