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REVIEW ARTICLE

Inflammation from the basics to the clinical: Advances and challenges in oxidative stress

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ABSTRACT

Introduction - In this review, one of the mechanisms that is generated in inflammation, oxidative stress, was analyzed. Inflammation is an immune system response, it is essential for survival and recovery, but it can cause damage to the body, due to oxidative stress that occurs when there is an imbalance between the production of reactive oxygen species and the body's ability to neutralize them with Endogenous antioxidants contribute to the development of chronic diseases such as cardiovascular, diabetes, autoimmune diseases, cancer, neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis.

Aim - Evaluate the literature about Inflammation from the basic to the clinical.

Methodology - Databases such as MEDLINE/PubMed and ScienceDirect regarding Inflammation were analyzed.

Results - Despite recent advances in the understanding of inflammation and oxidative stress, there are still important challenges in the study and treatment of these conditions, on the one hand, it is necessary to develop more precise biomarkers to evaluate oxidative stress and inflammation in the patients. While in the other, new therapeutic approaches are needed to modulate inflammation and oxidative stress more effectively and specifically.

Conclusion - That the study of inflammation and oxidative stress is crucial to understanding the pathophysiological bases of various chronic diseases and that advances in the field of inflammation and oxidative stress have provided new therapeutic perspectives for the treatment and prevention of chronic diseases. . .

Keywords: - Inflammation, oxidative stress, reactive oxygen species and chronic diseases.

INTRODUCTION

Inflammation is a complex biological response of the immune system to damage, infections or attacks. Although essential for tissue survival and recovery, chronic inflammation can cause damage to the body and contribute to the development of various diseases, such as cardiovascular disease, diabetes, autoimmune diseases and cancer. One of the mechanisms involved in inflammation is oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species and the body's ability to neutralize them.

INFLAMMATION: FUNDAMENTAL BASIS

"Inflammation is not a disease, but a nonspecific response that produces a healthy effect in the organism in which it occurs." Cohnheim (1839-1884) was the first researcher to use the microscope to observe swollen blood vessels in thin, translucent membranes, such as the mesentery and tongue of the frog. Shortly after, the research of Elie Metchnikoff and Paul Ehrlich demonstrated that both cellular factors (phagocytes) and serum factors (antibodies) were essential for defense against microorganisms. To these names must be added that of Sir Thomas Lewis, who, through simple experiments on the inflammatory response of the skin, established the concept that various chemical substances induced locally by the stimulus of an injury, such as histamine, which are mediating factors of vascular alterations of inflammation. This fundamental concept is the basis for the important discoveries of chemical mediators of inflammation and the possibility of using anti-inflammatory drugs[1,2].

Inflammation has two distinct phases: acute and chronic. Acute inflammation has a relatively short course; Its fundamental characteristics are the exudation of fluid and plasma proteins (edema), and the migration of leukocytes (mainly neutrophils). Chronic inflammation lasts longer and is characterized by the proliferation of blood vessels, fibrosis and tissue necrosis[1].

Acute inflammation is an immediate response of the body to an injury or infection. It is characterized by dilation of blood vessels, extravasation of fluids, and migration of inflammatory cells to the affected site. This initial inflammatory response is necessary to initiate the repair of damaged tissues and neutralize infections. However, if inflammation persists, it becomes chronic inflammation, which can lead to tissue damage and contribute to the development of chronic diseases[1].

OXIDATIVE STRESS: BASIC CONCEPTS

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the body's ability to neutralize them with endogenous antioxidants. ROS, like free radicals, can damage cells and tissues if not properly controlled. Oxidative stress has been implicated in chronic inflammation and various diseases, such as cardiovascular diseases, neurodegenerative diseases, diabetes, and cancer.

CONCEPT OF OXIDATION

Oxidation is a process in which a chemical substance loses (gives up) electrons, and reduction is a process in which the chemical

substance gains (gains) electrons. Oxidation and reduction occur simultaneously and the total number of electrons lost is equal to those gained. The chemical substance that gives up electrons is the reducing agent and the chemical substance that receives electrons is the oxidizing agent[4,3].

