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Oxidative Stress and Neurodegenerative Disease

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1. Introduction

In an oxidation-reduction balance, the antioxidant and oxidant molecules are in equilibrium in the organism. When a free radical increase causes an increase in the activity of the antioxidant systems, this leads to a state of redox homeostasis. The oxidation-reduction balance loss in the organism, caused by an excess of oxidants or a deficit in the antioxidant system, is defined as an oxidative-stress state, which is characterized by high levels of reactive species.

The oxidative-stress state has an important role in the development of many degenerative diseases, such as autoimmune disease, cancer, cardiac disease, and diabetes, but it also has a crucial role in the neurodegenerative diseases, such as Alzheimer's (Pan et al., 2011), Parkinson's (Sevcsik et al., 2011), Huntington's (Lee et al., 2011), lateral amyotrophic sclerosis (Zhao et al., 2011), multiple Sclerosis (Witherrick et al., 2010), and other processes related to pathological aging (Flovd et al., 2011).

Brain plasticity allows certain mental functions to work normally, e.g the learning and memory process. The synapses that form between the neurons are highly organized and are specific structures that permit fast and highly selective interactions between the cells in response to the constant environmental changes that produce neuroplasticity (Bruel-Jungerman et al., 2011). This allows the cells of the nervous system to be both functional and continuously structurally modified to establish new dendrites and synaptic connections. The brain plasticity process can be altered by oxidative stress, which produces oxidative damage, loss of process, synapse deaths, and alteration in the formation of new cells (Rivas-Arancibia et al., 2010).

The synaptic transmission involves the liberation of neurotransmitters from the presynaptic neurons and their detection by a specific receptor on the surface of the membrane of the postsynaptic neuron. Under conditions of homeostasis, the synaptic plasticity is regulated by changes in the amount of receptors in the postsynaptic membrane, changes in the form and size of the dendrite spines, and kinetic modulation of the protein synthesis and degradation.

The reactive species produce oxidation of lipids, proteins, and DNA in the cell, unfolding the proteins. The oxidation of the molecules that form the cell membrane alters its selective permeability, which leads to a loss of osmotic balance.

Smythies (1999) proposed the redox hypothesis of learning and neurocomputing. This hypothesis suggests that redox signals may control a mechanism involved in brain plasticity, in which the growth and elimination of synapses and dendrite spines depend on the redox state. The fate of a synapse depending in part on the redox balance means that if the oxidant-environmental cell produces an oxidative-stressed state, and the reactive oxygen species (ROS) cause elimination of spines. This has been demonstrated in alcoholism and neurodegenerative diseases (Götz et al, 2001). If the cell's environmental are antioxidant, synapses are preserved (Smythies, 1999) and increase the number of synapses, facilitating plastic brain phenomena. The central nervous system (CNS) is especially sensitive to the oxidants because of its high lipid content, high consumption of oxygen, and low levels of antioxidant enzymes. The hippocampus, substantia nigra, and the striatum are particularly vulnerable to oxidative stress (Rivas-Arancibia et al., 2010; Santiago-López et al., 2010). The vulnerability of these structures is probably caused by the neurochemical and metabolic characteristics of neural network. The hippocampus contains neurotransmitters such as acetylcholine and glutamate, and also has the ability to produce new neurons in the dentate gyrus, which make it susceptible to redox changes. This response is in part modulated by oxidative changes and an excess of reactive species block neurogenesis (Rivas-Arancibia et al., 2010). In the substantia nigra and the striatum, the normal metabolism of dopamine involves many oxidative reactions. In a state of redox balance, the dopamine oxidation does not disrupt normal metabolism of dopamine, because oxidized dopamine is converted by a complex series of reactions to neuromelanin. The loss of the redox balance causes oxidation of cytoplasmic dopamine in the presence of transition metals, with the formation of superoxide, hydrogen peroxide, and the hydroxyl radical. The dopaminergic neurons in the substantia nigra are involved in different functions such as learning and memory processes and motor control. With a loss of redox equilibrium, these neurons easily suffer oxidative damage and begin to produce a chain of events, in which the synthesis and metabolic path of dopamine contribute to the increase of the oxidative stress state because of quinone formation, making the nigroestriatal pathway much more vulnerable to damage in comparison to other brain structures (Santiago López et al., 2010).

2. Free radicals, reactive species formation, and cell signaling

A free radical is a species containing one or more unpaired electrons with the ability to exist independently (Halliwell, 2006, 2007). Free radicals are highly reactive, but despite their chemical reactivity, this reactivity changes over a wide spectrum. The first organic free radical was identified by Gomberg in 1900, the methyl triphenyl radical. More than 50 years ago, free radicals were described in living systems in a classic work by Commoner & Townsed published in Nature (1954). Subsequently, it was proposed that free radicals of oxygen (or reactive species of oxygen), could be formed as products of the enzymatic reactions of cell metabolism. At that time the theory was that the reactive oxygen species (ROS) could be the direct cause of many diseases, including cancer and almost any neurodegenerative process (Harman, 1956). In the 1960s and 1970s, free radicals began to be considered as important elements in biological systems. Among other findings, the enzyme superoxide dismutase (SOD) was discovered that converts the free radical

superoxide ($\bullet O_2^-$) into hydrogen peroxide (H_2O_2) (McCord & Fridovich, 1969). This finding convincingly proved the importance of the free radical in biological systems. The simplest of the free radicals is the hydrogen atom, with a single proton and a single unpaired electron. The elimination of a hydrogen atom from a biological molecule produces an unpaired electron on the atom or molecule to which the hydrogen atom was originally bonded.

The diatomic molecule of oxygen (O_2) is regarded as a radical because it has two unpaired electrons, each located in a different orbital, but the two have the same spin. This is why O_2 has a relatively low reactivity in contrast with other highly reactive radicals. The radicals can be formed by the loss of a single electron or by the gain of a single electron, each action from some stable molecule. A radical could donate its unpaired electron to another molecule or could also trap an electron from another molecule turning the latter into a free radical. The unpaired electrons increase the chemical reactivity of the molecule. It is the manifestation of the free radical to get to the most energetically stable state through pairing with another electron. Thus, many radical-radical and radical-molecule reactions take place as soon as two molecules of the reaction are found. In addition the molecules would be changed by this type of reaction. The high reactivity of free radicals causes their half-life to be brief, on the order of milliseconds, varying according to the type of free radical.

3. How are the reactive species formed?

In biological systems, free radicals and the intermediate products of the biological metabolism are formed. Both free radicals and metabolites are called reactive species. Those most often found are reactive oxygen species (ROS) and reactive nitrogen species (RNS). There are also reactive iron species (RIS) and reactive copper species (RCS) (Valko et al., 2007).

3.1 Reactive oxygen species (ROS)

About 60 years ago, it was not thought that the ROS were part of the biological system reactions because of their high reactivity and low selectivity. More than 90% of the oxygen that enters into the cells is used for the production of energy. The mitochondria produce more than 80% of the adenosine triphosphate (ATP) necessary in animal cells. During this process, four electrons are added to each molecule of O_2 resulting in the formation of two molecules of H_2O. During the phosphorylation oxidative process, 1% to 5% of the O_2 used by the mitochondria via complex I and III (Buetler et al., 2004) escape the respiratory chain to form the superoxide anion. Some of these molecules contain an unpaired electron, thus a free radical. The intermediate products have several levels of reactivity with non free radical species. Different ROS often coexist, and it is difficult to identify the specific species as responsible for a given biological effect. For example, different reactive oxygen species formed from the elimination of the superoxide can participate in different types of reactions during which cellular metabolism can suffer a oxidation or reduction process.

3.1.1 Superoxide anion

This is a relatively unreactive species but potentially toxic. It can start reactions that give rise to other reactive ROS. This new anion can be formed as a product of many reactions catalyzed enzymatically, as in flavoprotein reactions (Xanthine oxidase, aldehyde oxidase,

purine oxidase) (Behar et al., 1979; Korycka-Dahi & Richardson, 1981), oxidases and hydroxylases (diamino oxidase, galactose oxidase, cytochrome p450), and also those that can be formed in nonenzymatic reactions of oxygen with cysteine (Sáez et al., 1982) or riboflavin, as happens in the mitochondrial respiratory chain (Boveris, 1972).

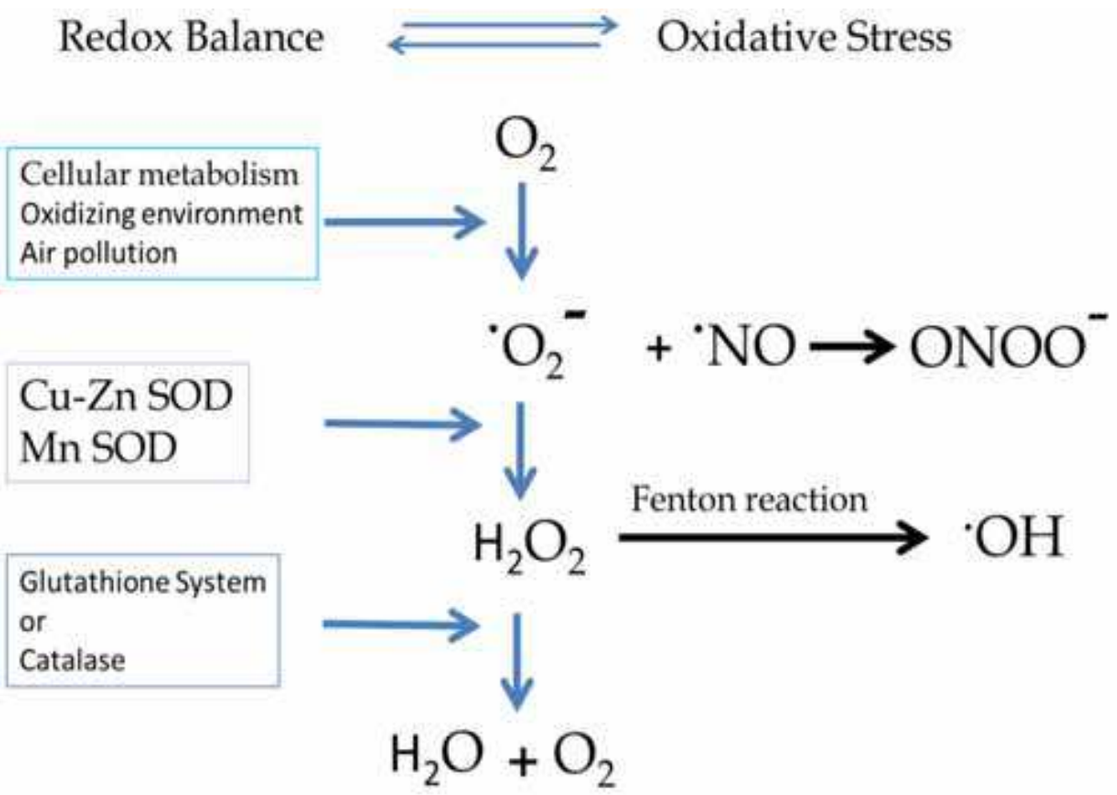
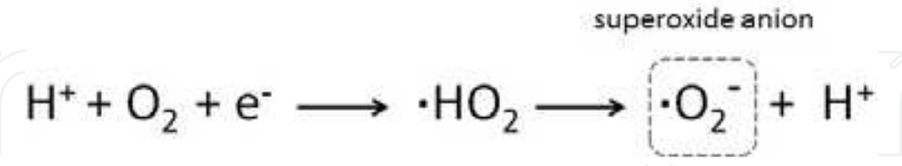


Fig. 1. Schematic oxidation-reduction reactions. Note the reduction reactions in a redox balance (left), and oxidation reactions in an oxidative stress condition (right)



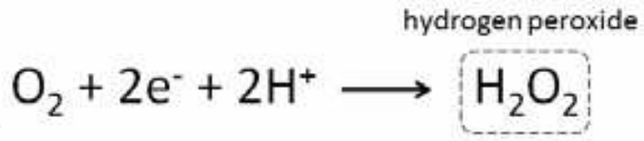
Reaction 1. Formation of Superoxide anion

3.1.2 Hydrogen peroxide (H_2O_2)

Hydrogen peroxide is not a free radical, but it is a reactive oxygen species that can easily diffuse through the membranes. In biological media it is formed by two pathways; 1) After the direct reduction of the oxygen by two electrons (reaction 2) and 2) By the catalyzation of the superoxide anion with SOD (reaction 3).

