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Review

Free radicals and their different effect: A literature based review.

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Abstract: Free radicals are reactive molecules with at least one unpaired free electron that are highly unstable. They are generated in the body by natural metabolism as well as external influences such as smoking, pesticides, pollution, and radiation. They react rapidly with DNA, lipids, and protein, which are all important components in our bodies. In this study we trying to summarize about the free radicals and also their different type of effects on body.

Keywords: Free radical, ROS, RNS, Oxidative stress, disease

1. Introduction

The regular cellular metabolism produces free radicals. A free radical is an atom or molecule that has one or more unpaired electrons in its valency shell or outer orbit and can exist without the help of other atoms or molecules. Because a free radical has an odd number of electrons and it is unstable, short-lived, and also extremely reactive. They can get electrons from another compounds to achieve stability because of their strong reactivity. As a result, the affected compound oxidized and becomes a free radical, setting off a chain reaction that eventually causes harm to the living cell [1]. Free radicals and other nonradioactive reactive species are made up of both ROS and RNS [2]. ROS and RNS have been demonstrated to have a dual role as helpful and harmful species based on their positive and negative impacts on biological systems [3]. They alter the structure of healthy cells [4], causing oxidation of lipids, amino acids, and nucleic acids [5].

A number of factors influence the quantity of free radicals generated [6]. Mitochondria are the primary location of ATP synthesis, which rises with age [7]. Following that, there has been a lot of data to indicate that biological systems have adapted to free radical cohabitation and have created various useful uses of free radicals in a variety of physiological activities [8-10](Table 1).

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Table 1. Some free radical diseases

Cancer
Atherosclerosis
Emphysema
Arthritis
Asthma
Ageing
Hypertension
Cirrhosis
Allergy
Cataract
Retinopathy
Macular degeneration

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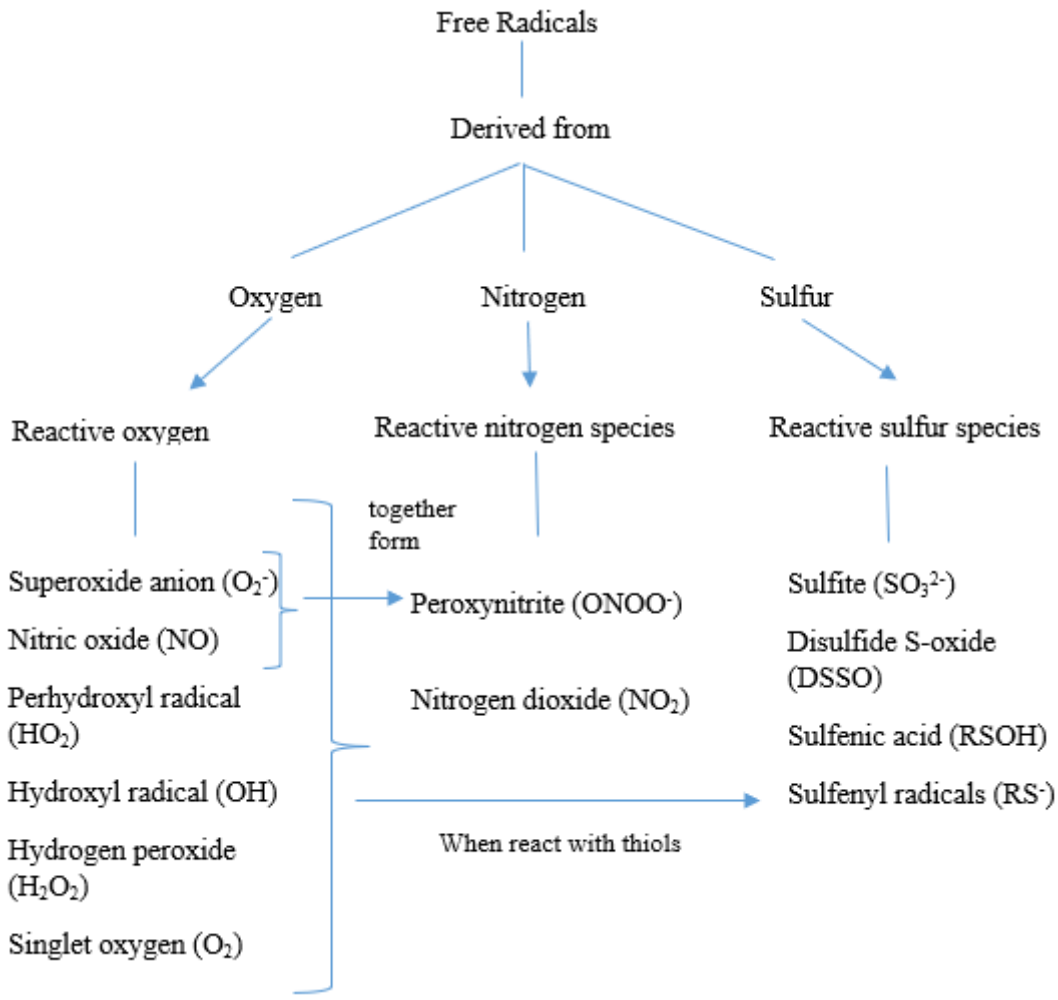