OXIDATION IN BIOLOGICAL SYSTEMS

In humans, oxidation is a dynamic process that is constantly carried out, in such a way that the agents causing oxidation are the so-called oxidants, as oxidants are reactive oxygen species (ROS) and reactive oxygen species. nitrogen (ERN). These reactive species (RS) are generated mainly within the organism (intracellularly and acting both inside and outside the cell) and are also stimulated by environmental agents. The ROS that occur in the body are caused by: normal metabolism (in the respiration chain at the mitochondrial level), hypoxia events, biological agents, immunological modifications, genetic alterations.

The reactive species produced in humans, ROS and ERN, can be beneficial or toxic, depending on the concentration and continuity in which they are produced; and they can be classified as radical and non-radical (Table 1).

Table 1. Reactive oxygen and nitrogen species according to Halliwell, B., & Gutteridge, JM (2015).

	Reactive Oxygen Species ROS	Reactive Species Nitrogen ERN
RADICALS	Superoxide anion •O2- Hydroxyl •OH Peroxyl •OOR Hydroperoxyl HO2 Alkoxyl •OR	Nitric oxide NO• (nitrogen monoxide) Nitrogen dioxide NO2•
NON-RADICAL	Hydrogen peroxide H2O2 hypochlorous acid HOCl Ozone O3 Singlet oxygen 1O2 form 1Δ Hypobromous acid (HOBr)	Nitrous acid HNO2 Peroxynitrous acid (ONOOH) Alkylperoxynitrites (RONOO) Nitrosyl cation NO+ Nitronium cation NO2+ Nitrosyl anion NO- Dinitrogen tetraoxide N2O4 Dinitrogen trioxide N2O3 Peroxynitrite anion ONOO- Nitrite NO2- Nitrate NO3-

Reactive oxygen and nitrogen species are essential for many normal biological processes, such as the activation of phagocytes, the metabolism of eicosanoids, or, forming part of a series of events in response to an invasion of microorganisms and foreign material, generating chemotactic factors, among others. They are also involved in cell signaling, however, they play an important role in the generation of cellular damage, initiating a wide variety of toxic oxidative reactions, such as the initiation of lipid peroxidation, inhibition of mitochondrial respiration, inhibition of mitochondrial activity of the Na+/K+ pump, inactivation of sodium channels and other protein oxidative reactions.

Under physiological conditions there is a balance between the formation of ROS, ERN and enzymatic and non-enzymatic antioxidants, as well as repair systems; however, when this balance is broken, so-called oxidative stress occurs[5,6,7,8]

OXIDATIVE STRESS (OS)

Rebeca Gerschman, between the 1950s and 1960s, postulated the theory of cellular damage due to oxygen toxicity and the decrease in antioxidants; Based on this theory, in 1985 Helmut Sies developed the concept of EO as a situation of imbalance with an increase in oxidants or a decrease in antioxidants[9].

Oxidative stress is the increase in the production of ROS and ERN or a decrease in antioxidant or repair systems, or a combination of these factors.

Oxidative stress leads to biochemical and physiological lesions which can deteriorate metabolism, causing oxidative damage to lipids, proteins and nucleic acids, which finally results in cell death and subsequently tissue damage[9,10,11] (Table 3).

Oxidative stress is associated with aging, exercise, ethanol intake, smoking and numerous human diseases, such as: ischemia, reperfusion, atherosclerosis, acute hypertension, hemorrhagic shock, diabetes mellitus, cancer, inflammation, Parkinson's disease, Alzheimer's disease, Huntington's disease, Wilson's disease, Friedreich's ataxia and multiple sclerosis, nephrotoxicity, acute renal failure, chronic renal failure, among other diseases[5.6,7,8.]

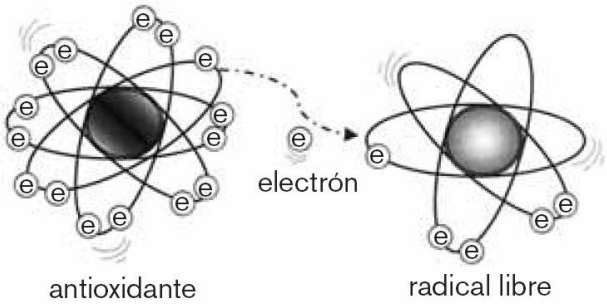
Up to this point, various ROS and ERN have been mentioned that are normally produced in living systems, and under conditions of oxidative stress, however, to prevent the oxidation of biomolecule there are antioxidant substances.

