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REVIEW ARTICLE

Mechanisms of Oxidative Stress in the Human Body: A Review

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ABSTRACT

Oxidative stress, an imbalance between pro-oxidant agents and antioxidant agents in which the pro-oxidant agents exceed the antioxidant concentration, has become a pivotal mechanism in the onset and advancement of several human illnesses. Although physiologically crucial for cellular communication, immune defense, and adaptability, excessive oxygen radical production surpasses antioxidant capability, leading to biomolecular damage and malfunction. This study seeks to thoroughly analyze the processes that induce oxidative stress in the human body, highlighting both endogenous and external sources, along with the complex association between oxygen radicals and the production of pro-inflammatory cytokines. Endogenous factors include mitochondrial electron leakage, NADPH oxidase activity, endoplasmic reticulum stress, peroxisomal metabolism, xanthine oxidase activity, cytochrome P450 uncoupling, and transition metal-mediated Fenton chemistry. Exogenous inducers, including cigarette smoke, air pollution, heavy metals, alcohol, food excess, psychological stress, and xenobiotic exposure, exacerbate oxidative stress, frequently interacting synergistically with endogenous processes. Simultaneously, inflammatory processes emerge not only as a result of reactive oxygen radical but also sustain their generation via cytokine signaling, NF-κB activation, inflammasome assembly, and the synthesis of peroxynitrite from nitric oxide, establishing a detrimental cycle of oxidative-inflammatory injury.

Keywords: Antioxidant defenses, Endogenous and exogenous stressors, Inflammatory pathways, Oxidative stress, Reactive oxygen species (ROS)

INTRODUCTION

The notion of oxidative stress has garnered much interest since Denham Harman's seminal showed the association between the production of free radicals and the aging process, introduced in the 1950s. Oxidative stress fundamentally refers to an imbalance between the generation of oxidants and the ability of antioxidant defense [1]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are essential for normal physiological functions, including cell signaling, host defense, and adaptation; however, an excess of these reactive molecules can surpass the capacity of antioxidant systems, leading to cellular dysfunction and tissue damage[2].

There are different species of free radicals, which include reactive oxygen species (ROS) and reactive nitrogen species (RNS), which play a role in oxidative and nitrosative stress. These species originate from several sources, both internal and external to the human body, with mitochondria and membrane-bound enzyme complexes acting as principal contributors under physiological settings [3].

Oxidative stress has been linked with the etiology of several human illnesses, including cardiovascular disorders, neurological diseases, malignancy , diabetes mellitus, and others. Moreover, cumulative oxidative damage has been significantly associated with aging and age-related functional deterioration [4].

Due to its extensive biological significance, comprehending the processes of oxidative stress induction is essential. These processes can be classified into endogenous sources, including mitochondrial malfunction, enzyme activity, and organelle stress responses, and external ones, comprising environmental contaminants, lifestyle variables, and radiation exposure. Oxidative stress frequently results from the interaction of these causes, exacerbated by insufficient antioxidant defenses [5].

Intrinsic Sources of Oxidative Stress

Oxidative stress mostly results from reactive oxygen radicals produced as byproducts of regular cellular metabolism. Under physiological circumstances, reactive oxygen species (ROS) are meticulously regulated by antioxidant enzymes and scavenging mechanisms. However, when their production surpasses neutralizing capabilities, they accumulate and provoke oxidative damage. Multiple essential endogenous systems facilitate the formation of reactive oxygen species (ROS) within the human body [6].

Electron Transport Chain in Mitochondria

Mitochondria serve as the essential center for cellular energy metabolism and provides the most substantial source of endogenous reactive oxygen species (ROS). In glucose oxidation and then phosphorylation, electrons are conveyed through different protein complexes I–IV of the electron transport chain (ETC) to finally reduce molecular oxygen to water [7].

This activity is very efficient; nonetheless, a minor proportion of electrons exit the chain prematurely, especially at complexes I (NADH:ubiquinone oxidoreductase) and III (cytochrome bc1 complex). The electrons interact with molecular oxygen to produce the superoxide anion ($O_2^{\bullet -}$) [8].

Superoxide is swiftly dismutated to (H_2O_2) either spontaneously or by superoxide dismutase (SOD). Hydrogen peroxide, while less reactive, may permeate membranes and, in the presence of transition metals like iron or copper, engage in Fenton chemistry to produce hydroxyl radicals (•OH), which are among the most deleterious reactive oxygen species (ROS) [9].

Mitochondrial DNA (mtDNA) is especially susceptible to reactive oxygen species (ROS) due to the absence of protective histones and its constrained repair mechanisms. Damage to mitochondrial DNA further undermines electron transport chain performance, establishing a detrimental loop of heightened reactive oxygen species production and compromised energy metabolism. Mitochondrial oxidative stress is closely associated with neurodegenerative illnesses, aging, and metabolic problems [10].

