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A NEW APPROACH TO THE TREATMENT AND PREVENTION OF MORPHOFUNCTIONAL CHANGES IN THE HEART AS A RESULT OF THE EFFECTS OF VARIOUS FACTORS OF THE EXTERNAL AND INTERNAL ENVIRONMENT (LITERATURE REVIEW)

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ABSTRACT

Cardiovascular diseases are the most common causes of morbidity and mortality worldwide. Redox dysregulation and a dyshomeostasis of inflammation arise from, and result in, cellular aberrations and pathological conditions, which lead to cardiovascular diseases. Despite years of intensive research, there is still no safe and effective method for their prevention and treatment. Recently, molecular hydrogen has been investigated in preclinical and clinical studies on various diseases associated with oxidative and inflammatory stress such as radiation-induced heart disease, ischemia-reperfusion injury, myocardial and brain infarction, storage of the heart, heart transplantation, etc. Hydrogen is primarily administered via inhalation, drinking hydrogen-rich water, or injection of hydrogen-rich saline. It favorably modulates signal transduction and gene expression resulting in suppression of proinflammatory cytokines, excess ROS production, and in the activation of the Nrf2 antioxidant transcription factor. Although H_2 appears to be an important biological molecule with anti-oxidant, anti-inflammatory, and anti-apoptotic effects, the exact mechanisms of action remain elusive. There is no reported clinical toxicity; however, some data suggests that H_2 has a mild hormetic-like effect, which likely mediate some of its benefits. The mechanistic data, coupled with the pre-clinical and clinical studies, suggest that H_2 may be useful for ROS/inflammation-induced cardiotoxicity and other conditions.

Key words: heart transplantation, ischemia/reperfusion injury, molecular hydrogen, oxidative stress, radiation-induced heart disease.

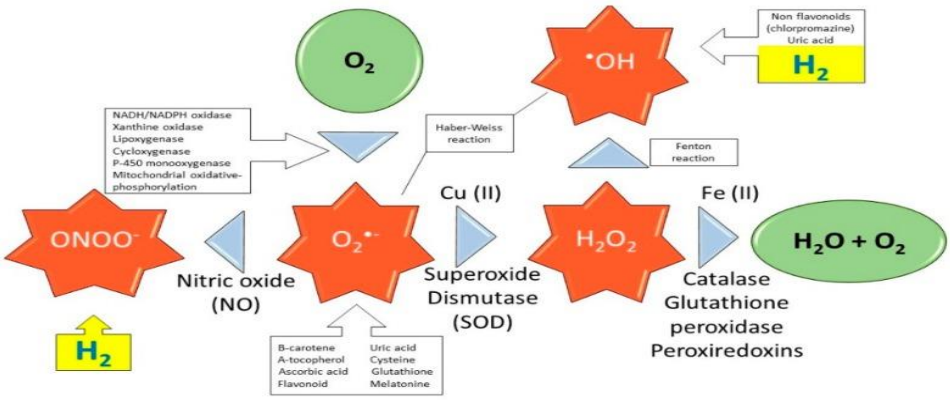
INTRODUCTION

According to statistics cardiovascular and oncological diseases are the main cause of more than 93% of morbidity and mortality worldwide [1,2]. One of the most widely used methods for treating patients with oncological diseases is radiotherapy, which uses ionizing radiation. This treatment damages cancer cells leading to their apoptosis and eventual healing of patients [3]. However, during irradiation of cancer cells, the surrounding healthy tissue may also be inadvertently affected which, in turn may cause serious health complications, including radiation-induced heart disease [4,5]. Ischemia/reperfusion (I/R) injury represents a condition in which tissues or organs are damaged due to being exposed to a period of ischemia followed by replenishment of oxygen-rich blood. I/R injury is implicated in the pathogenesis of various clinical issues including stroke, myocardial infarction, organ transplantation, and also in injuries to various organs such as the brain, heart, kidneys and skeletal muscles [6]. Therefore, research in this field, and the use of completely new techniques that will positively influence the effects of excessive free radical production on the cardiovascular system, can significantly improve the quality of life of both oncology and cardiology patients.

Molecular hydrogen (H_2) represents an effective and non-toxic molecule with wide potential for treating many reactive oxygen/nitrogen species (ROS/RNS)-related diseases, including diseases induced by irradiation [7,8]. Besides the antioxidant action, hydrogen also exerts its beneficial effects through reduction of inflammation and modulation of signaling pathways, thus providing cytoprotection [9]. The protective effects of H_2 have been investigated in pathological conditions such as cardiac fibrosis, hepatic injuries, neuronal diseases, radiation-induced diseases, diabetes, etc. [10], in which free radicals are casually involved. Ischemia and subsequent reperfusion of the heart represents another state in which an enormous number of tissue-damaging free radicals are produced. I/R could be an important situation in which to use H_2, helping to mitigate/alleviate the negative impact of toxic ROS/RNS [6]. The great advantage of using H_2 is also the wide spectrum of administration possibilities available to the organism – by inhalation, drinking H_2-rich water produced with pressure or using H_2-producing tablets, using H_2-rich saline solution, or taking an H_2 bath [8,11].

