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Invited Review

Impact of exercise training on redox signaling in cardiovascular diseases

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ABSTRACT

Reactive oxygen and nitrogen species regulate a wide array of signaling pathways that governs cardiovascular physiology. However, oxidant stress resulting from disrupted redox signaling has an adverse impact on the pathogenesis and progression of cardiovascular diseases. In this review, we address how redox signaling and oxidant stress affect the pathophysiology of cardiovascular diseases such as ischemia–reperfusion injury, hypertension and heart failure. We also summarize the benefits of exercise training in tackling the hyperactivation of cellular oxidases and mitochondrial dysfunction seen in cardiovascular diseases.

Contents

Abbreviations: 4-HNE, 4-hydroxy-2-nonenal; ATP, adenosine triphosphate; Cu ZnSOD, copper–zinc superoxide dismutase; ETC, electron transport chain; GPX, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; HNO, nitroxyl; MAO, monoamine oxidase; MDA, malondialdehyde; MnSOD, manganese superoxide dismutase; mtNOS, mitochondrial nitric oxide synthase; NADH, nicotinamide adenine dinucleotide; NAPDH, nicotinamide adenine dinucleotide phosphate; $NO^{\cdot}$, nitric oxide; $NO_2^{\cdot}$, nitrogen dioxide; NO^+, nitrosonium; NOS, nitric oxide synthase; NOX, NADPH oxidase isoform; iNOS, inducible NOS; eNOS, constitutive endothelial NOS; $O_2^{\cdot-}$, superoxide; $^{\cdot}OH$, hydroxyl radical; $ONOO^{\cdot}$, peroxynitrite; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; VO_2 max, maximal oxygen consumption.

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1. Introduction

Cardiovascular disease remains a major public health problem; acute myocardial infarction, hypertension and heart failure are among the leading causes of morbidity and mortality worldwide (Gerczuk and Kloner, 2012). According to the World Health Organization, over 7 million people die of cardiovascular disease every year (WHO, 2011), and this circumstance may however be more critical considering that the prevalence of cardiovascular diseases is expected to rise as the mean age of the population increases. Therefore, the fundamental mechanisms responsible for the pathophysiology and progression of cardiovascular diseases, as well as the development of pharmacological and non-pharmacological therapies, must be extensively studied.

Cardiovascular diseases are commonly described as multifactorial diseases characterized by activation of neurohumoral systems (i.e. sympathetic and renin–angiotensin–aldosterone systems), inflammation, cellular reprogramming and bioenergetics dysfunction (Chen et al., 2008; Churchill et al., 2010; Ferreira et al., 2008; Shen and Young, 2012). Common to these processes is increased oxidant stress, characterized by excessive generation of reactive oxygen and nitrogen species (ROS and RNS, respectively) and reduced antioxidant capacity. The purpose of this review is to outline the role of oxidant stress in cardiovascular diseases, and summarize evidence suggesting that exercise training counteracts the oxidant stress that is commonly observed.

2. Reactive oxygen and nitrogen species

ROS and RNS are classes of reactive radical and non-radical molecules that play a critical role in the cardiovascular physiology and pathophysiology. In an attempt to acquire stability, these unstable species tend to donate or steal electrons from other molecules, such as lipids, carbohydrates, proteins and nucleic acids, which usually results in structural remodeling of its molecular targets. ROS and RNS can be either friends or foes depending on concentration, location and context. Physiological levels of ROS and RNS are crucial in controlling several cellular processes including ion channel function, calcium transient, gene expression and protein activation (Droge, 2002; Wang et al., 2008; Yan et al., 2008). However, excessive intracellular ROS and RNS generation has been associated with a variety of diseases including cancer, metabolic, neurodegenerative and cardiovascular disorders (Zhang et al., 2011). Although high levels of both ROS and RNS cause cellular toxicity, these highly reactive and aggressive radicals differ in their composition, generation and sources.

ROS are highly reactive molecules formed from incomplete reduction of O_2, including free radicals containing one or more unpaired electrons such as superoxide ($O_2^{\cdot-}$) and hydroxyl radical ($^{\cdot}OH$) and non-radicals such as hydrogen peroxide (H_2O_2). One electron reduction of O_2 generates $O_2^{\cdot-}$, a highly reactive membrane impermeable molecule with short half-life in an aqueous environment. $O_2^{\cdot-}$ is quickly converted to H_2O_2 by the action of superoxide dismutase enzymes (SOD). Since H_2O_2 is more stable than $O_2^{\cdot-}$ and membrane permeable, it has an important role in cellular redox homeostasis and signaling, acting as a second messenger. Reaction of H_2O_2 with transition metals ions produces $^{\cdot}OH$, a very reactive and toxic ROS (Fenton reaction: $Fe^{2+} + H_2O_2 \leftrightarrow Fe^{3+} + OH + {}^{\cdot}OH$).