Figure 1: Types of free radicals. Free radicals are mainly three types such as Reactive Oxygen species, Reactive Sulfur species and Reactive Nitrogen species

1.1. Reactive Oxygen species

They are extremely reactive oxygen-containing compounds classified as superoxide, hydroxyl, and hypochlorite radicals [4]. They are produced as a result of enzymatic events that occur both within and outside the cell. Single oxygen, lipid peroxides, hydrogen peroxideand other non-radicals are examples of reactive oxygen species (ROS) [5]. Exogenous and endogenous production of ROS are both possible [6]. They are the principal by-product generated in aerobic organisms' cells, and they can trigger autocatalytic reactions. They start a chain reaction by reacting with nearby molecules such as protein, enzymes, and membrane lipids, converting them to free radicals and causing damage [4]. Environmental agents, ions, metals, chlorinated chemicals, radiation, and xenobiotics are examples of external sources [11]. Peroxisomes, microsomes, mitochondria, inflammation produced by cell activation and cytochrome P450 metabolism, [6]neutrophils, and eosinophils are all endogenous sources. Other sources include metal-catalyzed processes, X-rays and UV light irradiation, mitochondrial catalyzed electron transport reactions, macrophages and neutrophils during inflammation, and contaminants in the environment [12](Figure 1).

1.2. Reactive Nitrogen species

Reactive Nitrogen Species (RNS) are free radicals connected to septic shock, asthma, atherosclerosis, and other diseases. Reactive nitrogen species include nitric oxide and nitrogen dioxide, for example. Nitric oxide, a highly reactive free radical produced by the enzyme nitric oxide synthase (NOS), damages carbohydrates, lipids, proteins, and nucleotides, causing inflammation, adhesions, and tissue damage. It also suppresses platelet aggregation, relaxes artery and vein muscles, and nitric oxide donors, as vasodilating drugs, can play an important role in therapeutics [13].

1.3. Reactive Sulfur species

The oxidation of thiols and disulfides produces this sort of free radical. They have a high oxidation state of sulphur and are redox-active in nature. Some examples include disulfide, sulfenic acid, and thiyl radicals. They cause thiol proteins and enzymes to be inhibited because to the quick oxidation they undergo. According to several in vitro investigations, sulphur can exist in a variety of oxidation states ranging from 2 to +6 [14]. The number of electrons required for full reduction to thiol indicates the number of thiols that these species can reduce. Sulfite radicals and disulfide-S-oxide (DSSO) are two examples of secondary oxidation products with a greater degree. Sulfite induces a continuous and slow oxidation of lipids and sulfhydryls, according to many tests on muscle homogenates. Experimental evidence suggests that the mechanisms that cause the formation of reactive sulfur species may also play a role in the oxidation of lipids [15].

1.4. Oxidative stress

ROS can cause structural damage to cells, proteins, nucleic acids, membranes, and lipids at high quantities, causing a shift in oxidative metabolism towards pro-oxidants. Toxins, infections, disease, radiation, medication, chronic inflammation, strenuous physical activity, exposure to alcohol and pesticides, smoking, and a poor diet can all

contribute to a stressed state at the cellular level. Cells produce oxidants in a variety of ways, including xenobiotic metabolism, which detoxifies hazardous compounds, regular aerobic metabolism, which leaves around 10% of oxygen unutilized by the cell, and phagocyte oxidative burst, which denatures and destroys foreign components such as proteins [4].

