Chapter 1

Regulation of the Redox Environment

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Abstract

All organisms maintain a strict redox environment, crucial for cell physiology, by preserving the pro-oxidant compounds generated during cell metabolism and from antioxidant system elements. In pathophysiological conditions, the redox environment is altered, causing oxidative stress, cell damage, and eventually cell death. In this chapter, we review the elements involved in the redox environment, including the oxidant, antioxidant, and glutathione systems. In addition, we summarize the physicochemical bases of the redox environment and the biological functions of the glutathione cycle. Finally, we propose a redox environment regulation model that considers some regulated variables that are actively involved in maintaining the redox environment: reactive oxygen species, reactive nitrogen species, and the redox couple $GSH^2/GSSG$.

Keywords: Redox environment, oxidant system, ROS, antioxidant system, glutathione

1. Introduction

All organisms maintain a strict redox environment, crucial for cell physiology, by preserving the pro-oxidant compounds generated during cell metabolism and from antioxidant system elements. In pathophysiological conditions, the redox environment can be altered, causing oxidative stress, cell damage, and eventually cell death. Two regulated variables are actively involved in maintaining the redox environment: the concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the redox couple $GSH^2/GSSG$.

2. Main body

2.1. The redox system

Oxidizing system elements are free radicals and reactive species of various atoms or compounds such as oxygen, nitrogen, iron, copper, and glutathione (GSH). With respect to free radicals, they are molecules or molecular fragments containing one or more unpaired electrons in their atomic or molecular orbitals, which cause the molecule to be very reactive [1]. However, not all reactive species are free radicals: at a pH of 7.4 ± 0.1 they may be electroneutral molecules, able to donate electrons to free radicals, and oxidize transition metals present in cells. Although several groups of compounds are considered oxidants, those considered to be the most important from the physiological point of view are those compounds derived from oxygen and nitrogen: ROS and RNS. Under physiological conditions, the presence of ROS and RNS is required for diverse signaling pathways [2,3]. Among the most important elements of the oxidizing system in living organisms are superoxide anion radicals ($O_2^{\cdot-}$), hydroxyl groups ($^{\cdot}OH$), hydrogen peroxide (H_2O_2), nitric oxide (NO), and peroxynitrite ($ONOO^-$) groups.

The presence of an electron in molecular oxygen (O_2) forms the free radical superoxide ($O_2^{\cdot-}$), which is considered to be a primary ROS that can interact with other molecules to generate secondary ROS or RNS [2,3]. Various metabolic pathways within the cell generate $O_2^{\cdot-}$, but the principal incomplete reduction route occurs in the mitochondrial respiratory chain: between 1 and 4% of $O_2^{\cdot-}$ is formed by the incomplete reduction of the total O_2 consumed in complex I (NADH: ubiquinone oxide-reductase) and III (cytochrome C oxide-reductase). The production of $O_2^{\cdot-}$ is also promoted by enzymatic complexes like xanthine oxidase (EC 1.1.3.22), cytochrome P450, nitric oxide synthase (NOS), or monoamine oxidase (EC 1.4.3.10).

Figure 1 shows how $O_2^{\cdot-}$ promotes the formation of H_2O_2, $^{\cdot}OH$, and $ONOO^-$ by various chemical pathways.

