Review

Oxidative stress such as basic reaction of many among human diseases and ageing

Summary
Oxidation-reduction reaction (redox) represents the biochemical process fundamental for life . In aerobic organisms, oxygen is converted to water and ATP at the end of the respiratory chain. That provides the energy needed to maintain normal body function and metabolism. In redox reaction, oxygen is partially reduced to form superoxide, i.e. a stucture with unpaired electrons' number, also named "reactive oxygen species" (ROS). Normally, ROS production is balanced by some antioxidant substances (AOX), such as enzymes, some vitamins and several small-molecules that play important roles in antioxidant defense. On the contrary, ROS prevalence induces oxidative damage in some human proteins, lipidis, carbohydrates and DNA, responsible for cell's morbidity until death. Specifically, ROS. act in the pathogenesis of atherosclerosis, cancer, some brain diseases, such as Alzheimer's and Parkinson', obesity, insulin resistance, type 2 diabetes mellitus and others. ROS also prevail in human tissue with advancing age, favouring the healthy ageing. Thus, the redox reaction represents the "mother" of many among human diseases and healthy aging. At present, the giving of AOX to balance the ROS prevalence is uncertain if reduces their damages, even if long-term AOX-diet consumption, together moderate physical activity BMI reduction and reduction of food intake, is able to slow down the ROS injuries progressively increasing with advanced age.

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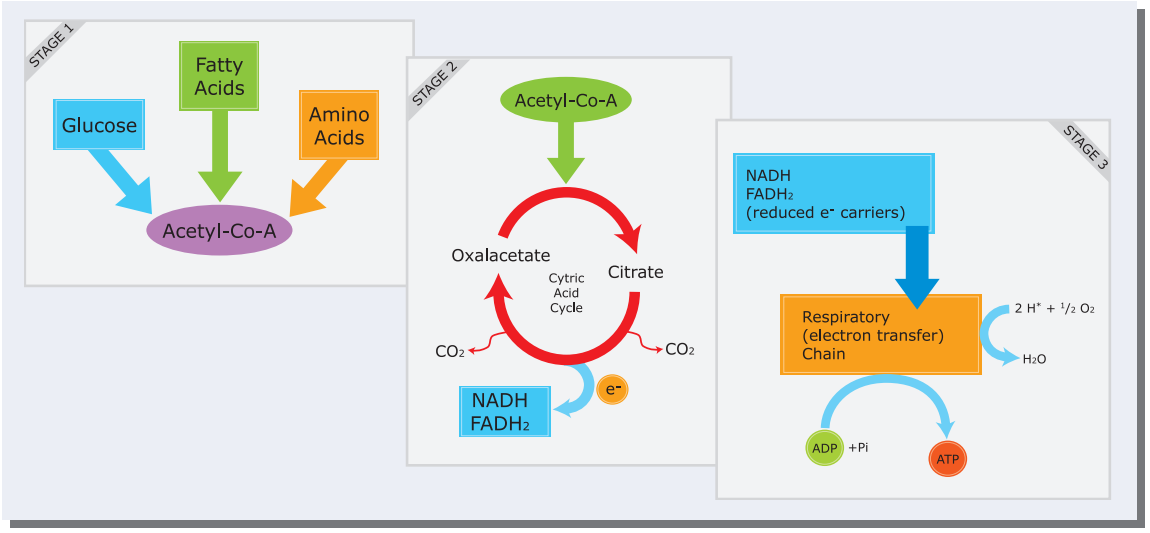
In aerobic organisms, oxygen is converted to water with energy production (ATP), at the end of the respiratory chain happening in the mitochondria. Respiratory chain happens in 3 successive stages (figure 1).
1 stage: nutrients (glucose, fatty acids, amino acids) are oxidized until the acetyl-CoA.
2 stage: Acetyl-CoA is oxidized in the citric acid cycle, with formation of Co_2. In the sequence of biochemical ractions of citric cycle, energy released is keeped means by the formation of NADH and $FADH_2$.
3 stage: These co-factors (NADH, $FADH_2$) subsequently are oxidized, releasing H^+ and electrons. In turn, these are transferred by the respiratory chain up to oxygen with H_2O, whereas ADP + Pi is turned in ATP (energy).

