Chapter

Diseases Related to Types of Free Radicals

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Abstract

The free radicals are reactive molecules with electron-rich groups produced during metabolic reactions occurring in the cells. These free radicals are collectively known as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Lipid peroxidation products and protein carbonyls species are under the group of ROS, and nitric oxide and peroxynitrites are under the group of RNS. The malondialdehyde that reacts with LDL-C indirectly induced the risk of atherosclerosis. The protein carbonyls acts as marker of protein oxidation and exerts damage to proteins. The nitric oxide plays an important role in DNA damage, inflammation, proliferation of cancer cells, and dysfunction of apoptosis. The peroxynitrites could induce the process of lipid peroxidation, DNA damage, and may exert chronic damage to all biomolecules. The aim of the present study is that the free radicals may react with biomolecules of the cells and play an important role in the development of chronic disease conditions in the humans.

Keywords: reactive oxygen species, reactive nitrogen species, oxidative stress, pathological conditions

1. Introduction

Free radical is a molecule with an unpaired electron and capable of high reactivity [1, 2]. Free radicals are found to be involved in alteration of redox system, induced DNA damage, activation of procarcinogens, these all markers of induction of cancer [3]. Some of the radicals are the superoxide (O^{-2}), hydroxyl (OH•), alkoxy radical (RO•), and nitric oxide (NO), and nonradical species are hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and peroxynitrites (ONOO—), which play an important role in the development and progression of different pathological conditions [4]. NO-induced dose-responsive DNA strand breakage and deaminations of cytosine to uracil and 5-methylcytosine to thymine account for the mutagenicity of nitric oxide toward bacteria and mammalian cells [5]. Antioxidants are proved that reduce the actions of reactive oxygen and nitrogen species, which are capable of damaging cells and tissues [6]. The proteins contain nitrotyrosine residues accumulate in cells which disrupts multiple regulatory pathways [7].

Nitroxidative stress maker species are actively engaged in the chronic disease complications, and their toxicity is reduced by antioxidants which have protective effects [8]. The enzymes of NADPH oxidases, xanthine oxidase, uncoupled nitric oxide synthase, and mitochondria act as markers of reactive oxygen species production in all metabolic cells [9]. Free radicals thus adversely alter lipids, proteins, and DNA and trigger a number of human diseases [10]. Peroxynitrites are the leading molecule of reactive nitrogen species by enhancing the process of lipid peroxidation, DNA

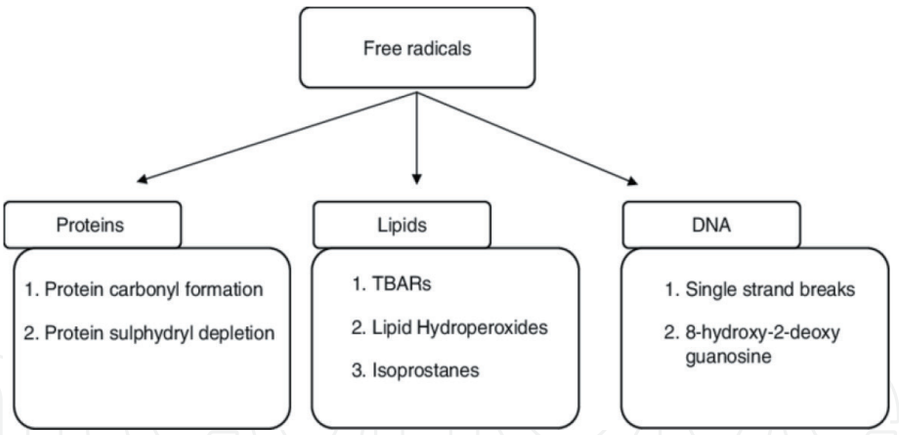

Figure 1.
Impact of free radicals on biomolecules present in cells leads to formation of adducts, markers of various diseases [19].

damage, and protein oxidation and act as molecular target for drug development for cardiovascular, inflammatory, and neurodegenerative diseases [11]. In the cells, the interaction of excess superoxides with excess nitric oxide results in the generation of peroxynitrite which specify the chronic disease conditions of stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, and neurodegenerative disorders [12]. The reduced glutathione, glutathione disulfide, and glutathionylated proteins act as markers of redox imbalance are directly proportional to oxidative stress [13].