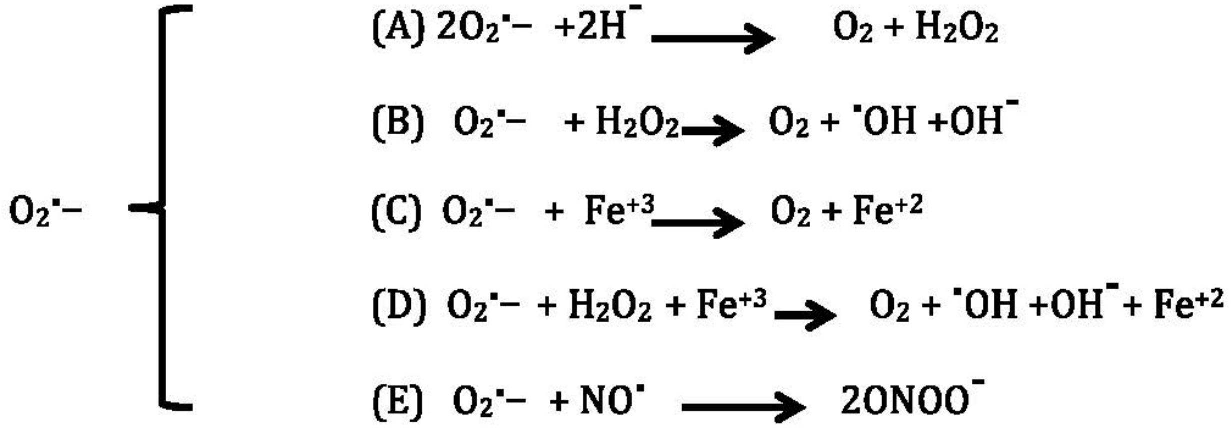

Figure 1. Reactive oxygen and nitrogen species formation from the superoxide anion radical. A) $O_2^{\cdot-}$ dismutation, which can be formed spontaneously or can be catalyzed by SOD. B) Haber-Weiss reaction. C) Fe^{+3} to Fe^{+2} reduction. D) Fenton reaction. E) Peroxynitrite ($ONOO^-$) formation.

In addition to forming ROS and RNS, $O_2^{\cdot -}$ can also inactivate enzymes involved in the antioxidant system, or in metabolic and signaling pathways such as catalase (EC 1.11.1.6), glutathione peroxidase (EC 1.11. 1.19), glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12), ornithine decarboxylase (EC 2.1.3.3), and adenylyl cyclase (EC 4.6.1.1) [1,4]. For example, H_2O_2 is formed by spontaneous dismutation or catalyzation by superoxide dismutase (SOD, EC 1.15.1.1). Although this compound has practically no oxidative effect on biomolecules, it plays a major role in the oxidative stress process by generating $^{\cdot}OH$ groups. When H_2O_2 molecules pass through cell membranes, they reach compartments containing transition metals, such as Fe^{+2} or Cu^{+}, which can oxidize them and induce the formation of $^{\cdot}OH$ radicals. Thus, $^{\cdot}OH$ radicals may be formed through pathways involving $O2^{\cdot -}$ radicals or H_2O_2 [1,2,3,5].

The neutral form of the hydroxide ion (OH^-) is an $^{\cdot}OH$ group with high reactivity (10^7-10^{10} M^{-1} s^{-1}) and a very short half-life (10^{-9} s) [6]. Thus, when $^{\cdot}OH$ groups are produced *in vivo*, they react near their site of formation and are very toxic to biomolecules such as DNA, proteins, and membrane phospholipids.

Many investigators consider NO to be radical because it contains an unpaired electron in its $2\pi_y^*$ orbital. When NOS (EC 1.14.13.39) metabolizes the conversion of L-arginine to L-citrulline, NO radicals are formed [7]. Under physiological conditions, NO is involved in processes such as neurotransmission, blood pressure regulation, defense mechanisms against pathogens, and immune response regulation [2]. In aqueous media, NO has a short half-life but in a hypoxic environment it presents greater stability with a half-life of more than 15 s [8]. The toxic effect of NO is in fact closely related to the formation of the secondary RNS $ONOO^-$, which occurs when NO is overproduced. $ONOO^-$ has a very high reaction constant (7×10^9 $M^{-1}s^{-1}$), making it a powerful membrane-oxidizing agent that produces lipid peroxidation [2]. In fact, the reaction between $ONOO^-$ and carbon radicals ($^{\cdot}CO_2$) produces the secondary RNS, a nitrite radical ($^{\cdot}NO_2$). These radicals mediate protein nitrotyrosilation by reacting with the hydroxyl group of the tyrosine amino acid (TyrOH) to produce the tyrosyl free radical ($Tyro^{\cdot}$), which can then be neutralized by another $^{\cdot}NO_2$ [9].

2.2. Antioxidant system

In aerobic organisms, various processes such as growth, cell differentiation, apoptosis, and immune response require low concentrations of oxidants such that an increase generates a state of oxidative stress that causes cellular malfunction and even death. Therefore, an antioxidant system capable of neutralizing ROS and RNS is essential to the optimal function of many cellular operations.