Comparatively, RNS are a family of molecules primarily derived from nitric oxide ($NO^{\cdot}$), a small and uncharged molecule mainly generated by $NO^{\cdot}$ synthase (NOS). $NO^{\cdot}$, at physiological levels, has a pivotal role in the maintenance of vascular and cardiac function. However, excessive $NO^{\cdot}$ levels cause cellular toxicity through its ability to react with other radicals. Due to this high versatility, there is a range of RNS molecules produced from $NO^{\cdot}$ including peroxynitrite ($ONOO^{\cdot}$), nitrogen dioxide ($NO_2^{\cdot}$), nitroxyl (HNO) and nitrosonium (NO^+). When both $NO^{\cdot}$ and $^{\cdot}OH$ are produced in the cells, $^{\cdot}OH$ reacts with $NO^{\cdot}$ in a much faster rate than SOD generating $ONOO^{\cdot}$, a potent oxidizing radical in cardiac and vascular cells.

3. Oxidant stress in the cardiovascular system

The term "oxidant stress" describes conditions that result from the spatio-temporal imbalance between free radical generation [reactive atoms/ions/molecules with unpaired electrons or unstable bonds] and its detoxification through enzymatic and non-enzymatic systems. Studies using cell culture and experimental animal models clearly support the role of oxidant stress in the onset and progression of cardiac diseases (Churchill et al., 2005; Churchill and Szweda, 2005; Yogalingam et al., 2013). Moreover, patients with acute myocardial infarction or heart failure usually display increased levels of oxidant stress characterized by accumulation of lipid peroxidation byproducts [i.e. malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE)] and exacerbated carbonylation of proteins compared to health individuals (Brioschi et al., 2012; Lu et al., 2010).

Exacerbated oxidant stress also plays pivotal role in the pathophysiology of hypertension. High concentration of ROS and RNS affects several downstream signaling molecules including ion channels, protein phosphatases, protein kinases and transcription factors, which impairs vascular function by modulating vascular smooth muscle cell growth, migration, inflammation, apoptosis and cell death (Paravicini and Touyz, 2006). Moreover, increased free radicals generation enhances vascular calcium signaling, thereby altering vascular contractility and tone (Touyz, 2005).

Some cardiotoxic effects of oxidant stress have been attributed to the activation of signaling pathways that harmfully affects cardiac contractility. Both *in vivo* and *ex vivo* cardiac contractions are decreased after treating hearts with oxidizing agents. Increased ROS and RNS can result in direct oxidation or nitrosylation of many calcium regulatory and contractile proteins in failing hearts (Steinberg, 2013). In fact, $ONOO^-$ decreases maximal force development of the intact heart and the contractility in isolated human ventricular myocytes (Hong et al., 2007; Kanski et al., 2005). These responses are linked to increased nitration of tyrosine residues of sarcomeric proteins such as troponin I, troponin C and myosin heavy chain. Early studies using skinned rat cardiac muscles show that O_2^- depresses maximal calcium-activated force (MacFarlane and Miller, 1992). More recently, it has been shown that excessive O_2^-, H_2O_2 and $ONOO^-$ are major contributors to oxidant stress-mediated myocardial contractile failure (Avner et al., 2012; Doroszko et al., 2010).

Elevated ROS and RNS generation also disrupts cardiac bioenergetics. Specific forms of free radicals (i.e. H_2O_2, O_2^-, NO and $ONOO^{\cdot}$) produced by mitochondria during acute (ischemia–reperfusion injury) and chronic (heart failure) cardiovascular diseases can react with phospholipids presented in the mitochondrial inner membrane and generates highly reactive lipid peroxidation by-products (i.e. 4-HNE), thus contributing to mitochondrial dysfunction. Moreover, excessive O_2^- and NO production inhibits mitochondrial electron transport chain at multiple sites and also causes mitochondrial permeability transition (Brown and Borutaite, 2007). Working in a positive feedback loop, the disruption of mitochondrial electrochemical gradient by ROS and RNS stimulates local production of free radicals and therefore propagates the mitochondrial-mediated cell death signaling.

4. Redox signaling

Based on a large body of evidence, it is now recognized that under physiological conditions, the reversible reduction–oxidation