NADPH Oxidases (NOX Family)

A significant source of reactive oxygen species (ROS) is the NADPH oxidase (NOX) enzyme family. In contrast to mitochondria, which produce reactive oxygen species mostly as byproducts, NOX enzymes intentionally create superoxide by transferring electrons from NADPH to molecular oxygen. This process is crucial for immune response, especially in neutrophils and macrophages, where the "respiratory burst" generates substantial quantities of reactive oxygen species (ROS) to eliminate invading pathogens [11].

Seven isoforms of NOX exist (NOX1–5, DUOX1, DUOX2), each characterized by unique tissue distribution and regulation mechanisms. For instance, NOX2 is essential in phagocytes, whereas NOX4 is prevalent in the renal and vascular system. Dysregulation of NOX activity results in excessive buildup of reactive oxygen species (ROS), which contributes to chronic inflammation, hypertension, endothelial dysfunction, and fibrosis [12].

Endoplasmic Reticulum (ER) Stress and Protein Misfolding

The endoplasmic reticulum is essential for protein folding, lipid production, and calcium regulation. Protein folding necessitates disulfide bond formation, which involves electron transfer and thus generates reactive oxygen species, including hydrogen peroxide. In stressful conditions- such as nutritional scarcity, hypoxia, or excessive protein load, the endoplasmic reticulum (ER) accumulates misfolded proteins, initiating the unfolded protein response (UPR) [13].

The UPR seeks to reestablish ER homeostasis via three signaling pathways facilitated by PERK (protein kinase R-like ER kinase), ATF6 (activating transcription factor 6), and IRE1 (inositol-requiring enzyme 1). Nonetheless, chronic ER stress leads to calcium efflux into the cytoplasm, disrupting mitochondrial function and increasing ROS generation. Furthermore, UPR signaling might initiate pro-oxidant pathways, hence exacerbating oxidative stress [14].

The interplay between the endoplasmic reticulum and mitochondria is increasingly acknowledged in metabolic disorders, neurodegenerative illnesses, and cancer.

Peroxisomal Metabolism

Peroxisomes are specialized organelles that participate in lipid metabolism, namely in the β-oxidation. This process happened for very-long-chain fatty acids and the detoxification of reactive chemicals. In contrast to β-oxidation that occurs in mitochondria, peroxisomal fatty acid catabolism produces hydrogen peroxide directly via acyl-CoA oxidases. Under typical conditions, H_2O_2 is converted into water and oxygen by catalase [15].

Nonetheless, peroxisomal malfunction or excessive lipid substrate flow results in H_2O_2 buildup, which can permeate the cytoplasm and trigger oxidative damage. Moreover, peroxisomes are intricately associated with mitochondria and the endoplasmic reticulum, establishing redox-sensitive communication networks [16].

Xanthine Oxidase (XO)

Xanthine oxidase, a molybdenum-dependent enzyme, plays a pivotal role in purine metabolism by catalyzing the transformation of hypoxanthine into xanthine and subsequently into uric acid. In this process, XO donates electrons to oxygen, resulting in the formation of superoxide and hydrogen peroxide as byproducts [17].

In normal physiology, XO activity facilitates the formation of uric acid, an antioxidant present in plasma. Excessive activation of XO after ischemia-reperfusion damage, inflammation, or metabolic abnormalities skews the equilibrium towards pro-oxidant activity. Increased XO activity has been associated with endothelial dysfunction, atherosclerosis, and gout. Pharmacological inhibitors of xanthine oxidase, such allopurinol and febuxostat, are therapeutically significant for managing hyperuricemia and mitigating oxidative stress-induced vascular damage [18].

Cytochrome P450 Enzymes

The cytochrome P450 (CYP) enzyme family facilitates the metabolism of xenobiotics, pharmaceuticals, and endogenous substrates, including steroids and fatty acids. Transferring of electrons from NADPH through cytochrome P450 reductase to oxygen, generating a highly reactive oxygen species that facilitates substrate hydroxylation [19].

Despite stringent regulation, this process may become "uncoupled," leading to electron leakage to oxygen and the production of O_2^- and H_2O_2. Specific pharmaceuticals and toxins intensify this uncoupling, resulting in CYP-mediated oxidative stress. Acetaminophen overdose generates N-acetyl-p-benzoquinone imine (NAPQI), resulting in glutathione depletion and significant hepatotoxicity. Consequently, CYP activity serves as a crucial detoxifying mechanism and a possible factor in oxidative damage [20].

