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Review Article

Oxidative Stress as "Mother" of Many Human Diseases at Strong Clinical Impact

Abstract

Oxidative stress, characterized by the production in excess of free radicals, is the main aspect of all living systems which use oxygen to convert biochemical energy coming from nutrients into adenosine triphosphate. In turn free radicals, also called reactive oxygen species , induce oxidative damage to some cellular macromolecules, as lipids, proteins, and DNA .Increased reactive oxygen species serum concentration has been implicated in the pathogenesis of some, common human diseases, included both healthy and diseased ageing. The most frequent pathologies involved are: atherosclerosis, cancer, Alzheimer's and Parkinson's Diseases and chronic obstructive pulmonary disease. Together with these, other, less frequent diseases can be interested, as chronic fatigue syndrome, lateral amyotrophic sclerosis and skin diseases. Therefore oxidative stress, that is an imbalance of an essential biochemical reaction physiologically happening in the human body, can be considered as one of the sources of the most common human pathologies and of the aging process.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic Lateral Sclerosis; CFS: Chronic Fatigue Syndrome; COPD: Chronic Obstructive Pulmonary Disease; EGFR: Epidermal Growth Factor Receptor; LDL: Low Density Lipoprotein; OS: Oxidative Stress; NAD: Nicodin Amide Dinucleotide; NO: Nitric Oxide; PD: Parkinson's Disease; ROS: Reactive Oxygen Species; SOD-1: Super Oxide Dismutase-1; T2DM: Type 2 Diabetes Mellitus; VEGFR: Vascular Endothelial Factor Receptor; VSMC: Vascular Smooth Muscle Cell;

Introduction

Likewise the 1991 Gulf War, known as a "mother of all battles", oxidative stress (OS) can be considered as a "mother" of many human diseases life threatening. OS is a condition in which oxidation exceeds the anti-oxidant reactions, causing an imbalance between oxidative and anti-oxidant systems, with prevalence of reactive oxygen species ROS [1-5]. These include: peroxide, superoxide, hydroxyl radical, singlet oxygen and others. Under normal conditions ROS are maintained at physiological levels by several endogenous antioxidant systems, as superoxide dismutase, catalase, glutathione peroxidases, lacto-peptidases, glutathione reductase and others [6]. However, if active ROS are excessively generated, the balance between the formation and the removal of these species is lost. Generating oxidative damage (disruption between antioxidant defenses and ROS production) [7]. ROS can be generated from both endogenous and exogenous sources. Endogenous ROS are produced in normal metabolic reactions. Exogenous ROS derive by exposure to cigarette smoke, environmental pollutants, consumption of alcohol in excess, exposure to ionizing radiations, viral and bacterial infections, and others [8]. Individual, hereditary factors, and lifestyle are the main determinants of OS. Useful methods to evaluate OS include [9,10]. A) Measurement of ROS; B) Detection of oxidized DNA and lipids; C) Quantification of anti-oxidants. These ROS can attack some molecules in biological membranes and tissues, thus inducing various diseases [7,11]. Afterwards, we refer on some pathologies favored by detrimental effects of ROS, responsible for morbidity and death of total population [12-19]. We also refer on healthy ageing connected to OS in different ways [20,21] (Figure 1).

Atherosclerosis

Atherosclerosis is the result of the oxidation of the low density lipoproteins (LDL) present in the arterial wall and produced by ROS. The LDL-oxidation induces, in turn, the expression of adhesion-molecules, the proliferation and migration of smooth muscle cells, the oxidation of lipids, the endothelial dysfunction (apoptosis) and

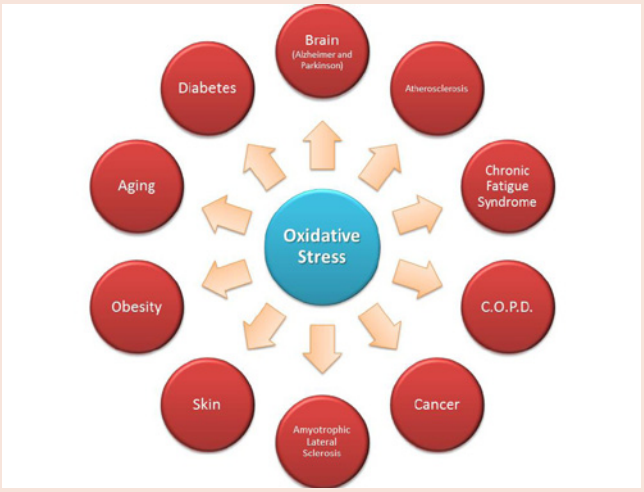

Figure 1: The greater number of human pathologies favoured by oxidative stress.