Many enzymes produce hydrogen peroxide from oxygen, such as xanthine oxide reductase, superoxide dismutase, glucose oxidase, D-amino acid oxidase, uricase (Battaner et al., 1990; Fridovich, 1986; Janolino & Swaisgood, 1975; Romero-Alvira et al., 1987) and may also result

from chemical reactions such as the autoxidation of ascorbic acid catalyzed by copper (Korycka-Dahi & Richardson, 1991).

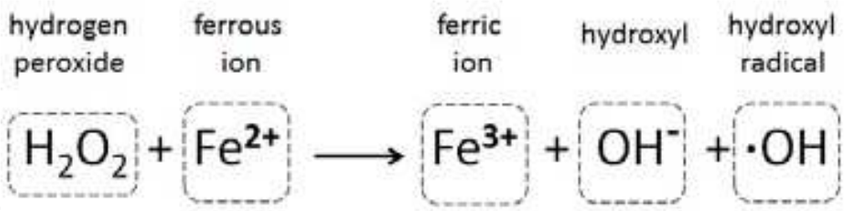


Reaction 2. Reduction of oxygen

Reaction 3. Dismutation of superoxide anion

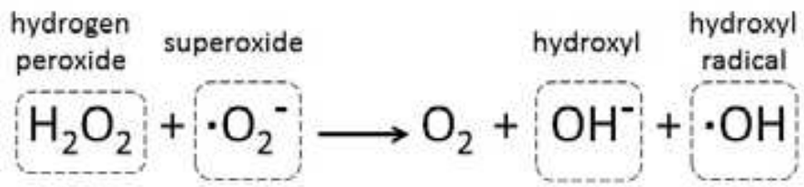
3.1.3 Hydroxyl (•OH)

This is the most reactive species, with an average life estimated of about 10^{-9} seconds (Liochev & Fridovich, 1994). Because of Its high reactivity its chemical action is confined to the vicinity of the site of production. It can be formed in vivo as a result of high-energy radiation (x-ray, gamma ray), which can cause homolytic breakage of water. UV light does not have enough energy to split a water molecule but it can split oxygenated water into two molecules of the hydroxyl radical. At the biological level, the most important hydroxyl radical formation is the Fenton reaction (Halliwel & Guteridge, 1992) (reaction 4).



Reaction 4. Hydroxyl radical formation. Fenton reaction

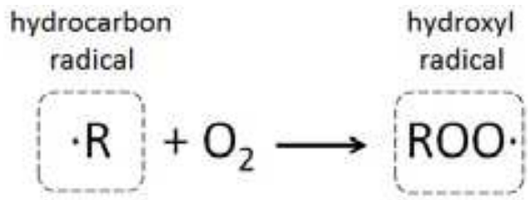
Hydrogen peroxide and the superoxide radical can form the hydroxyl radical by the Haber-Weiss reaction (Wardman, 1996) (Reaction 5):



Reaction 5. Hydroxyl radical formation, the Haber-Weiss reaction. This reaction is catalyzed by metals such as iron or copper

3.1.4 Peroxyl radical (ROO•)

The peroxyl radicals are probably the most abundant in biological systems, and they are not as reactive as the ROS. They originate from the addition of oxygen to any hydrocarbon radical (reaction 6). This radical has a relatively long half-life (on the order of seconds).



Reaction 6. Production of the peroxyl radical

3.1.5 Oxygen singlet ($^1O_2$)

This is an excited form of molecular oxygen. It is not a free radical and it is formed in vivo by the action of light on oxygen molecules in the presence of photoactivators, such as riboflavin (Aurand et al., 1977). Its half-life is about 10^{-6} seconds, depending on the nature of the surrounding matrix. It can interact with other molecules by transferring to them its excitation energy or by chemically combining with them. It can form in the oxidation of NADPH in the microsomes by the activity of several enzymes such as xanthine oxidase, lactoperoxidase, lipoxygenase, and prostaglandin synthetase.

3.1.6 Nitric oxide (•NO)

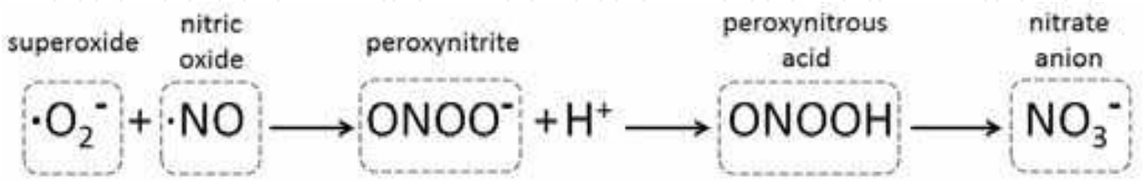
It is a lyophilic and water-soluble gas, with an average half-life of 3 to 5 seconds. Enzymatically formed from arginine, its reaction is catalyzed by nitric oxide synthase (NOS). The NOS has three isoforms. The neuronal nitric oxide synthase (nNOS) or type I, the inducible nitric oxide synthase (iNOS) or type II, and the endothelial nitric oxide synthase (eNOS) or type III. They are constitutively expressed. Their activity is regulated by the intracellular concentration of calcium (Bredt et al., 1991). The inducible nitric oxide synthase (iNOS) or type II is expressed in the macrophages when they are stimulated by cytokines, lipopolysaccharides, or other immune substances. It is also is found in other tissues, such as brain tissue and endothelium (MacMicking et al., 1997). Its expression is regulated at both the transcriptional and posttranscriptional level, which involves the transcription by redox signaling as an increase in reactive species and cytokines, such as nuclear factor kappa B (NF-kB) and the MAP kinases (MacMicking et al., 1997). Nitric oxide plays a fundamental role in the regulation of local blood flow, inhibits platelet aggregation, is a neurotransmitter, and is produced by activated macrophages that contribute to the primary immune defense. Another effect of the •NO radical is its ability to react with the iron of intracellular protein, mainly mitochondrial. Most of the enzymes that possess a heme prosthetic group can be inactivated by nitric oxide. Nitric oxide can react with nucleic acids leading to mutations and DNA breakage and it can also cause necrosis (Tang et al., 2011).

The •NO radical has an important antiinflammatory action, and it has the ability to cause cellular and tissue dysfunction by a proinflammatory effect. To understand this double effect it has been proposed that the regulatory and antiinflammatory effects of nitric oxide occur when it has a direct impact on a biological molecule (Grisham et al., 1999), which occurs under physiological conditions in which the production of •NO is low and a redox

balance is present. However, upon the loss of the redox balance when the concentration of •NO increases, the •NO has indirect effects through metabolites associated with RNS, and they may react with oxygen or the superoxide radical, which occurs during oxidative stress and an inflammatory response (Tweedie et al., 2011).

3.1.7 Peroxynitrite (•ONOO-)

Nitric oxide can generate the peroxynitrite anion (•ONOO-) by reaction with the superoxide anion (Gryglewsli et al., 1986; Miles et al., 1996).



Reaction 7. Formation of peroxynitrite anion

4. Free radical production

There are many ways by which organisms are exposed to the effects of oxygen free radicals. Free radicals can be produced through several chemical processes, both within and outside the organism. The same cell is potentially more than one source of production of a free radical. Depending on the origin of its production, the peroxynitrite can be in equilibrium with its conjugate acid (ONOOH). In neutral solution it is a powerful oxidizing agent able to nitrate tyrosine residues, nitrating and oxidizing guanosine, degrade carbohydrates, initiate lipid peroxidation, and fragment DNA (Beckman & Koppenol, 1994, 1996).

The production of $\bullet O_2$- and •NO in vivo is different. The peroxynitrite production always occurs when there is an excess of one or the other (Grisham et al., 1999). Some authors established that both reactions of oxidation and nitration mediated by the peroxynitrite are influenced largely by the relative flow of production of $\bullet O_2^-$ and •NO (Jourd'Heuil et al., 2001). They also established that the highest rates of oxidation occur with an excess of •NO, producing oxidation through the •OH and from the peroxynitrite $\bullet NO_2$ formed. However, the reaction of peroxynitrite with CO_2 is the most important way that the peroxynitrite decomposes in vivo (Lymar & Hurst, 1995), forming the end product $\bullet N_2O_3$, which is a potent nitrating agent.

In addition to the reactions of oxidation, the peroxynitrite has the ability to nitrate phenolic compounds under physiological conditions, such as the rings of tyrosine (Goldstein et al., 2000). Tyrosine residues are oxidized by the radical derivatives of the peroxynitrite forming the radical tyrosyl, which in turn reacts with •NO to form 3-nitrotyrosine. The nitration mediated by peroxynitrite in vivo might be inhibited by a relative overproduction of $O_2^{-\bullet}$ because of competition between them by the radical tyrosyl, by which the formation of 3-nitrotyrosine would be inhibited when the rate of formation of $\bullet O_2^-$ exceeded that of •NO (Goldstein et al., 2000) in the exogenous and endogenous sources (Freeman & Crapo, 1982).

4.1 Exogenous ROS production

Many antineoplastic agents (Dedon & Goldberg, 1982), such as the adriamycin, bleomycin, daunorubicin, and other antibiotics (Doroshow & Hochstein, 1982) depend on quinoide

groups or joining metals for their activity. Some of the effects of these drugs have been attributed to their ability to reduce oxygen to superoxide, the hydroxyl radical, and hydrogen peroxide. The irradiation of organisms by electromagnetic radiation (x-rays and gamma rays) or by particle radiation (electrons, protons, deuterons, and neutrons) also cause free radicals (Bielsky & Gebieki, 1977).

Environmental factors, such as photochemical air pollutants as ozone, hyperoxia, pesticides, tobacco smoke, solvents, anesthetics, and aromatic hydrocarbons are a source of reactive species. These agents have free radicals, such as in tobacco smoke, or become reactive species with cellular metabolism and detoxification processes (Mason, 1982). An important source of reactive species that deserves special importance is environmental pollution (Searing & Rabinovitch, 2011; Bhalla, 1999) because it has been shown that an oxidation environment, in which we live in polluted cities, is associated with chronic-degenerative diseases. An example is ozone pollution (Bhalla & Gupta, 2000). Studies have shown that ozone pollution causes serious damage to human health and is a determining factor in the progression of neurodegenerative diseases (Zawia et al., 2009; Schwela, 2000). This gas acts to produce ROS in the body, causing an increase in oxidants, increasing the state of oxidative stress in the organism and thus contributing to increase the neurodegenerative process in the patient (Cretu et al., 2010).

4.2 Endogenous ROS production

Autoxidation of small molecules. There are a variety of soluble components able to produce phosphorylation in the cell, such as thiols, hydroquinone, catecholamines, flavins, and tetrahydropterins. In all these, the superoxide radical is the radical primarily formed by the dioxygen reduction by these molecules (Baccarini, 1978). Hydrogen peroxide is also produced as a byproduct from the disproportionation of the superoxide radical, either spontaneously or enzymatically catalyzed by superoxide dismutase (SOD).

4.2.1 Soluble enzymes and proteins

Enzymes, such as xanthine oxide reductase, aldehyde oxidase, flavinprotein dehydrogenase, and tryptophan dioxygenase, generate free radicals during their catalytic cycle (Massey et al., 1989). During ischemia, calcium stimulates the activation of proteases leading to changes in the activation of these enzymes (Warner et al., 2004) causing cell damage and death.

