

Environmental Factors as Inducers of Oxidative Stress

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Prolonged elevated oxidative stress (OS) possesses negative effect on cell structure and functioning, and is associated with the development of numerous disorders.

Keywords: oxidative stress ; reactive oxygen species ; antioxidants

1. Introduction

Oxidative stress (OS) is defined by the production and accumulation of Reactive Oxygen Species (ROS) in biological systems above the capacity of cells and tissues to neutralize ROS presence to a safe level [1]. Reactive Oxygen Species (ROS) are molecular oxygen (O_2)-derived characterized by high reactivity towards other molecules. ROS comprise free radicals such as superoxide anion radical ($O_2^{\bullet-}$) and hydroxyl radical ($\bullet OH$), and nonradical molecules such as singlet oxygen (1O_2) and hydrogen peroxide (H_2O_2). Singlet oxygen (1O_2) is the excited state of ground state triplet molecular oxygen (3O_2), and is generated via absorption of energy sufficient to reverse the spin of one of its unpaired electrons what leads to the formation of singlet state where two electrons possess opposite spin [2]. Superoxide anion radical ($O_2^{\bullet-}$) is generated by one-electron reduction of molecular oxygen (O_2), what results in the production of a charged ionic species ($O_2^{\bullet-}$) possessing a single unpaired electron and a negative charge [3]. Hydrogen peroxide (H_2O_2), a compound possessing an oxygen-oxygen single bond [4], is generated from dismutation of $O_2^{\bullet-}$ [3]. H_2O_2 can be decomposed via Fenton reaction to OH^- and $\bullet OH$ with Fe^{2+} oxidation, or can react with $O_2^{\bullet-}$ to form $\bullet OH$, OH^- and O_2 [2]. Hydroxyl radical ($\bullet OH$) possesses a single unpaired electron and is generated by oxidation of water (H_2O) or hydroxide ions (OH^-), or by decomposition of hydrogen peroxide (H_2O_2) via Fenton reaction [5][6].

In living organisms, ROS are produced during indigenous metabolism to serve as signalling molecules, but can be also generated at high concentrations due to exposure to environmental stress factors (radiation, pollution, pathogens, etc.) [7]. Generated ROS include singlet oxygen (1O_2), superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\bullet OH$), and are characterized by different reactivity. 1O_2 is a highly reactive form of oxygen possessing two electrons with opposite spins, and oxidizing molecules via reaction with double bonds [8][9]. Although $O_2^{\bullet-}$ is not a strong oxidant, it can undergo dismutation to H_2O_2 that can decompose to form a $\bullet OH$, one of the strongest oxidants. $O_2^{\bullet-}$ can also react with nitric oxide radical to form a peroxynitrite, also considered a powerful oxidant [8]. The elevated production of ROS and oxidative stress cause detrimental effect on organisms due to the damage of cellular macromolecules, with oxidation of lipids, proteins and nucleic acids. In human, the occurrence and development of many diseases such as obesity, atherosclerosis, diabetes mellitus type 2 (DMT2), rheumatoid arthritis, cancer and neurodegenerative diseases are associated with oxidative stress [10]. To cope with oxidative stress, organisms developed defence mechanisms (**Figure 1**) involving anti-oxidant enzymes, as well as non-enzymatic molecules. The human enzymatic anti-oxidant mechanisms include enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd) and thioredoxins (Trx), with glutathione (GSH) serving as electron donor and used in reactions catalysed by GPx. The non-enzymatic anti-oxidant system in human body is composed of anti-oxidant proteins, such as proline-rich proteins and ferritin, and low-weight anti-oxidant molecules synthesized indigenously, such as coenzyme Q_{10} , α -lipoic acid, melatonin and bilirubin. Moreover, addition of external low-weight anti-oxidant molecules, such as N-acetylcysteine, resveratrol, β -carotene, tocopherols and ascorbic acid, can strengthen the capability of indigenous defence system against OS.

