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| RESEARCH ARTICLE

Review Article: Role of Oxidative Stress in Cell Biology

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| ABSTRACT
Oxidative stress is a fundamental concept in the field of cell biology and pathophysiology, which refers to the presence of an imbalance between the production of reactive oxygen species (ROS) and the ability of the biological system to detoxify these reactive intermediates or repair the resulting damage. This disturbance in the redox state of the cell can lead to the generation of toxic effects through the production of peroxides and free radicals, which subsequently damage essential cellular components such as nucleic acids, lipids, and proteins. Oxidative stress can arise from various sources, both endogenous and exogenous. Endogenously, ROS is generated as a byproduct of normal cellular metabolism, particularly during oxidative phosphorylation in the mitochondria, whereas exogenous sources of oxidative stress include smoking, air pollution, exposure to ultraviolet or ionizing radiation, intense physical exercise, and psychological stress. When the production of ROS overwhelms the cell's antioxidant defenses, the resulting oxidative stress can have detrimental effects on cellular function and viability. Oxidative stress has been implicated in the pathogenesis of numerous disease states due to the disruption of normal signaling pathways that induce DNA damage and trigger apoptotic or necrotic cell death cascades. The deleterious effects of oxidative stress are not limited to acute events but also contribute to the development of chronic diseases. Furthermore, oxidative stress-induced DNA damage can lead to genomic instability and the activation of oncogenic signaling cascades. The physiological role of oxidative stress in cellular function is complex, as it can also serve as a signaling mechanism to maintain homeostasis. Moderate levels of reactive oxygen species can act as secondary messengers, triggering adaptive responses that enhance cellular antioxidant defenses and promote cell survival. However, when oxidative stress reaches a critical threshold, it can overwhelm these protective mechanisms and lead to abnormal cellular activities and, ultimately, cell death.

| KEYWORDS

Apoptosis, Cellular metabolism, DNA damage, Free radicals, Reactive oxygen species (ROS)

| ARTICLE INFORMATION

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1. Introduction

1.1. *Oxidative stress*

Oxidative stress is the result of increasing intracellular concentrations of ROS that cause damage to lipids, proteins, and DNA (Yun et al., 2020). ROS is a super anion, and hydroxyl and hydrogen peroxide radicals are among the most negative effects (Demirci-Cekic et al., 2022). During development, most organisms are protected by enzymatic and non-enzymatic antioxidants (Silva and Silva, 2023). Natural antioxidants are usually insufficient for preventing oxidative damage to organisms. Antioxidant supplements that use slower oxidation or inhibit the oxidation of cell

substrates have been shown to protect against damaging hepatic cells or carcinogenesis (Gulcin, 2020; Akbari et al., 2022).

Oxidative damage from oxidative stress to biological molecules leads to abnormal activity and initiation of cell death. This is determined by an imbalance between the generation of free radicals, including active ROS, and the activity of the antioxidants (Kıran et al., 2023; Sadiq, 2023). Intracellular ROS are produced by enzymes (mitotic enzymes, NADPH oxidase, xanthine oxidase, etc.) and non-enzymatic (UV) pathways and play many physiological functions within brain cells (Varol, 2020). Oxygen regeneration and toxicity depend on its electronic structure. In a stable rhythmic atmosphere, the two outer orbital electrons have the same spin (Napolitano et al., 2022).

Reducing forms of oxygen-containing free radicals are very stable and require or need to accept electron donors (Martemucci et al., 2022). With this in mind, they are very active and have a very short lifespan. There is a slight decrease in oxygen radicals, superoxygen, and hydroxyl radicals; monomorphic oxygen, or ozone, is not radical, but it can easily be converted to free radicals and can be called ROS (Chang and Xia, 2024). The high functional activity of ROS and the rapid interaction of chemical reactions with biological molecules are rapidly uptake by cells for signal transduction or control by a highly potent antioxidant system. Excessive production of ROS and/or a defect in the antioxidant system can lead to the oxidation of protein, DNA, or lipid peroxidation, which may significantly affect cell homeostasis (Juan et al., 2021; Pisoschi et al., 2021; Sadiq, 2023).