4.2.2 Mitochondrial electronic transport chain

In healthy tissue, one of the main sources of free radicals are the mitochondria. This is because these organelles are responsible for more than 90% of cellular oxygen consumption and the radicals in biological systems always, ultimately are generated by the metabolism of oxygen by this route.

Most mitochondrial hydrogen peroxide comes from the disproportionation of the superoxide radical (Boveris & Chance, 1973). The generation of the superoxide radical by mitochondria occurs when the conveyors of the respiratory chain, located in the inner mitochondrial membrane, are highly reduced (Turrens & Boveri, 1980).

Four complexes are responsible for electronic transport in the respiratory chain. The production of radicals has been observed in the mitochondria isolated in complex I (Turrens & Boveri, 1980) and in complex III (Boveris & Chance, 1973). For complex I, the

most likely candidates as free radical generators seem to be iron-sulfide centers, whereas complex III has been discussed intensively to determine if they could be a semiquinone (Boveris & Chance, 1973) or cytochrome b (Nohl & Jordan, 1986; Turrens, 2003; Ghouleh et al., 2011).

4.2.3 Electronic transport of the endoplasmic reticulum and nuclear membrane systems

Both systems of intracellular membranes contain cytochromes P450 and b5, which can oxidize unsaturated fatty acids (Capdevila et al., 1981; Ghouleh et al., 2011) and xenobiotics (Chignell, 1979). The cytochromes P450 and b5 are the most powerful oxidizers in vivo, although they can also act as reducing agents. There are several actions that activate molecular oxygen species (Ghouleh et al., 2011) generating oxygen electrophílics in turn by radicals that can be released into the cell (Dolphin, 1988).

4.2.4 Peroxisomes

Peroxisomes are cellular sources of the production of hydrogen peroxide because of their high concentration in oxidases, none of which uses superoxide as a precursor. These enzymes include the D-aminoacid oxidase, urate oxidase, L-a-hydroxyacidic oxidase, and acyl-fatty-Coenzyme A oxidase (Boveris et al., 1973).

Peroxisomal catalase is the enzyme that metabolizes most of the hydrogen peroxide generated by the peroxisomes oxidases (Freeman & Crapo, 1982; Frei, 1994).

4.2.5 Plasma membrane

Free radicals generated extracellularly must cross the plasma membrane before reacting with other cellular components and can then start toxic reactions. Unsaturated fatty acids present in the membrane and transmembrane proteins with oxidizable amino acids are likely to be altered by free radicals. These reactions affect the properties of the membranes by changing their permeability and decreasing the potential of the membranes, making secretory functions stop, and inhibiting metabolic processes in the cells. All this is caused by lipid peroxidation or the oxidation of important structural proteins (Freeman & Crapo, 1982).

5. Antioxidant systems and loss of redox balance

In the presence of the oxygen, organisms have been forced to develop mechanisms for their protection against the ROS. Antioxidants are biological substances that are able to compete for oxidizable substrates and inhibit oxidation (Halliwell & Gutteridge, 1984). Antioxidant systems can be divided into enzymatic and nonenzymatic (Somogyi et al., 2007). The first are the SOD, glutathione peroxidase, catalase, and thioredoxin. Nonenzymatic types include vitamins, proteins, and amino acids, which are less reactive but in greater concentration in contrast to the enzymatic types, which have a high reactivity with the ROS, but are in lower concentrations.

Antioxidant systems counteract the activity of the ROS, thus maintaining the oxidation-reduction balance. These systems can be endogenous and exogenous. The most important endogenous antioxidant systems are the enzymes superoxide dismutase, catalase, and glutathione peroxidase.

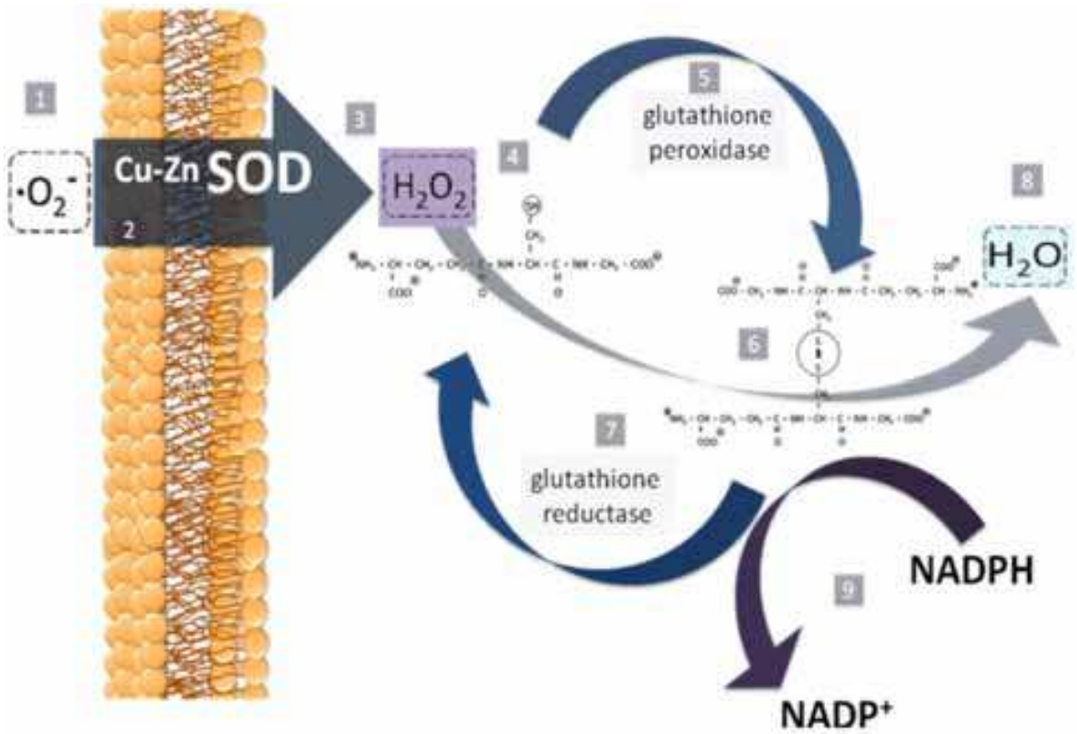


Fig. 2. Shows an oxygen free radical (1), which in the presence of the enzyme Cu-Zn SOD (2) gives rise to peroxides (3) that react with reduced glutathione (4) and are catalyzed by the enzyme glutathione peroxidase (5) resulting in oxidized glutathione (6) and water (7). The peroxides (3) that can be toxic to the cell are removed. The oxidized glutathione (6) in the presence of glutathione reductase (8) and NADPH (9), which hosts an electron, allows the oxidized glutathione to return to its reduced form

5.1 Endogenous systems

5.1.1 Superoxide dismutase (SOD)

The catalytic role of the SOD was discovered by McCord and Fridovich in 1969. The SOD is an enzyme that catalyzes the reduction of the superoxide anion, which is produced in the body as the resulting product of oxidative phosphorylation, either derived from UV radiation or during inflammation, by transforming the superoxide anion into a product such as hydrogen peroxide that is metabolized easily to water by glutathione peroxidase (GPx) and catalase (CAT).The SOD is present in different forms, such as copper-zinc SOD and manganese SOD (Mn-SOD). The Cu-Zn SOD is found in the cytosol and the cell membrane, has a molecular mass of 32 kDa with two identical subunits. The Mn-SOD is located in the mitochondrial matrix (Grisham et al., 1999; Halliwell & Gutteridge, 1989; Ohno et al., 1994) and has a molecular mass of 88 kDa with four identical subunits (Ohno et al., 1994). It acts as a first line of defense in the detoxification of the superoxide anion and seems to be involved in processes of tumor removal or cellular differentiation.

5.1.2 The glutathione antioxidant system

The glutathione antioxidant system is formed by reduced glutathione and the activity of the enzyme glutathione reductase that reduces the oxidized glutathione and glutathione

peroxidase, which along with the reduced glutathione contributes to the elimination of peroxides. Glutathione (GSH) is a tripeptide compound of glutamic acid, cysteine, and glycine that has many important functions within cells (Fig. 3). Glutathione serves as a reducer, conjugates to drugs to make them more soluble in water, is involved in the transport of amino acids across cell membranes (γ-glutamyl cycle), is a substrate for the peptide-leukotrienes, serves as a cofactor for some enzyme reactions, and as an aid in the reorganization of protein bridges.

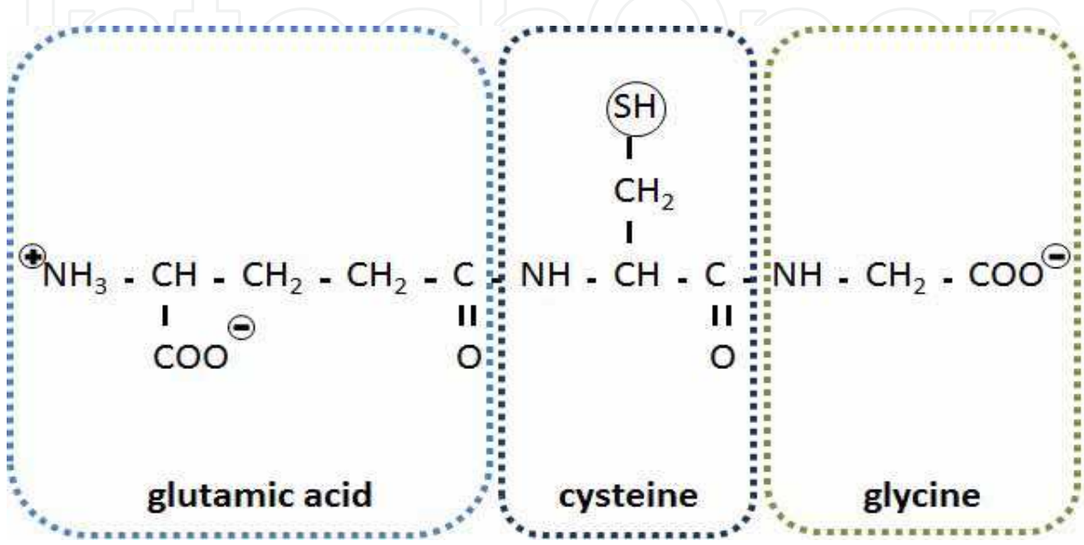
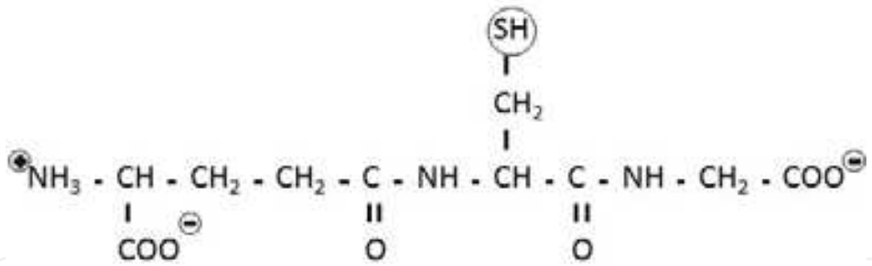


