Experimental Gerontology 48 (2013) 45–54

Contents lists available at SciVerse ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Oxidative stress in surgery in an ageing population: Pathophysiology and therapy

Franklin Rosenfeldt [a,*], Mark Wilson [a], Geraldine Lee [a], Christina Kure [c], Ruchong Ou [a], Lesley Braun [a], Judy de Haan [b]

[a] Cardiac Surgical Research Unit, Department of Cardiothoracic Surgery, Alfred Hospital, Department of Surgery, Monash University, Melbourne, Australia
[b] Oxidative Stress Laboratory, Diabetic Complications Division, Baker IDI Heart and Diabetes Institute, Melbourne, Australia
[c] Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne Australia

ARTICLE INFO

Article history:
Received 26 December 2011
Received in revised form 8 March 2012
Accepted 14 March 2012
Available online 23 March 2012

Section Editor: A. Simm

Keywords:
Oxidative stress
Surgery
Ageing population
Antioxidant capacity
Therapy

ABSTRACT

Reactive oxygen species (ROS) play an important role in the regulation of normal cellular function. When ROS are produced in excess they can have detrimental effects, a state known as oxidative stress. Thus ROS play both physiological and pathophysiological roles in the body. In clinical practice oxidative stress and its counterpart, antioxidant capacity can be measured and can guide remedial therapy. Oxidative stress can have a negative impact in all forms of major surgery including cardiac surgery, general surgery, trauma surgery, orthopedic surgery and plastic surgery; this is particularly marked in an ageing population. Many different therapies to reduce oxidative stress in surgery have been tried with variable results. We conclude that in surgical patients the assessment of oxidative stress, improvement of the understanding of its role, both positive and negative, and devising appropriate therapies represent fruitful fields for future research.

1. Introduction

Reactive oxygen species (ROS) play an important role in the regulation of normal cellular function. When ROS are produced in excess they can have detrimental effects, a state known as oxidative stress. In this review we outline the physiological and pathophysiological role of ROS and how oxidative stress and its counterpart, antioxidant capacity can be measured. We then summarise the involvement of oxidative stress in surgery and review the biochemical and clinical benefits of reducing this stress.

2. Oxidative STRESS

2.1. What is oxidative stress?

Oxidative stress in the body represents an imbalance between the production of reactive oxygen species (ROS) and the ability of the antioxidant defence mechanisms to detoxify the reactive intermediates. An excess of ROS can damage all cellular components, including proteins, lipids, and nucleic acids. The greater the oxidative stress, the more severe the resulting cellular damage; moderate oxidation can trigger apoptosis, more intense stresses may cause necrosis.

2.2. Reactive oxygen species

Within a cell, ROS are generated from a divergent range of sources including the enzymatic activation of cytochrome C, NADPH oxidases, xanthine oxidase, the dysregulation of eNOS and leakage from mitochondria. During normal metabolic processes, mitochondria play an essential physiological role in metabolism by supplying energy for optimal cellular function (Fernández-Checa et al., 1998; Valko et al., 2007). Metabolism involves various reductive-oxidation (redox) reactions where the removal (oxidation) or addition (reduction) of an electron occurs in order to maintain cellular homeostasis. However, dysregulation of ROS metabolism, particularly within mitochondria, can have severe consequences for mitochondrial function and ultimately cellular integrity. Indeed, a link has been established between mitochondrial dysfunction, elevations in mitochondrial ROS production and several pathologies such as endothelial dysfunction (Widlansky and Gutterman, 2011), neurodegeneration (Orsucci et al., 2011), cellular aging (Terzioglu and Larsson, 2007), the damage associated with cerebral ischemia-reperfusion (Chen et al., 2011) and diabetes (Naudi et al., 2012) and its complications (Forbes et al., 2008), Many of the damaging effects of mitochondrially produced ROS may arise from their interactions with mitochondrial proteins (Gu et al., 2010) as well as mitochondrial DNA (mt-DNA) (Costa et al., 2011).

Molecules with an unpaired electron are referred to as oxidants or free radicals, however, it is now increasingly appreciated that 2-electron or non-radical reactive oxygen species such as hydrogen

* Corresponding author.
E-mail address: f.rosenfeldt@alfred.org.au (F. Rosenfeldt).

0531-5565/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.exger.2012.03.010

peroxide can also play important roles, not only in cell signalling but when present at higher concentrations, in cellular injury (Mak and Newton, 2001). During regular metabolic reactions, molecular oxygen is used to generate adenosine triphosphate (ATP) from adenosine diphosphate (ADP), a process known as oxidative phosphorylation, but also results in the generation of the superoxide radical ($O_2^{\cdot-}$) (Obayan, 2004). Through dismutation reactions with antioxidants (see later, Section 2.3) ROS such as superoxide anions ($O_2^{\cdot-}$), generate hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH•), a third generation radical derived from H_2O_2, in the presence of iron (Thannickal and Fanburg, 2000) (Fig. 1). In low concentrations these ROS have important roles in regulating normal cellular function. For example, ROS such as superoxide anions, hydroxyl radicals and H_2O_2 are involved in response to noxious conditions such as hypoxia and the destruction of cells infected with viruses. Reactive nitrogen species (RNS) such as nitric oxide (NO) produced by nitric oxide synthase (NOS) influence vascular tone and inflammation (Cooke et al., 2003; Valko et al., 2007).

Recent data suggest an important role for ROS in the process of autophagy, an important pro-survival process, where cells selectively remove damaged mitochondria, missfolded proteins and toxic metabolites. In this process, ROS trigger the early responses of autophagic processes by eliminating potential sources of pro-apoptotic stimuli (Marchi et al., 2012). However, surplus production of these ROS/RNS results in the destruction of proteins, DNA and lipids which can lead to cellular damage and disease.

