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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 (Flov d 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 (Brue l-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 environment is 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 nigrostriatal 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 & Townsend 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 ($\bullet\text{O}_2^-$) 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 (H₂O₂)

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 ($\cdot\text{OH}$)

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 (Halliwell & Gutteridge, 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 ($\bullet NO$)

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 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- κ B) 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 $\bullet NO$ 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 $\bullet NO$ 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 $\bullet NO$ is low and a redox