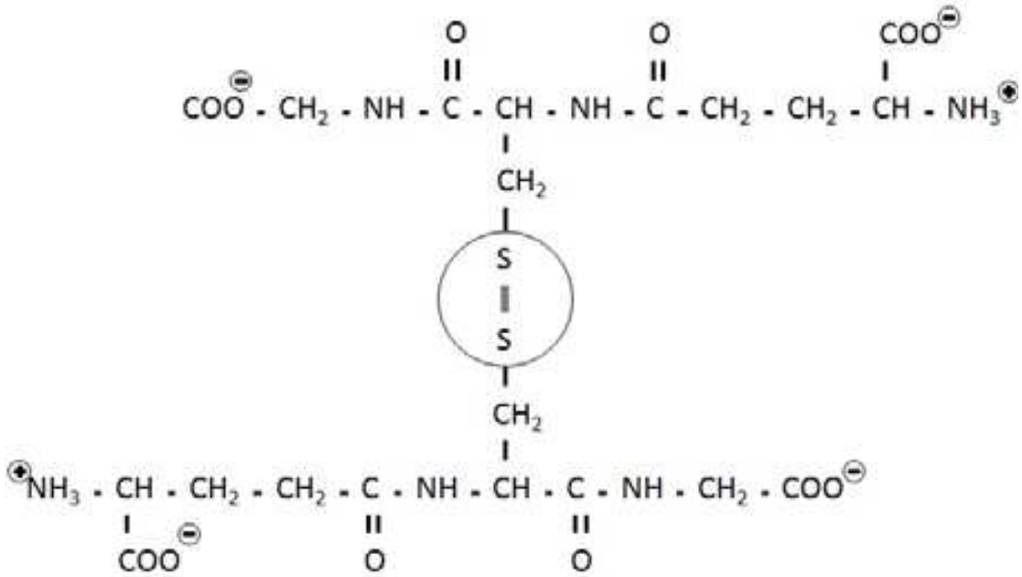
Fig. 3. Structure of glutathione

The role of GSH as a reducing agent is important especially in a highly oxidizing environment. The sulfhydryl of GSH can be used to reduce peroxides. The resulting form of oxidized GSH consists of two molecules of disulfide linked together (GSSG). Glutathione reductase uses NADPH as the cofactor to reduce GSSG to two molecules of GSH. Therefore, the pentose phosphate pathway is important to produce the NADPH required for glutathione reductase. Glutathione peroxidase is a selenium-dependent enzyme that catalyzes the reduction of H_2O_2 or lipoperoxide (L-OOH) using the reduced glutathione (GSH).

Oxidized glutathione is reduced by glutathione reductase that uses NADPH (from the pentose phosphate pathway) as an electron donor, thus maintaining the ratio GSH /GSSG (Fig. 4). There are at least three forms of glutathione peroxidase dependent on selenium; an intracellular form, extracellular (GPx-C), or plasma (GPx-P) that has specific activity for phospho-lipoperoxides (GPx-PH), usually associated with the membrane and although its activity is the same, has structural differences. The GPx-C and GPx-P are tetrameric enzymes composed of four identical subunits with each containing a selenium atom attached covalently to a molecule of cysteine. The sequence of amino acids in the subunits of the GPx-C is different from the sequence of the GPx-P. The separate subunits have no catalytic activity. The GPx-PH is a monomer enzyme that also has an atom of selenium and catalytic activity (Stepanik & Ewing, 1993). The GPx-C has higher affinity for H_2O_2 than for lipoperoxides, and the GPx-P has a similar affinity for the two substrates. The GPx-C and GPx-P are used as substrates for H_2O_2 and the lipoperoxides. They are not able to use the phospholipoperoxides (PHL-OOH) that are the major substrates for the GPx-PH (Maiorino et al., 1991).



(a)



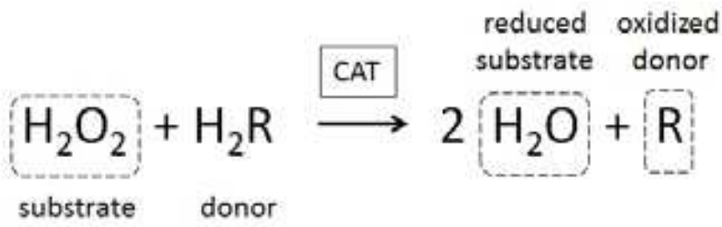
(b)

Fig. 4. (a) Reduced glutathione structure (GSH). (b) Oxidized glutathione structure (GSSG)

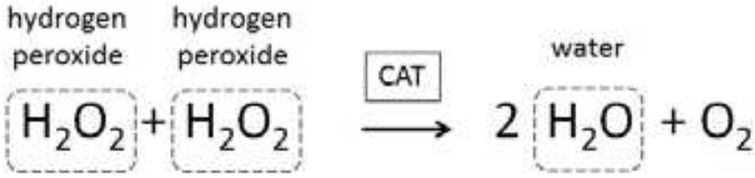
5.1.3 Catalase

Catalase (CAT) or hydrogen peroxide oxidoreductase is one of the more abundant enzymes in nature and is widely distributed in the human body. Its activity varies depending on the tissue, highest in the liver and kidneys, lowest in connective tissue and the lining, and practically nonexistent in the nervous tissue. At the cellular level it is located in the mitochondria and peroxisomes, except in erythrocytes, where it is located in the cytosol. This enzyme is a tetrameric metaloprotein of four identical subunits that are held together by noncovalent interactions. Each subunit contains a prosthetic group of protoporphyrin IX. Catalase is involved in the destruction of hydrogen peroxide generated during cellular metabolism. It has two features; the catalytic and the peroxidative. Both can be represented by reaction 9.

The general reaction covers the substrate reduction taking hydrogen atoms from a donor, and the products are the reduced substrate and the oxidized donor. In the catalytic reaction, the donor is another molecule of H_2O_2. This reaction can only be accomplished by the enzyme in its tetrameric form.



Reaction 9. Destruction of hydrogen peroxide by catalase



Reaction 10. Catalytic reaction of the enzyme catalase on hydrogen peroxide

In the peroxidative reaction the enzyme can be used as donors of hydrogen to methanol, ethanol, formic acid, and formaldehyde. This reaction can be with monomers, dimers, and tetramers. Glutathione peroxidase (GPx) and glutathione reductase (GRd) are part of an antioxidant system (GPx-GRd), and catalase (SOD-CAT). It has been observed that both systems fail to act simultaneously. The CAT acts in the presence of high concentrations of H_2O_2, and the GPx at low concentrations, which shows an inverse correlation in the activity of two enzymes.

5.2 Exogenous systems

Antioxidant vitamins, along with glutathione, comprise a group of reducing agents able to donate electrons to oxidized species such as free radicals and the lipoperoxides, thus neutralizing their destructive oxidative potential (Chao et al., 2002).The most significant exogenous antioxidant systems are vitamins A, C, and E, and some metals such as copper and selenium. The last is a cofactor for the enzyme glutathione peroxidase.

Vitamin A. It can be derived from retinol of animal origin and comes from different plant carotenes. The main sources of vitamin A are fish liver oils, liver of mammals, and milk. In plants it exists in the form of carotene (provitamin). It has an important role in vision. In the form of retinoic acid, vitamin A is effective in the treatment of acne and other skin conditions.

Vitamin E is a substituted lipid isoprenoid of the tocopherol family. Its biologically active form is D-alpha tocopherol, whose phenolic hydroxyl is responsible for the antioxidant effects. Vitamin B12 is plentiful in the yolk of eggs, whole milk, the offal of mammals, and fish oils. It is essential for humans (Mayes, 1997). The activity of vitamin E is one of the first barriers against the peroxidation of the polyunsaturated fatty acids. Mitochondrial, endoplasmic reticulum, and plasma membrane phospholipids have affinities to alpha-tocopherol, so it is highly concentrated in these sites (Nenzil et al., 2001). Tocopherols act by interrupting free radical chain reactions because of their ability to transfer a phenolic hydrogen to a peroxide free radical. Vitamin E can be in the form of phenoxy or phenoxyl free radical, in unreversible intermediate reactions that presuppose the transformation of the vitamin to its final harmless products. Tocopherols and selenium act synergistically

allowing the organism to have its antioxidant activity (Hoenyet et al., 2005). Selenium is required for the normal pancreatic function (Rayman, 2000), which is necessary for the proper digestion of lipids. Though it is known that the levels of vitamin E are correlated with the ability to digest and absorb lipids. Because of its hydrophobic nature a deficiency of tocopherols is found in processes such as hepatic cholestasis and cystic fibrosis or bowel resections. Recent work shows the close relationship of the increase in the requirement of vitamin E and selenium with the intake of unsaturated fatty acids, aging, and the degenerative diseases such as atherosclerosis (Penn et al., 2003), Alzheimer's disease (Butterfield et al., 2002), or prostatic carcinoma (Thomas, 2004).

Vitamin C or L-ascorbic acid is a derivative of glucose. It is essential in the human diet. It is a lactone, in which the hydroxyl associated with the double bond groups function as agents with a high reducing potential, allowing it to participate in the direct reduction of oxygen, thus functioning as a donor substrate in the reactions of the peroxidases (Mayes, 1997). The mechanism of action of this vitamin yields a higher antioxidant level because it includes the inhibition of the formation of the superoxide radical or nitrosamines during digestion. In addition, it is the agent that reduces the phenoxy radical formed during vitamin E activity (Chao et al., 2002). Vitamins C and E are classified as antioxidant switches because they act by stopping the formation of free radical chain reactions (Shite et al., 2001), trapping them and reducing them, unlike the preventive antioxidants (which include peroxidase enzymes) to prevent the initiation of the sequence of reactions. Tocopherols work in an environment of high oxygen partial pressure, whereas beta-carotene works at low O_2 partial pressures.

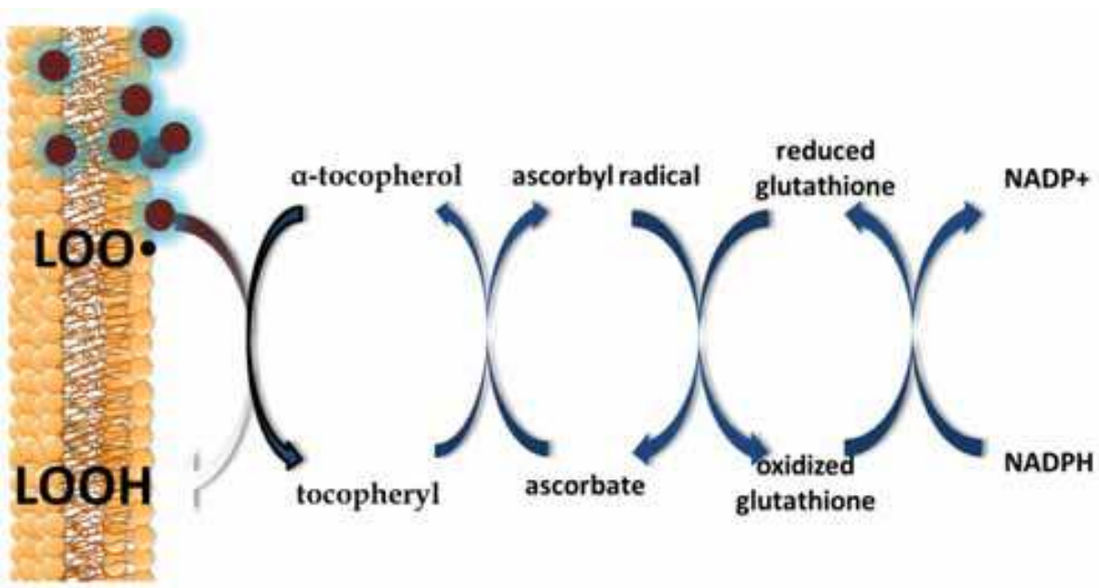


Fig. 5. Action of tocopherol on lipid peroxides and regeneration in the presence of ascorbate and reduced glutathione

6. Role of the reactive species in cellular signaling

The mechanisms of oxidation-reduction and free radicals play an important role in cell physiology (Kovacik & Wells, 2006), from the renewal of membranes, cellular plastic phenomena, cell migration, synthesis and release of some hormones, increase in transcription

of cytokines during inflammatory processes, the participation in cell signaling (Stone & Yang, 2006; Biniert et al., 2006), and the mechanisms of second messengers (Smythies, 1999; Chiarugi & Fiaschi, 2007).