In these chemical reactions, a reagent loses electrons, whereas other reagent acquires these same (figure 2). As consequence, the reagent's atoms (that are most stable in the round state) become unstable. In turn, the unstable atoms, also named as Reactive Oxygen Species (ROS), aim to stability by losing or purchasing an electron, by redox (or oxidation-reduction reactions) reactions. These are a family of reactions transfering electrons from diverse antioxidant agents to unstable atoms to restore their stability[1].
In addition to the mitochondrial respiratory chain, there are other endogenous sources of ROS (also named superoxides or free radicals) production. In particular, when leukocytes encounder microorganisms or other pathogens invading our body, they

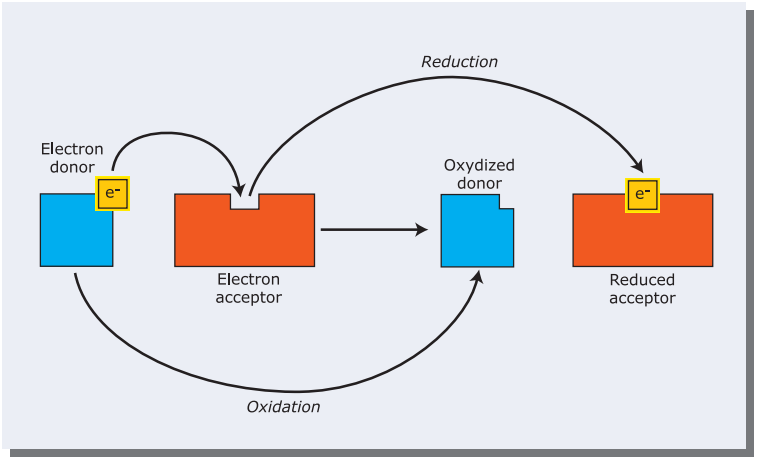
Figure 1. Three stages driving to the energy production from the fundamental nutrients (glucose, fatty acids, amino-acids) to citric acid cycle, and H_2O + ATP.



start to generate large amounts of superoxides. Additionally, there are a few external sources of superoxide, especially cigarette smoke.

Disturbances in the normal redox reaction can cause toxic effects, through the production of ROS not entirely balanced. ROS are highly reactive due to the presence of unpaired valence shell electrons, able to damage proteins, lipids, DNA structure, until the cells' death[2]. In normal conditions, cells are able to defend themselves against ROS damage through some antioxidants, such as superoxide dismutases, catalases, lactoperoxidases, glutathione peroxidases and others. Small molecule antioxidants, such as ascorbic acid, tocopherol, polyphenols also play important role as cellular antioxidants[3]. The steady-state concentration of the oxidant substances is mantained at non-toxic levels by a variety of antioxidant defences. On the contrary under some abnormal conditions and with advancing age, low levels of antioxidants, or inhibition of the antioxidant agents cause O.S., that may damage or kill cells. That can happen for disruption between antioxidant defences and ROS production, for deficient antioxidant defences and/or for increase in ROS production (figure 3). It mostly comes in common human diseases, such as atherosclerosis, cancer, Alzheimer's and Parkinson's diseases, chronic fatigue syndrome, plaques' rupture, chronic pulmonary disease, and chronic ischemia. In addition, O.S. itself contributes to the aging process (figure 4).

Figure 2. Typical example of oxidation-reduction reation with transfert of electrons of donor to acceptor.