The ROS requires oxygen for its formation and play an important role in human health and disease [14]. The development of increased ROS production with the simultaneous dysfunction of mitochondria has been exhibited in the pathogenesis of disorders [15]. Every cell especially vascular cells are involved in the higher production of free radicals implicated in the pathogenesis of ischemic heart disease, atherosclerosis, cardiac arrhythmia, hypertension, and diabetes [16]. The scavenging role of hydrogen peroxide is performed by catalase and decreases catalase activity results in aggregation of hydrogen peroxide leads to formation of oxidative distress [17]. The aerobic metabolic reactions are faced to greater a concentration of oxygen generates and is increased oxidation it leads inflammation, mitochondrial dysfunction, and chronic kidney diseases [18]. The purpose of the present review is to investigate the role of free radicals in various physiological and pathological diseases like neurodisorders, cancer, renal, cardiovascular, and immunological dysfunctions (**Figure 1**).

2. Oxidation and cancer

The reactive oxygen and nitrogen species (RONS) are synthesized in greater concentration by reducing antioxidant defense, and formation of redox imbalance leads to oxidative damage to the DNA and proteins in the oral squamous cell carcinoma [20]. In animals, ROS may influence cell proliferation and cell death through the activation of several signaling pathways in the development of carcinogenesis [21]. The higher level of ROS is directly proportional to the suppression of antioxidant enzymes and significant role of oxidative-induced injury in the breast cancer [22]. The prolonged exposure and intake of tobacco is strongly associated with decreased status of antioxidant enzymes, increased oxidative stress markers with the pathogenesis of oral cancer [23]. The strong correlations of ROS and RNS with lowered antioxidants are found in oral precancer and cancer [2] (**Figures 2–3**).

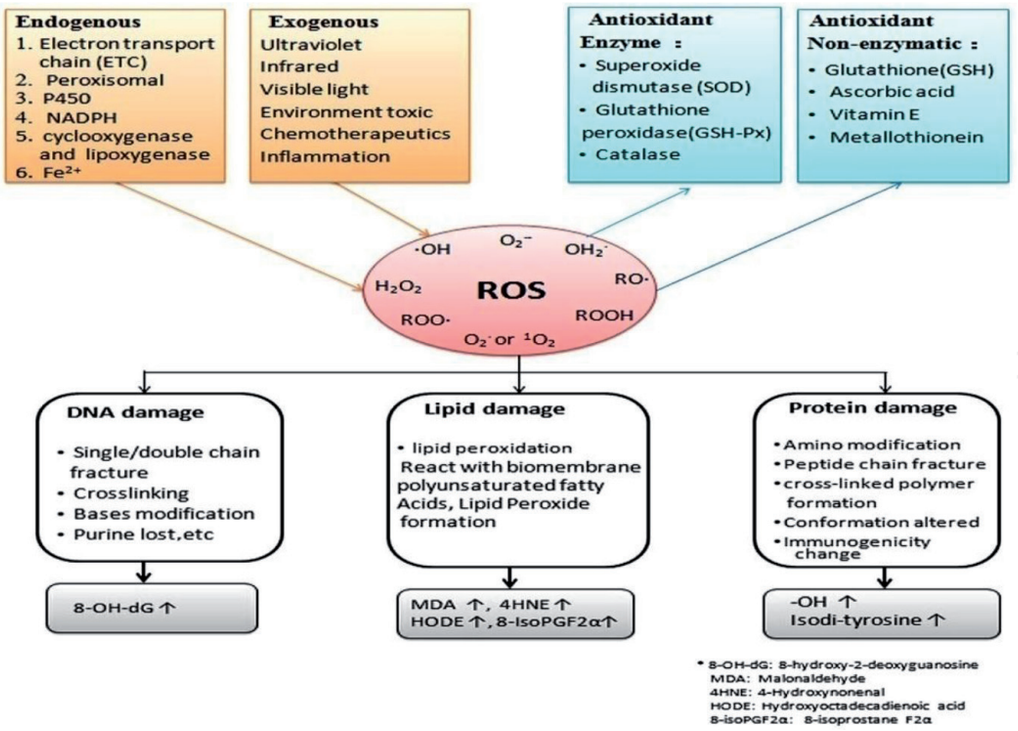

Figure 2.
The functions of free radicals on biomolecules and its consequences [24].

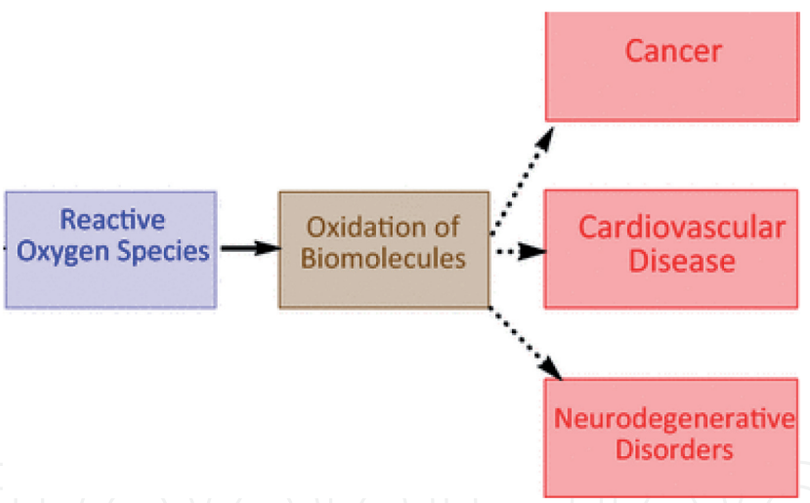

Figure 3.
Reactive oxygen species are involved in the development of various pathological disorders [38].