The ROS are characterized by their dual nature, which depends on the redox state of the organism. In a balanced oxidation-reduction reaction, the main effects of the ROS in the cell are through their actions in signaling pathways. These oxidant signals can easily be offset through antioxidant systems, To restablish a redox equilibrium, the ROS causes the expression of antioxidant enzymes and related defense mechanisms. At low concentrations the ROS are involved in many physiological functions. It has been suggested that the main effects of the ROS in cells are through interactions they have with different signaling pathways and not by their direct action on macromolecules (Maher, 2000). Both phenomena do coexist. There is evidence that living organisms have not only adapted to coexist with free radicals but they also have generated several mechanisms for using free radicals in different physiological functions (Halliwell & Gutterdge, 2007; Kirkwood, 2005).

Infectious diseases possibly were a mechanism of natural selection in the early stages of human civilization. The ROS participate directly in the defense mechanism against infections. They are part of a respiratory burst and are important modulators of the inflammatory response. Resident glia in the brain in normal situations are produced by ROS and its role in the brain is to counter cell damage. In addition, they participate in other functions, such as the regulation of vascular tone, the monitoring of the oxygen pressure, and the expansion of signal transduction. Signal transduction mediated by reactive species regulates the response to oxidative stress, which keeps the redox balance within homeostatic limits (Droge, 2002). For all this, the homeostatic regulation of the oxidation-reduction balance has a special importance of keeping the delicate balance between the adaptive advantages of the biological use of free radicals and their harmful effects. One of the most important discoveries is that the ROS can regulate gene expression of several bacterial genes, which is generated by H_2O_2 (Christman et al., 1985). For mammals, small amounts of $\bullet O_2^-$ and H_2O_2 increase the production of interleukin 2 (IL-2), which is an important factor of lymphocyte growth, possibly as a response to the activation of the nuclear factor kappa B (NFκB) that occurs in the presence of the ROS (Schreck et al., 1992).

The term "redox signaling" is used to describe a process of regulation, that involves processes of oxidation-reduction. This type of signaling is used by a wide range of microorganisms, including bacteria, and its most common use by the cell is the generation of antioxidant defenses to restore the original state of redox homeostasis after a temporary exposure to the ROS (Droge, 2002). The interaction of various components of antioxidant systems (Mendiratta et al., 1998a, 1998b) is effective for the recycling of components and is sufficient to cope with the stress caused by the ROS for long periods in the life of an organism (Soberman, 2003). Aging and particularly inflammatory, chronic diseases cause an alteration in the maintenance of redox state, which causes mechanisms of progressively aggravated pathology.

As mentioned, the ROS generate cellular events, such as the activation of the pathway of the MAP. These consist of four subfamilies sensitive to the ROS and are identified as kinases regulated by extracellular signaling (ERK1-2), kinase c-Jun NH2 - terminal (JNK), and kinase p38 kinase big MAP type 1 (BMK1 or ERK5). Each family has its trigger mechanism and then modulates specific cellular functions (Suzaki et al., 2002). We will discuss the physiological role of the ROS and the path of the BMK1 or ERK5 kinase in neuronal cells. There is evidence, found in experiments in PC12 cells, of different intracellular signaling

steps identified in the path of the MAP kinases, where the ROS are involved (Suzaki et al., 2002).

The activation of the pathway of the BKM1 stimulated by the ROS depends on the presence of c-Src, a protein kinase encoded by the gene Src, and that becomes involved in the internalization of the signals to the nucleus through the phosphorylation of other proteins, including second messengers. When the ROS present in the cells interact with the c-Src, this causes activation of the kinase, which in turn has an immediate effect on the activation of the BMK1 through key intermediates to continue the internalization of the signal initiated by the ROS. Below is shown the cascade of the MEKK3 and MEK5 kinases (Suzaki et al., 2002). The BMK1-ERK5 possesses a amino acid motif TEY of physiological importance because it is on this site where atoms join with the phosphorous kinase MEK5 (Lee et al., 1995; Zhou et al., 1995). This, when phosphorylated, acquires the ability to cause the activation of the MEF2C and MEF2A, both belonging to the family of MEF2 transcription factors, and to cause the translocation at the nucleus, which is involved in the expression of genes of c-Jun and c-Fos, themselves part of the family of the AP1 (Silva, 2001). Components of this family have a common binding site on the DNA that results in the expression of neuropeptides and neurotrophins, synthesis and expression of receptors to various ligands, activation of transcription factors, the synthesis of various enzymes involved in the production of neurotransmitters, such as thyroxine hydroxylase, a limiting enzyme in the production of catecholamines and the formation and polymerization of proteins to the cytoskeleton (Silva, 2001). In endothelial cells, oxidative stress is involved in the formation

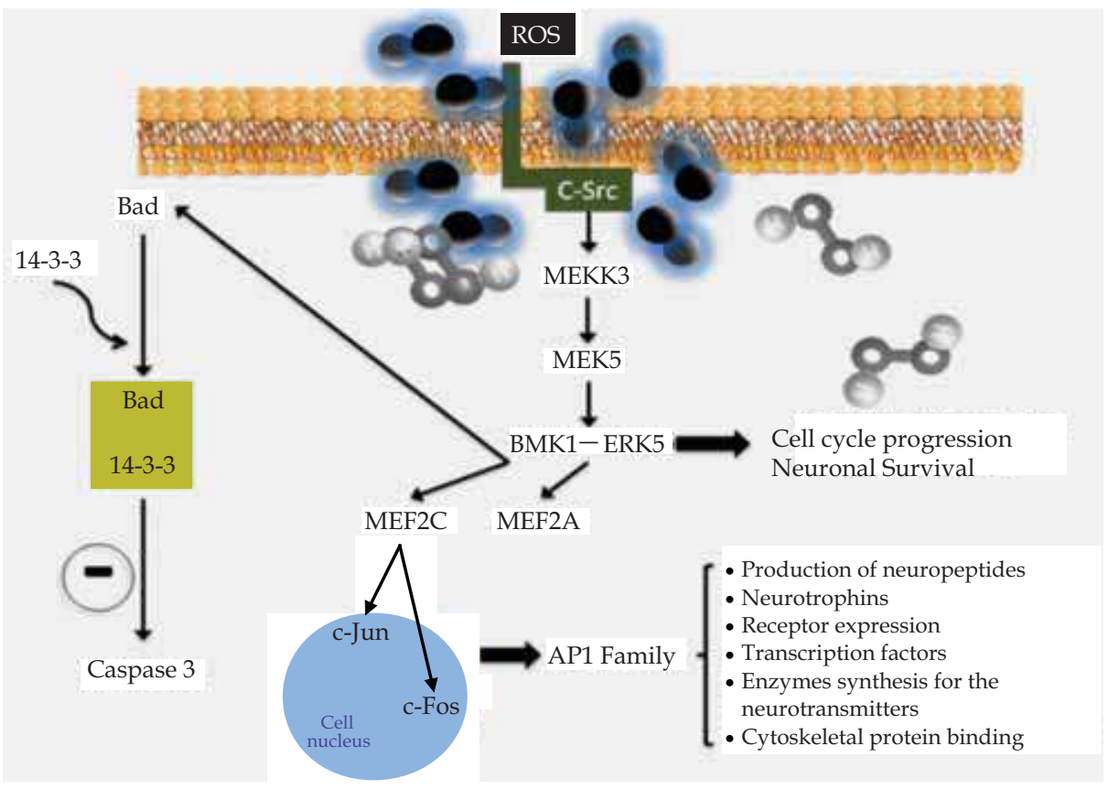


Fig. 6. Shows the action of reactive species on cellular signaling. In this example we can observ the effects of ROS on the AP1 family mediated by the pathway of MEKK3

of BMK1 (Yan, 1999) and this is able to phosphorylate Bad, a protein involved in the signaling of apoptosis. The scaffold 14-3-3 protein binds to Bad when it is phosphorylated and stops it from having proapoptotic activity. The nonphosphorylated Bad is able to travel to the mitochondria, causing the release of cytochrome C, a crucial step for the activation of caspase 3 (Xinchun et al., 2004). This evidence can suggest that the protective role and antiapoptotic action of BMK1-ERK5 is generated by the ROS (Liu et al., 2003).

7. Inflammation response and oxidative stress

The inflammatory response is a natural and important process in the repair of tissues and a fundamental mechanism of defense of the organism against infections and harmful agents. When the inflammatory response is not limited a process of chronic inflammation is established. In the animal model of oxidative stress, caused by exposure to ozone on healthy animals, chronic oxidative stress is able to cause an inflammatory response and dysregulation of the same answer (Rivas-Arancibia et al., 2010). It is widely reported that chronic inflammation produces ROS that lead to a state of oxidative stress. This change in the redox balance, causing activation of the signaling pathways of the cell, causes a perpetually inflammatory state. Maintaining the redox balance is important for cell signaling and adequate transcriptional activity (Chung et al., 2009). The ROS and other reactive species regulate the expression of proinflammatory cytokines, such as TNFα, IL-1β, IL-6, and IL-8, and the cell-adhesion molecules, such as the adhesion intercellular-1 (ICAM-1) and E-selectin molecules. Several biological states cause an increase in the amount of proinflammatory cytokines. Aging causes an increase in the levels of cytokines such as TNF-α, IL-1β, IL-6, gamma interferon (IFNγ), the beta-transforming growth factor (TGFβ), and acute phase proteins (Bruunsgaard et al., 2003). High levels of IL-6 have been associated with neuronal atrophy and chronic inflammatory states such as diabetes type 2 and atherosclerosis (Devaux et al., 1997; Willette et al., 2010). The C-reactive protein (CRP) levels increase with ageing, and high levels of chronic diseases are found associated with ageing, heart disease, and Alzheimer's disease (Ridker et al., 2001).

Activation of transcription factors that are sensitive to redox signals generate the production of inflammatory mediators, such as interleukin-1β (IL-1β), Interleukin-6 (IL-6), necrosis tumor-α factor (TNF-α), cycle-oxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS), and the cell adhesion molecules(CAMs) (VCAM-1, ICAM-1, and P- and E-selectin) (Salminen & Kaarniranta, 2010). NF-κB is a transcription factor activated by a wide variety of stimuli, such as oxidative stress, infection, and inflammation. This activation plays a key role in regulating the immune response (Salminen & Kaarniranta, 2010). NF-κB is composed of a heterodimericprotein complex containing a DNA-binding domain and a domain of acidic transactivation formed by the heterodimer polypeptides RelA-p65 and p50. Normally NF-κB is linked to a protein of the IκB family in cytoplasm, which inhibits its activation (Baldwin, 1996). When IκB is degraded, the NF-κB is freed and causes its translocation to the nucleus, where the NF-κB can bind to a promoter and start the transcription of specific genes that encode for proinflammatory mediators. Activation of tNF-kB is usually transient, but chronic activation produces changes in the inflammatory response. Protein-generated NF-kB and COX-2, TNF-α,e, and IL-1β and IL-6 are also potent activators of the same pathway, creating a vicious cycle (Handel et al., 1995, Fisher et al., 1996). There is evidence showing that aging increases the degradation of

NF-kB because of phosphorylation of IKB by NIK-IKK and MAPKs (Kim et al., 2000). There are other transcription factors involved in the inflammatory response. The family of the forkhead box O (FOXO) is evolutionarily conserved and integrated by FOXO1, FOXO3a, FOXO4, and FOXO6 in mammals (Van der Heide et al., 2004). The FOXO activation causes the transcription of genes involved in the regulation of the cell-cycle metabolism, cell death, and resistance to oxidative stress (Hedrick, 2009). The activation of these factors of transcription is regulated by growth factors through the phosphorylation of protein kinase B (PKB) (also known as Akt). This formation of phosphoinositide 3-kinase (PI3K) leads to the translocation of FOXO in the cytoplasm to the nucleus (Salih & Brunet, 2008). Both protein-kinase PI3K and Akt are able to mediate many signals of cell survival through inhibition of apoptosis processes (Lawlor and Alessi, 2001). However, little is known about how PI3K-Akt regulates levels of the ROS in cells. FOXO1 reduces the degree of oxidative stress increasing the amount of mRNA coding for Mn-SOD and catalase (Burgering & Medema, 2003). FOXO3a and FOXO4 protect quiescent cells in vitro from oxidative stress. FOXO3a directly activates the transcription of antioxidant enzymes Mn-SOD, catalase, and peroxiredoxin 3 (Prx3) (Marinkovic et al., 2007). This suggests that FOXO also has an important role in the redox balance. Both PI3K and Akt protein kinase are able to mediate many signals of cell survival through inhibition of apoptosis processes (Lawlor & Alessi, 2001).
The hypothesis of molecular inflammation can facilitate a better understanding of the aging process and related diseases such as dementia, cancer, osteoporosis, gingivitis, and vascular diseases.

