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Endogenous Antioxidants: A Review of their Role in Oxidative Stress

Tomás Alejandro Fregoso Aguilar,
Brenda Carolina Hernández Navarro and
Jorge Alberto Mendoza Pérez

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Abstract

Oxidative stress (OxS) constitutes a disturbance caused by an imbalance between the generation of free radicals and antioxidant system, which causes damage to biomolecules. This, in turn, may lead the body to the occurrence of many chronic degenerative diseases. Therefore, it is very important to know the functioning of those endogenous (and exogenous) antioxidants systems to prevent such diseases. Due to evolutionary conditions in living beings, among other functions have been developed and selected defense systems against the deleterious action of free radicals. Such systems are intrinsic in cells (at level intracellular and extracellular) and act together with the dietary exogenous antioxidants. All these antioxidant systems have very important role in preserving the oxide/reduction equilibrium in the cell. To understand the role of the transcription factor Nrf2 in regulating the processes of antioxidant defense, it must also know the role of many of the endogenous antioxidants that occur because of its activation. Therefore, this chapter makes a literature review of the most important general aspects of endogenous antioxidant systems, which will provide another point of view from which to approach the study and treatment of many chronic degenerative diseases, such as diabetes, hypertension, and Parkinson.

Keywords: oxidative stress, endogenous antioxidants, free radicals, catalase, glutathione

1. Introduction

The aerobic organisms use mitochondria as the main generator of energy for the realization of its vital functions. To do this, these organelles produce ATP through reactions of oxidation and reduction and attach to the tricarboxylic acid cycle with the electron transport chain. This happens due to the oxidation of the food and of the NADH and FADH₂, produced in different metabolic pathways, such as glycolysis, β -oxidation, and the same Krebs cycle. However, these reactions invariably result in the generation of reactive oxygen species (ROS) compounds that are unstable by having final layer of electrons unpaired and that, in trying to stabilize itself sequester electrons from other biomolecules, making them also destabilize and, therefore, is no longer able to perform their duties properly, thus altering the homeostasis and, ultimately, causing cell death. Due to the current oxidant characteristics of the atmosphere on our planet, organisms are affected by imbalances in the oxidation-reduction reactions, not only on many of their metabolic reactions but also on external factors, such as microbial infections, xenobiotics, toxins from the diet, radiation, environmental pollution, and so on. All this in conjunction can contribute to the generation or aggravation of many diseases, such as cancer, diabetes, Parkinson and so on [1]. Other authors theorize that this imbalance in redox reactions has worked as an evolving pressure in order to develop effective mechanisms to eliminate the oxygen toxicity; this allowed the evolution of higher forms of living organisms, which are much more specialized and protected against negative actions of ROS (**Figure 1**) [2, 3].