Atherosclerosis

Primarily, the increased ROS production induced by dysfunction of respiratory chain is involved in the atherosclerotic process. That happens for increased serum levels of LDL-oxidation, responsible for endothelial dysfunction. This also favours the vasoconstrictive and pro-thrombotic effects achie-

Figure 3. Equilibrium between antioxidants (AOX) and reactive oxygen species (ROS) in normal circumstances (high). Imbalance of redox reaction, for the ROS prevalence (left-low) or the AOX reduction (right-low).

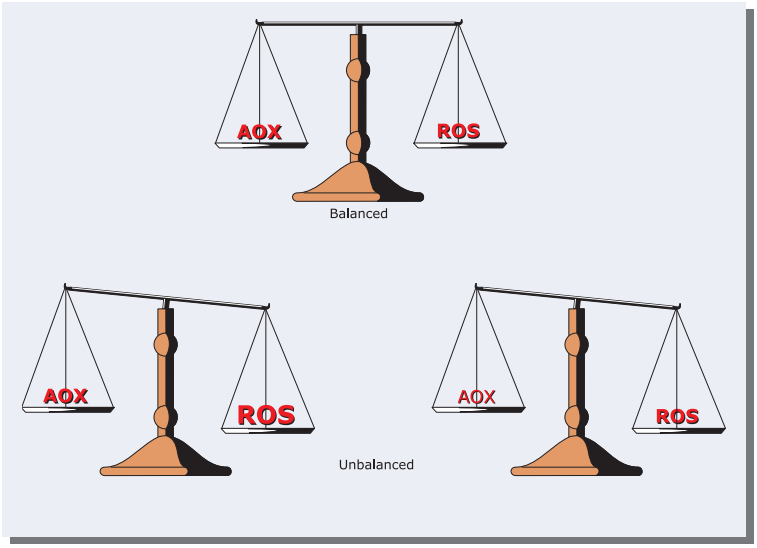
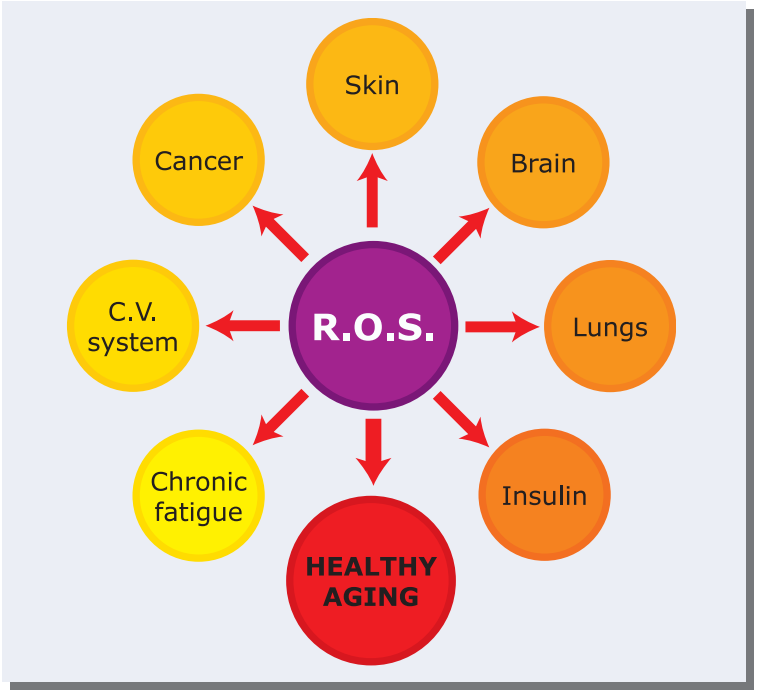


Figure 4. Leading pathologies favoured by the ROS action on human structures.



