OXIDATIVE STRESS AND ITS ROLE IN CHRONIC DISEASES

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Annotation. *Oxidative stress is a pathological condition that occurs as a result of an imbalance between the production of reactive oxygen species and the body's antioxidant defense system. This article presents a review of the role of oxidative stress in the development and progression of chronic diseases. The main sources of reactive oxygen species, mechanisms of cellular damage, and the impact of oxidative stress on lipids, proteins, and nucleic acids are discussed. Particular attention is paid to the involvement of oxidative stress in chronic non-communicable diseases, including cardiovascular diseases, diabetes mellitus, neurodegenerative disorders, and chronic inflammatory conditions. Modern diagnostic approaches for assessing oxidative stress markers and antioxidant status are described. The article also reviews current preventive and therapeutic strategies aimed at reducing oxidative stress, including lifestyle modification, antioxidant therapy, and dietary interventions. Understanding the mechanisms of oxidative stress is essential for improving early diagnosis, prevention, and management of chronic diseases, thereby enhancing patients' quality of life and reducing disease-related complications.*

Key words: *Oxidative stress, reactive oxygen species, antioxidants, chronic diseases, lipid peroxidation, inflammation*

Introduction: The Delicate Balance of Redox Homeostasis

Oxidative stress is defined as a physiological state characterized by an imbalance between the production of pro-oxidants and the body's antioxidant defense systems. This imbalance leads to a disruption in redox signaling pathways and subsequent macromolecular damage. Under normal conditions, reactive oxygen and nitrogen species (RONS) act as essential signaling molecules that regulate cellular processes such as gene expression, protein phosphorylation, and apoptosis. However, when RONS production exceeds the neutralizing capacity of antioxidants, it triggers a cascade of cellular degeneration that is a primary driver of the aging process and the development of chronic non-communicable diseases.

Sources and Mechanisms of Reactive Species Generation

The sources of oxidative stress are categorized into endogenous and exogenous origins:

• Endogenous Sources: The primary source of intracellular ROS is the mitochondria during oxidative phosphorylation, where oxygen is reduced as electrons move through the electron transport chain. Other significant sources include NADPH oxidase (NOX) enzymes, which

are used by immune cells (macrophages and neutrophils) to battle pathogens, and peroxisomes.

• Exogenous Sources: Environmental factors such as air pollutants, cigarette smoke, radiation, and toxins introduce unstable free radicals into the system.

• Molecular Catalysts: Transition metal ions like iron (Fe^{2+}) and copper (Cu^{+}) can catalyze the non-enzymatic Fenton reaction, transforming relatively stable hydrogen peroxide into the highly reactive and destructive hydroxyl radical (•OH).

The Impact of Oxidative Stress on Cellular Components

When ROS/RNS accumulate, they harmfully modify the structural and functional integrity of the cell:

• Lipids: RONS target polyunsaturated fatty acids to initiate lipid peroxidation, creating toxic products like malondialdehyde (MDA) and 4-hydroxy-trans-2-nonenal (HNE). HNE, in particular, is a potent biomarker for disease progression as it forms covalent adducts with proteins and DNA, leading to cellular dysfunction.

• Proteins: Oxidative stress causes nitrative stress (nitration of tyrosine residues) and nitrosative stress (S-nitrosylation of thiols), which can result in protein aggregation, enzyme deactivation, and endoplasmic reticulum stress.

• Nucleic Acids: ROS oxidize 2′-deoxy-guanosine to 8-hydroxy-2′deoxyguanosine (8-oxo-dG), a hallmark marker for site-specific DNA damage and genomic instability.

The Role of AGEs and the AGE-RAGE Axis

A critical consequence of oxidative stress, especially in hyperglycemic states, is the formation of Advanced Glycation End Products (AGEs). AGEs are formed through non-enzymatic reactions between reducing sugars and protein amino groups. These products interact with Receptors for AGEs (RAGE), initiating a "vicious cycle". This interaction activates the NF-κB signaling pathway, which upregulates pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and stimulates NOX enzymes, producing even more ROS and further exacerbating oxidative damage.