The antioxidant system is divided into two subsystems: enzymatic and non-enzymatic. Within the non-enzymatic antioxidant system are organic compounds such as ascorbic acid, α-tocopherol, carotenoids, flavonoids, and reduced GSH. While enzymes such as catalase (EC 1.11.1.6), glutathione peroxidase (GPX, EC 1.11.1.19), and SOD are considered the first line of enzymatic antioxidant defense, other enzymes, such as glutathione reductase (GR, EC 1.6.4.2), glutathione S-transferase (GST, EC 2.5.1.18), and thioredoxin reductase (EC 1.6.4.5) [1,2,5,10], also contribute to defense. Thus, maintaining the oxidation concentration of an organism at homeostasis is complex and must be executed within narrow limits. Figure 2 shows an overview of the interactions between the oxidant and the antioxidant system.

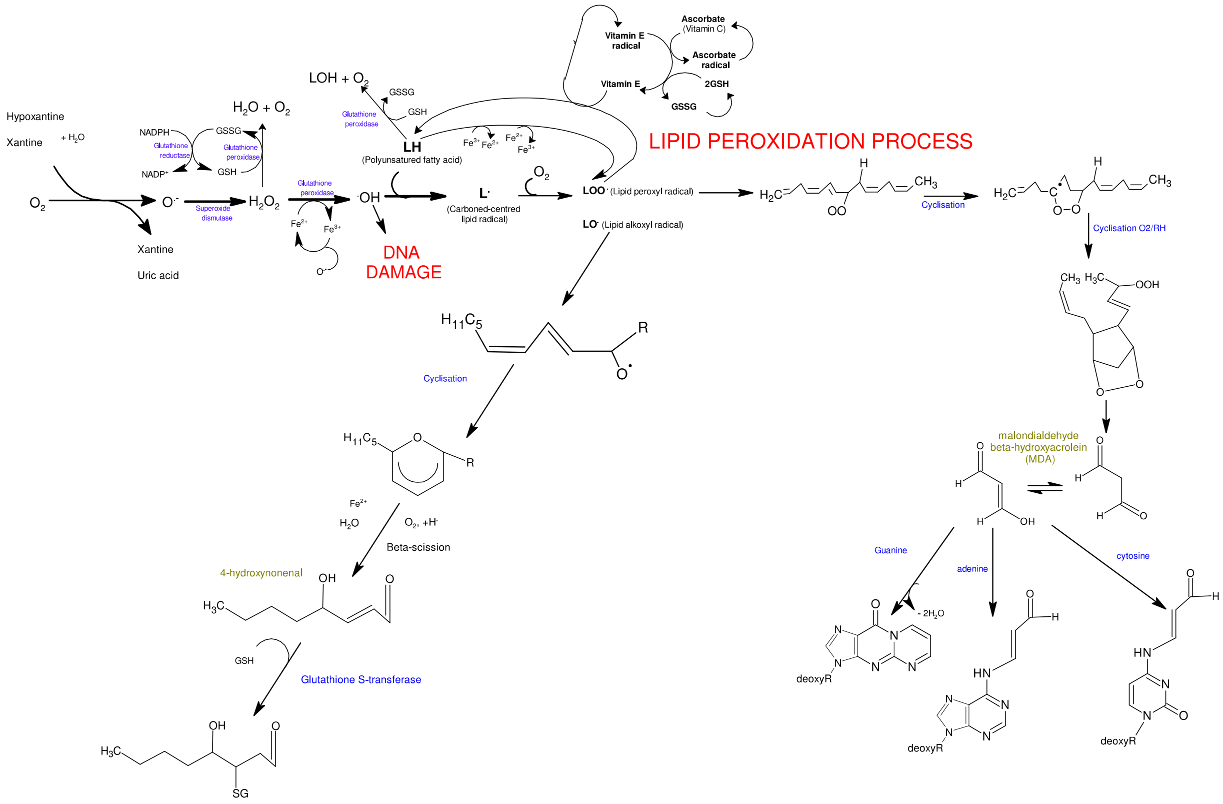

Figure 2. Reduced glutathione (GSH) role and the participation of other antioxidants (lipoic acid, vitamins C and E) in the ROS formation and lipid peroxidation. Reaction 1: $O_2^{\cdot -}$ is formatted from the O_2 reduction process mediated by the NAD(P)H oxidase and xanthine oxidase complex or produced by no enzymatic pathways such as those involving semi-ubiquinone in the mitochondrial respiratory chain. Reaction 2: $O_2^{\cdot -}$ is dismutated by superoxide dismutase (SOD) to H_2O_2. Reaction 3: H_2O_2 is neutralized by glutathione peroxidase (GPX) using GSH as cofactor. Reaction 4: Oxidized glutathione (GSSG) is reduced to GSH by reductase glutathione (GR) using NADPH.