ving the conditions of vascular dysfunction[4,5]. These processes tend to increase with advancing age and in the presence of some conditions, such as cigarette smoking, and worsed by some metabolic disease, such as diabetes mellitus. The progressive endothelium dysfunction with advancing age was recently confirmed by Donato et al., that evidenced the age-dependent raised concentration of Nitrosodyne (a cellular marker of O.S.) in aged healthy subjects in comparison with young healthy individuals[6]. The consequent ROS over-production yelds both reduction of endothelium-dependent vasodilation and platelet-dependent thrombus formation[7]. ROS also contributes to the increase in lipid oxidation, vascular remodeling, smooth muscle proliferation and expression of adhesion molecules. Another study referred that ROS are able to facilitate the conversion of human macrophages into foam-cells[8], that represents a premature phase of atherosclerotic process. But, ROS over-production also predisposes to acute vascular injury, such as acute coronary syndromes (ACS), by favouring thrombocyte aggregation, leukocyte adhesion, and smooth muscle cell proliferation[9]. Further, oxidized LDL influences some citokynes' relase, such as IL-1β, IL-6 and TNF-α, responsible for acute inflammatory processes[10]. Finally, ROS are able to modulate matrix metalloproteinase degradation and could contribute to the instability of atherosclerotic plaques[11,12].

Cancer

Another important action of ROS is their cytotoxic effects acting in some forms of cancer. Particularly, a carcinogenous role may partly exert by ROS during their metabolism. Furthemore, the oxidative damage to cellular DNA can lead mutations and may play an important role in the initiation and progression of multistage carcinogenesis[13]. On the other hand, most cancer cells exhibit overproduction of ROS, which is throught to provide favourable conditions for cancer cells'

growth. Some AA. hypothesized also that the increased ROS generation may make cancer cells highly vulnerable to exogenous ROS-modulating agents, producing changes in DNA, its modification, and rearrangement , gene duplication and the activation of some oncogenes. Some evidences also suggest that transformed cells use ROS signals to drive proliferation and other events required for tumor progression.

Brain diseases

Alzheimer's disease

Researches in Alzheimer's disease have recently demonstrated compelling evidence of the importance of oxidative processes in its pathogenesis. Cellular changes show that ROS over-production is an event that precedes the appareance of the hallmark pathologies of the disease, such as neurofibrillar tangles, and senile plaques[14]. The intervent of O.S. in the pathogenesis of Alzheimer's disease evidenced by these findings :

1) the alteration of mitochondrial function and the formation of superoxide radicals;
2) the excessive H_2O_2 production;
3) the increased lipid peroxidation and membrane alterations;
4) the pro-aggregating effect of ROS on beta/An protein of C-terminal fragment. Particularly, Hydrogen peroxide (H_2O_2) appears to be implicated in the aetiology of Alzheimer's disease, for its actions in the modifications of proteins, lipids, and DNA sequence, that contribute to the loss of synaptic functions.

Parkinson's disease

O.S. has been proposed as one of several hypotheses for Parkinson's disease. It may be reasonable to assume that they can cause point mutation and/or overexpression of certain genes, which initiate degeneration and death of dopaminergic neurons. Altered ubiquination and degradation of some proteins have also been implicated as key to dopaminergic cell death of the disease. Furthermore, O.S. contributes to the cascade of events leading to dopamine cell degeneration characteristic of Parkinson's disease. It is intimately linked to other components of the degenerative process too, such as mitochondrial dysfunction, excitotoxicity, nitric oxide toxicity and inflammation. But, these evidences indicate that sometimes it is difficult to determine wether O.S. leads to or is consequence of these events[15].