1.5. Sources of free radicals

ROS can come from both endogenous and external sources. Various cellular organs that consume oxygen, such as mitochondria, peroxisomes, and the endoplasmic reticulum is substantial, are endogenous sources of ROS [16].

1.6. Mitochondria

Mitochondria is the major source of free radicals. Complex I (NADH dehydrogenase) and complex III (superoxide radicals) are the two key sites in the electron transport chain where superoxide radicals are formed (ubiquinone cytochrome c reductase). When electrons are transferred from complex I or II to coenzyme Q or ubiquinone (Q), a reduced version of coenzyme Q is formed (QH_2). In the Q-cycle, the reduced form of QH_2 has been regenerates to coenzyme Q through an unstable intermediate of semiquinone anion $^{\bullet}Q^{-}$. The superoxide radical is generated when the synthesized Q donates electrons to molecular oxygen. Superoxide is not produced by enzymes, hence the higher the metabolic rate, the more ROS is produced [17](Figure 2).

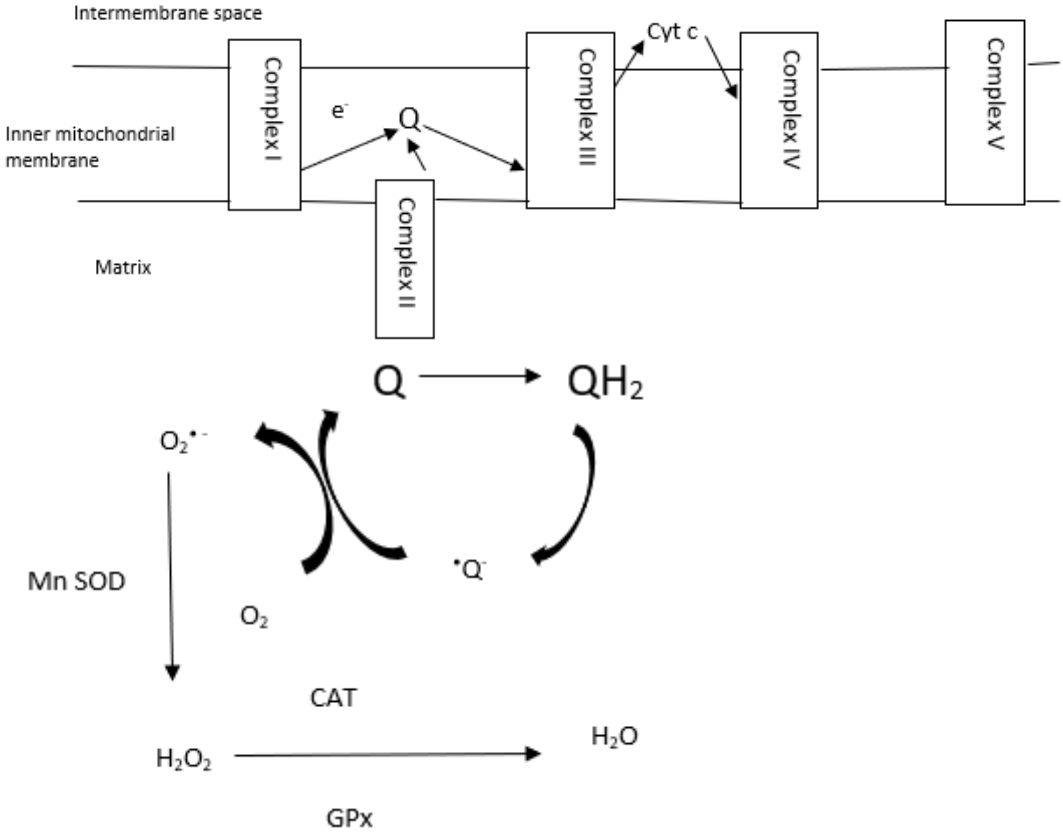

Figure 2: Generation of free radicals mitochondria.

1.7. Peroxisomes

The respiratory system pathway in peroxisomes has been include the transformation of electrons from different metabolites to oxygen, resulting in the formation of H_2O_2, but basically it is not linked to oxidative phosphorylation to produce ATP, certain releasing free energy in the form of heat [18]. It produce peroxide as a by pro-uct of fatty acid and other molecules.