8. Loss of the redox balance

The free radicals interact with other cell components, such as proteins, DNA, and lipids, to form multiple catabolic products. An example of these is lipid peroxidation resulting in lipid hydroperoxides and aldehydes that interact with the sulfhydryl groups of proteins causing the loss of protein functionality and thus perpetuating cell damage. The increased levels of calcium and nitric oxide stimulates the production of inflammatory interleukins causing gliosis and increasing the state of oxidative stress. This causes damage and cell death (Sugaya et al., 1998; Ryter et al., 2007), thus establishing a cycle through a chain of oxidative reactions that involve both neurons and glia. These are involved in the maintenance of the damage that extends into adjacent tissue cells.

8.1 The role of mitochondria in oxidative stress

Mitochondria play a critical role in maintaining cellular homeostasis. This organelle is an important cellular source of energy in producing ATP. In addition they maintain the intracellular levels of calcium within appropriate ranges to mediate cell signaling and control neuronal excitability and synaptic function. In the brain there is a metabolic coupling between vascular substrates, providing oxygen and glucose and the metabolic needs of the brain tissue, formed by neurons and glia alike (Foster et al., 2006).The sequence of events that occurs after neural stimulation includes an initial decrease of oxygen in areas of high demand for this gas (for example, those first stimulated) and a large further increase of oxygen associated with a wide field of arterial vasodilatation. These events are closely related to mitochondrial activity through the production of H_2O_2 as a signaling molecule (Foster et al., 2006).

Like other cells, nerve cells use ATP as a source of energy for biochemical processes involved in various cell functions, and produce ROS as a result of oxidative phosphorylation. The electrical excitability and structural changes, coupled with the synaptic complexity of neurons yields unusual demands in cellular systems that produce or respond to ATP and ROS. Mitochondria in axons and presynaptic terminals provide for sources of ATP to pump ions that are concentrated in these structures to quickly restore the subsequent ion gradients for depolarization and neurotransmitter release. Mitochondria also play a role in the regulation of synaptic functions because of their ability to regulate calcium levels and the production of ROS (Mattson & Liu, 2002).

Neurons in the brain are highly vulnerable to metabolic changes so that a mitochondrial disorder, which causes a decrease in the production of ATP, represents a clear threat to the viability of the neurons and glial cells, the functionality of neural networks, and consequently the normal functions of the brain can be changed. The alteration in the regulation of calcium levels by the failures of the mitochondrial buffer and the release of mitochondria-bound calcium contributes to a severe injury of brain tissue in response to excitotoxicity by glutamate, oxidative stress, or metabolic damage such as trauma. Similarly, an abnormal increase in the generation of ROS by the mitochondria also puts at risk cell viability because many shock-mechanism absorbers might be overwhelmed (Kann & Kovács, 2007).The result is an oxidative damage to the structural and regulatory proteins of the cell membranes that modulate the redox state, and can lead to abnormal activity in various ionic channels. Another event that puts cell viability at risk is the formation of the mitochondrial permeability-transition pore (mPTP), which occurs in response to a mitochondrial overload of calcium in the presence of high levels of ROS. The mitochondrial permeability-transition pore is characterized by an increase in nonspecific permeability in the inner mitochondrial membrane, loss of membrane potential, a possible rupture of the outer membrane, and a severe mitochondrial swelling. When the opening of the mPTP is transitory, the release of cytochrome C from the intermembranal space can activate the caspase cascade that leads to apoptosis. If the opening of the mPTP is prolonged, the mitochondrial content is reduced by quickly causing necrosis (Kann & Kovács, 2007).

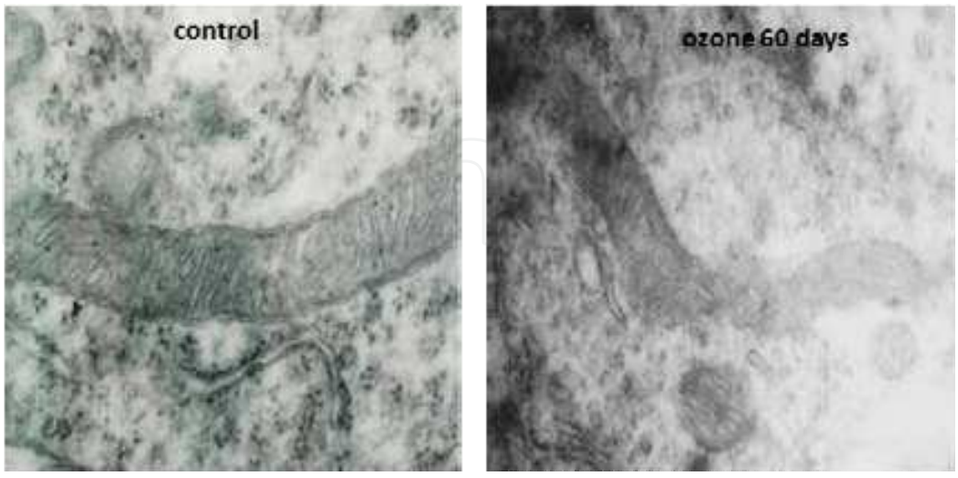


Fig. 7. Electronic microphotography that shows the effects of an oxidative stress state caused by ozone exposure on the neuron mitochondria of the rat hippocampus (30.000x). Observe the loss of the external mitochondrial membrane and damage of the mitochondrial crests after exposure to ozone (right)

9. Oxidative stress state and neurodegenerative process in an animal model

9.1 Ozone as a model for oxidative stress

Various methods have been used to deal with the study of oxidative stress and its biological significance in the organism. This ranges from biochemistry, cell culture, and animal models to clinical studies. Ozone exposure causes the generation of ROS (Chen & Qu, 1997; Kennedy et al., 1992; Pryor, 1994; Pryor & Church, 1991; Romieu et al., 1998, Saintot et al., 1999) and the formation of relatively stable products (Bocci, 2006; Pryor et al.,1995) able to oxidize DNA, proteins (Kanofsky & Sima, 1993), and lipid membranes (Postlethwait et al., 1998), which if they are not offset causes damage and cell death. In the epithelial lining of the lung, the fluid is characterized by high concentrations of antioxidants, mainly ascorbic acid and glutathione (GSH) (Bocci, 2006). To react with these antioxidants a portion of the inhaled ozone is destroyed. The pulmonary antioxidant defenses are able to neutralize the damage, depending on the dose and exposure time, but when they are overwhelmed a chain of chemical reactions begins that leads to the formation of ROS, caused by secondary exposure to ozone. The ROS pass into the blood, and through the bloodstream reach all the organism, producing a state of widespread oxidative stress (Rivas-Arancibia et al., 2000, 2003). The mechanism of toxicity of ozone is explained as a cascade of reactions (Pryor et al., 1995) in which inhaled ozone reacts with molecules in the fluid of the epithelial lining producing ROS and toxic byproducts, which in turn are able to cause other reactions in the blood. This cascade of reactions is responsible for the toxic effects of ozone both in the lung microenvironment and throughout the body (Ballinger et al., 2005; Bocci, 2006; Pryor et al., 1995). Although the majority of the studies on the effects of oxides of carbon, sulphur, nitrogen, and ozone were made in animals, they indicate that damage may be caused in humans when air pollution increases. Oxidative stress caused by acute or prolonged exposure to ozone causes alterations in the brain plasticity that are manifested by the deficit in the learning processes, memory, and motor activity behavior (Rivas-Arancibia et al., 2000; Dorado-Martínez et al., 2001). Exposure to low doses of ozone over a long time causes a process of progressive neurodegeneration (Angoa-Pérez et al., 2006; Pereyra-Muñoz et al., 2006, Rivas-Arancibia 2010).

Brain tissue is most vulnerable to oxidative damage caused by its high consumption of oxygen, a high metabolic rate, and low levels of antioxidant enzymes, such as SOD, glutathione peroxidase, and catalase. A large increase of lipid peroxidate levels is caused by an increase in ROS, because of the brain's high content of polyunsaturated fatty acids that are highly susceptible to oxidation. Different brain structures show differences in their response to oxidative damage (Hermida-Ameijeiras et al., 2004).

There is clear evidence that air pollution causes an oxidizing environment for humans. High levels of contamination in highly populated cities are correlated with the rise of a number of pathologies, such as autoimmune, degenerative, and neurodegenerative diseases. When using a model of oxidative stress, produced by ozone exposure to low doses (0.25 ppm) for 4 hours daily for different times (7, 15, 30, 60, and 90 days), healthy animals developed a process of progressive neurodegeneration that depends on the exposure time (Angoa-Perez et al., 2006; Pereyra-Muñoz et al., 2006; Rivas-Arancibia et al., 2010, Santiago-Lopez et al., 2010).

The increase in the levels of oxidized lipids, proteins, carbohydrates, and nucleic acids are used as indicators of the state of oxidative stress. Levels of antioxidant enzymes and their activity are used as indicators of antioxidant capacity. The determination of oxidized

biomolecules and the activity of antioxidant systems clearly determine the redox state in which an individual is found, e.g. we can find high levels of oxidized lipids or proteins, but these can be accompanied by an increase in the activity of the SOD and glutathione peroxidase, or an increase in the levels of reduced glutathione. This indicates that oxidative stress is compensated for because the increase of the prooxidants is accompanied by an increase in the antioxidant systems, which leads to a balanced redox system and tissue changes that are reversible. If the oxidation of the biomolecules increases and there is a decrease in the activity of antioxidant systems, we can then infer that there is a loss of redox balance that produces a state of oxidative stress. This is important to define because many experimental models do not consider these effects and the results are often contradictory. As an example of the models that used ozone, the administration of high doses of this gas in animals may cause a strong antioxidant response and then the increase in the levels of antioxidants has a repair effect on the organism. However, in Wistar rats more than 2-years old, this response causes a severe neuronal and endothelial damage because older animals have a decreased antioxidant activity level in a chronic oxidatively stressed state, and this also occurs in chronic-degenerative diseases.

Another important factor is the dose and exposure time. In healthy young animals exposed to low doses of ozone for 4-h daily for a prolonged time, a chronic oxidative stress state is generated that causes a process of progressive neurodegeneration. This degenerative process becomes irreversible after 30 days of exposure to this gas. Though animals are no longer exposed to ozone the damage continues to make progress. The progressive neurodegeneration process is shown in figures 8,9,10 in which oxidative stress, depending on the time of exposure to ozone, increases the immunoreactivity to p53 and the translocation of p53 to the nucleus, indicating an increase in cell death by apoptosis.