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is emerging as the most dominant disorders of our time, particularly in women. CFS is characterized by a number of symptoms including headache, joint pain, gastrointestinal and/or visual disturbances, and cognitive dysfunction. Immune response can also to be impaired[16] in this state. The role of O.S. in CFS is emerging but still uncertain. Theoretically, it can cause mitochondrial dysfunction responsible for decline in the efficiency of antioxidant enzyme systems[17]. Recently, it was demonstrated that patients with CFS have significanly elevated levels of F_2-isoprostanes, a series of prostaglandin-isomers related to free-radicals[18]. A number of antioxidants can be given for therapeutic aim, such as vitamins C and E, selenium, Ginko-Biloba and a-lipoic acid. Several supplements also should be considered for potential therapeutic intervention, including selenium (necessary to support glutathione peroxidase activity) or Ginko-Biloba, a powerful antioxidant with strong neuroprotective properties. Plant-based antioxidant support should be maximized through dietary-intake in this condition. The immune cell function recently appared as important diagnostic marker for CFS.

Insulin-resistance and obesity

In addition, O.S. has been linked to obesity, insulin-resistance and metabolic syndrome. The link between O.S. and insulin resistant condition seems to induced by the inflammatory state[19]. Several clinical trials have demonstrated the improvement of insulin-sensitivity in insulin resistant and diabetic patients treated with antioxidants. Skalicky et al. confirmed that high levels of free radicals together with low antioxidant capacity were detected in obese adults[20]. Meigs et al also found that O.S. is associated with insulin-resistance in individuals at average or elevated risk of diabetes, even after acounting for BMI[21]. It is known that initially, insulin resistance is compensated by hyperinsulinemia, with normal glucose tolerance. Impaired glucose tolerance occurs when either the insulin resistance increases or compensatory insulin secretory responses decreases or both occur. In these eveniences, serum glucose levels also increase, inducing a rise in ROS production. In turn, that can wor-

sen both insulin action and secretion, thereby accelerating the progression to overt type 2 diabetes. Referring to the obesity, it was found that bariatric surgery performed in obese patients, reducing inflammatory citokines' levels, decreases both insulin-resistance and O.S. levels[22]. That evidences the direct reports between O.S. and obesity. O.S. reduction after biliopancreatic diversion seems to be related to the regulation of glucose fluctuation resulting from intestinal by-pass. Two mechanisms seem to contribute to the improvement in insulin resistance after biliopancreatic diversion: a short term mechanism is due to bypass; a long term mechanism dependent from decreased fat mass and resulting changes in release of molecules associated with adipose tissue.

Chronic pulmonary disease

O.S. and inflammation are also the major hallmark of chronic obstructive pulmonary disease (COPD). Particularly ROS, either directly or via the formation of lipid peroxidation products may play a role in enhancing the inflammation, through the activation and phosphorylation of mitogen activated protein kinases. In turn, these two conditions induce hypersecretion of mucus, alveolar- epitelial permeability and apoptosis. In the long run, that produces broncho-pulmonary degeneration with respiratory insufficiency. In addition, O.S. may have a role in the poor efficacy of corticosteroids[23] in COPD.

Ageing

Although the fundamental mechanisms are still poorly understood, a growing body of evidence points toward ROS as one of the primary determinants of aging of some macromolecules, such as DNA, proteins, carbohydrates, and lipids. The consequent age-dependent accumulations of mutations of these induce a loss of their function, with chronic pathologic conditions occurring in ageing and acceleration of cells' death. According to these evidences, Hartman firstly proposed "the free radical theory of aging"[24]. That favors a great number of acute and chronic diseases including: diabetes mellitus, atherosclerosis, distinct cancer types, chronic obstructive pulmonary disease, human immunodeficiency, Alzheimer's and Parkinson's disease and cerebrovascular disease, as well as many degenerative processes inducing healthy aging.

Oxidative damage in aged organisms also happens in specific cellular organelles, as the mitochondria (mitochondrial theory of aging). In fact, mitochondrial function and morphology are progressively impaired with advancing age. Mutations especially happen in mitochondrial DNA. In view of age-related decreases in mitochondrial protein synthesis, in mitochondrial transcripts and expression of genes involved in mitochondrial turnover, the rate of this might determine the susceptibility and mutations of mitochondria, controlling the rate of cells' aging[25]. But independendly from any aging-theory, human cells suffer from at least 10,000 hits of free radicals daily. The number increases with advanced age, and jointed to certain pro-oxidant factors, such as smoking, alcoholism, eccessive drugs' consumption, masculine gender, chronic stress and others.