The incorrectly synthesized proteins are different for each neurodegenerative disease. The β-Amyloid, which forms extracellular brain plugs, as well as tangles of tau protein, is an important component of intracellular synapses, a histopathological feature of the disease that is associated with embedded in an intracellular portal called Roy's body of the brainstem, neocortical region, and spinal cord (Sharma et al., 2022; Gilbert et al., 2023). It should be noted that some synthesized proteins are not simply associated with a specific disease. Therefore, α-sinucrane accumulation (sinus disease) is also known as Roy's body dementia and multi-line atrophy (Gomez and Ibba, 2020; Rajab et al., 2020). Tau aggregates are not only Alzheimer's disease and result from a number of neurodegenerative disorders but are manifested by major age-related disorders, progressive supranuclear palsy (PSP), and temporary chromosome-related dementia. The Alzheimer family is also associated with changes in beta-amyloid production (Virgilio et al., 2022; Darricau et al., 2023; Badihian et al., 2024).

To confirm the importance of proteins in neurodegenerative diseases, histopathological features of Huntington's disease include the synthesis of the Huntington protein. All of these neurotransmitters are composed primarily of protein fibers and are generally non-toxic, and toxic small forms of a few of these proteins cause cellular diseases and neurodegeneration in these diseases (Höhn et al., 2020; Churkina et al., 2022). Uncoordinated proteins can be implanted and replicated in neurons and other astrocytes in prion-like mechanisms (Hu et al., 2024). Most of these proteins play a physiological role in the form of monomers. Therefore, Alpha-synuclein appears to be important in synaptic transmission and mitochondrial bioenergetics (Srinivasan et al., 2021).

Tau is a microtubule-associated protein that strengthens microtubules and promotes axon release (Jiménez, 2023). The conversion of these proteins into toxic forms requires fusion, and tau requires phosphorylation (Boyarko and Hook, 2021). This is a specific process that contains many components that can depend on the oxidative state of the cell; beta-amyloid or alpha-synocrin compounds can be composed of iron ions such as copper, iron, and zinc (Nesci et al., 2021). Variable metals can produce ROS, and, in view of this, negatively synthesized proteins require ROS for their synthesis, but they also cause ROS to be produced (Alfei et al., 2024). One of the major problems associated with neurodegenerative diseases is early diagnostic biomarkers and, importantly, incorrectly synthesized protein testing as a potential biomarker for neurodegenerative diseases and the acquisition of oxidative stress products (Kulenkampff et al., 2021; Doroszkiewicz et al., 2022; Karaboğa and Sezgintürk, 2022). There are several roles for ROS and oxidation products in pathology, coagulation mechanism, and accumulation of abnormal binding proteins (Wang and Zennadi, 2020; Beura et al., 2022).

1.2. Free radicals

Free radicals are active chemicals with unpaired electrons in the outer layers. ROS are compounds that contain a single oxygen (Tripathi et al., 2021). In addition, reactive nitrogen species (RNS) such as ONOO-, radical peroxide (ROO-), nitrogen monoxide (NO), and copper, sulfur, and iron species increase ROS in addition to disruption of redox balance (Kwon et al., 2021; Mandal et al., 2022). Additionally, a growing database of data indicates that the production of active oxygen forms through mitochondria is essential for metabolic use, and these types destroy cell components by initiating death (Venditti and Di Meo, 2020; Tian et al., 2022; Al-Hetty et al., 2023). Studies showed that about 2-3% of these can escape the chronic antioxidant system and damage cells, lipids, proteins, and nucleic acids (Zahra et al., 2021; Jomova et al., 2023). On the other hand, natural hazards can produce forms of ROS and other oxidizing chemicals, such as air pollution, UV rays, and cigarette smoke (Zahaba, 2024).

1.3. Lipid peroxidation reaction

Lipid peroxidation is a common term for a process in which free radicals such as polyunsaturated fatty acids (PUFAs) release hydrogen from carbon dioxide and oxygen to produce peroxyl fatty radicals and hydrogen peroxide (Angelova et al., 2021). According to scientific research on this topic, the main endemic sources of ROS, progenitor membranes, vesicles, and peroxisomes have been investigated (Angelova et al., 2021). The whole process of lipid oxidation can be easily divided into three stages: initiation, distribution, and termination (Wang et al., 2023). Peroxy radicals have the ability to release hydrogen from fat molecules in the presence of many metals, including iron and copper. The radicals eventually react with hydrogen to form lipid peroxides (Martemucci et al., 2022). Cytotoxic aldehyde is formed when these radicals sometimes react with another lipid molecule, reacting with other FRs to form a stable end product of almond aldehyde (MDA). Another LPO product produces low-density lipoprotein (LDL) 4-hydroxynonenal (4hn) that can cause harmful cell damage (Misso et al., 2020; Podgrajsek et al., 2024).