the alteration of vasomotor activity [22-24]. In confirmation of the role of ROS in the progressive endothelium dysfunction we underline the increased Nitrosodine (a cellular marker of OS) concentration in aged subjects in comparison with young healthy individuals [25]. Further, oxidized-LDL influences the release of some cytokynes', such as IL-1β, IL-6 and TNF-α, responsible for acute inflammatory processes of arterial wall. Another mechanism through which OS participates to atherogenesis consists in the production of trascription factors, as nuclear factor xB (NF-xB) and activator protein 1, which participate in the expression of adhesion molecules as vascular cellular adhesion molecules (VCAM-1), intracellular adhesion molecules (ICAM-1) and other cytokines acting in smooth muscle cells of atherosclerotic vessels [26,27]. In addition, ROS are able to modulate matrix metalloproteinases (MMPs) degradation and could contribute to the instability of atherosclerotic plaques [28,29]. The role plays by OS in the atherosclerotic process was confirmed by the use of statins in atherosclerosis. As well as the cholesterol levels' reduction, these drugs also lead to an increase of NO production and inhibit LDL oxidation [30].

Cancer

The cancer-induction is a multifactorial process that involves several factors, as genetic, physical, chemical and environmental factors. Recent knowledge's in ROS biology and tumor genesis suggest that free radicals control various aspects of tumor development including inflammation, transformation, survival, proliferation of cancers' cells, invasion, angiogenesis, and metastasis [31-33]. Specifically, free radicals directly or indirectly act, via DNA damage, on gene expression and signaling at the cellular levels [9]. In succession, the main effects of ROS on tumor genesis and some clinical their complications are reported:

Proliferation. OS effects on several biochemical pathways, such as epidermal growth factor receptor (EGFR) or mTOR, that involve key signaling proteins favoring cells' reproduction [34]. **Metastases**. ROS contributes to increased cell's motility, migration and invasion of cancer-cells, resulting in tumor expansion and metastases [35]. **Neo-angiogenesis**. Tumors produce many pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), its receptor (VEGFR), angiopoietin, MMPs, fibroblasts growth factor and others. Of these, VEGF has emerged as the crucial role in the regulation of neo-angiogenesis. MMPs are a family of enzymes that proteolytically degrade some components of the extracellular matrix, favoring neo-angiogenesis. That happens by degradation of the vascular basement membrane of the extracellular matrix in order to allow endothelial cells to migrate and invade into the surrouding tissue. In this connection, a recent study pointed out that ROS increase VEGF levels and so favour angiogenesis [36-38]. **Effects on mRNA**. But, OS inducing ROS over-production are involved in cancer development through the changes produced in microRNA (mRNAs) [39,40]. Concerning this topic, Favaro et al. recently confirmed that several ROS-related mRNAs are involved in various modalities of cancer-growth [41]. **Physio/chemical therapy**. The majority of agents used to kill cancer cells (ionizing radiations, most chemotherapeutical agents and some targeted therapies) work (through either directly or indirectly) generating ROS that block key steps in the cell cycle [42]. In this connection, current evidences support that antioxidants protect normal cells against the insults of chemotherapy and radiotherapy [42]. On the other hand, these same prevent tumorigenesis and increase lifespan [43].

Insulin resistance and diabetes

Previous investigations provide convincing evidence about the relationship between mitochondrial pro-oxidant agents production and insulin resistance [44].The link between OS and insulin resistant conditions seems to be the inflammatory state [45]. In confirmation of the role of OS in metabolic disorders, Meigs et al., demonstrated that this is associated with insulin resistance in individuals at average or elevated risk of diabetes [46-49]. Initially, the condition of insulin resistance is compensated by hyperinsulinemia with normal glucose tolerance. Impaired glucose tolerance occurs when either insulin resistance increases or compensatory insulin secretory response decreases or both occur, accelerating the progression to overt type 2 diabetes mellitus (T2DM).

