Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular and Cellular Cardiology 44 (2008) 954–967
Journal of Molecular and Cellular Cardiology
www.elsevier.com/locate/yjmcc

Review article

Late sodium current inhibition as a new cardioprotective approach

Sharon L. Hale [a,b,1], John C. Shryock [c,*,1], Luiz Belardinelli [c], Michael Sweeney [d], Robert A. Kloner [a,b]

[a] *The Heart Institute of Good Samaritan Hospital, Los Angeles, CA 90017, USA*
[b] *The Keck School of Medicine, Division of Cardiovascular Medicine, University of Southern California, Los Angeles, CA 90017, USA*
[c] *Cardiovascular Therapeutics, Inc, 1651 Page Mill Road, Palo Alto, CA 94304, USA*
[d] *Depomed, Inc., 1360 O'Brien Drive, Menlo Park, CA 94025, USA*

Received 20 November 2007; received in revised form 5 March 2008; accepted 21 March 2008
Available online 8 April 2008

Abstract

There is increasing evidence that the late sodium current of the sodium channel in myocytes plays a critical role in the pathophysiology of myocardial ischemia and thus is a potential therapeutic target in patients with ischemic heart disease. Ranolazine, an inhibitor of the late sodium current, reduces the frequency and severity of anginal attacks and ST-segment depression in humans, and unlike other antianginal drugs, ranolazine does not alter heart rate or blood pressure. In experimental animal models, ranolazine has been shown to reduce myocardial infarct size and to improve left ventricular function after acute ischemia and chronic heart failure. This article reviews published data describing the role of late sodium current and its inhibition by ranolazine in clinical and experimental studies of myocardial ischemia.

Keywords: Late I_{Na}; Late sodium current; Ranolazine; Ischemia; Angina; MERLIN; Calcium overload; Cardioprotection

Contents

1. Introduction . . . 955
2. Dysregulation of intracellular Na^+ and Ca^{2+} homeostasis during ischemia: The role of the late sodium current . . . 955
3. Inhibition of the late sodium current by ranolazine . . . 956
4. Effects of ranolazine at other channels, membrane transporters and receptors . . . 957
   4.1. Calcium channels, NCX, and NHE . . . 957
   4.2. Human Ether-a-go-go Related Gene (hERG) current (I_{Kr}) . . . 957
   4.3. Adrenergic, opioid, and serotonin receptors . . . 958
   4.4. Fatty acid oxidation . . . 958
   4.5. Summary . . . 958
5. Anti-ischemic effects of ranolazine in experimental animal models . . . 958
   5.1. Acute myocardial ischemia . . . 958
      5.1.1. Isolated heart preparations . . . 958
      5.1.2. Intact animal models . . . 959
   5.2. Myocardial stunning . . . 959
   5.3. Ranolazine and heart failure . . . 960
   5.4. Summary . . . 960
6. Clinical perspective . . . 960

* Corresponding author. Tel.: +1 650 384 8508; fax: +1 650 384 8040.
E-mail address: john.shryock@cvt.com (J.C. Shryock).
[1] These authors contributed equally to this work.

0022-2828/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.yjmcc.2008.03.019

7. Evidence from clinical trials that ranolazine reduces angina . . . 961
7.1. Early clinical studies . . . 961
7.2. The MARISA, CARISA, ROLE, and ERICA studies . . . 961
7.2.1. Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) . . . 961
7.2.2. Combination Assessment of Ranolazine in Stable Angina (CARISA) . . . 962
7.2.3. Ranolazine Open Label Experience (ROLE) . . . 962
7.2.4. Efficacy of Ranolazine in Chronic Angina (ERICA) . . . 963
7.3. Ranolazine in non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS): the MERLIN-TIMI 36 outcome trial . 963
7.4. Summary . . . 963
8. Conclusions and future directions . . . 964
References . . . 964
Glossary . . . 976

1. Introduction

This review presents evidence that inhibition of the late sodium current (late I_{Na}; see Glossary) in the heart is beneficial to reduce electrical and mechanical dysfunction during ischemia. The pathophysiological role of late I_{Na} to increase Na^+ and Ca^{2+} overload during myocardial ischemia is summarized. Studies showing that ranolazine, the first selective late I_{Na} inhibitor approved for human use, is beneficial in preclinical models of ischemia, infarction, heart failure and arrhythmias are discussed, and clinical trials of the efficacy and safety of ranolazine are reviewed. For additional reviews of the cardioprotective and neuroprotective roles of Na^+-channel blockers the reader is referred to [1–7].