Table 2. Cellular targets of ROS and ERN (Günthern and Mogado, 2007)

WHITE	EFFECTS
Unsaturated amino acids with thiol groups	o Protein denaturation o Breakage of covalent bonds o Inhibition of cell permeability and organelles
Nitrogenous bases	o o Alterations in the cell cycle o Mutations
o Carbohydrates	o Changes in the protoplasmic portion of the cell membrane
o Unsaturated lipids	o o Oxidation of cholesterol and fatty acids o o Formation of covalent bonds between lipids o Alterations in the permeability of biological membranes
o Vitamin cofactors	Reduced availability of redox cofactors derived from nicotinamide and flavin
o Neurotransmitters	Decreased availability of neurotransmitters such as catecholamines and serotonin
o Antioxidants	Decreased availability of antioxidants, including alpha-tocopherol and carotene
o Proteins	o Breaking of peptide chains o Denaturation
o DNA	o Breaking chains o Modification of bases
o Hyaluronic acid	Change in synovial fluid viscosity
o	

ANTIOXIDANTS

Antioxidants are defined as those substances that, present in low concentrations compared to those of an oxidizable substrate (biomolecules), delay or prevent oxidation[12], by donating an electron in order to make the ER more stable (Scheme 1).



Scheme 1. Interaction of free radicals with antioxidants (Velásquez et al., 2004).

The chemical defenses capable of maintaining the oxidant/antioxidant balance of the body can be classified into enzymatic antioxidants, non-enzymatic antioxidants, and repair mechanisms.

As enzymatic antioxidant agents there are: the enzyme superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione transferase, glutathione reductase (GR) and paraoxonase (PON1).

Non-enzymatic antioxidants are divided into those obtained through the diet (exogenous) and those that are synthesized in our body (endogenous). Both are classified into: water-soluble and fat-soluble antioxidants (Table 3).

Enzymatic repair systems: repair oxidized DNA and proteins[11]. Among the DNA repair enzymes are endonucleases, exonucleases and methionine sulfoxide reductase[12].

VITAMIN C (ASCORBATE OR ASCORBIC ACID)

Ascorbate can exist in three redox states: L-Ascorbate, ascorbyl radical and dehydroascorbate acid. You can remove the .O2-,. OH, H2O2, ROO., NOO. and also extinguish $^1O_2$[13,14].

Most animals can synthesize ascorbate from glucose, but some primates and man have lost the enzyme for the last step of biosynthesis (gulonolactone oxidase).

Table 3. Non-enzymatic antioxidants.

	Exogenous	Endogenous
Water soluble	Flavonoids and polyphenols	Uric acid
	Vitamin C	Bilirubin
Fat soluble	Vitamin E	Coenzyme Q10
	Carotenoids	

Vitamin C is a water-soluble molecule, which interacts with practically the same oxyradicals as Vitamin E, but with the additional advantage of its ability to regenerate the reduced variant (antioxidant) of vitamin E by interacting with the tocopheryl radical to regenerate the α-tocopherol to its active state. However, it is important to consider that in the presence of transition metals, such as in hemolysis, vitamin C is capable of facilitating the production of free radicals, apparently without connection with an increase in lipoperoxidation[15].

TIOLS (GLUTATHIONE)

Glutathione is a tripeptide of γ-glutamic acid, γ-cysteine and γ-glycine that constitutes the most abundant major cellular non-protein thiol; it is maintained at a millimolar concentration. It is found in reduced form (GSH) and oxidized form (GSSG). Glutathione has several functions, including; It participates in the formation and breakdown of disulfide bridges in proteins and its antioxidant activity is due to the reducing capacity of the thiolic group of cysteine.

It can act as an antioxidant in enzymatic reactions (such as with glutathione peroxidase). Protects the oxidation of essential SH groups of proteins. It is one of the most active non-enzymatic antioxidants and directly traps H2O2, .OH, .O2-, chlorinated oxidants. The ability of GSH to carry out singlet 1O2 quenching reactions has also been described, returning it to its non-reactive basal state (triplet)[14,15].

When GSH reacts with oxidants it is oxidized to GSSG, which is toxic to cells, so they tend to maintain a low GSSG/GSH ratio, by reducing GSSH to GSH with glutathione reductase[14,15].