1.8. Endoplasmic reticulum

ROS are produced by endoplasmic reticulum enzymes such as cytochrome p-450 and b5 enzymes, as well as diamine oxidase [19]. Erop1p is another most important thiol oxidase enzyme that catalyzes the pass of electrons from the dithiols to molecular oxygen, resulting in H_2O_2 [20].

1.9. Making of free radicals

Free radicals are created when a chemical bond is broken in such a way that every fragment retains one electron, when a radical is cleaved to produce another type of radical, and also when the redox reactions occur [21,22] (Figure 3).

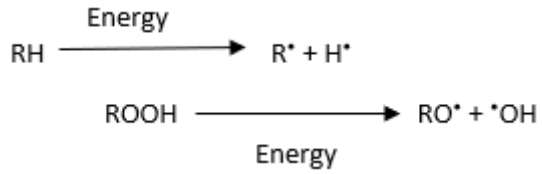

Figure 3: Chemical Generation of free radicals.

1.10. Free radicals in different type of disease

Atherosclerosis, inflammatory conditions, certain cancers, and the aging process have all been linked to oxidative stress [8]. All type of inflammatory diseases (arthritis, glomerulonephritis, vasculitis, adult respiratory diseases syndrome, lupus erythematosus), ischemic diseases (stroke, heart diseases, intestinal ischema), acquired immunodeficiency syndrome, hemochromatosis, organ transplantation, emphysema, high blood pressure, gastric ulcers and preeclampsia, neuropathic pain are now thought to be linked to oxidation [23].

1.11. Cancer

Free radicals allow genetic material to be modified and mutated, resulting in cancer tissue damage. There may be a link between the DNA oxidized product and tumor size, according to research [24]. By reacting with DNA's components, free radicals damage its bases and deoxyribose backbone, which can lead to oncogene activation and chromosomal abnormalities, which encourage cancer further [25]. These radicals can even affect the normal transcription of a gene by forming hydroxylated DNA bases. Other alterations include strand breakage, sugar lesions, and the creation of protein-DNA crosslinks [2]. When a cell divides with a broken DNA strand, the cell metabolism changes and the duplication pattern changes[4]. Antioxidants are thought to have a key role in tumor prevention.

1.12. Diabetes

Free radical damage contributes considerably to ß-cell malfunction, dysglycemia in the pre-diabetic condition, insulin resistance, and type 2 diabetes [26]. Some variables, such as leptin and free fatty acids, are reported to be in higher amounts in diabetic patients, resulting in a high concentration of ROS [27].

1.13. HIV (AIDS)

Excessive production of free radicals can cause inflammation, damage the cellular membrane, deplete the protective mechanism, and trigger apoptosis [28]. The interaction of Kupffer cells with glycoprotein 120 of SIV and HIV-1 can also result in the release of proinflammatory cytokines and chemokines. It is the primary cause of CD4+ lymphocyte depletion [29].

1.14. Cardiovascular disease

Cardiovascular disease (CVD) has a multifactorial etiology and is linked to a number of risk factors such as hypercholesterolemia, smoking, diabetes, hypertension, stress, poor diet and also physical inactivity, to name a few [29,30]. Recent study findings have sparked a heated discussion as to whether oxidative stress has been the primary or secondary cause of several cardiovascular disorders [30] unsaturated fatty acids make up a large portion of blood's low-density lipoproteins (LDL), and their oxidation plays an important role in atherosclerosis [31]. Endothelial cells, macrophages and smooth muscle cells are the three most important cell types in the vessel wall, and they can generate free radicals that cause lipid peroxidation [32].

1.15. Carcinogenesis

ROS and NOS like superoxide anion, hydroxyl radical, hydrogen peroxide and nitric oxide, as well as their biological metabolites, aid in carcinogenesis. Free radicals have also been implicated in carcinogenesis, mutation, and transformation by a number of researchers; it is evident that their availability in a biosystem may leads to mutation, transformation, and eventually cancer [8]. It's imperative to know free radical reactions as one of several mechanisms that lead to human cancer, and to consider research into their role in cancer as a strategy to prevent the start or progression of cancer [33].

