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The Pathogenesis of Xenobiotic-Induced Oxidative Stress in the Cardiac Microenvironment

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Abstract

The heart functions to ensure optimal perfusion of every organ while maintaining elasticity and compliance. Mainly composed of cardiac myocytes, fibroblasts, endothelial and vascular cells, the heart has the highest energy demand of all organs. Thus, it requires a high rate of adenosine triphosphate (ATP) production to maintain normal physiological function. Using oxidative phosphorylation, the heart produces ATP and concomitantly produces reactive oxidative species (ROS). Therefore, normal homeostasis and mitochondrial metabolism make the heart extremely susceptible to intrinsic and extrinsic oxidative stress. Exogenous foreign agents or aberrantly expressed endogenous molecules are characterized as cardiac xenobiotics (CX) which promote cardiac-specific toxicity. CX enter the body via nutritional and drug intake or environmental exposure and cause an imbalance in ROS production and antioxidant protection within the cardiac microenvironment. Chronic ROS exposure alters the cellular and molecular physiology of key detoxifying enzymes which modify cardiovascular structure and function. The heart has a tightly controlled antioxidant system that manages ROS and maintains homeostasis within the cardiac microenvironment. This strictly regulated system consists of endogenous enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and exogenous antioxidants such as vitamins, minerals, polyphenols and carotenoids derived from nutritional sources. Sustained levels of cardiac xenobiotics can result in chronically imbalanced ROS production that outpaces the antioxidant system. Over time this imbalanced system results in irreversible cellular and subcellular damage, altering cardiac

structure and function and increasing the risk of cardiac dysfunctions such as maladaptive left ventricular hypertrophy, cardiac fibrosis and heart failure.

Keywords: Xenobiotics; Cardiac; Reactive Oxidative Species (ROS); Detoxifying Enzymes; Antioxidants

Abbreviations: ATP: Adenosine Triphosphate; ROS: Reactive Oxidative Species; SOD: Superoxide Dismutase; GPx: Glutathione Peroxidase; CX: Cardiac Xenobiotics

Introduction

Maintenance of cardiac output to ensure adequate perfusion of the heart itself and every organ in the body is the ultimate function of the heart. The heart is a compliant and elastic organ with both mechanical and electrophysiological functions. It is mostly composed of cardiac myocytes (highest volume of mitochondria), cardiac fibroblasts, mast cells, endothelial cells, and vascular cells. In addition to its cellular composition, the cardiac microenvironment is composed of subcellular organelles and macromolecules, which play a vital role in adenosine triphosphate (ATP) production. ATP production and enzymatic synthesis are critical for proper signal transduction, cell to cell communication, and maintenance of cellular membrane integrity. The heart has a high metabolic demand; thus, it continuously produces ATP via oxidative phosphorylation, which creates the highest rate of production of reactive oxidative species (ROS) [1]. This demand, coupled with low levels of cardiac detoxifying enzymes, makes the heart extremely susceptible to oxidative stress. ROS and key detoxifying enzymes are primarily produced and located within the mitochondria, where cardiac cellular metabolism occurs. Mitochondrial ATP production produces hydroperoxyl, hydroxyl, peroxynitrite radicals, superoxide anion, hydrogen peroxide and carbon dioxide [2]. In addition to this intrinsic oxidative stress, the heart is susceptible to high levels of external oxidative stress from hypertension-induced pressure overload, cardiac toxicants, and xenobiotics. Therefore, homeostatic regulation of cardiac metabolism requires a tightly regulated microenvironment with a cardiac-specific antioxidant system. Detoxifying enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), are part of the first line defense against ROS-mediated cardiac injury [3]. Endogenous mechanisms within the cardiac microenvironment and exogenous antioxidant mechanisms from natural sources can modulate ROS production and oxidative stress derived from metabolic and detoxifying activity. High metabolic demand increases cardiac susceptibility to oxidative stress of cardiac toxicants and xenobiotics.