Transition Metals and Fenton Reaction

Transition metals, especially iron and copper, are essential in redox biology but also facilitate the development of detrimental reactive oxygen species (ROS). The Fenton reaction involves the reduction of hydrogen peroxide by ferrous iron (Fe^{2+}), producing hydroxyl radicals (•OH) and ferric iron (Fe^{3+}). The Haber–Weiss reaction also combines superoxide and hydrogen peroxide in the presence of iron to produce •OH radicals [21].

Excessive iron buildup, as in hemochromatosis or frequent blood transfusions, surpasses ferritin storage capacity and amplifies Fenton chemistry. Likewise, copper imbalance in Wilson's illness induces oxidative stress in the liver and brain. These reactions are especially deleterious when hydroxyl radicals indiscriminately assault DNA, proteins, and lipids, precipitating permanent cellular damage [22].

External Inducers of Oxidative Stress

Alongside intrinsic metabolic activities, the human body is perpetually subjected to environmental and lifestyle stresses that exacerbate the generation of reactive oxygen species (ROS). Exogenous inducers can surpass antioxidant defense systems and interact synergistically with endogenous processes, resulting in prolonged oxidative stress and heightened disease risk [23].

Environmental Contaminants

1. Cigarette Smoking

Cigarette smoke is a significant exogenous source of free radicals and oxidants, comprising over 10^{14} reactive molecules each puff. The gas phase is characterized by free radicals including nitric oxide (NO•) and superoxide, whereas the tar phase comprises stable semiquinone radicals that engage in redox cycling to perpetually produce reactive oxygen species (ROS) [24].

2. Airborne Particulate Matter (PM)

Air pollution, particularly fine particulate matter ($PM_{2.5}$ and PM_{10}), substantially adds to oxidative stress. These particles comprise transition metals (iron, copper, and vanadium) and organic molecules (polycyclic aromatic hydrocarbons, or PAHs) that facilitate the generation of reactive oxygen species (ROS) [25].

Particulate matter exposure stimulates alveolar macrophages and epithelial cells, resulting in the generation of superoxide, hydrogen peroxide, and pro-inflammatory cytokines. The oxidative-inflammation axis correlates with cardiovascular morbidity, diminished lung function, and metabolic syndrome in populations subjected to elevated pollution levels [26].

3. Heavy Metals

Toxic metals, including cadmium, lead, arsenic, and mercury, indirectly provoke oxidative stress by depleting glutathione, blocking antioxidant enzymes, and impairing mitochondrial function [27].

Factors Associated with Lifestyle

1. Alcohol Consumption

The metabolism of ethanol produces reactive oxygen species via many mechanisms. The principal enzyme, alcohol dehydrogenase (ADH), converts ethanol into acetaldehyde, which is further processed by aldehyde dehydrogenase (ALDH), resulting in the production of NADH. Elevated NADH levels increase the leakage of electrons. Furthermore, ethanol is processed by CYP2E1, which generates reactive oxygen species (ROS) [28].

2. High-Fat/High-Carbohydrate Diets

An excessive intake of saturated fats and carbohydrates induces the formation of reactive oxygen species (ROS) via mitochondrial overload, endoplasmic reticulum (ER) stress, and NADPH oxidase (NOX) activation. Hyperglycemia facilitates protein glycation, resulting in the formation of advanced glycation end-products (AGEs), which interact with RAGE receptors and enhance reactive oxygen species (ROS) production through NADPH oxidases [29].

3. Psychological Stress

Despite being less apparent, psychological stress triggers oxidative stress through the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Stress hormones, including cortisol and catecholamines, elevate mitochondrial reactive oxygen species production, weaken antioxidant defenses, and enhance inflammatory signaling [30].

4. Exposures to Pharmaceuticals and Chemicals

Numerous pharmaceuticals and xenobiotics are powerful inducers of oxidative stress. Acetaminophen overdose produces NAPQI through CYP2E1 metabolism, resulting in glutathione depletion and hepatotoxicity [31].

5. Inflammatory Pathways and Reactive Oxygen Species

Inflammation and oxidative stress are closely linked, creating a self-reinforcing cycle in which reactive oxygen species (ROS) stimulate inflammatory signaling, while inflammation enhances ROS generation. This reciprocal interaction is fundamental to several chronic illnesses, including cardiovascular problems, diabetes, neurodegeneration, and cancer [32].

The Respiratory Burst in Immune Cells

A prominent connection between inflammation and reactive oxygen species (ROS) is established through the respiratory burst in phagocytes. Neutrophils, macrophages, and monocytes employ this method to swiftly generate reactive oxygen species (ROS) as a component of host defense [33].