2.3. Non-enzymatic antioxidant system

Inside the cell, several nucleophilic organic compounds, such as vitamin A, vitamin E, ascorbic acid, and dihydro lipoic acid, function to neutralize reactive species. For example, α-tocopherol, commonly known as vitamin E, is the most active of tocopherols [11]. It has a chroman ring, which is responsible for its antioxidant activity, while the carbon phytyl side chain of vitamin E remains anchored to the cell membrane (Figure 3). Furthermore, α-tocopherol is the lipid antioxidant that most potently inhibits *in vitro* lipid peroxidation propagation, and it is the dominant tocopherol found in the bloodstream.

Vitamin C or ascorbic acid is essential for the synthesis of various proteins such as collagen, oxytocin, and vasopressin. Its antioxidant capacity lies in the tocopheryl radical reduction that is anchored to cell membranes (reactions 8 to 12 of Figure 2). In addition, ascorbic acid can reduce nitrites and inhibit the formation of nitrosamines [12].

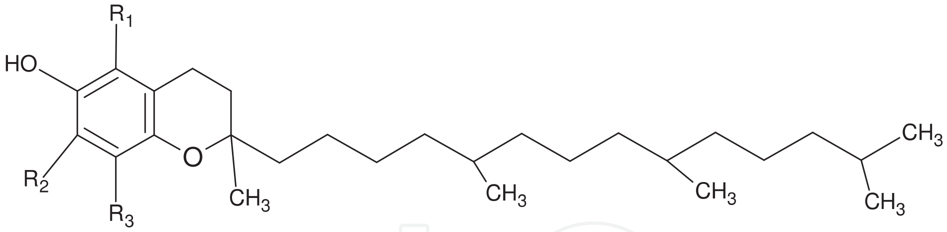

Figure 3. α-tocopherol structure (2R, 4'R, 8'R-tocopherol).

Dihydrolipoic acid (DHLA) or 6,8-dimercapto-octanoic acid is an organic compound that acts as a cofactor for some enzymes. The high electron density in the two SH groups gives the molecule characteristics of a nucleophile, which favors the 1,2-dithiolane-ring formation of the α-lipoic acid (LA) (chemical name: dithiolane-3-pentanoic acid), when it interacts with reactive species. LA and DHLA exhibit direct free radical scavenging properties, and as a redox couple, with a low redox potential of −0.32 V, is a strong reductant [13]. At a concentration of 0.05–1 nM, DHLA neutralizes the species $^{\cdot}OH$, $LOO^{\cdot}$, $ONOO^{-}$, and hypochlorous acid; furthermore it can form stable complexes with Mn^{+2}, Cu^{+2}, Zn^{+2}, and Fe^{+2}, preventing oxidative interactions between these transition metals and biomolecules. Finally, LA/DHLA also functions as an antioxidant by regenerating ascorbic acid when it reduces dihydroascorbate and the semidihydroascorbic radicals [12].

Now we move on to GSH, one of the most important antioxidant organic compounds because of its dependence on the cell redox environment.

2.4. The reduced glutathione-oxidized glutathione (GSH^2/GSSG) ratio and the reduction–oxidation (redox) environment

2.4.1. The physicochemical basis of the redox environment

Cellular processes in aerobic organisms depend on oxidation processes, which promote the mobilization of electrons from organic molecules to oxygen; this produces the energy required to maintain cellular processes. In general, the presence of redox couples controls electron flow, but a reducing environment is also necessary: the redox environment is the sum of all the redox states of the reduction–oxidation couple that are inside the cell (intracellular redox environment) or in the extracellular fluid (extracellular redox environment).