Antioxidant therapy (supplement-drugs)

An antioxidant agent is a molecule that may protect the cells against the effects of free radicals . Much substances may act as antioxidants; among these there are: Vitamin A, Vitamin C, Vitamin E, β-carotene; some minerals (selenium, zinc, manganese) polyphenols; phytochemicals products (included fruits vegetables, nuts, grains, fish), and some enzymes (superoxide dismutase, catalase, glutatione peroxidase, etc.). Their use to prevent oxidative diseases is controversial. In fact, high doses of β-carotene seems to increase the rate of lung cancer[26]. On the contrary, the use of Vitamin E appears to reduce the rise of heart disease[27]. In other states, such as Alzheimer's disease, the evidence of vitamin E is mixed[28,29]. That seem to confirm the uncertainties about the effective role of antioxidants in some diseased conditions favoured by oxidative damage. In accordance with some AA., the antioxidant capacity of plasma is insensitive to dietary supplementation with antioxidants or antioxidant-rich food[30]. On the contrary, Frei of Pauling Institute affirmed that these substances are effective in to prevent oxidative damage and inhibit chronic disease. In fact, many in vitro disease shown that antioxidant-drugs, such as ascorbic acid, α-tocopherol, β-carotene, and flavonoids, may act as effective antioxidants in biological systems[31]. Referring to some frequent age-diseases, researches in Alzheimer have recently demonstrate compelling evidence on the importance of oxidative processes in its pathogenesis. Cellular changes show

that O.S. in an event that precedes the appearance of the hallmark pathologies of the disease, such as neurofibrillar tangles, and senile plaques . Since Alzheimer is a multifactorial disease, Maczurek et al. have been recently suggested that rather a combination than a single drug treatment might be most beneficial for these patients[32]. Among many suggested add-on treatment to alfa-lipoic acid (ALA), phytonutrients (polyphenols) with antioxidant and anti-inflammatory properties might quite promising treatments[33]. O.S. also contributes to the events' cascade leiding to dopamine cell degeneration responsible for Parkinson's disease. However, O.S. is intimately linked to other components of the degenerative process, such as mitochondrial dysfunction, excitotoxicity, nitric oxide toxicity and inflammation. Therefore, it is difficult to determine wether O.S. leads to or is consequence of these events. Concerning this, O.S. and Parkinson's disease appear to be mutually binded. Referring to the cardiovascular disease alone, at this time the scientific data not justify the use of antioxidants for cardiovascular risk reduction. This position is consistent with the recommendations that have made by AHA in 2004[34]. But, a significant reduction of cardiovascular disease can be achieved by the long-term consumption of diets suggested by AHA Dietary Guidelines[35], and balancing energy intake with regular physical activity[36].

In conclusion, the balance between antioxidants and pro-oxidants is of a great importance in mantaining the physiological functions to reduce the rate and the progression of some frequent diseases and extending the lifespan. On view of that, the imbalance between the production and the removal of ROS, that increases O.S., could be considered such as "*the mother of many human diseases and healthy aging*". In other words, redox reactions appear to be such a fundamental biochemical processes happening in organisms for live. When peroxides production abnormally increases, O.S. also happens. This seems to emerge such as one of the primary determining both ageing and some common (related) diseases, until the prevalence of death on life-lengthening. But, several investigations performed in the last years, showed that antioxidants alone are unable to decrease the age-and-non-age related levels of oxidative damage. Nevertheless, their use together physical activity, BMI reduction, and reduced food intake (caloric restriction), are requested to minimize and slow the detrimental effects of impaired redox reactions, that increase with advanced age. Their beneficial effects on oxidative damages seem to be also evident in non-aged subjects. TiM

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