THE SUPEROXIDE RADICAL ANION AND THE SUPEROXIDE DISMUTASE

The enzyme superoxide dismutase (SOD), discovered by McCord and Fridovich, is the first antioxidant that protects against oxidative damage, because it accelerates the transformation of the superoxide anion radical into hydrogen peroxide[16].

$$O2^- + .O2^- + 2H \xrightarrow{S.O.D.} H2O2 + O2$$

In the above reaction, one molecule of superoxide is oxidized to give rise to O2, while another is reduced to give rise to H2O2. The reaction is diffusion limited due to the reaction constant (2 x 109 M-1 s-1).

In the phagocytes of the immune system (activated neutrophils, eosinophils and macrophages), when faced with a stimulus, they experience an increase in oxygen consumption, mainly in the plasma membrane, where the enzyme NADPH oxidase[17] produces, at the expense of electrons from the pentose pathway and basal oxygen, oxygen free radicals. The extracellular production of O2•- represents more than 90% of the oxygen consumption of the activated cell[18].

$$NAD\ PH + 2\ O_2 \longrightarrow NADP+ + 2\ O_2- + H+$$

NADPox

In the vascular endothelium: through endothelial NADPH oxidase[19].

$$NAD\ (P)H + 2\ O_2 \longrightarrow NAD(P) + H+ + 2\ .O2–$$

Cytochrome P450-dependent oxygenases[20].

NITRIC OXIDE

Nitric oxide (NO·), also known as nitrogen monoxide, is a colorless gas relatively soluble in water, an obligatory intermediate of the nitrogen cycle. NO· is a lipophilic free radical. It is not very reactive and diffuses through the membrane and cytoplasm. It reacts slowly with the thiol groups or sulfhydryls of some proteins.

He does not. It can form other ERNs, such as nitrate when reacting with O2 and peroxynitrite (ONOO-) when reacting with O2·-, the nitrosonium cation (NO+), the nitroxyl anion (NO-)[21]

Nitric oxide is a molecule of great importance in biological systems, it participates in signaling systems. At concentrations of 10-7 M it functions as a messenger in the central and peripheral nervous system, in addition, it exerts multiple antiatherogenic effects: vasodilation, inhibition of platelet aggregation, inhibition of smooth muscle fiber proliferation and decrease in the production of chemotactic protein. of monocytes (MCP), among others.

Nitric oxide is formed by the immune system and inhibits essential enzymes such as terminal oxidases and other hemoproteins that bind oxygen and enzymes with Fe-S centers such as aconitases[22], and together with ROS it influences multiple effects of inflammation and immune response.

ADVANCED GLYCOSYLATION PRODUCTS (AGEs)

Non-enzymatic glycosylation of proteins, also called glycation or Maillard reaction. AGEs (advanced glycosylation end products) increase the formation of ROS since they are compounds unknown to the effector cells of the immune response, which promotes their activation and the production of RL. AGEs are generated through the reaction between a carbohydrate (monosaccharide) and a protein or lipid. These compounds are formed when food is cooked and also in the body as age increases or in pathological states such as hyperglycemia.

At the beginning of the 20th century, Louis Camille Maillard (1872-1936) studied the combination of sugars with other biomolecules and described the molecular bases of these reactions, which later took his name. A decade later, in 1922, the Italian chemist Mario Amadori (1886-1941) determined the arrangement that bears his name and that describes the first stages of the combination of reducing sugars with primary amino groups belonging to different molecules[23].

The reaction between an aldehyde group of a monosaccharide and a free amino group (the reactive amino groups can be the α-NH2 group of the N-terminal protein or the Є-NH2 group of the lysine residue depending on their availability and conditions of the medium) a molecular arrangement known as the Schiff base is produced. These bases are unstable and undergo a slow intramolecular rearrangement that forms ketoamines or fructosamines (Amadori compounds), this reaction is reversible; The persistence of the conditions that give rise to Amadori compounds favors their accumulation and transformation, through non-enzymatic and irreversible reactions, into advanced glycosylation products (AGEs). The latter are chemically stable molecules (covalent complexes), therefore, they do not degrade.

INTERACTION BETWEEN INFLAMMATION AND OXIDATIVE STRESS.

Inflammation and oxidative stress are closely related. Chronic inflammation can lead to excessive production of ROS, leading to oxidative stress. In turn, oxidative stress can activate inflammatory pathways, generating a vicious cycle that contributes to the development of chronic diseases. Additionally, various inflammatory cells release enzymes and inflammatory mediators that can increase oxidative stress in affected tissues.