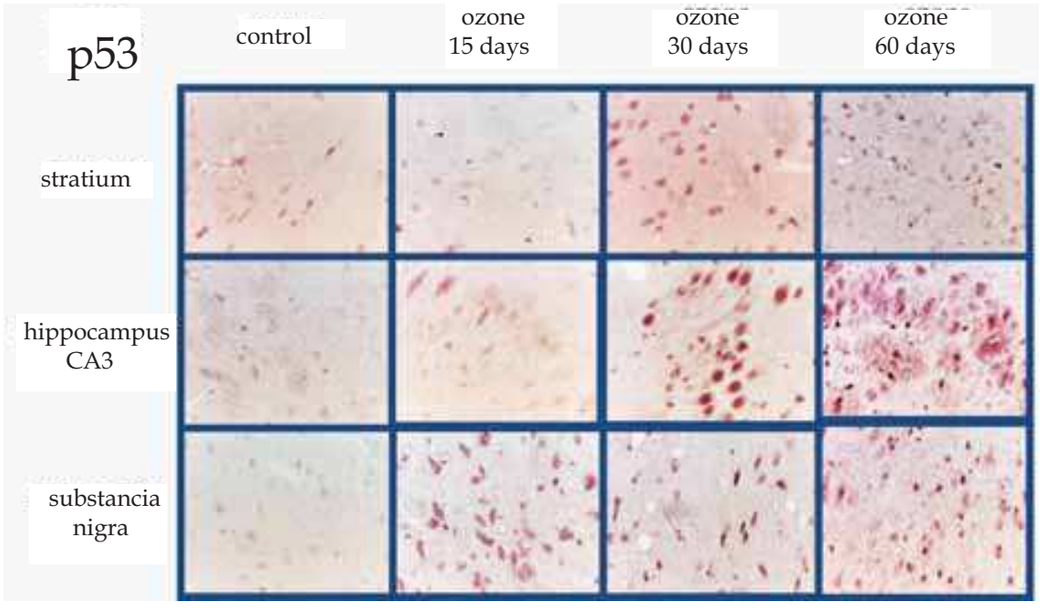


Fig. 8. The effect of oxidative stress on P53 immunoreactivity caused by chronic exposure to low ozone doses for different times (15, 30, and 60 days) in different brain structures (striatum, hippocampus, and substatia nigra). Note immunoreactivity increases in the nucleus as a function of the time of exposure to ozone

This result shows that oxidative stress by itself is able to produce damage and neuronal death, which is accompanied by the loss of regulation of the inflammatory response and by changes in astrocytes and microglia.

We can therefore conclude that oxidative stress caused by ozone produces a state of progressive neurodegeneration, which is characterized by neuronal death, changes in the microglia, loss of regulation of the inflammatory response, and loss of the ability of brain to be repaired.

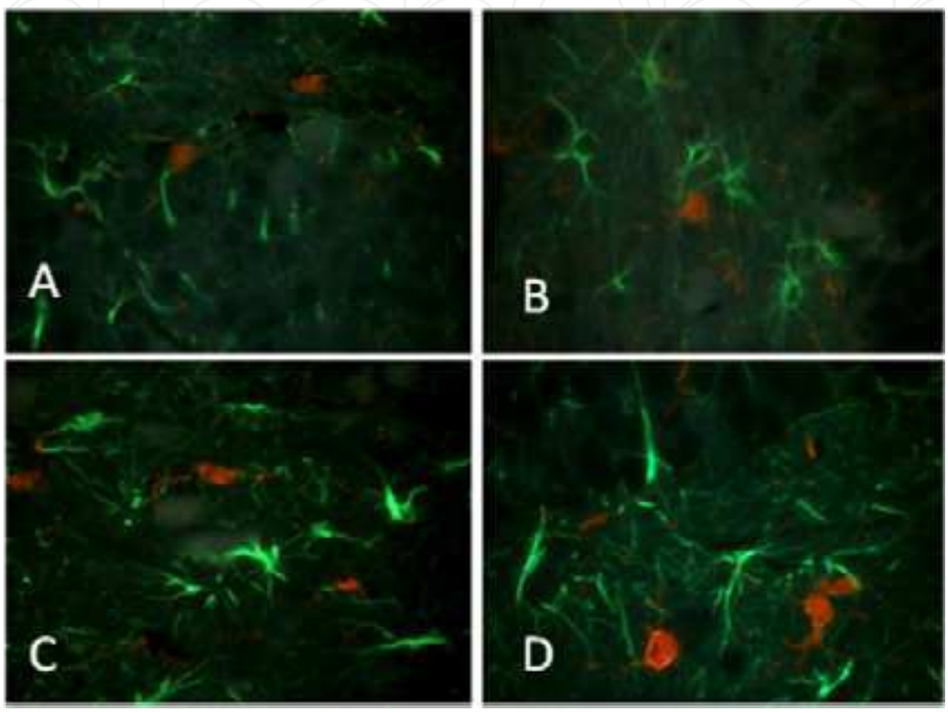


Fig. 9. Double micrograph that shows the effects of oxidative stress on astrocytes (green) and microglia (red) in the rat hippocampus exposed chronically to low ozone doses. Control (A) 30 days (B) 60 days (C), and 90 days (D) of ozone exposure (40x). Note that oxidative stress causes morphological changes in astrocytes and phenotypic changes in microglia

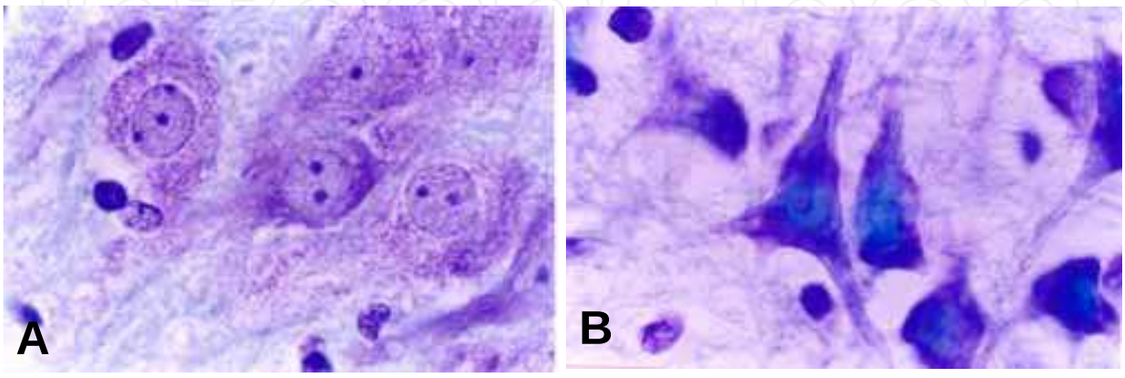


Fig. 10. Micrograph that shows the effects of oxidative stress on the hippocampal neurons of the rat exposed to ozone for 30 days. Control (A) and 30 days of ozone exposure (B) (100x)

10. Neurodegenerative diseases

Neurodegenerative diseases (diseases in which nerve cells degenerate and die) have a variety of symptoms, can affect different parts of the brain, and the causes are multifactorial and still are not entirely clear. All of them have in common the altered mitochondrial function, increased oxidative damage, presence of abnormal aggregates of proteins and proteasomes, alteration in the metabolism of iron, and changes and dysregulation of inflammation and exitotoxicity. All these form a vicious cycle and can initiate cell death and quickly recruit other cells in its destructive purpose. Oxidized proteins are usually removed by the proteasomes. Inhibition of the proteasomes by a redox state alteration leads to an accumulation of abnormal proteins and ROS production. The ROS-producing agents can initiate neurodegeneration because the ROS causes damaged mitochondria, producing an increase in the Ca^{2+}, and inhibiting the function of the proteasomes. The iron in several areas of the brain increases with age and with other metals promotes oxidation, and with this the aggregation of various proteins.

10.1 Oxidative stress and Alzheimer's disease

Alzheimer's disease is characterized by the pathogenic presence of intracellular tangles of tau protein containing hyperphosphorylated and extracellular senile plaques formed primarily by β-amyloid oligomers. Different scenarios have been proposed that explain the causes involved in the development of the disease; one is oxidative stress. There are several studies suggesting that accumulation of free radicals in excess formed during normal metabolism is able to cause oxidation of proteins, DNA and RNA, lipid peroxidation, and modification of sugars, thus generating massive neuronal death in the hippocampus, associated with parts of the neocortex (Praticò, 2008). The formation of senile plaques is caused by the intracellular and extracellular accumulation of insoluble beta amyloid in the brain. The peptide beta amyloid is generated by the splitting of the amyloid precursor protein (APP) that involves the enzymes alpha, beta, and gamma secretases (Rajendran, 2008). There are multiple forms of oligomerization that can be found in the beta amyloid peptide. This peptide can play various physiological and pathological roles depending on

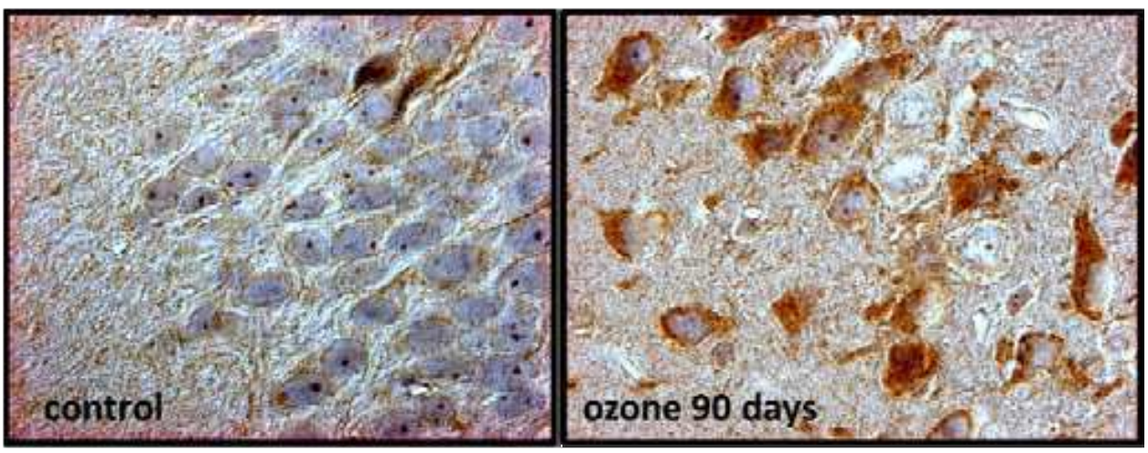


Fig. 12. Microphotography that shows the effects of a chronic, oxidative-stress state on the expression of the insoluble form of β-amyloid 1-42 immunoreactivity in a healthy rat exposed to low ozone doses for 4 h daily for 90 days

the path of its formation. The beta amyloid may deposit in specific regions of brain as amyloid plates that form. Break up of the APP is in two phases; a nonamyloidogenic pathway and an amyloidogenic pathway (Rajendran, 2008). In the nonamyloidogenic pathway, the alpha secretase cleaves in the position of the amino acid 83 from the side carboxyl terminal producing a long ectodominion amino (N) - terminal (sAPPα). The result of this process is the formation of C83, which is retained by the membrane to be cut by the gamma secretase forming short fragments of p3. The breakdown by the alpha secretase occurs in the region of beta amyloid.

The amyloidogenic pathway is an alternate way of rupturing of the APP that leads to the generation of beta amyloid. This path is caused by the beta secretase that cuts in the amino acid 99 allowing the release of sAPPβ in the extracellular space. Subsequently the rupture of this fragment between residue 38 and 43 by γ-secretase releases an intact peptide Aβ. The full length of the β-amyloid peptide is 40 residues ($A\beta_{40}$), with 10% a variant of 42 residues ($A\beta_{42}$). This latter variant is more hydrophobic and easily causes formation of fibrils and is the form of this peptide which predominates in beta amyloid plaques (Rajendran, 2008; Tillement et al., 2010).

Lower levels of the intracellular β-amyloid peptide produce the internalization of the amyloid precursor protein. This internalization is mediated by a low density receptor-related lipoprotein 1B (LRP1B), one of the members of the LDL family, This receptor typically joins the precursor protein of amyloid in the plasma membrane to prevent the internalization of the beta amyloid peptide by reducing its production. The failure of these mechanisms and the association of the tau protein causes the internalization of extracellular protein neurons, which gives rise to the production and outsourcing of the insoluble beta amyloid isoform.