The enzyme NADPH oxidase (NOX2) is pivotal to the respiratory burst. Upon activated by pathogens or inflammatory signals, NOX2 assembles at the phagosomal or plasma membrane, transferring electrons from NADPH to molecular oxygen, therefore generating superoxide anion ($O_2^{\bullet-}$). Superoxide is dismutated into hydrogen peroxide (H_2O_2), which can subsequently be transformed into the very lethal hypochlorous acid (HOCl) by myeloperoxidase (MPO). These reactive chemicals are essential for microbial eradication but may potentially induce collateral tissue damage if released extracellularly or generated in excess [34].

Pro-Inflammatory Cytokine Signaling

Reactive oxygen species and inflammation are interconnected at the molecular level via cytokine-mediated signaling pathways.

- Cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), activate intracellular pathways that induce reactive oxygen species (ROS) generation [35].
- In contrast, ROS function as secondary messengers, increasing cytokine gene expression and release. For instance:
- TNF-α stimulates mitochondrial reactive oxygen species generation and enhances NOX enzyme expression.
- IL-1β activates NOX and induces mitochondrial failure, perpetuating oxidative imbalance [36].

NF-κB Pathway and Oxidative Stress

The transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) serves as a primary regulator of inflammation. NF-κB activation is very sensitive to redox conditions [37].

- Under resting circumstances, NF-κB is confined in the cytoplasm by inhibitory IκB proteins.
- Reactive oxygen species (notably hydrogen peroxide) activate IκB kinase (IKK), resulting in the degradation of IκB and the nuclear translocation of NF-κB [38].

Activated NF-κB stimulates the production of pro-inflammatory cytokines, adhesion molecules, and NOX isoforms.

This not only sustains inflammation but also amplifies reactive oxygen species-generating mechanisms, establishing a feedback loop integral to chronic inflammatory conditions such as atherosclerosis and autoimmune disorders.

Inflammasomes and Reactive Oxygen Species

Inflammasomes are multiprotein complexes that detect cellular stress and trigger inflammatory responses. The NLRP3 inflammasome is especially pertinent to oxidative stress [39].

- Reactive oxygen species (ROS) function as principal upstream activators of NLRP3.
- Activated NLRP3 facilitates the cleavage of pro-caspase-1 into active caspase-1, which then converts pro-IL-1β and pro-IL-18 into their mature, pro-inflammatory forms.
- Mitochondrial failure, potassium efflux, and lysosomal rupture together contribute to reactive oxygen species (ROS) formation, hence associating oxidative stress with inflammasome activation [40].

Persistent Inflammation and Systemic Oxidative Stress

In acute inflammation, the formation of reactive oxygen species (ROS) is meticulously controlled and temporary, facilitating pathogen elimination and tissue restoration. In chronic inflammation, sustained reactive oxygen species production surpasses antioxidant defenses, resulting in systemic oxidative stress [41].

Illustrations encompass:

- Atherosclerosis: Oxidized low-density lipoproteins (oxLDL) produced by reactive oxygen species (ROS) facilitate macrophage absorption and foam cell production, perpetuating vascular inflammation [42].
- Obesity and metabolic syndrome: Enlarged adipocytes secrete cytokines (TNF-α, IL-6) that activate macrophages and NOX enzymes, establishing an oxidative-inflammatory cycle [43].

Nitric Oxide and Peroxynitrite in Inflammatory Processes

Reactive nitrogen species (RNS) exacerbate oxidative damage linked to inflammation.

- Inducible nitric oxide synthase (iNOS) is increased in activated macrophages, resulting in the production of substantial quantities of nitric oxide (NO•) [44].
- In the presence of superoxide, nitric oxide (NO•) reacts swiftly to produce peroxynitrite ($ONOO^-$), a formidable oxidant that may nitrate proteins, damage DNA, and inactivate mitochondrial enzymes.

Peroxynitrite is a key mediator of endothelial dysfunction, neurotoxicity, and chronic inflammatory injury [45].

Resolution of Inflammation and Redox Equilibrium

Remarkably, reactive oxygen species (ROS) are not solely harmful; they can contribute to the resolution of inflammation. Suboptimal levels of reactive oxygen species (ROS) function as signaling molecules to initiate antioxidant responses, encourage macrophage polarization towards an anti-inflammatory phenotype (M2), and aid in tissue healing [46].

The transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) antagonizes NF-κB by enhancing the expression of antioxidant enzymes (e.g., SOD, catalase, glutathione peroxidase). The equilibrium between NF-κB and Nrf2 signaling dictates whether inflammation resolves or evolves into a chronic and deleterious condition [47].

CONCLUSIONS

Oxidative stress results from intricate interactions between internal and external causes, closely associated with inflammation and chronic illness. Enhancing antioxidant defenses while minimizing reactive oxygen species (ROS) production is essential for prevention and treatment. Comprehending these systems provides avenues for precise treatments to enhance health and mitigate aging-related deterioration.

DISCLOSURE

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