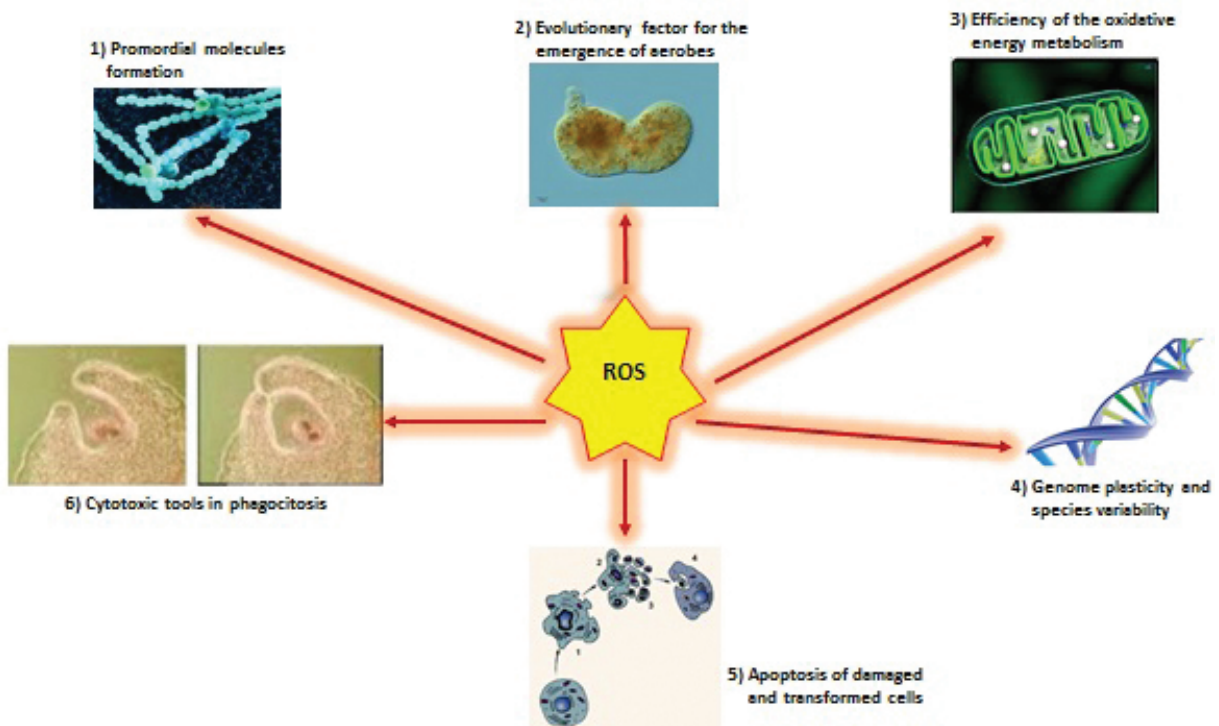


Figure 1. Evolving pressure of ROS in evolution of life in oxygen-rich atmosphere [2].

The reactive oxygen species can be either endogenous or exogenous [4, 5]. The transport chain of mitochondrial electron is the main source of endogenous ROS; the reduction in O_2 to H_2O_2 is carried out in four steps during which occur ROS and are as follows:

1. $O_2 + e \rightarrow O_2^\circ$ Superoxide radical
2. $O_2^\circ + H_2O \rightarrow H_2O^\circ$ Hydroperoxyl radical
3. $H_2O^\circ + e + H \rightarrow H_2O_2$ Hydrogen peroxide
4. $H_2O_2 + e \rightarrow OH^\cdot + OH^\circ$ Hydroxyl radical

Thus, these ROS being unstable, seek its stabilization capturing electrons from other biomolecules, altering its function, and therefore, strategies have been developed to maintain low concentrations of these ROS, thanks to the activity of endogenous antioxidant agents that may be of a protein or nonprotein nature. In **Figure 2**, it is described in a general way, the way in which they can generate ROS from the mitochondrial respiratory chain and it's debugging by some endogenous antioxidants [6–9].

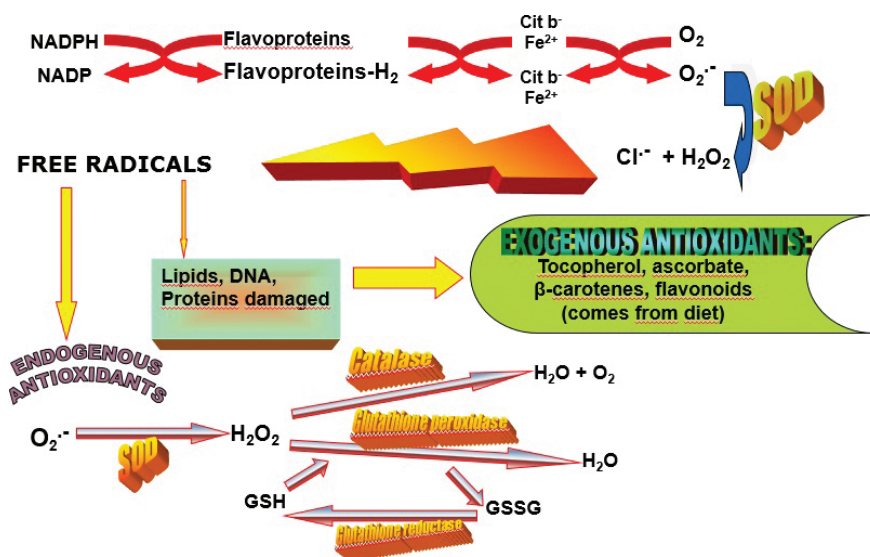


Figure 2. Formation of free radicals from the mitochondrial respiratory chain (modified from Ref. [10]).