This article summarizes the most recently published literature about using H_2 in different ROS/RNS-related diseases such as I/R injury, radiation-induced heart disease, and the potential using of H_2 in transplantations and in grafts storage, which is closely connected with I/R injury. We also briefly discuss some of the molecular mechanisms of H_2 and the viable potential for H_2 in clinical situations.

Oxidative stress occurs as a result of a dyshomeostasis between ROS/RNS and the antioxidant self-defense system. This dysregulation is considered a causative common denominator for many pathological processes, as it impairs cellular and organ function [12]. ROS are byproducts of oxygen reduction, which occurs during normal cellular metabolism. These ROS/RNS include superoxide anion ($O_2^{\bullet-}$), hydroxyl ($^{\bullet}OH$), peroxyl ($RO_2^{\bullet}$), alkoxyl ($RO^{\bullet}$) radicals, and nitric oxide ($NO^{\bullet}$), and other non-radical species, which can function as oxidizing agents, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$), and peroxynitrite ($ONOO^-$). The primary sources of ROS are mitochondrial respiration, NADH/NADPH oxidase, and xanthine oxidoreductase (Figure 1) [13]. Mitochondria are constantly exposed to high levels of ROS which, if unregulated, n cause mitochondrial DNA damage and cellular apoptosis [14].



Production of ROS: effect of antioxidants and selective action of H_2. Schematic reactions of ROS production by action of enzymes during respiration in mitochondria. Green color represents non-radical molecules, red color represents ROS created from normal respiration, yellow color indicates action of H_2.

ROS serve vital roles in modulating cell signaling pathways [15], gene expression, cell proliferation, apoptosis [16], DNA synthesis, cellular migration and invasion, tumor metastasis and angiogenesis [17,18]. Oxidative stress and/or nitrosative stress can activate several transcription factors, including nuclear factor (NF)-κB, activator protein 1, p53, hypoxia-inducible factor 1-α (HIF-1α), matrix metalloproteinases, peroxisome proliferator-activated receptor-γ, β-catenin/Wnt, and nuclear factor erythroid 2-related factor 2 (Nrf2) [19,20].

Hydroxyl and nitrosyl radicals, either by a direct reaction or by triggering a radical chain reaction, are the major contributors to the destruction of important biomolecules. Cellular redox dysregulation is one of the most important contributors to the pathogenesis of cardiovascular and metabolic diseases [2]. It has a causal role in various vascular diseases such as hypertension, diabetic vasculopathy, hypercholesterolemia and atherosclerosis. ROS mediate various signaling pathways that underlie cardiovascular pathophysiology [2]. Peroxynitrite

plays a decisive role in the pathogenic mechanism for conditions such as stroke, myocardial infarction and chronic heart failure [22]. Indeed, acute and chronic excessive intracellular increases of ROS are implicated in the initiation and progression of cardiovascular diseases. For example, excessive ROS impair endothelial and vascular smooth muscle cell functions

Radiation and Radiation-Induced Heart Disease

It has been demonstrated that a number of factors including intense exercise, cardiac infarction, cessation of blood flow, organ transplantation, inflammation, and radiation exposure can cause acute oxidative stress [14]. Radiation therapy is a primary method used to manage cancer; however, many noxious effects are inevitably linked to radiation exposure [15]. Radiation-induced symptoms are associated with increased ROS and inflammation during radiotherapy, which significantly impair the patient's quality-of-life [16]. Exposure to a high dose of radiation over a short time is associated with acute radiation syndrome, whose symptoms are initially manifested as severe diarrhea and fluid loss [16].

The noxious consequences of radiation occur from either direct or indirect effects, which account for most of the damage [7]. Radiation induces a direct detrimental effect by directly damaging critical biomolecules including DNA, proteins, and lipids [7]. The indirect detrimental biological effect is attributed to toxic hydroxyl radicals (•OH) generated from radiolysis of H2O [9], which is estimated to account for 60–70% of the radiation-induced cellular damage. The hydroxyl radical is one of the most reactive ROS and reacts rapidly and indiscriminately with biological macromolecules. These biomolecules include DNA, which produces 8-hydroxy-2′-deoxyguanosine (8-OHdG, a biomarker of carcinogenesis) membrane lipids [11], as well as amino acids, and proteins. These reactions lead to the formation of various secondary ROS [12], which can result in severe health impairments due to cellular injury and irreversible damage in susceptible cells and organs [33]. Biomarkers such as malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARs), etc. are indices of lipid peroxidation and membrane damage, which lead to pathological changes in membrane permeability [4].