1.4. Sources of Oxidative Stress

While the origins are quite different, oxidative stress can damage lipids, proteins, and DNA (Demirci-Cekic et al., 2022). In contrast, free radicals are required for every aerobic organism. Therefore, balance is important to body health (Di Meo and Venditti, 2020). External or natural sources of stress have different chemicals that ultimately lead to different disorders (Garcia-Caparros et al., 2021).

Other natural sources of stress include pesticides and natural chemicals that are toxically affected by the modification of biomolecular peroxides and scavenging enzymes (Sule et al., 2022). In addition, the capability of active metal to produce ROS or nitrogen monoxide radicals was studied (Liu et al., 2022). Internal stresses are manifested by inflammatory mechanisms and/or processes (Zhazykbayeva et al., 2020). In addition, several studies have demonstrated the role of cell culture in modulating oxidative stress mechanisms (Varesi et al., 2022). In fact, metabolic processes can produce a variety of ROS levels. It also causes a variety of damages, including double DNA fragmentation and mutations common in human cancer (Zhao et al., 2023). The non-enzymatic reaction of the mitochondrial respiratory chain on the enzymatic process of ROS production includes NADPH oxidase, nitrogen monoxide (eNOS), and lipophilic (Aranda-Rivera et al., 2022).

Natural production of ROS is complicated because reactive oxygen species can be beneficial in metabolism and detrimental to cells (Sies et al., 2022). It should be noted that the negative impacts of ROS and the role of antioxidants in moving from one region to another are a form of false yin-yang (Tan et al., 2022). One beneficial role of oxidative stress is related to protection against infectious diseases and pathogens (Rudrapal et al., 2022). Immune cells, especially neutrophils, respond to a chain reaction in the exocrine cells, which leads to a process known as respiratory failure (Al-Shehri, 2021). In this process, macrophages or neutrophils produce large ROS amounts. NADPH is well-known as part of respiration (Mortimer et al., 2021). It showed that ROS can act as a second transmitter of intracellular signaling mechanisms by acting as an anticancer agent, causing cell aging and apoptosis (Pourbagher-Shahri et al., 2021). In contrast, lower H2O2 levels act to signal the molecule to promote cellular proliferating, segregation, or migrating. However, ROS biology reveals that cells are complex (Sadiq, 2023).

1.5. ROS species

The most effective species given that thiol-type RNS production is associated with ROS, scavenger tools, and antioxidant reducing formation of RNS or lower nitrostric conditions. These radicals remove foreign substances within the cell for the benefit of the body (Pálla et al., 2024). Increasing evidence points to the important roles of intracellular processes like vasodilatation (Hu et al., 2022). On the other hand, excess levels of these free radicals can have a detrimental effect on the biological structure, as discussed previously (Martemucci et al., 2022). Indeed, the target of RONS is highly sensitive to proteins, which are the main mechanism of cell proteins. However, ROS-mediated thiol conversion, especially oxidative stress, is caused by cysteine residues (Aranda-Rivera et al., 2022).

Depending on the oxidative state of the cell, the thiol group of a cysteine residue is either reduced to a free thiol (-SH) by an antioxidant defense mechanism or converted to another post-translational oxidant (ox-PTM) (red) (Kükürt et al., 2021). Protein oxidation is well characterized in the neurodegenerative brain. For example, carbonyl proteins and 3-nitrotyrosine have been identified in Alzheimer's disease (AD) and Alzheimer's disease. Indeed, proteolytic pathways in the Alzheimer's brain include creatine kinase, glutamine synthase (GS), ubiquitin carboxy-terminal hydrolase L-1 (UCHL1), lα-enolase, and dihydropyrimidinase-associated protein BB (CK). Craytin kinase (isoform), α-enolase and triphosphate isomerase are involved in the process of intracellular energy production, and low levels of ATP (adenosine triphosphate) deplete AD neurons in the brain (Hinarejos et al., 2021; Mi et al., 2024). Proteomic studies also showed that PD proteins (deficient in tryptophan and cysteine residues) synthesized α-sinucrane with methionine to form methionine sulfoxide in the cerebral parenchyma. Methionine oxidation has an effect on suppressing protein fibrosis. This may lead to the accumulation of α-sinucranone, which may affect the onset and progression of PD (Pu et al., 2023; Lopes et al., 2024).