Biomolecules in living organisms are highly exposed to oxidative stress, which is the main cause of damage to nucleic acids, proteins, carbohydrates, and polyunsaturated lipids, which finally develops cells mortality [11]. Reactive species derived from molecular oxygen (ROS) and nitrogen (RNS) have been deeply studied and new radical species such as chlorine (RCS), bromine (RBS), and sulfur-derived species have also been identified.

The “Free radicals” are molecular compounds with one-electron deficiency also denominated impaired electron in their outer orbital, examples of ROS are superoxide anion, hydroxyl radical, and hydrogen peroxide; nitric oxide and peroxynitrite are included in RNS.

Curiously, free radicals while having important chemical differences share similar mechanisms for damage at the level of biomolecules [11]. The oxidation of amino acid residues, the

subsequent formation of protein aggregates by cross-linking and the production of protein fragments may result in the loss of activity and inactivation of enzymes and metabolic pathways, finally ending up with cell death [12].

Some authors have reported that at a physiological level there is a relation between the inactivation mechanisms by antioxidant system and the generation of ROS. This is related with a higher production of ROS when an organism presents harmful conditions, resulting in high oxidative stress conditions. In addition, if ROS are accumulated, the endogenous antioxidant defenses will not be enough. And immediately, oxidative modification in cellular membrane or intracellular molecules is performed in order to equilibrate the ROS antioxidant defense mechanisms [13].

In this chapter, a brief updated description is made of the main endogenous antioxidants, such as glutathione, lipoic acid, bilirubin, ferritin, superoxide dismutase, catalase, glutathione peroxidase, among others, as well as their participation in various pathological processes.

2. Endogenous nonprotein antioxidants

Four well-known main antioxidant mechanisms against oxidative damage have been largely studied (1) sequestration of transition metal ions, (2) scavenging and quenching of ROS and RNS, (3) ending of chain reactions by free radicals, and (4) molecular repairing of radical's damages.

2.1. Glutathione

GSH (L- γ -glutamyl-L-cysteinyl-glycine) is a non-protein thiol that reaches millimolar concentrations in most cell types. Its reduced form (GSH) is biologically active. It functions as an antioxidant defense against reactive oxygen/nitrogen species (ROS/RNS) as also with detoxication enzymes like GSH peroxidases and GSH-S-transferases [14, 15]. The GSH/glutathione disulfide is the major redox couple in animal cells [16].

Mitochondrial protection is exerted by GSH versus radicals and oxidant species by the contribution of a group of nutrients that can directly or indirectly protect mitochondria from oxidative damage and improve mitochondrial function [17]. The protection mechanism of these molecules prevents the generation of oxidants, scavenging free radicals, or inhibiting oxidant reactivity. Other mechanism includes increasing cofactors of mitochondrial enzymes that increase the kinetic constant of enzyme activity, which represents a protecting mechanism from further oxidation. The activation of enzymes such as hemeoxygenase 1 and NAD(P)H:quinone oxidoreductase 1, neutralize ROS and increase mitochondrial biogenesis [18].

2.2. Alpha-lipoic acid (LA)

Alpha-lipoic acid (LA) can deliver antioxidant activity in nonpolar and polar mediums and present antioxidant effect in its oxidized (LA) and reduced (DHLA [dihydrolipoic acid])

forms [19]. LA can actuate its antioxidant effect in any subcellular compartment of the body [20], and it is effective in recharging enzymes in the mitochondria [21]. Diabetes mellitus and neurodegenerative diseases can be controlled with LA due to the antioxidant properties of lipoate/dihydrolipoate system, influencing the tissue concentration of the reduced forms of other antioxidants. However, some evidences indicate that lipoic acid might also counteract NF- κ B (Nuclear factor kappa-light-chain-enhancer of activated B cells) activation triggered by oxygen shock [22].