2.1 Free radical cause nitric oxide

The nitric oxide (NO) has dual role in health and disease and depends on its concentration. Nitric oxide is the active marker of the development of cancer by induction of angiogenesis, blood vessel formation during physiological and pathological processes [25]. NO may modulate tumor DNA repair mechanisms by upregulating p53, poly (ADP-ribose) polymerase, and DNA-dependent protein kinase (DNA-PK). The role of NO in cancer will have profound therapeutic implications for the diagnosis and treatment of disease [26]. Alterations in the NO metabolism and to increase protein nitration may contribute to the mutagenic processes and promote lung carcinogenesis [27]. NO promotes intravasation and angiogenesis to enhance cancer cell growth and increase the properties of cancer cells [28].

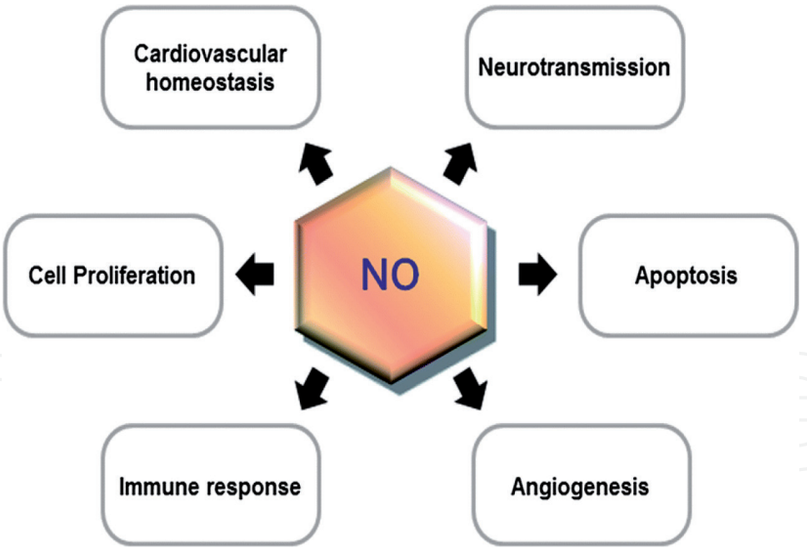

Figure 4.
The role of nitric oxide in various diseases of humans [57].

In lung cancer, a high level of NO is linked to chronic stages of cancer cells and protective role in the survival and proliferation of tumor cells by inhibiting apoptosis, increasing cell migration, and invasion [29]. NO and its role in carcinogenesis and tumor progression, as well as dietary chemopreventive agents have NO-modulating properties with safe cytotoxic profile [30]. The nitric oxide synthase 2-mediated production of NO/reactive nitrogen oxide species (RNS) is heavily involved in cancer progression and metastasis in different types of tumor (**Figure 4**) [31].

2.2 Free radical cause peroxynitrites

Peroxynitrites (ONOO—) could able to cause DNA strand breaks and oxidize cellular thiol groups in viable rat thymocytes in a dose-dependent fashion [32]. ONOO— is actively involved in the disturbances of signaling pathways of epidermal growth factors indirectly induced the process of tumorigenesis [33]. The combined effects of nitric oxide and oxidized LDL forms increase the concentrations of peroxynitrites that leads to glutathionylation of p21 ras proteins which results in aberrant activation of p21 [34]. The S-nitrosylation of PTEN, Bcl_2 enhanced DNA mutation, and inhibition of apoptosis results in cell proliferation and cell survival [35]. The peroxynitrite could modify the DNA and increase the DNA adducts which act as antigens is one of the factors for the autoantibody induction in cancer patients [36]. Levels of peroxynitrite and nitrosylhemoglobin can be used as highly informative markers of disease prognosis and therapeutic approach [37].