1.6. Antioxidants

There are two types of antioxidants: enzymatic antioxidants and non-enzymatic antioxidants, which control free radical reactions and protect the body from ROS. Enzymatic antioxidants inhibit lipid peroxidation of the precursor membrane by acting as scavengers of free radicals from intracellular and external sources (Sundaram Sanjay and Shukla, 2021). Non-enzymatic antioxidants are divided into intrinsic (metal antioxidants) and extrinsic (complementary antioxidants) (dietary antioxidants) (Ayoka et al., 2022). The body's immune system produces nutrients and non-enzymatic antioxidants like alpha-lipoic acid, melatonin, L-arginine, coenzyme q10, uric acid, albumin, transferase, and birilbin (Teleanu et al., 2019). The body contains trace elements (selenium, manganese, and zinc), vitamins (A, E, and C), omega-3 and omega-36, fatty acids, and carotenoids form is produced. Low glutathione (GSH) is a non-enzymatic antioxidant produced mainly by intracellular fluid (Mirończuk-Chodakowska et al., 2018; Shakoor et al., 2021).

Antioxidants are chemical molecules that slow down autoxidation by preventing the formation or growth of free radicals (Parcheta et al., 2021). Free radicals are continuously produced by many biological or chemical processes and can occur simultaneously in nature (Nimse and Pal, 2015). There are many factors that contribute to the formation of free radicals. For example, smoking, drinking alcohol or certain foods, exposure to UV and ionizing radiation (for example, light), low-molecular ozone or other metals, annealing, iron depending on Fenton reaction, etc (Żukowski et al., 2018; Martemucci et al., 2022). It plays an important role in many physiological, biological, and pathological conditions. In biological systems, they are generally defined as active molecules that contain oxygen, nitrogen, and sulfur (Rani et al., 2021). As a result, they are associated with many different human diseases. Therefore, the formation of free radicals can be regulated in a variety of ways by antioxidants. Antioxidant efficacy is related to initiation potency, rate constants, redox volume, and dissolved antioxidants (Nauser and Gebicki, 2020).

In this case, plant foods that contain many antioxidants, such as tocopherol, ascorbic acid, glutathione, or natural antioxidants, can prevent human diseases (Akbari et al., 2022). In addition, natural antioxidants have been shown to be effective supplements in cosmetics, diets, and nutritional supplements (Hoang et al., 2021). Purbic acid and coumarin extracts are natural compounds. The first is orange pigment found in algae and fungi, and the second is found in a variety of plant sources, especially green plants (Islam et al., 2924). These compounds and their derivatives exhibit a wide variety of biological functions, including antibacterial, antiviral, antitumor, antifungal, and

cellular toxicity, as well as anti-inflammatory, anti-allergic, anticarcinogenic, hepatoprotective, and antioxidant activities (Alibi et al., 2021; Tariq et al., 2021; Wahab et al., 2024). Ionizing radiation is used in medicine and industry, for example, for the diagnosis and treatment of cancer, as well as for cell nutrition. There are several ways medication can reduce the harmful effects of radiation exposure (Gharban and Al-Shaeli, 2021; Omer, 2021).