2.3. Coenzyme Q

Coenzyme Q (CoQ) is a benzoquinone derivate localized in the mitochondrial respiratory chain as well as in other internal membranes. CoQ is directly involved in energy transduction and aerobic adenosine triphosphate (ATP) production because it transports electrons in the respiratory chain and couples the respiratory chain to oxidative phosphorylation [23]. This compound is considered as an endogenously synthesized lipid soluble antioxidant, present in all membranes. The protective effect is extended to lipids, proteins, and DNA mainly because of its close localization to the oxidative cellular events [24]. In the inner mitochondrial membrane, CoQ has at least four different functions such as a redox carrier, antioxidant, activator of uncoupling proteins, and being a factor influencing the permeability transition pore (PTP). Also, it is proposed that lysosome contains a NADH-dependent CoQ reductase involved in translocation of protons into the lysosomal lumen [24].

2.4. Ferritin

Ferritin is an iron-binding protein. Which consists of its cytosolic form of two subunits, termed H and L. Twenty-four ferritin subunits assemble to form the apoferritin shell. Each apoferritin molecule is sequestering iron atoms [25]. The main function of ferritin is to limit Fe (II) available to participate in the generation of oxygen-free radicals (ROS). It is not surprising that oxidant stress activates multiple pathways of ferritin regulation. In addition, it is proposed that ferritin provokes gene and protein alterations that coordinately limit oxidant toxicity. Some studies had demonstrated that exposure to heme group causes ferritin synthesis in endothelial cells and concordantly reduced their cytotoxic response to hydrogen peroxide [26, 27].

2.5. Uric acid

Uric acid is an intermediate product of the purine degradation pathway in the cell. Uric acid is degraded further by the enzyme uricase but there is evidence that in humans and great apes, the uricase gene was inactivated during hominoid evolution [28]. According to different demonstrations, uric acid and albumin are the two major antioxidants in human plasma, contributing 24% and 33%, respectively, of the total antioxidant activity [28]. It is well established that high blood levels of uric acid in humans protects cardiac, vascular, and neural cells from oxidative injury [29, 30]. The ability of urate to scavenge oxygen radicals and protect the erythrocyte membrane from lipid oxidation was first described by Kellogg and Fridovich [31], and was characterized further by Ames et al. [32].

The antioxidant effects of uric acid have been proposed particularly in conditions such as multiple sclerosis, Parkinson's disease, and acute stroke [13, 33–35]. While chronic elevations in uric acid are associated with increased stroke risk [36, 37], acute elevations in uric acid may provide some antioxidant protection. As a demonstration of this, cultured rat hippocampal neuronal cells were protected from oxidative stress with uric acid [38], and administration of uric acid 24 hours prior to middle artery occlusion also attenuated brain injury induced by acute ischemia in rats [38]. Uric acid is an antioxidant mainly in a hydrophilic environment, which is probably a major limitation of the antioxidant function of uric acid.

2.6. Bilirubin

Heme oxygenase-1 (HO-1) is the enzyme that generates carbon monoxide, iron, and biliverdin using the heme fraction as a substrate [39], and biliverdin reductase that reduces biliverdin to bilirubin being this molecule the ending product of the heme degradation. Bile pigments are potent *in vitro* scavengers of free radicals [39] reinforcing the concept that HO-1 is a crucial inducible antioxidant system engaged to assist against oxidative injury and other forms of cellular stress. Bilirubin has a role in the prevention of ischemic injury in isolated hearts [40], attenuation of oxidative damage in cultured cells [41], and modulation of airway smooth muscle contractility [42]. Also, bilirubin defends neurons against hydrogen peroxide-mediated damage [43], where a redox cycle between biliverdin and bilirubin appears to amplify this protective effect [44]. Recently, administration of biliverdin *in vivo* demonstrates to protect rat kidney, liver, and gut from ischemia-reperfusion injury [45–47]. *In vitro* experiments gave evidence that bile pigments scavenge NO and NO-related species [48]. Epidemiological studies sustain a beneficial action of bilirubin against the development of cardiovascular disease and cancer [49, 50].

The protection of bilirubin against classic coronary heart disease risk factor was demonstrated by Troughton et al. [51] and an increase of serum total bilirubin level is associated with the decrease of peripheral arterial disease [52]. Elevated serum bilirubin concentration protects from different coronary and microvascular dysfunctions and possibly against coronary atherosclerosis [53].