Cardiac Xenobiotics and Oxidative Stress

Cardiac xenobiotics (CX) are exogenous foreign agents or aberrantly expressed endogenous compounds which promote cardiac-specific toxicity [4]. The primary modes of cardiac xenobiotic entry are achieved via the environment, nutrition, and/or drug exposure. CX drug-exposure's wide range of classes include anticancer drugs (i.e. doxorubicin), ethanol, psychoactive drugs (i.e. methylenedioxymethamphetamine a.k.a. “ecstasy”), and catecholamines [5]. Both pulmonary and extrapulmonary CX environmental exposure have demonstrated decreases in cardiac heart rate variability. The inhalation of toxic particles extends its damage to cardiovascular tissue promoting cardiac arrythmias, altering cardiac repolarization, and increasing blood pressure [6]. Nutrition also exposes the heart to oxidants, and it has been well established that diets high in trans and saturated fats promote cardiovascular disease (CVD). Research shows that different types of athletes exhibit different xenobiotic profiles based upon diet, designed to enhance performance and recovery [7]. Based upon the amount consumed and physiological and/or pathological state of the consumer, nutrition can be beneficial and/or deleterious. Thus, there is an association between CX exposure, normal cardiovascular physiology and increased prevalence of CVD [8].

Reactive oxidative species are free radicals and non-radical derivatives produced as a by-product of cellular metabolism; and at low levels promote cell growth, but at high levels can promote tissue injury and reduce cell function. Under physiological conditions, ROS production, detoxifying enzymes (i.e. SOD), and antioxidants (i.e. carotenoids) carefully balance intracellular ROS to maintain cellular homeostasis [9]. Under pathological conditions, there is an increase in pro-oxidant to antioxidant ratio; mitochondrial energy metabolism is altered; and the heart reverts to fetal metabolism switching from beta-oxidation to glucose oxidation. Various biomarkers of oxidative stress provide indirect evidence for the effect of ROS in CVD. For example, the

overexpression of GPx indicates the capacity to detoxify ROS prevents myocardial infarction, myocyte hypertrophy, and fibrosis [3]. Increased levels of 8-hydroxy-2′-deoxyguanosine, a marker of ROS-induced oxidative damage, are also present in CVD [10]. Increased ROS production that is not counterbalanced by antioxidants can alter cellular homeostasis and cause deleterious genetic and epigenetic mutations that are responsible for cell cycle regulation and antioxidant enzyme protein synthesis [11]. Oxidative stress can alter the backbone and side chains of proteins, and these structural alterations promote functional changes that alter the integrity of macromolecules, affect cell membrane permeability, and exacerbate oxidative damage [12,13]. Chronic oxidative stress results in irreversible and fatal damage of macromolecules which promotes maladaptive cardiac hypertrophy, extensive cardiac fibrosis and heart failure [14].

Conclusion

In a normal physiological state, cardiac mitochondrial metabolism is accompanied by concomitant ROS production, which requires a strictly regulated antioxidant system to maintain homeostasis and prevent irreversible damage of macromolecules within the cardiac microenvironment. CX-induced toxicity generates excessive ROS production and creates a harmful imbalance of the regulatory system, causing cardiac-specific oxidative stress. The primary endogenous systems use key detoxifying enzymes such as SOD, GPx and CAT to regulate ROS production and exogenous antioxidants consisting of vitamins, minerals, polyphenols and/or carotenoids derived from nutritional sources to maintain homeostasis.

Unregulated CX exposure can invoke irreversible damage of macromolecules in the cardiac microenvironment promoting a sequence of events leading to maladaptive cardiac remodeling, which negatively impairs cardiac contractility and compliance. Thus, it remains essential to clearly characterize the endogenous and exogenous antioxidants responsible for managing cardiac oxidative stress; determine the role of dietary intervention on ROS production; and to provide alternative strategies to maintaining optimal protection against CX-induced oxidative stress.

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