Chapter 8
Relationship Between Redox Regulation and β-Adrenergic Responses in the Heart

Belma Turan

Abstract Catecholamines have physiologically important effects on the performance of the heart through the activation of adrenergic receptors. In general, it is known that sympathetic nervous system activation modulates the signaling pathway that controls excitation–contraction coupling (ECC) in the heart. Coordinated myocyte handling of Ca\(^{2+}\) is essential for efficient ECC in the heart. A growing body of knowledge on cardiac β-adrenergic receptor (β-AR) signal transduction demonstrates that the agonist-bound β-AR selectively interacts with the stimulatory G protein (G\(_s\)), which activates adenylyl cyclase (AC), catalyzing cAMP formation. Subsequently, activation of cAMP-dependent protein kinase A (PKA) leads to phosphorylation of regulatory proteins involved in cardiac ECC and energy metabolism. Published data have shown that the altered cardiac responses in pathological conditions are closely related to the function of the β-AR system. From the current literature it is clear that the β-AR system and its importance in regulating cardiac function under both physiological and pathophysiological situations has attracted the attention of many investigators. Ca\(^{2+}\) functions as a critical second messenger in mediating fast intracellular responses in all tissues through signaling proteins to coordinate cell function with different intracellular mechanisms. In addition, the identification of oxidatively sensitive proteins that modulate intracellular signaling mechanisms and the associated generation of reactive oxygen species (ROS) are critical to understanding how cells respond to oxidative stress. Therefore, any disturbance in the intracellular ionic homeostasis due to the excess ROS, was shown to result in the occurrence of impaired cardiac contractile activity. Since β-ARs and AC are known to participate in the regulation of cardiac function, it is possible that the β-AR-linked signal transduction pathway is also affected by ROS.

Introduction

Cardiovascular disease is the leading cause of death of most humans. However, differences in age, heart size, physiological status, and other factors confound
comparisons leading to variable and conflicting conclusions (see review by Chu et al. 2005). Myocellular Ca\textsuperscript{2+} cycling is a primary determinant of normal cardiac contractile function and any abnormality in this process is likely associated with cardiac dysfunction and heart disease (Marks 2001; Chu et al. 2005; Wold et al. 2006). Furthermore, it is well known that functional changes of heart have been associated with altered expression and/or activity of Ca\textsuperscript{2+} handling proteins (Choi et al. 2002; Eisner et al. 1998; Wehrens and Marks 2003; Yaras et al. 2005).

Contraction and relaxation of heart muscle cells are regulated by Ca\textsuperscript{2+} cycling between the cytoplasm and sarcoplasmic reticulum (SR). Therefore, myocyte mishandling of Ca\textsuperscript{2+} is a central cause of both contractile dysfunction and arrhythmias under pathological conditions (Pogwizd et al. 2001). β-Adrenergic stimulation is a major physiological mechanism to meet increases in circulatory demand, acting through positive inotropic and lusitropic effects. β-Adrenergic signaling and myocellular Ca\textsuperscript{2+} homeostasis are importantly linked because β-adrenergic receptor (β-AR) stimulation regulates the activity and expression of Ca\textsuperscript{2+} handling proteins. Although the β-adrenergic signal transduction pathway in the heart is known to participate in regulating cardiac performance by identifying, amplifying, and transmitting the catecholamine-initiated signals, this system is impaired under both chronic and acute pathological conditions (see review by Dhalla et al. 1997).

A large number of studies have demonstrated the role of reactive oxygen species (ROS) in the pathogenesis of the cardiovascular diseases. The risk factors for cardiovascular disease can widely depend on many factors such as contents of daily diets and/or environmental conditions of the individuals. Most recently, these factors became important in the early prevention of cardiovascular diseases. Oxidative stress, the imbalance between ROS production and breakdown by endogenous antioxidants, has been implicated in the onset and progression of cardiovascular diseases. Antioxidant therapy has shown promise in preventing the development of several different heart diseases. Thus, this article will attempt to explain the relationship between redox regulation and β-adrenergic responses in heart under oxidative stress.

**Heart and β-Adrenergic System**

It is well documented that coordinated myocyte handling of Ca\textsuperscript{2+} is essential for efficient excitation–contraction coupling in the heart. Since cardiac pump is able to alter its function in response to any requirement in the body and the regulation of contractile function of individual myocytes obtained by modulation of intracellular Ca\textsuperscript{2+} signaling, the characteristics of regulation induced by adrenergic stimulations are very important for maintaining the normal heart function in humans.

The sympathetic nervous system plays a central role in regulating heart function and response to most types of stress through β-AR stimulation. Binding of β-adrenergic agonists to receptors in the heart activates adenylyl cyclase (AC) via a stimulatory G protein. On the other hand, it is known that the altered responses of the