3. Endogenous protein antioxidants

This chapter provides an overview of the three protein antioxidants (with enzymatic activity), which are the first line of defense against oxidative stress on the body: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase.

3.1. Superoxide dismutase (SOD)

Superoxide dismutases (SODs) are a group of key enzymes functioning as the first line of antioxidant defense by virtue of the ability to convert highly reactive superoxide radicals (dismutation) into hydrogen peroxide and molecular oxygen [54]. They have identified four isozymes of superoxide dismutase: (i) SOD1 is a metalloprotein binding copper and

zinc ions that are localized in the cytosol of the cell [55, 56], (ii) SOD2, localized in the mitochondria and it is associated with the manganese or iron ions [56, 57], (iii) SOD3, localization is extracellular and is also associated with the copper and zinc, although it has a high molecular weight [56, 58] and it has high affinity for heparin and heparin sulfates [59], and (iv) SOD4 associated with nickel and found in various aerobic bacteria found in soil of class of *Streptomyces* [60, 61].

SOD1 (associated Cu/Zn) is present in a lot of Gram-negative bacteria pathogens and eukaryotes [62], although protists appear to lack SOD1 [63]. Plants contain SOD1 in the cytosol and in the chloroplast [64] and also been found in plant peroxisomes [65]. Animal cells possess dimeric SOD1 in the cytoplasm and in the nucleus, the intermembrane space of mitochondria [66] and peroxisomes [67]. However, the precise intracellular location of SOD1 is responsive to the metabolic state of cells and tissues [68]. SOD2 may be associated to Mn, Fe, or two ions (Mn/Fe).

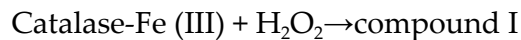
SOD1 (associated with Cu/Zn) requires Cu and Zn for its biological activity; the loss of Cu results in its complete inactivation and is the cause of multiple diseases in human and animals [69]. It has a molecular weight of about 32 kDa. This group of enzymes works together with glutathione peroxidase and catalase to convert the superoxide radical into hydrogen peroxide. This enzyme has also been identified as a cause of familiar forms of amyotrophic lateral sclerosis (ALS) due to copper homeostasis is altered. Indeed, the total amount of copper ions in the mouse spinal cord, a region the most affected by ALS, is significantly elevated by expressing SOD1 [70, 71].

SOD2 has a molecular weight of about 96 kDa [59]. The SOD4 associated with Ni was discovered in *Streptomyces* [72] but has also been found in some genera of actinobacteria and cyanobacteria [73]. There is evidence that SOD2's levels to be regulated by MAPK activity in vitro [74, 75], also substances such as anthocyanins, polyphenols, alkaloids, and phytoalexins, are responsible for the induction of SOD2 mRNA expression; SOD2 can be induced by some inflammatory cytokines [76, 77], including tumor necrosis factor (TNF)- α , which may compensate for the inflammatory effect. The valine-to-alanine substitution in SOD2 Ala-16Val single nucleotide polymorphism (SNP) decreases the transport efficiency of the enzyme into the mitochondria and modifies the antioxidant defense against ROS. This process is an important pathophysiological mechanism in development and progression of diabetes and its complications [78, 79].

The SOD3 enzyme has many physiological effects; there are studies that reported reduced cardiovascular damage by recombinant administration of SOD3 [80, 81]. In the lung, mice with decreased levels of SOD3 had a significantly shortened life span and experienced death associated with lung edema under conditions of hyperoxia [82].