Historically, the term redox state has been used to define the redox environment; however, based on physicochemical studies, Schafer and Buettner defined the redox state as the reduction potential of a redox couple [14]. Figure 4 shows the half-cell reduction potential ($E_{PC1/2}$) change of the redox pair involved in maintaining the redox environment, which involves the transfer of two electrons.

The next redox couple is involved in maintaining the redox environment because the curves generated show a third-order model. The pK_a group is over the physiological pH and the reduced oxidized ratio is 1:100, 1:1000, or greater:

1. NADPH/NADP$^+$ system considering a 0.1-mM concentration.
2. Reduced thioredoxin/oxidized thioredoxin (TrxSH$_2$/TrxSS) system considering a 15-μM concentration.
3. GSH^2/GSSG system considering a 3-mM concentration.

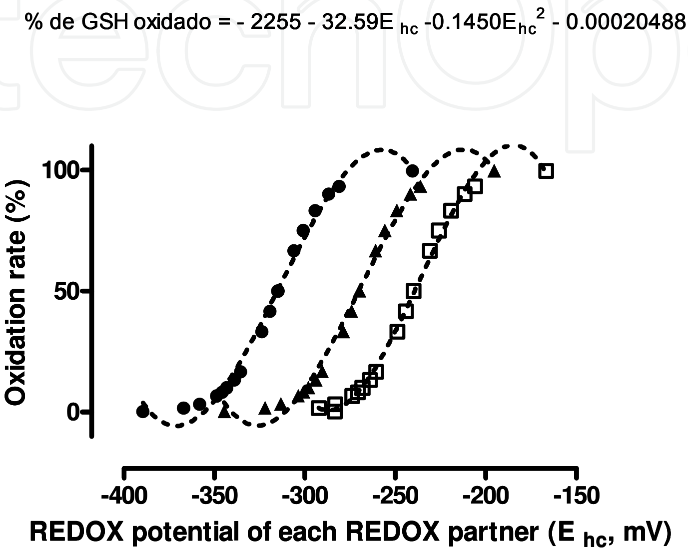

Figure 4. Theoretical reduction potentials of redox couple involved in maintaining the redox environment in response to the oxidized pair proportion increase. Symbol (·) represents the pair NADPH/NADP$^+$, symbol (▲) represents the pair TrxSH$_2$/TrxSS, and symbol (□) represents the pair GSH^2/GSSG. Modified from [14].

Furthermore, although all three intracellular buffer systems contribute to maintaining the redox environment, the most influential couple appears to be GSH^2/GSSG: it had the highest concentration, indicating that it better buffered the potential changes in the range between −300 and −100 mV. Interestingly, varying the reduced pair concentration caused changes in the $E_{PC1/2}$ that are perfectly associated with various processes like cell proliferation, differentiation, apoptosis, and necrosis [14–19].

2.5. The GSH cycle and biological functions

The synthesis of reduced GSH (γ-L-glutamyl-cysteinyl-glycine) occurs in the cell cytoplasm and involves two ATP-dependent enzymatic steps (Figure 5).

GSH synthesis begins when amino acids (e.g., glutamate, cysteine, and glycine) enter the cell. While glutamate and glycine may enter the cell by secondary active transport, cysteine enters by a neutral amino acid transport mechanism. (Some glutamate transporters can also transport cysteine.) In fact, cysteine is considered the limiting amino acid for GSH synthesis because it is present at a lower concentration in the plasma and has a lower Km [20].

Once amino acids have entered the cell, γ-glutamylcysteine synthetase (γ-GCL, EC 6.3.2.2) produces γ-glutamylcysteine. This formation process involves two steps: the interaction