Synthesis of soluble β-amyloid is altered during this phase and increases the synthesis of the insoluble, unfolded β-amyloid as part of the insoluble plates of the β-amyloid. The loss of redox homeostasis, both endogenous or exogenous, produces a state of chronic oxidative stress that increases the production of ROS and RNS, causes a reduced expression or activity of antioxidant systems, accelerates ageing, and plays a key role in the pathogenesis and the course of Alzheimer's disease by the altering of many signaling metabolic pathways in the cell by promoting mutations or altering the postransductional mechanisms. The chronic disruption of the oxidation-reduction balance, causes bad protein folding, products of advanced glycosylation, overload of peroxidation of saturated fatty acids (hydroxynonenal, HNE) (Liu, 2008), oxidation of cholesterol, disturbances in the insulin receptor to cause insulin resistance, and oxidation of LDL receptors involved in the reentry of peptide or the APP (Liu, 2008). We can infer that Alzheimer's is the final manifestation of a series of oxidative alterations of metabolism, which involve different biomolecules, in which the loss of the oxide-reduction balance plays a decisive role in the formation of the phosphorylated tau protein and insoluble beta amyloid .

10.2 Environmental toxics and Parkinson's disease

The initiation and development of the Parkinson disease's (PD) is still uncertain. The pathophysiology is complex and multifactorial and often differs among affected individuals. A large number of studies have provided evidence that loss of redox regulation contributes to all forms of PD, but it has not yet been determined whether the ROS are a primary event or a consequence of the pathogenic factors. An overproduction of ROS is unquestionably an important mediator in cell death in PD (Berg, 2004). It has been suggested that the PD

pathogenesis may involve two processes; damage from a specific disease or that combined with damage associated with normal aging. The PD is the result of neurodegeneration in specific areas of the brain (substantia nigra, pars compact, and putamen) resulting in a decrease of dopamine (Cui, 2004). Factors involving dopamine, neuromelanin, increase in the deposits of iron in the substantia nigra, a decrease of ferritin and glutathione (GSH), a deficiency in the role of the complex I mitochondrial respiratory chain, mitochondrial dysfunction and excitotoxicity may be the cause or result of the ROS. Toxins such as paraquat, MPTP, and rotenone have proven to increase the risk of PD in humans. Studies with animal models and cells reveal the oxidative and inflammatory properties of these toxins, and their ability to activate glial cells that subsequently destroy the neighboring dopaminergic neurons. The activity of the complex I mitochondria is deficient in the substance nigra (SN) in PD and can be associated with a genetic abnormality or be the result of oxidative stress. The postulate of a defect in the mitochondrial DNA is still uncertain. It has been shown in the culture of dopaminergic cells that the decrease of glutathione, from the selective loss in the activity of the mitochondrial complex I is an important feature of PD.

10.2.1 Dopaminergic system

Dopamine (DA) is a catecholamine that plays an important role in the human brain as an inhibitory neurotransmitter, particularly involved in the regulation of motor function. It is synthesized in the nerve terminals from tyrosine, the precursor of the amino acid dopaminergic neurons. The synthesis begins with the formation of L-DOPA, through the action of tyrosine hydroxylase and the biopteridines. The former enzyme is the limiting enzyme in the synthesis of dopamine. The activity is strictly controlled. L-DOPA is metabolized to form DA by an aromatic amino acid decarboxylase. In the nerve terminals, the DA is stored in synaptic vesicles with an acid content because it prevents the autoxidation of the DA until it is released. The action ends with the uptake of DA by a membrane transporter and the subsequent reuse or catabolism by the enzyme monoamino-oxidase (MAO) or the catechol-o-methyltransferase (COMT). Within the brain, dopaminergic systems are involved in processes of motivation, learning, memory, and motor control. It is estimated that dopamine is > 80% of the total content of catecholamines in the brain. The greatest risk of the DA is that this catechol group oxidizes easily through a process that involves the transfer of an electron to oxygen. Thus, this oxidation results in the formation of an superoxide anion, hydrogen peroxide, hydroxyl radical, and other ROS that are able to generate a state of oxidative stress and start a process of neurodegeneration.

10.2.2 Dopamine as a source of ROS in the CNS

Mechanisms through which the DA stimulates the production of ROS have been proposed. These depend on the presence or absence of enzyme mediators. It is known that the DA of the SN and the striatum (STR) is deaminated by the enzyme MAO located in the outer membrane of the mitochondrion. This reaction has resulted in the production of a superoxide radical, hydroxyl radical, and hydrogen peroxide (Graham, 1978). Proposed mechanisms through which the DA stimulates the production of ROS depend on the presence or absence of enzyme mediators.

The endogenous dopamine-derived N-methyl(R)salsolinol is one of the most studied derivatives of DA for two reasons. It is present in the human brain and can easily become a neurotoxin able to cause cell death. It has been proposed that this compound can be formed

by an enzymatic pathway that involves a synthase or a nonenzymatic pathway by the condensation of the DA with acetaldehyde (Naoi et al., 1996).Another derivative of the DA is the tetrahydropapaveroline (THP), which is obtained from enzymatic catabolism. The THP by itself is able to cause necrosis in neuroblastom cells and is related to the pathogenesis of Parkinson's disease. Derivatives of the metabolism of DA act as proneurotoxins in the development of Parkinson's disease. It is known that certain components of tobacco smoke may react with these proneurotoxins preventing its activation. This may explain the beneficial effect of smoking on the incidence of Parkinson's disease (Hermida-Ameijeiras et al., 2004).

10.2.3 The autoxidation of dopamine

Another mechanism through which DA can contribute to the formation of ROS is its spontaneous autoxidation. The DA is a molecule of the catechol group that can easily oxidize nonenzymatically to form a series of electrochemical type quinoide species. The initial step in the oxidation of the DA involves a reaction with molecular oxygen to form two molecules of the superoxide anion and DA-o-quinone. The formation of the superoxide anions during the autoxidation of the DA leads to the production of hydrogen peroxide by the dismutation of superoxide. The DA-o-quinone then undergoes an intramolecular clyclization to form 5,6-dihydroxiquinoline, which is subsequently oxidized by the DA-o-quinone to form dopaminochrome. This compound undergoes a rearrangement to form 5,6-dihydroxyindole, which in turn is oxidized to an indole quinone. The next

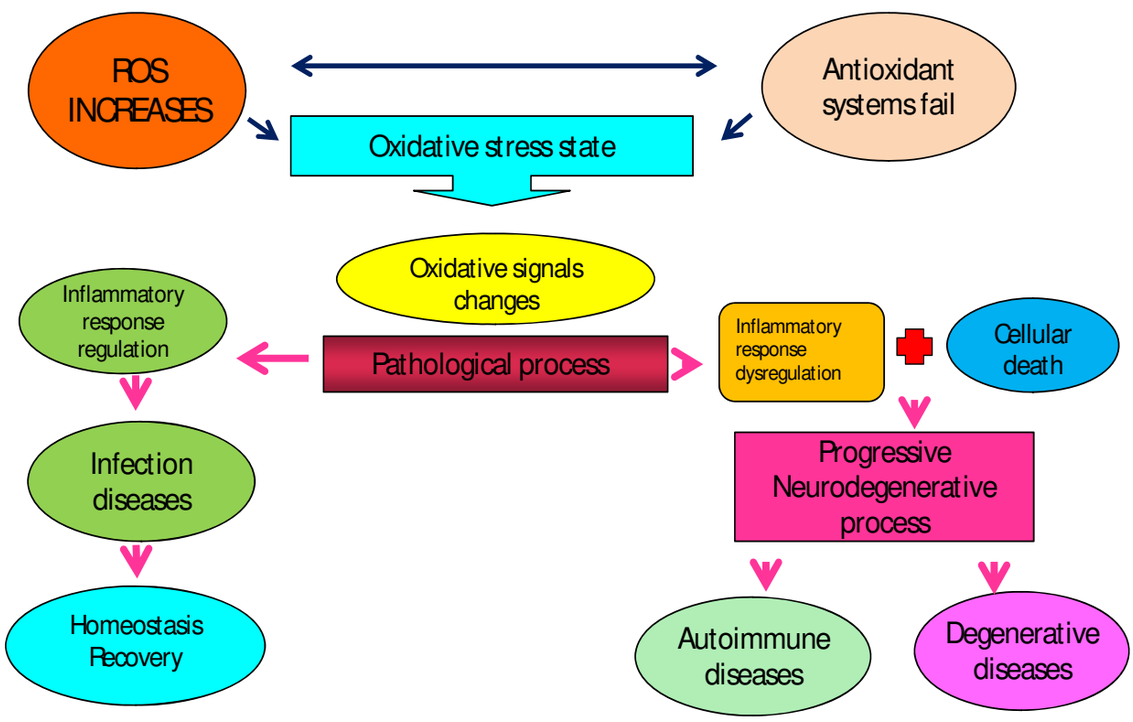


Fig. 13. Showing the effect of oxidative stress on the pathological process and the pathway that is followed depending on the regulation or nonregulation of the inflammatory responses

polymerization process eventually leads to the generation of a dark pigment called neuromelanin. The dark appearance of the SN is caused by the presence of this pigment containing products derived from the oxidation of the cysteinyl-DA. When the autoxidation of the DA takes place in the presence of L-cysteine, the DA-o-Quinone undergoes a nucleophilic attack by the thiol of the amino acid group to form cysteinyl-DA. This differs from normal oxidation of the DA to form neuromelanin (Hermida-Ameijeiras et al., 2004).

11. Conclusions

In a balanced oxidation-reduction system, reactive species have an effect as signaling or a regulator of both the glia and neurons in internal signaling pathways, act as regulators of the immune response, which includes inflammatory response, and as regulators of the cell cycle, neuroplasticity, and metabolism. The short-term loss of the oxidation-reduction balance causes an increase in the activity of antioxidant systems to counteract the oxidative stimulus. The endogenous increase of the antioxidant systems play a restorative role of the organism. An enlightening physiological example of this is the repairing role of exercise in chronic degenerative diseases, which is explained by a rise in free radicals as a consequence of an increase in endogenous antioxidant systems.

The loss of the redox balance (as shown in the model of oxidative stress caused by ozone) implies a loss of regulation of the inflammatory response, which then causes a reparative and self-limiting response. This becomes a perpetual response, a vicious cycle, in which there is mitochondrial failure that leads to a lack of ATP, an increase in the state of oxidative stress, loss of regulation of inflammatory markers, blocking of antioxidant systems, inability to synthesize new proteins, disorders of the proteasome, accumulation of misfolded proteins, and the conformational change in key receptors involved in metabolism and cell signaling. All of them, established slowly over time, can produce chronic degenerative diseases and neurodegenerative diseases as a manifestation of a series of alterations caused by multiple factors, including that of the establishment of a state of chronic-oxidative stress. This plays a key role in the loss of the regulation of cell signaling, of the different responses that lead to neuronal death and loss of brain repair and the altering of the process of neurogenesis. All these are clinically manifested into neurodegenerative diseases long after the vicious cycle has started. The discovery of early oxidative markers specific to each neurodegenerative disease can allow an early diagnosis and break the vicious cycle established by oxidative stress. This can be seen occurring in the near future for the treatment and detection of these diseases.

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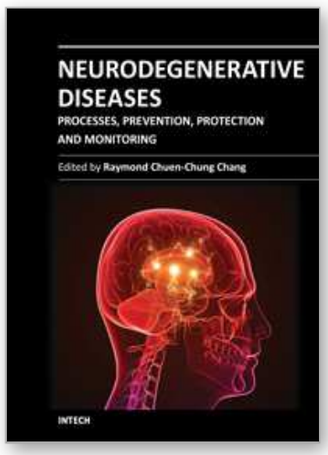

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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