Among them, antioxidants can be used as radioprotectors that are effectively removed by releasing free radicals or absorbing radiation (Shivappa and Bernhardt, 2022). The potency of antioxidants against free radicals can be tested in vivo or in vitro for abnormalities such as high costs, complications, and behavioral doubts (animal sacrifice) (Martemucci et al., 2022). Antioxidants can be considered chemical compounds that are categorized according to their mechanism of action (Gulcin, 2020). Basic antioxidants (scavengers) are chemical compounds that prevent oxidation, whereas secondary antioxidants (chain scavengers) are indirectly oxidized by splitting of hydroperoxide into nonradical compounds; the preparation of a major antioxidant by donating hydrogen or electrons, neutral oxygen neutral, triple oxygen uptake, and UV rays by absorption (Gulcin, 2020; Pisoschi et al., 2021; Valgimigli, 2023). Vitamins E and A can be classified as a multi-functional antioxidant as they exhibit protective antioxidant activity in both their primary and secondary modes of action (de Almeida Torres et al., 2022; Chu et al., 2023).

1.7. Mechanism of Action of Antioxidants

Antioxidants play a direct role in reducing the types of ROS. Free radicals with oxygen and carbon centers in lipids are a common type of oxidizing agent (Ali et al., 2020). Initiation, distribution, and termination are known as the three mechanisms involved in lipids. The antioxidants work by blocking or breaking down the region (Costa et al., 2021). Antioxidants that break the chains inhibit this process by preventing the spread of large chains or destroying large chains (Chib et al., 2020).

1.8. Antioxidant enzyme

Potentially, ROS puts the body at risk of oxidative stress. ROS production can be derived from mitochondria and various enzymes, including xanthine and NADPH oxidase, and chitochrome p450 (Fukai and Ushio-Fukai, 2020; Aranda-Rivera et al., 2022). These enzymes work specifically to produce specific undesirable effects for biological chemical activities. To overcome danger, testicles modified complex antioxidants (Gulcin, 2020). With respect to the enzymatic component of this immune system, the promotion of oxidative stress is characterized by the stimulation of NFB-mediated (Hojo et al., 2023). The basis of the biochemistry of these antioxidants is the rapid conversion of superoxide (O_2) anions into hydrogen peroxide (H_2O_2) in the presence of SOD, which makes hydroxyl radicals more harmful. H_2O_2 itself is a powerful oxidant that penetrates the membranes and must be cleared to the cells immediately to prevent an accumulation of ROS, and removing H_2O_2 that is influenced by catalase or glutathione peroxidase, which is present in the testicles (Carmo de Carvalho et al., 2022; Islam et al., 2022; Andrés et al., 2023). Glutathione (GST) causes binding in electrical activity by sulfhydryl groups on various substrates in preparation for cellular release (Parcheta et al., 2021). This function is important in removing lipid peroxides and the metabolism of heterologous organisms. SOD can enhance immunity and stem cells (Panahi et al., 2020; Nethravathy and Dakshayini, 2023). The significance of the SOD has been demonstrated in mice exposed to stresses in the testicles (Hamza and Diab, 2020). Therapy resulted in increasing cytochrome c leakage from mitochondria and DNA strand fractures in these viral cells compared to wild-type control (Gualtieri et al., 2021). Leakage of testicular mitochondria is further emphasized by much higher testicles (Gualtieri et al., 2021; Kaltsas, 2023).

2. Conclusions

The study of oxidative stress has emerged as a critical area of inquiry within the biomedical sciences, offering profound insights into the intricate mechanisms underlying both physiological processes and the pathogenesis of a vast array of diseases. There is increasing evidence that the abnormal production of free radicals, such as the superoxide anion and hydroxyl radical, leads to increased stress on cellular structures and causes changes in molecular pathways that underpin the development of numerous important human diseases, including cardiovascular disorders, neurological conditions, and cancer, as well as the process of physiological aging. However, the field of study has seen a significant amount of progress and advancement in recent years, with a wealth of new research and discoveries that have expanded our understanding of the underlying principles and

mechanisms at play. Hence, as the field continues to evolve and new issues are explored, there is a growing need for further studies and analyses to build upon these recent findings and address the remaining gaps in knowledge. One of the key areas that require additional investigation is the examination of the latest developments within the field, as highlighted by the observation that understanding the latest developments in a field can help researchers explore ideas and attain new research ideas. Moreover, the need for such studies is further underscored by the assertion that further studies based on recently published articles are needed. This sentiment is echoed in the literature, with one study emphasizing the importance of helping the reader link the present work with the larger body of knowledge that was portrayed in the Introduction" and highlighting the need to suggest further work that needs to be done based on the new knowledge gained from the research.

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