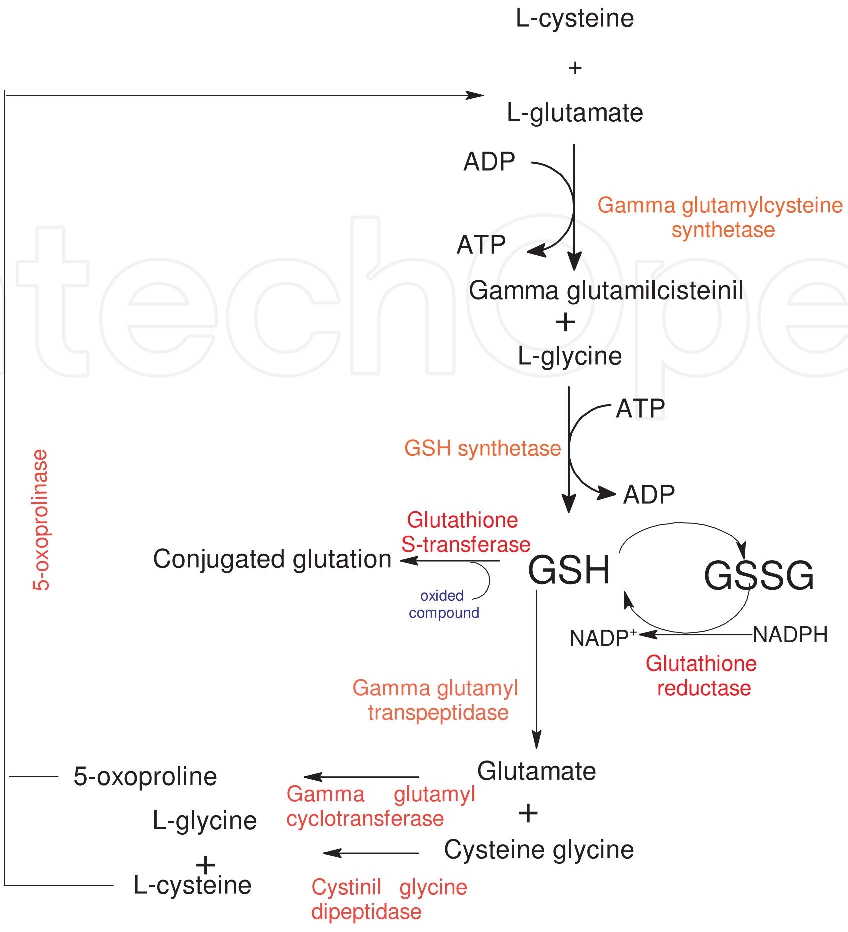

Figure 5. Reduced glutathione (GSH) cycle. Glutathione reductase (GR); glutathione S-transferase (GST), and oxidized glutathione (GSSG).

between glutamate and ATP in the presence of Mg^{2+} to form γ-glutamylphosphate (intermediate) and the intermediate interaction with cysteine and ADP release [21]. The first step is the most important in the formation of GSH because γ-GCL is the GSH synthesis-limiting enzyme. γ-GCL is a heterodimeric enzyme composed of a catalytic subunit called a heavy subunit (γ-GCL_H Mr ≈ 73 kDa) and a regulatory subunit or light subunit (γ-GCL_L Mr ≈ 31 kDa). The activity of γ-GCL depends primarily on the substrates and is inhibited by GSH. Specifically, the activity of γ-GCL_L is controlled by kinases such as protein kinase A (PKA) and protein kinase C (PKC) [22].

Thermodynamically, two processes can occur once the γ-GCL is formed: it may form GSH when it combines with glycine, acting as GSH synthetase (GS, EC 6.3.2.3), or it may interact with the γ-glutamyl cycle transferase to form 5-oxo-L-proline and L-cysteine. The prevailing way depends on the K_m of each enzyme; under physiological conditions, the K_m of GS is 12 times higher than that of γ-glutamyl cycle transferase. Thus, more than 95% of the time, GSH formation is promoted [23].

Once GSH is synthesized, there are several processes in which it participates:

1. Hydrolyse plasma GSH hydrolysis for cell GSH *in novo* synthesis; for example, when hepatocytes secrete GSH, another cell can hydrolyze it in its precursors (cysteinyl-glycine and glutamate) by γ-glutamyl-transpeptidase (γ-GT, EC 2.3.2.2) that are expressed on the outer plasma membrane. Compounds, such as cysteinyl-glycine or its S-conjugates, may be subject to peptidases, causing them to form free amino acids that can be introduced into the cell and initiate GSH formation [23,24].

2. Detoxify electrophiles to conjugate electrophiles with α and β unsaturated carbonyls by glutathione S-transferase (GST, EC. 2.5.1.18). This reaction results in electrophile removal and glutathione S-conjugate metabolism by the γ-GT enzyme and cysteinyl-glycine peptidase [24]. However, this process is not always beneficial for the cell because sometimes more toxic species can be produced, as we will discuss later.