3.2. Catalase (CAT)

Catalase is a tetrameric porphyrin-containing enzyme that is located mainly in peroxisomes. It catalyzes the conversion of H_2O_2 to water and molecular oxygen in two steps [59, 83, 84]:



The presence of bound NADPH in each subunit may help protect the enzyme from being inactivated by H_2O_2 [83]; the highest activity of this enzyme appears to be in the liver and erythrocytes [85]. Some reports indicate that factors such as stress and brain-derived neurotrophic factor (BDNF) are involved in the antioxidant capacity of many antioxidants endogenous; to this respect, Hacıoglu et al. [86] studied a murine model where mice with BDNF deficiency under stress conditions showed an increment in CAT enzyme activity with respect to stressed wild-type mice, indicating that the ability to scavenge free radicals was diminished; and this suggest that normal wild-type mice have a better stress tolerance than BDNF heterozygous mice [86]. Catalase along with other antioxidant enzymes have been considered as biomarkers of oxidative stress in various organs; for example, in streptozotocin-induced diabetic rats, hepatic levels of these enzymes are dramatically reduced, although treatment with various plants can ameliorate this effect [87, 88]. For several decades, it was established that the levels of many antioxidant enzymes, including catalase, decline with age [89]. To this respect, Casado et al. [90] reported that in elderly patients with ischemic disease, COPD, and other diseases typical of old age, SOD levels are increased, but CAT levels are decreased; a phenomenon which they interpreted as a compensatory effect to balance the antioxidant system.

3.3. Glutathione peroxidase (GPx)

This enzyme can exist in two forms: selenium-dependent and selenium-independent, each with different subunits and different active sites [84, 91]. GPx catalyzes the reduction of H_2O_2 or organic peroxide (ROOH) to water or alcohol [59, 92]; this process occurs in the presence of GSH, which is converted into GSSG (oxidized glutathione) during this reaction. The reaction has special significance in the protection of the polyunsaturated fatty acids located within the cell membranes where the enzyme functions as a part of a multicomponent antioxidant defense system within the cell [93]. There are four isoforms in humans, cytosolic and mitochondrial (GPx1), cytosolic (GPx2), extracellular (GPx3), and the phospholipid peroxide (GPx4) [91, 94, 95]. The kidney and liver are the organs with the highest amount of GPx [85]. It is known that there is a competition between GPx and Cat for H_2O_2 as a substrate [59]. It has been found that in many other organs and tissues, such as the dorsal root ganglion (GDR), the GPx is the first enzyme that is activated under high levels of EROS, indicating the importance of this enzyme as a first line of defense against stress oxidative [96, 97]. Furthermore, have been found associations in the levels of this enzyme with skin diseases such as vitiligo; Asian vitiligo patients showed lower levels of GPx than the controls, but no difference was shown between populations of Caucasian vitiligo patients and Asian vitiligo patients [98].

Recent studies have involved GPx4 in carcinogenic processes, including the ferroptosis (nonapoptotic form of cell death that can be triggered by small molecules, which inhibit the biosynthesis of glutathione or GPx4); it was found that inactivation of GPx4 is crucial for the ferroptosis development and that overexpression of this enzyme blocks the action of the RSL-3,

small GTPases called RAS, which is attacked by oncogenic RAS selective lethal (RSL) molecules; however, how RSL3 bind GPx4 to inhibit its activity is not known [99, 100].

4. Conclusions

As the reader will notice, endogenous antioxidants work as one big system that complements its main constituents to maintain redox balance in the body. When ROS levels rise and threaten the homeostatic processes of the human body, endogenous antioxidants are activated. The majority of them are expressed when some factors, such as factor Nrf2, are activated. However, endogenous antioxidants also work together with exogenous antioxidants from diet to decrease levels of ROS.

Reactive oxygen species could have or have not harmful effects, but they can also play a role in signaling different growth factors. This conclusion is supported by the hypothesis that decreased levels of ROS may lead to degenerative diseases, generating an interesting concept that ROS must be regulated but not eradicated.

In this chapter, some functional generalities of endogenous antioxidants were reviewed, and some aspects of their activity were discussed under conditions of high ROS levels; from this it follows that, although all of them work together, perhaps protein antioxidants, which have enzymatic activity, such as superoxide dismutase, catalase, and glutathione peroxidase, constitute the first line of defense against the oxidative stress.

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Author details

Tomás Alejandro Fregoso Aguilar^{1*}, Brenda Carolina Hernández Navarro¹ and Jorge Alberto Mendoza Pérez²

*Address all correspondence to: fisiobiologo@hotmail.com

¹ Departamento de Fisiología, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, Mexico

² Departamento de Ingeniería en Sistemas Ambientales, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, Mexico

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