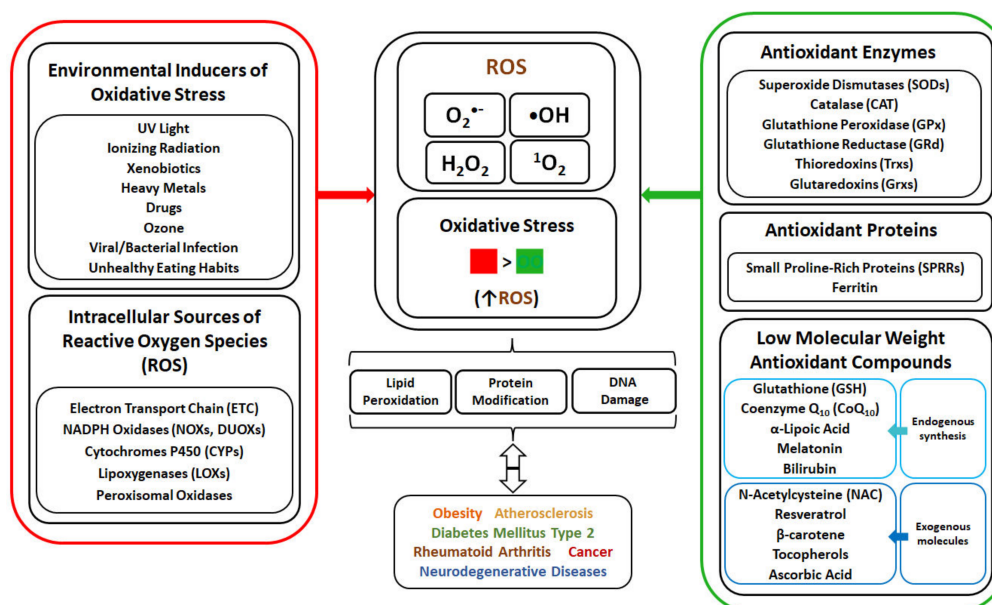


Figure 1. The overview of oxidative stress (OS) generation in human, with various environmental factors as the cause of OS, with different ROS types and different intracellular sites for ROS generation, OS relation with the disease's occurrence, and anti-oxidant mechanisms involving enzymatic and non-enzymatic molecules.

2. Environmental Factors as Inducers of Oxidative Stress

Environmental factors, such as radiation (ultraviolet, ionizing), tobacco smoke, xenobiotics and other pollutants as well as infections, are inducers of ROS generation and oxidative stress (**Figure 1**).

Ultraviolet (UV) light, a part of electromagnetic radiation spectrum with wavelength range of 100 nm to 400 nm, is divided into UVA (320–400 nm), UVB (290–320 nm) and UVC (220–290 nm) light. The sources of UV light can be natural (sun) or artificial (phototherapy, sunbeds, arc welding, germicidal lamps). UV radiation can be absorbed by cellular components resulting in their conversion into the excited state, performing chemical reactions with ROS generation. UV rays can be also absorbed by photosensitizers (endogenous and exogenous), which in their excited state, can abstract hydrogen to form free radicals, or can transfer energy with O_2 to form 1O_2 [11]. UV-induced reactive oxygen species contribute to the damaging effect of UV towards the skin [12].

Ionizing radiation (IR), including gamma and X rays, is the radiation capable of inducing atom ionization via reactions of electron ejection [13]. The sources of IR are radiotherapy, nuclear accidents, atomic bombing, soil radioisotopes and cosmic rays [14][15]. Ionizing radiation causes radiolysis of water and linear energy transfer (LET)-mediated generation of reactive chemical species ($\bullet OH$, H_2O_2 , $O_2^{\bullet -}$) that can damage macromolecules (nucleic acids, proteins, lipids) [16]. IR-generated reactive species cause cellular damage with detrimental effect on living organisms [13].

Xenobiotics, represented by polycyclic aromatic hydrocarbons and pesticides, are organic substances being foreign to living organisms and possessing structural abilities to induce oxidative stress in organs and tissues. Polycyclic aromatic hydrocarbons (PAHs) are formed during incomplete combustion processes of fuels and from traffic emissions [17]. PAHs undergo oxidation into phenolic intermediates which are converted via semiquinone anion radicals into quinones, with generation of superoxide anion radicals and H_2O_2 [18][19]. Pesticides (herbicides, insecticides, fungicides, etc.), used in agriculture for crop protection, can be found as contaminants in air, water and food. The mode of oxidative action of pesticides, with herbicide paraquat as an example, is the induction of mitochondrial damage and the redox cycle involving quaternary ammonium nitrogen atoms and a bipyridyl ring in paraquat structure, what leads to production of ROS and paraquat radicals [20].