3. Detoxify hydrogen peroxide by glutathione peroxidase (GPX, EC 1.11.1.19) [25].

4. Maintain ascorbic acid and vitamin E levels [11,12].

5. Communicate intracellular processes as internal modulator of several signaling pathways [26].

6. Modulate NMDA receptors in the central nervous system [27].

7. Transport metals (e.g., Cu^{+2}, Hg^{+2}, Pb^{+2}, and Zn^{+2}) [28].

GSH mitochondrial concentration is approximately 11–15 mM. Entry of GSH into the mitochondria is dependent on electroneutrality conveyors such as tricarboxylic or dicarboxylic acids [28]. In general, the GSH/GSSG ratio is greater than 10 for cells and organelles like mitochondria and nuclei, whereas the endoplasmic reticulum has a lower GSH/GSSG ratio between 1 and 3 [14].

2.6. Redox system regulation model

For several years, physiologists have sought to establish a simple model for studying physiological variables in comparison with cybernetic models [30].

The generalities of the model are presented in Figure 6. To be regulated, any physiological variable requires the following characteristics:

1. A value that fluctuates over a narrow range.

2. A sensor that reports to a comparator, which compares the variable value to a set point.

3. An integrator center that sends information loops to the input (feedback) or output (feed forward) elements so that these loops will activate variables that are generally controlled to keep the regulated variable within a narrow range.

Although this model is generalized for all physiological variables, it may be adapted for use with intracellular variables.

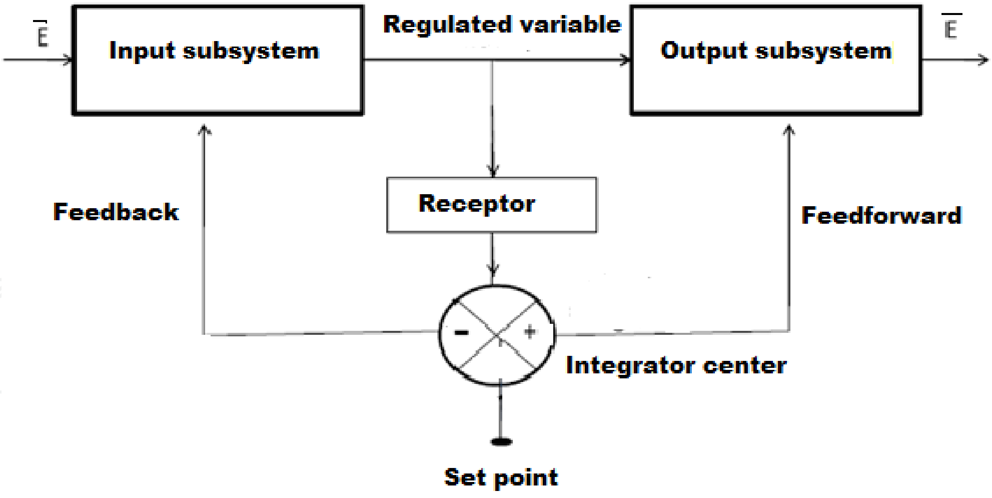

Figure 6. Control systems general model. Modified from [30].