Obesity

A recent editorial of Youn et al., hypothesized that ROS generated in vascular smooth muscle cells (VSMC) play an important causal role in the development of obesity, causing a condition of overweight due to leptin-resistance, glucose intolerance and inflammation [50]. On the other hand, the expansion of visceral adipose tissue caused by over-consumption of nutrients, generate an increase of visceral adipose tissue. As visceral fat stores expand, adipocytes generate increased ROS levels and metabolic syndrome [51]. Therefore, two conditions (OS and obesity) can be considered reciprocally as cause and effect one of another [52,53].

Neurodegenerative diseases

Neurodegenerative diseases indicates a loss of nerve structure and function, leading to a progressive brain damage and neurodegeneration. Apart from environmental or genetic factors, OS largely contributes to neurodegeneration. Particularly, ROS have been implicated in the progression of Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS).

Alzheimer's disease

Several studies showed that OS plays a central role in the neuropathological lesions of AD. There are: beta-amyloid peptide deposits (also called as senile plaques), happening at early stage of AD and neurofibrillary tangles, typical of the late stage [54]. Recent evidences suggest that OS may also favour AD pathogenesis by disruption of homeostasis of some metals (such as iron, zinc and copper) and ROS accumulation in the mitochondria (mitochondrial dysfunction) [55,56]. Therapeutically, it is evidenced that some compounds, as Mitoquinone mesylate reduces beta-amyloid accumulation decreasing OS [57,58]. Other drugs acting against AD as OS antagonists are Sirtuin-1, and omega-3 fatty acids [59,60].

Parkinson's disease

Most of cases of PD are idiopathic. Exposure to some substances (as pesticides, organic solvents, toxins) viral and bacteric infections play also a role. Obviously, aging di per se is an important factor

that ROS stimulate physiological adaptation to physical exercise [79]. In accordance with these controversial effects of free radicals on healthy ageing, it must be also relate on the conflicting results obtained by the antioxidant supplementation. A recent meta-analysis show no evidence to support the use of vitamin and antioxidant supplements for prevention of age-related diseases [80]. But, a meta-analysis on the risk of Alzheimer's disease shown that dietary intakes of vitamin E, vitamin C, and beta carotene can lower the risk of this disease [81]. Therefore, the effectiveness of anti-oxidants' treatment to contrast age-related diseases is still uncertain and further studies are requested [82].

Other diseases

OS also intervenes in other pathologic conditions frequently occurring among human diseases, such as chronic fatigue syndrome, chronic obstructive pulmonary disease, and skin disease .

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is an emerging disorder, particularly frequent in women. The syndrome is characterized by incapacitating fatigue of at least 6 months duration. It can affect every major system in the body, with neurological, immunological, hormonal, gastro-intestinal, musculoskeletal and pshycological problems [83]. The pathophysiology of the syndrome remains elusive. Initially, Holmes et al. proposed persisting infections as cause [84]. Smith et al. hypothesized a possible association between leukocyte antigen and CFS [85]. But, OS is certainly involved in CFS pathogenesis. In this area, Kennedy et al. recently reported high levels of OS in patients suffering of this patholology [86]. Particularly, OS produced in the muscle appears to be a primary target of CFS. In fact, the sarcolemmal and sarcoplasmic membranes of CFS patients clearly present signs of OS [87]. The mitochondrial respiratory chain is the major site of ROS production in muscle cells [88].

Chronic obstructive pulmonary disease

It is known that the pathogenesis of chronic obstructive pulmonary disease (COPD) depends on the interaction between environmental and genetic factors. Among the firsts , the most important factor of COPD acting in the western world is the cigarette smoking and the inhalation of combustion products [89]. Concerning this, OS plays an important role through injury to the respiratory apparatus [90]. Lipid peroxidation is the leading expression of OS happening in patients with COPD. That results in the degradation of polyunsaturated fatty acids, and leads to the alterations in the structure and permeability of the membrane. In turn, the alterated structure-permeability of membrane results in loss of ion-exchange selectivity, release in the contents of organelles, and formation of cytotoxic products, such as malondialdehyde and isoprostanes [91,92].