Direct and indirect effects of radiation induce excessive production of eicosanoids (e.g., prostaglandins, prostacyclin, thromboxane and leukotrienes), which are endogenous mediators of inflammation, vasodilation or vasoconstriction, vascular permeability, and microthrombus formation [4]. Radiation injury to the myocardium is caused chiefly by these inflammatory aberrations in the microvasculature, leading to the activation of thrombin signaling and subsequent release of selectins and adhesion molecules [7]. This induces adhesion and

extravasation of leukocyte transmigration of circulating monocytes resulting in vascular permeability and vasomotor changes in endothelial cells, which further induces leukocyte trafficking [8]. In the presence of elevated cholesterol, invading monocytes transform into activated macrophages and form fatty streaks in the intima [1]. Other pathological aberrations following irradiation include loss of alkaline phosphatase activity of capillary endothelial cells, and various pro-thrombotic changes such as production and release of von Willebrand factor (vWF), as well as a decreased production of thrombomodulin (Tm) and adenosine diphosphatase (ADPase) [7]. These changes further result in microthrombi, occlusion of vessels, reduced vascular density, perfusion defects, and focal ischemia, all of which lead to progressive myocardial cell death and fibrosis [11]. Cardiotoxic effects due to radiation exposure are collectively referred to as radiation-induced heart disease (RIHD).

Therefore, harmful effects of mediastinal irradiation include coronary artery disease, pericarditis, cardiomyopathy, valvular disease, conduction abnormalities [41], myocardial degeneration, perivascular and interstitial fibrosis [4], and chronic impairment of cardiac pump function [19]. Radiation-induced myocardial damage can occur 6-10 weeks after irradiation [22]. These noxious effects are related to dose, volume and technique of chest irradiation [11].

Cardiovascular injury due to radiation is the most common cause of adverse events among cancer survivors. Clinical studies of radiotherapy reveal regional perfusion defects in proportion to the radiation exposed area in non-symptomatic breast cancer patients [8]. Key factors responsible for the establishment of cardiovascular injury include oxidative stress, inflammation, and epigenetic modifications, and all have been linked to potential treatments [11,21,24]. Similar to the heart, the lungs are also very susceptible to radiation injury, which can result in radiation pneumonitis. Development of interstitial pneumonitis increases according to radiation dose, especially single-fraction total body irradiation at higher dose rates and higher total lung doses [5].

Methods of Radiation Protection The increase in the prevalence of RIHD underscores the necessity to develop and procure new therapeutic methods to mitigate the noxious impact of radiation. The indirect effect of radiation exposure, i.e., high production of free radicals, is considered the primary mediator of radiation toxicity. Therefore, the blocking and scavenging of free radicals are the most important components in an effective protection strategy [17]. Highly effective radiation protectants with low toxicity are strongly desired and have always been emphasized in the field of radiation [15].

Free radical scavengers are able to act preventively and/or therapeutically. Many chemical substances can operate as free-radical scavengers to protect cells and tissues against oxidative damage. Research has identified many types of antioxidants including ascorbic acid, tocopherols, polyphenols, and thiols such as glutathione [25]. Some natural antioxidants such as vitamins, polyphenols, flavonoids, etc. often have fewer toxic effects but also provide lower radioprotection [4]. Therefore, an ideal radioprotectant should be one that is effective yet with few harmful side effects. Medical gases such as carbon monoxide (CO), hydrogen sulfide (H_2S), and, as will be discussed later, molecular hydrogen (H_2), may be used to attenuate the harmful effects of oxidative stress and radiation [11].

Irradiation induces upregulation of myocardial connexin-43 (Cx43), a decline of microRNA (miRNA)-1 and an increase of miRNA-21 levels [2]. This may be due to radiation-induced oxidative stress and/or inflammation, which result in these pathological changes and often accompany cardiovascular disease [8, 10]. Treatment with aspirin and atorvastatin attenuates the irradiation-induced upregulation of myocardial Cx43 protein and miRNA-21 possibly via amelioration of oxidative stress and inflammation [6, 12]. It also suppresses expansive remodeling by inhibition of macrophage infiltration [7, 13]. The sulfhydryl compound amifostine is the only radioprotectant registered for use in humans, and has shown good radioprotective effects [8, 14]. Unfortunately, it is not without significant side effects such as hypertension, nausea and vomiting, which understandably limits its clinical use [9, 15,24].

Oxidative and inflammatory stress are also underlying causative factors in myocardial I/R injury. Cardiac myocytes, for their physiological function, require copious amounts of ATP; hence, a high density of mitochondria are needed to accommodate their high energy requirement. As such, these mitochondria, filled with reactive intermediates and pro-apoptotic signals, are intimately involved in I/R injury [16]. The inner mitochondrial membrane is responsible for maintaining mitochondrial transmembrane potential, and is usually impermeable to ions and proteins [17,20]. However, under stress, the opening of the mitochondrial permeability transition pore (mPTP) creates a non-selective channel between the inner membrane of the mitochondrion and the sarcoplasm. Consequently, a loss of the electrochemical gradient, production of ROS, Ca^{2}+ overload, and formation of apoptosomes ensue [20,21,24].

Production of free radicals through partial reduction of oxygen during I/R is well understood. These highly reactive ROS can rapidly overwhelm the cell’s endogenous antioxidant self-defense system. This creates cellular injury by

damaging lipids, proteins, DNA, and RNA. The xanthine oxidase substrates, xanthine and hypoxanthine, accumulate during ischemia, which triggers xanthine oxidase activation and consequently more ROS production [22]. These ROS can also elicit the opening of the mPTP resulting in a positive feedback loop of increased ROS production from the mitochondria ("ROS-induced ROS release") [18, 19].

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