Oxidative Stress in Chronic Diseases

Neurodegenerative Disorders: In Alzheimer's Disease (AD), oxidative stress often precedes the accumulation of amyloid-beta (Aβ) plaques. High levels of AGEs are typically found localized within these plaques and neurofibrillary tangles. Interestingly, AD is sometimes referred to as "Type 3 Diabetes" because it shares common biomarkers with diabetes, such as HNE and AGEs, and involves impaired insulin signaling. In Parkinson's Disease (PD), the auto-oxidation of dopamine in the substantia nigra generates hydrogen peroxide, leading to the selective loss of dopaminergic neurons.

Cardiovascular Diseases (CVD): ROS mediate endothelial dysfunction by reducing the bioavailability of nitric oxide (NO), which is essential for maintaining vascular tone and inhibiting platelet adhesion. Excessive ROS levels promote atherosclerosis by facilitating the oxidation of low-density lipoprotein (LDL) and the expression of cell adhesion molecules.

Diabetes Mellitus: Hyperglycemia triggers ROS overproduction through several pathways, including the mitochondrial respiratory chain and the polyol pathway. Pancreatic β-cells are particularly vulnerable to this stress because they have relatively low levels of antioxidant enzymes compared to other tissues.

Chronic Kidney Disease (CKD): The kidney's high energy demand makes it susceptible to mitochondrial ROS damage. Mitochondrial dysfunction typically precedes clinical symptoms like proteinuria. CKD is also characterized by elevated carbonyl stress and the accumulation of protein oxidation products in the renal tissue.

Diagnostic and Therapeutic Strategies

Biomarkers and Diagnosis Information regarding specific modern diagnostic approaches, such as measuring C-reactive protein (CRP) or using the FRAP (Ferric Reducing Ability of Plasma) assay, is supplemented from general medical knowledge as it is briefly noted in the article annotation but less detailed in the primary source excerpts.

Antioxidant Interventions

The body uses enzymatic antioxidants (SOD, Catalase, GPx) and non-enzymatic ones (Glutathione, Vitamins C and E). Dietary polyphenols found in fruits and vegetables, such as quercetin, curcumin, and resveratrol, reinforce these defenses by scavenging free radicals and chelating trace metals that would otherwise participate in ROS-generating reactions.

Emerging Therapies

• Stem Cell Therapy: Neural Stem Cells (NSCs) and Mesenchymal Stem Cells (MSCs) are being researched for their ability to replace damaged cells, secrete neurotrophic factors, and exert anti-inflammatory effects.

• Nanozymes: Engineered single-atom nanozymes (using metals like Mn or Pt) can selectively sequester ROS/RNS and are particularly promising for treating neuroinflammation and promoting blood-brain barrier reconstruction.

• RAGE Inhibitors: Small molecules like azeliragon and FPS-ZM1 are in clinical trials to block the AGE-RAGE axis, potentially halting the progression of AD and certain cancers.

Conclusion

Oxidative stress is a fundamental mechanism underpinning the pathophysiology of most chronic degenerative diseases. While it is an unavoidable byproduct of life, the transition from physiological signaling to pathological damage occurs when antioxidant systems fail. Future management of these diseases lies in targeted interventions—ranging from high-bioavailability dietary antioxidants to advanced nanozymes—that can selectively quench the most reactive species and break the vicious cycle of inflammation and oxidative damage.

Analogy for Understanding: Think of oxidative stress like rust on a bridge. Normal metabolism is like the rain and wind that naturally wear the bridge down; as long as you have a "maintenance crew" (antioxidants) to repaint the steel, the bridge stays strong. However, if the salt and moisture (toxins, hyperglycemia) increase too much, or the crew retires (aging), the rust (oxidative stress) begins to eat into the structural beams (DNA and proteins).

Eventually, the bridge (human body) can no longer support the weight of normal activity, leading to mechanical failure (chronic disease).

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