Although ROS can target any component of the cell, they generally react with the first structure they encounter, frequently the lipid components of cell or organelle membranes, although proteins and DNA are often targets, particularly in mitochondria where mt-DNA is in close physical proximity to sites of ROS production. However proteins, both structural and enzymatic are vulnerable to free radical-mediated denaturation, which results in the subsequent loss of important cellular functions, such as growth, division and repair. ROS such as superoxide, hydroxyl radicals and other oxygen free radicals are known to cause DNA base hydroxylation, crosslinking or scission of DNA strands that can lead to disruption of cellular integrity and lysis through processes such as apoptosis and necrosis (Marchi et al., 2012). Indeed, ROS are known to affect apoptotic pathways, and in particular, the expression of important pro-apoptotic mediators. In particular, H_2O_2 is known to promote apoptosis through the activation of the MAP kinase pathways, and JNK in particular (Pantano et al., 2003).

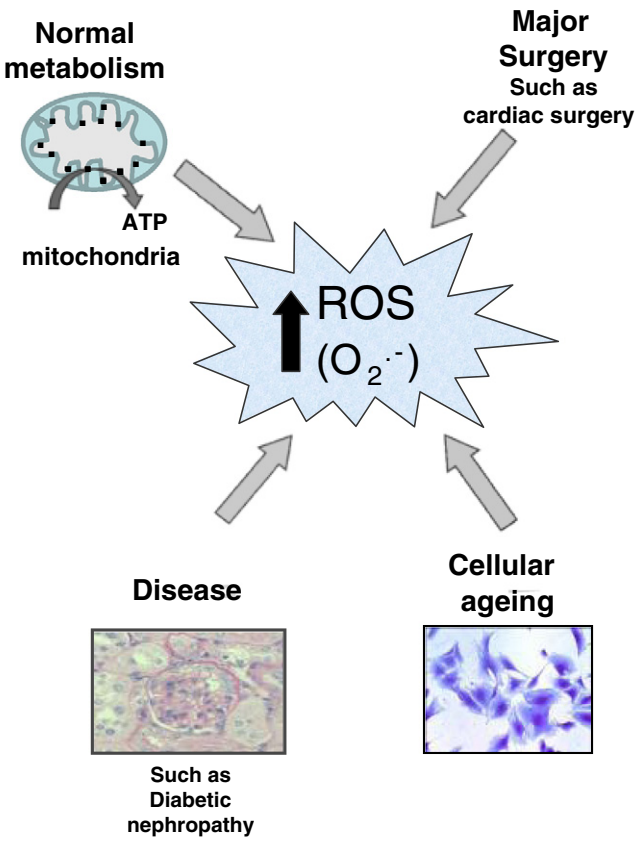

Fig. 1. Generation of reactive oxygen species.

2.3. Antioxidant defences

To prevent cellular damage, the body has developed inbuilt defence mechanisms comprised of endogenous antioxidants to counteract the destructive effects of oxidants and maintain optimal health (Sies, 1997; Valko et al., 2007). In order to reach a level of cellular homeostasis or "redox equilibrium", various intrinsic defence systems involving enzymatic and non-enzymatic pathways with protective and repair mechanisms are involved (Sies, 1997; Valko et al., 2007) (Table 1). Perhaps the most intensively studied cellular antioxidants are the enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). These enzymes located in cells and bodily fluids, work together to prevent oxidative damage by limiting ROS levels. As part of the antioxidant pathway, SOD accelerates the conversion of superoxide to H_2O_2 in a first step; while catalase and GPx convert H_2O_2 to water in the second step of the pathway (Fig. 2) (de Haan et al., 2003; Finkel and Holbrook, 2000). The thioredoxin/peroxiredoxin system of antioxidant enzymes is yet another system of particular relevance to the neutralization of ROS and the maintenance of ROS homeostasis within a cell (Kang et al., 1998). The thioredoxin (TRX) system consists of TRX, TRX reductase (TrxR) and NADPH (Yamawaki et al., 2003). This is particularly relevant to the maintenance of ROS homeostasis within mitochondria where TRX2, TrxR2 and NADPH are located and Prx3 and Prx5 are targeted to the mitochondrial matrix. Furthermore, non-enzymatic antioxidants such as phenolic compounds, vitamin C (ascorbic acid), vitamin E (α-tocopherol) and glutathione confer protection by intercepting and converting oxidants to non-radical end products or transferring radicals to areas where their damaging effects will be less detrimental (e.g. from a hydrophobic to aqueous phase) (Sies, 1997). The glutathione redox cycle for example breaks the chain of reactions which form reactive species by lowering H_2O_2 levels and in turn lowering hydroxyl radical formation (Fernández-Checa et al., 1998).

CoQ_{10} is an important vitamin-like substance found predominantly in mitochondrial membranes and is involved in various mitochondrial functions including the production of ATP, ROS scavenging, gene regulation and enhancing immune system function (Boreková et al., 2008). Since mitochondria are highly susceptible to ROS damage, CoQ_{10} is an important antioxidant in the protection of mitochondrial function. Furthermore, CoQ_{10} protects the stability of cell membranes, protects DNA from free radical-induced oxidative damage and is capable of recycling and regenerating other antioxidants, such as ascorbic acid

Table 1
Enzymatic and non-enzymatic antioxidants.

Enzymatic antioxidants	Non-enzymatic antioxidants	
	Lipophilic	Hydrophilic
Superoxide dismutase	Vitamin E	Vitamin C
Glutathione peroxidase	Ubiquinol (Coenzyme Q_{10})	Albumin
Catalase	Flavinoids	Uric acid
Peroxiredoxin		
Glutathione peroxidase		
Ascorbate peroxidase		