Ranolazine is an antianginal drug that acts to reduce the late (i.e., persistent), but not the early (i.e., peak or transient), influx of sodium through cardiac sodium channels in myocardial cells. In patients, ranolazine reduces the frequency of anginal attacks, increases time to ST-segment depression during a treadmill exercise test, and improves exercise tolerance. Ranolazine is the first antianginal agent capable of producing anti-ischemic effects without altering heart rate or blood pressure. In experimental animal studies, the drug has been shown to reduce myocardial infarct size and to improve left ventricular function both after acute ischemia and during chronic heart failure.

2. Dysregulation of intracellular Na^+ and Ca^{2+} homeostasis during ischemia: The role of the late sodium current

Myocardial ischemia is characterized by an imbalance of oxygen supply and demand that leads to a dysregulation of ionic homeostasis in myocardial cells, which when severe and prolonged, is followed by marked cellular depolarization and death [8]. An early event during ischemia is a rise in the cytosolic Na^+ concentration [1,9–11]. Increases of late I_{Na} and Na^+ influx via sodium–hydrogen exchange (NHE) in response to intracellular acidification both contribute to the rise of cytosolic Na^+ content during ischemia [12,13]. As cytosolic Na^+ increases, the influx of Na^+ and efflux of Ca^{2+} via the cell membrane sodium–calcium exchanger (NCX) decrease, whereas the efflux of Na^+ and influx of Ca^{2+} via NCX increase. Hence, entry of Ca^{2+} into the myocardial cell via NCX and L-type Ca^{2+} channels may exceed Ca^{2+} efflux and precipitate cellular Ca^{2+} overload. Cellular Ca^{2+} overload is believed to be a major contributor to the impairment (decrease) of left ventricular (LV) relaxation caused by ischemia/reperfusion [8,14,15]. As a result, LV wall tension during diastole is abnormally elevated, compression of the vascular space is increased, and blood flow to the ischemic myocardium during diastole is further reduced. Calcium overload caused by ischemia also has adverse consequences for myocardial electrical activity. Cellular Ca^{2+} overload may lead to recurrent spontaneous releases of calcium from the sarcoplasmic reticulum [16,17], which, in turn, cause delayed afterdepolarizations [18] that may lead to triggered activity, increased beat-to-beat variability of action potential duration (APD), and ventricular tachycardia. Thus, myocardial cell Ca^{2+} overload has a direct role in causing electrical and mechanical dysfunction of the ischemic myocardium (Fig. 1) [1,15,19–22].

Much evidence indicates that myocardial cell Ca^{2+} overload caused by ischemia and reperfusion can be prevented by inhibition or cardiac-specific ablation of NCX [23,24], blockade of membrane Na^+ channels [2,25–29], or reduction of NHE [13], thus indicating that increased Na^+ entry into cells is a proximate cause of Ca^{2+} overload. This hypothesis is supported by findings that myocardial cell Na^+ content increases during ischemia [9,10,27,28,30], and that impaired inactivation of Na^+ channels during hypoxia [31,32] is responsible for the excessive Na^+ entry. Both tissue hypoxia and reperfusion of ischemic myocardium are reported to generate metabolites (e.g., palmitoyl-L-carnitine and lysophosphatidylcholine) [33,34] and reactive oxygen/nitrogen species (e.g., hydrogen peroxide and nitric oxide) [35–38] that act to increase the "late" component of the Na^+ channel current (late I_{Na}) in ventricular myocytes. Late I_{Na} has been studied at whole cell and single channel levels [e.g., 39–42]. Late I_{Na} flows into myocytes through Na^+ channels that fail to inactivate properly. Transient openings of many Na^+ channels create the inward current responsible for the upstroke of the cellular action potential. When a small fraction (as few as two per cell) of these channels either fails to inactivate or reopens during the plateau of the cardiac action potential (AP) when Na^+ channels are normally closed, the resultant late Na^+ current slows repolarization of the AP and increases APD [42,43], the heterogeneity of repolarization and formation of early after-depolarizations (EADs) [36,44–47], and cellular Na^+ loading [47]. Transient, late (persistent), and resurgent Na^+ currents have different characteristics [48,49] but the Na^+ channels responsible for these currents in individual studies have not been shown to be different. However, late openings of Na^+