Heavy metals (HMs), such as Pb, Cd, Cr, Hg and As, are contaminants released from industry (effluents, waste product storage) to the surroundings (atmosphere, soil, water) and affecting human beings [21]. Accumulation of HMs ions in body induces oxidative stress within a range of mechanisms, including inhibition of antioxidant enzyme expression (by Cd), interaction with cofactors and/or disulphide bonds in antioxidant enzymes (e.g., Pb, Hg), haemoglobin autooxidation (by Pb^{2+}), binding to sulfhydryl groups ($-SH$) and reducing thiol pools (through Cd^{2+} or Hg^{2+}), generating glutathione-thiyl radicals (via $Cr(VI)$), changing the oxidation state of HMs with formation of H_2O_2 and hydroxyl radicals (through Cr or As), affecting calcium homeostasis and stimulating oxidative enzymes (by Hg), cytokine-mediated ROS generation (via Cd^{2+}),

and others [18][22][23]. Heavy metal-induced oxidative stress and macromolecules modification/degradation are the cause of many diseases, amongst which are cancer, cardiovascular disease, neurological disorders and chronic inflammation [24].

Drugs used for illness treatment are also the source of ROS generation in human body [25]. Anti-neoplastic agents, such as doxorubicin and cisplatin, are used for the treatment of different types of cancer. Doxorubicin, a representative of anthracycline antibiotics, generates ROS by undergoing mitochondrial reductase-mediated one-electron reduction to anthracycline semiquinone free radicals, that can react with O_2 to form $O_2^{\cdot-}$ or H_2O_2 . Doxorubicin can also interact with Fe^{3+} to form Fe^{2+} -doxorubicin free radical, that can reduce oxygen. Oxidative stress induction is the mechanism of doxorubicin cardiotoxicity [25]. Cisplatin, a platinum containing drug, was reported to increase the ROS level, via NADPH oxidase or xanthine oxidase [25][26]. Oxidative stress induction in the proposed mechanism of cisplatin nephrotoxicity and ototoxicity [26][27].

Smoking, with cigarette smoke containing nicotine, ammonia, acrolein, phenols, acetaldehyde, polycyclic aromatic hydrocarbons, polyphenols, hydrogen cyanide, heavy metals, etc., is another source of ROS production and oxidative stress occurrence [28][29]. The tobacco smoke contains gas phase and tar phase. The gas phase contains short-lived radicals, superoxide anion and nitric oxide, which react together to form highly reactive peroxyxynitrite. The tar phase contains stable semiquinone radicals and iron (Fe^{2+}). Semiquinone radicals reduce O_2 to $O_2^{\cdot-}$, that can dismutate into H_2O_2 , which in turn can react with Fe^{2+} via Fenton reaction to form $\cdot OH$ [29][30]. Oxidative stress is considered as a crucial factor in the pathogenesis of smoking-related disorders, such as lung cancer, chronic obstructive pulmonary disease and atherosclerosis [31].

Ozone (O_3) is a gaseous tropospheric pollutant, generated through reactions between intense solar radiation and pollutants (nitric oxides, sulphur oxides, carbon oxides, volatile organic compounds) produced from combustion of fossil fuels [32][33]. Contact of O_3 with biological matrix results in creation of H_2O_2 and lipids oxidation products [34]. Ozone exposure-induced oxidative stress is associated with neurodegenerative diseases [33][35].

The infections by viruses or bacteria can be also the cause of oxidative stress in human body. The body can be infected by viruses, such as DNA and RNA viruses, which enter and replicate inside host cells [36][37]. ROS are generated during viral infection via inducing activation of phagocytes [36] or via mediation of viral proteins expressed in host cells to support viral life cycle [37]. Oxidative stress occurring during bacterial infection is described for *Helicobacter pylori*, a gram negative, stomach-infecting bacterium. *H. pylori* infection results in oxidative stress via the immune and gastric epithelial cells producing ROS in an attempt to kill the bacteria, and via bacterial virulence factors inducing epithelium cellular responses and ROS generation [38].

Unhealthy dietary patterns, based on overconsumption of high-carbohydrate and high-fat food, are associated with increased risk of overweight and obesity occurrence and development of diabetes mellitus type 2 (DMT2) and cardiovascular diseases. High-fat or high-carbohydrate diets results in the elevated influx of substrates into mitochondrial respiration and increased donation of electrons to electron transport chain, leading to the electron leakage at complex III and elevated superoxide ($O_2^{\cdot-}$) generation. [39]. NADPH oxidase (NOX), an enzyme converting molecular oxygen to its superoxide radical, is also involved in nutrient-based ROS generation [40]. High-calorie diets may alter oxygen metabolism and are considered as one of the main factors leading to excessive ROS production [41].

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