Skin disease

Skin is a largest human body organ that provides an interface between the environment and the body. For its position, skin is a major target for toxic insults. Physical and chemical agents produce OS in skin. These include gaseous airborne environmental pollutants, UV, solar radiations, food contaminants, cosmetic products, drugs, and others. The consequent release of ROS is involved in the favoring the onset of PD. But, in all PD variants, OS is the underlying mechanism that leads to cellular dysfunctions [61]. The major sources of ROS, in PD are: dopaminergic cells' metabolism, mitochondrial dysfunction and neuroinflammation [62]. Specifically, OS happening in dopaminergic neurotransmitters, results in modification of intracellular macromolecules whose functions are important for cell survival. In detail, Dopamine is able to modify a number of proteins linked to pathophysiology of PD, such as α-synuclein, parkin and others [63,64]. In addition, Dopamine metabolites have been shown to induce proteosomal inhibition, which can lead the cells to undergo apoptosis [65]. Finally in the disease's progression, Neuromelanin (the last product of Dopamine oxidation) can be accumulated in the nigral region (pars compacta) as expression of death's neurons in this region, favouring PD [66]. Another source of OS associated with the pathogenesis of PD is the mitochondrial dysfunction [62]. Neuronal loss happening in PD is also associated with chronic neuroinflammation controlled by microglia [67]. For these complicated connections between PD and ROS, it is difficult to determine whether OS leads to or is a consequence of neurodegeneration [68].

Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive injury and death of lower motor neurons in the spinal cord on brainstem, and upper motor neurons in the motor cortex. The causes of ALS are unknown but, among the mechanisms inducing this, OS is certainly involved [69,70]. An increased Nitrosodine (a marker for oxidative damage) levels, was found to demonstrate the primary role of OS in the ALS beginning [71]. DNA damage induced by elevated levels of hydroxyl-deoxyguanosine was described too [72]. In addition, the hypothesis that OS is a cause of ALS was indirectly confirmed by the discovery that mutation of anti-oxidant enzyme superoxide dismutase-1 (SOD-1) was found in a significant ALS cases [73]. The mechanism by which mutant enzyme leads to motor neuron degeneration was recently identified in the neuronal mitochondrial damage induced by the SOD-1 mutation [74]. Excitotoxicity, mitochondrial dysfunction, protein aggregation, cytoskeletal dysfunction and others are other mechanisms implicated in motor neuron injury.

Ageing

Although the mechanisms inducing ageing are poorly understood, a growing body of evidence points ROS as one of the main determinants of this condition. The effect is attained by the OS acting on some macromolecules, such as DNA, proteins, carbohydrates, and lipids. The age-dependent accumulation of ROS induces a loss of human organs' function, with chronic changes of physiological conditions and acceleration of cells death. In this regard, Hartman firstly proposed the "free theory of aging" [20]. Particularly, oxidative damage in aged organisms happens in specific intracellular organelles, as the mitochondria [75]. But, several evidences does not support this statement [76]. In contrast with Hartman theory of ageing, recent evidences shown that increasing ROS generation can increase longevity even rather than reducing [77,78]. In favour of the positive effects of ROS on healthspan, Gomez-Cabrera et al. demonstrated

pathogenesis of a number of human skin diseases (SD), including cutaneous neoplasia [93,94].

Antioxidant treatment

Antioxidants are molecules which can safety interact with free radicals or terminate the chain reaction before vital molecules are damaged. The main antioxidants are vitamin E, beta carotene and vitamin C. Selenium, glutathione, flavonoids, lipoic acid and ubiquinol are also included. The body cannot manufacture the micronutrients, so they must be supplied in the diet. Antioxidants may exert their effect on biological systems by different mechanisms including electron donation, metal ion chelation, or indirectly by inhibiting the activity or expression of free radicals generating enzymes or enhancing the activity or expression of intracellular antioxidant enzymes [95].

Conclusive Remarks

Conclusively OS, as disturbance in the balance between the ROS production and antioxidant defense, is characterized by a prevalence of free radicals on antioxidant compounds. That induces an oxidative damage to some molecules, such as lipids, proteins and DNA, and represents a common denominator involved as pathogenetic mechanism responsible for most frequent human diseases. The process is also a main responsible for healthy and diseased ageing. Therefore, it represents the principal collateral cause of most diseases and death of people. Neverthless, despite the beneficial effects of several anti-oxidants on ROS action, at present none effective defense against their detrimental effects there is and further experiences are need to solve the question.

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