Inflammation and oxidative stress consist of distinct biochemical cascades; both processes are closely intertwined and operate in parallel,

particularly in the brain, which is more prone to oxidative stress[24]. Evidence of oxidative stress in the brain {such as ROS and markers of brain damage}[25,26] is generally found alongside evidence of inflammation (such as activated immune cells, cytokines and other inflammatory mediators, etc.)[27,28]. So there is much to learn about inflammation and oxidative stress, in their interactions at these two main known points of convergence, which in turn explains their tendency to occur together and reinforce each other, triggering oxidative stress activates the inflammatory responses and vice versa.

Microglia are cells of the central nervous system that function as elements of the immune system, producing ROS as defense agents against pathogens. or their markers[29]. If the antioxidant capacity of cells is overwhelmed by ROS, oxidative stress causes subsequent damage to essential molecules and tissues[30].

AIM

Evaluate the literature on the topic: Inflammation from the basics to the clinical.

METHODOLOGY

Databases such as MEDLINE/PubMed and ScienceDirect regarding Inflammation were analyzed.

RESULTS

LATEST ADVANCES IN THE STUDY OF OXIDATIVE STRESS AND INFLAMMATION

In recent years, numerous studies have been conducted to better understand the underlying mechanisms of inflammation and oxidative stress. It has been shown that certain environmental factors, such as diet, tobacco, and pollution, can increase oxidative stress and chronic inflammation. In addition, new molecules and signaling pathways involved in the regulation of inflammation and oxidative stress have been identified.

OXIDATIVE STRESS AND SIGNALING PATHWAYS

Oxidative stress can modulate a wide variety of biological processes by signals on the cell surface with changes in gene expression. HE suggest multiple signaling pathways. In fact, ROS can be defined as a true second messenger that regulates several cascades of nuclear transcription factor transduction signals, including modulation of the Ca2+ signal, protein kinase and phosphatase pathways[31].

Some oxidation processes are reversible and may play a role in the dynamic regulation of events resulting in variation of the redox condition within the cell. Such variations can cause changes in signaling proteins and modify transductional pathways.

ROS in general and hydrogen peroxide in particular, are second messengers for various physiological and pathological stimuli, such as inflammatory cytokines, angiotensin, growth factors, ionizing radiation, etc.[32]. For example, platelet-derived growth factor increases intracellular hydrogen peroxide levels in vascular smooth muscle cells and induces tyrosine phosphorylation and stimulation of serine/threonine kinase[33]. The Ras G-protein acts as a mediator of the ROS signal, activating a cascade of kinases, including various members of the MAP-kinase family[34]. In the case of ERK5 or BMK1 (large MAP kinase), hydrogen peroxide appears to be an exclusive activator[35]. Homocysteine is an

independent risk factor for atherosclerosis that induces oxidative stress[36]. These observations suggest that ROS may mediate specific signaling pathways within the cell, as well as, proteins may be differently sensitive to oxidation depending on their content of cysteine residues, their conformation, and the intensity of oxidative stress[37]. Therefore, the possible specific signal may be mediated by oxidative stress. Different agents induce oxidative stress to stimulate tyrosine kinase activity, induce phosphorylation on tyrosine residues and activate protein kinase C, c-Src, raf-1 and MAPK[38]. Baas and Berk demonstrated that superoxide radical increases MAPK activity in vascular smooth muscle cells. Treatments with antioxidants inhibit the generation of superoxide radicals and block the activation of MAPK.

CHALLENGES IN THE STUDY AND TREATMENT OF OXIDATIVE STRESS AND INFLAMMATION

Despite advances in understanding inflammation and oxidative stress, there are still significant challenges in the study and treatment of these conditions. On the one hand, it is necessary to develop more precise biomarkers to evaluate oxidative stress and inflammation in patients. Furthermore, new therapeutic approaches are needed to modulate inflammation and oxidative stress more effectively and specifically.

CONCLUSION

The study of oxidative stress and inflammation is crucial to understanding the pathophysiological bases of various chronic diseases. Oxidative stress and inflammation are closely interrelated and both play a key role in the development and progression of chronic diseases. Advances in the field of inflammation and oxidative stress have provided new therapeutic perspectives for the treatment and prevention of chronic diseases associated with these processes.

CONFLICTS OF INTEREST:

None

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