1.16. Rheumatoid arthritis

Chronic inflammation is a feature of RA, and the disease progresses as a result of the creation of ROS and RNS at the site of inflammation. When the levels of prostaglandins and isoprostanes in synovial fluid and serum were compared to controls, it was discovered that oxidative damage plays a significant role in RA [2].

1.17. Aging

According to research, free radical destroy to cells causes the degenerative changes that accompany aging [34]. A significant number of illnesses and disorders, as well as the aging process itself, have been linked, either directly or indirectly, to such reactive and possibly harmful substances. Numerous investigations have demonstrated that ROS play a significant role in brain aging, neuronal cell death, and neurodegenerative diseases [35].

1.18. Parkinson's disease

There has been evidence of increased levels of pro-oxidants in the brains of Parkinson's disease patients [36]. The increased damage of DNA, lipids, and proteins due to oxidative stress has been linked to this condition.

1.19. Huntington's disease

Due to the involvement of free radicals, there has been an increase in F_2 isoprostanes levels in the cerebro-spinal fluid of HD patients, [37] as well as a threefold increase in lactate concentrations in the basal ganglia and cortex, leading to the conclusion that HD patients have a defect in oxidative phosphorylation [38].

1.20. Alzheimers's disease

Due to the accumulation of amyloid in AD patients, oxidizing circumstances can promote protein cross-linking and aggregation of ßamyloid protein and other proteins, which can also cause neural membrane disintegration due to the oxidation of the side chains of membrane lipids, resulting in cell lysis [39]. There has been a considerable change in the brain's cortex proteins, as well as in the lymphocytic DNA damage of AD donors [40,41].

1.21. Fatigue and Illness

Chronic fatigue and muscular pain, such as chronic fatigue immunodeficiency syndrome (CFIDS) and myofascial pain syndrome (MPS), can occur when mitochondrial energy production is disrupted or distorted. This is thought to be due to cellular damage produced by free radicals [4]. The interaction with high affinity receptors found on macrophages and monocytes increases the production of free radicals [42].

1.22. Nephropathy

Oxidative stress has a crucial impact in renal illnesses such as chronic renal failure, uremia, glomerulonephritis, and proteinuria. Heavy metals including mercury, cadmium, and lead, as well as transition metals like copper, iron, and cobalt, have been discovered to cause nephropathy in various forms. Other medications, such as gentamycin, vinblastine, cyclosporine, and others, cause nephrotoxicity by causing oxidative damage to the lipids through peroxidation [2]. Low-density lipoproteins and other lipids are oxidized by reactive oxygen species, which promotes diabetic nephropathy. Endogenous antioxidants in plasma reduce the rate of oxidation [43].

1.23. Pulmonary diseases

Free radical damage to cells is thought to be part of the source of inflammation in the bronchioles, and studies suggest that this could lead to chronic obstructive pulmonary disease (COPD) and asthma [4]. The activation of certain redox transcription factors including NF-kappa B and specific kinases by oxidants may result in an increase in inflammation [2].

1.24. Lipid peroxidation

In the oxidative stress, lipid peroxidation causes oxidative damage to cellular membranes, lipoproteins and also some other molecules which are contain lipids. Lipid peroxidation is a reaction in which oxidants such as reactive oxygen species or non-radical species attack lipids and also having carbon-carbon double bonds,

particularly polyunsaturated fatty acids which are involve hydrogen removal from a carbon, resulting in hydroperoxides and lipid peroxyl radicals [44]. Lipid peroxidation seems to be a chain reaction that occurs when free radicals react with the unsaturated fatty acids which are present in cell membranes, causing them to oxidize and break down. Lipid peroxidation processes start with free radicals and end with them [45].

1.25. Fatal damage

Birth abnormalities and increased embryo fragmentation caused by free radicals have been linked to oxidative stress. Oxidants can alter critical transcription factors as well as gene expression, impacting embryo development in the early stages [13]. They play an important role in the mechanisms that cause fetal growth limitation [2].

2. Conclusion

Normal metabolism produces free radicals (ROS/RNS), which are implicated in a variety of physiological and pathological situations. Free radicals damage our body macromolecules such as DNA, fat and protein which are essential for our body. Free radicals generate different diseases that are harmful for human beings which are cataracts, cancer, diabetes mellitus, neurodegenerative diseases and cardiovascular diseases etc. More in-depth research and analysis of free radicals is needed to better understand their properties and mechanisms.

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