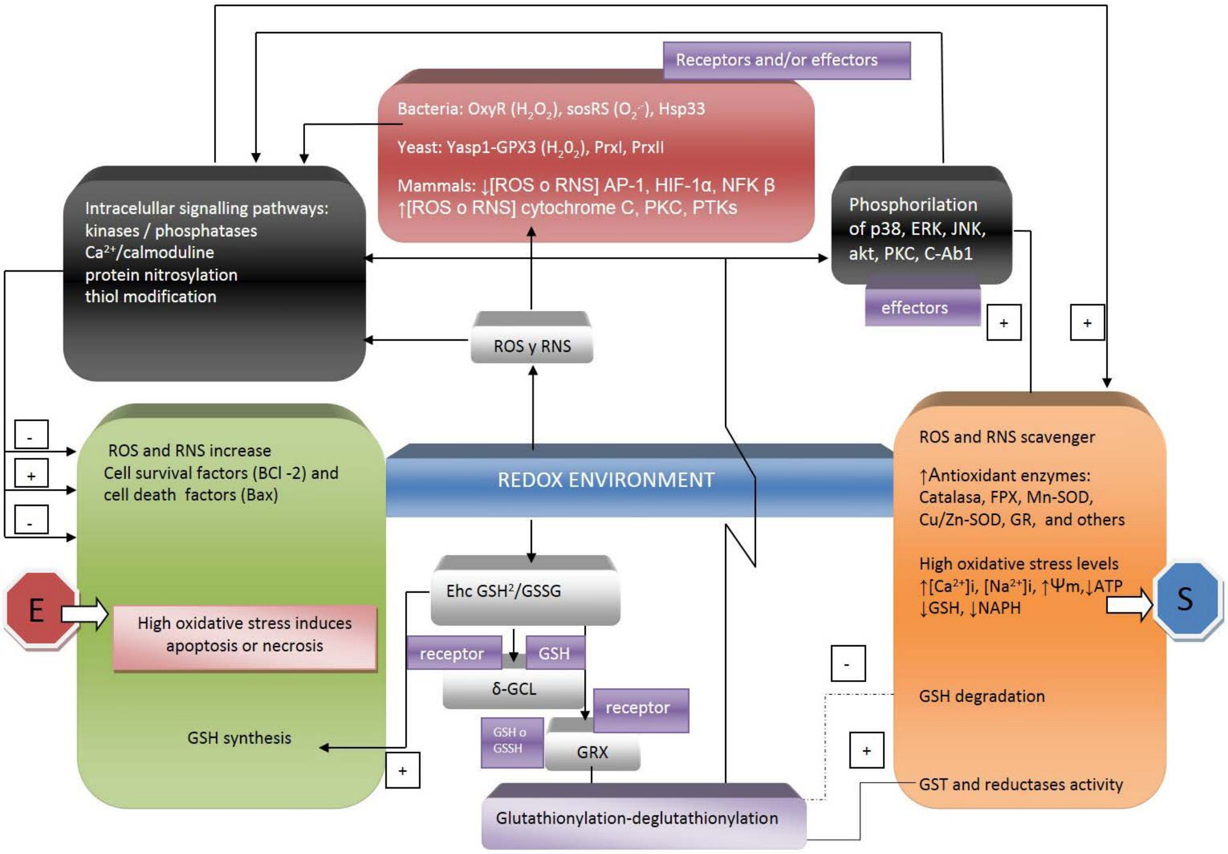

Figure 7. Redox environment regulation model proposed. Our model considers the GSH and ROS as regulated variables, which are sensed by intracellular proteins. Both act as receptors and integrators. In turn is produced a response to compensate the $E_{PC1/2}$ reduction or to increase ROS production to maintain the redox environment.

In particular, our research group considers the intracellular redox environment as a regulated variable since it has the elements described above. In Figure 7, we present the proposed model.

In our model we consider two actively regulated variables involved in maintaining the redox environment: ROS and RNS concentrations, and the couple GSH^2/GSSG $E_{PC1/2}$ redox.

ROS and RNS are sensed in microorganisms predominantly by proteins like oxyR, sosRS, Hsp33, PRXI, PrXII, and the Yap1-GPX3 complex. These proteins not only act as receptors, they also modulate signaling pathways. The final function of intracellular communications is to reduce the reactive species generation and/or neutralize them by stimulating the expression of antioxidant enzymes. Furthermore, it has been proposed that these routes activate cell survival pathways to prevent death, although in extreme oxidative stress apoptosis is favored even above necrosis.

This representation using the basis of a cybernetic model is new, and it allows the correlation of the effects of all systems, especially the GSH cycle to maintain homeostasis of the redox environment.

Finally, we can conclude that the redox environment is an essential variable to the entire system: maintaining a good immune response [31] and suitable neurogenic events [32], controlling growth, behavior, propagation, and differentiation of tumor cells [33], and most of all ensuring the correct function of organelles like the endoplasmic reticulum [34]; however, the redox environment has also been related with some undesirable events such as drug resistance in certain tumor cells [35]. Therefore, continued study of the redox environment is important to uncovering its role in signal transduction, disease, and health.

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