2.3 Free radical cause lipid peroxidation

Lipids are major structural components of the membranes and are highly addictable to oxidation by the presence of reactive double bonds [39]. The malondialdehyde (MDA), product of lipid peroxidation, reacts with low-density lipoproteins and indirectly induced the process of atherosclerosis [40]. The high level of oxidative stress is directly proportional to progression of tumor stages in lungs and pulmonary parenchyma [41]. The lipid peroxides are one of the ROS that enhance the DNA damage through mutations which results in decreased expression of tumor suppressor genes or increased expression of oncogenes [42]. ONOO— is the initiator of induction of lipid peroxidation which disrupts the membranes and lipoproteins.

These ONOO— and MDA collectively act as cytotoxic as well as mutagenic in cancer progression [43]. The formation of oxidative stress due to imbalance of redox system in the cells through increased lipid peroxidation has been associated with human health and diseases, including cancer [44]. The lower levels of cholesterol was detected in cancer cells and suspectible to attack of free radicals enabling the penetration of RONS into the interior of the cell, inducing pro-apoptotic factors [45].

3. Neurodegenerative diseases

3.1 Free radical cause peroxynitrites

The combined effects of peroxynitrite and sulfur-containing amino acids have been implicated in Parkinson's disease by performing the synergistic toxicity to a neuronal cell line [46]. The protein nitration in the form of nitrotyrosine residues is by the actions of peroxynitrite. Increased concentrations of both protein carbonyls and 3-nitrotyrosine have been reported in various neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [47]. The decreased activity of antioxidant enzymes with the simultaneous increase in the concentrations of peroxynitrites leads to disturbances of oxidative phosphorylation was observed in the brain mitochondria [48]. The modification of the monomers, destabilize microtubules, and major alterations in neurodegenerative diseases is performed by peroxynitrites [49]. The effects of S-nitrosylation on neuronal excitation are due to stimulation of ionotropic glutamate receptors and toxic Aβ peptides in Alzheimer's disease [50].

3.2 Free radical cause nitric oxide

In the lower doses, nitric oxide acts as a neurotransmitter of the neuronal cells, and it exerts antimicrobial activity invading microbes in macrophages [51]. Nitric oxide played an important role in the modulation of CO_2-mediated cerebral blood flow [52]. Nitric oxide is a physiological signaling molecule produced from L-arginine by enzyme of nitric oxide synthase (NOS). This enzyme occurs in three forms as neuronal (nNOS), endothelial (eNOS), and inducible nitric oxide synthase (iNOS). It increases the cGMP levels by acting as vasodilator and is involved in the neurotransmission between nervous system cells [53]. The positive association of oxidative stress and neurodegenerative conditions was observed in multiple sclerosis, stroke, and neurodegenerative disorders [54]. The ROS is actively involved in the oxidative damage to amyloid beta peptides, marker in the Alzheimer's disease [55]. The most abundant neurotransmitter in central nervous system is glutamate which acts as the initiator of NO formation, and H_2S is highly expressed in brain which is involved in the pathogenesis of various neurological disorders [56].

3.3 Free radical cause lipid peroxidation

The brain oxidative damage contributes to AD pathogenesis by the Aβ accumulation and amyloid plaque formation in the Alzheimer's disease of Tg2576 mice [58]. The imbalance of functioning endogenous antioxidant system leads to accumulation of free radicals, which not only induces the process of lipid peroxidation but also plays a central role in neurodegeneration [59]. Lipids are critical for plasticity and function of neuronal development. The abnormalities in lipid metabolism contribute to the pathogenesis of several neurodegenerative disorders like Alzheimer's disease and Parkinson's disease [60]. The relationship between lipid

alterations in energy metabolism and mitochondrial dysfunction in neurodegenerative disorders [61]. Deposition of abnormal aggregated proteins and disruption of metal ion homeostasis are highly associated with oxidative stress [62]. The antioxdant and free radicals of lipid peroxidation and cognition, and cognitive response to an exercise intervention program, in adults with coronary artery disease at risk of dementia [63]. The brain is more susceptible to lipid peroxidation due to its high oxygen consumption, high level of redox metal ions, reduced antioxidant defense mechanism, and high level of polyunsaturated fatty acids [64].

4. Cardiovascular diseases

4.1 Free radical cause nitric oxide

Decreased concentrations of nitric oxide may cause constriction of coronary arteries and contribute to provocation of myocardial ischemia in coronary artery disease patients. The nitric oxide present in lower amounts exerted the vascular inflammation that could lead to oxidation of lipoproteins and foam cell formation that leads to the development of the atherosclerotic plaque [65]. These ROS actively involved in atherogenesis through their formation from enzymes of xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and nitric oxide synthase [66]. The peroxynitrites directly increases sarco/endoplasmic reticulum calcium (Ca^{2+} ATPase) sarco/endoplasmic reticulum calcium (SERCA) activity by S-glutathiolation and irreversible oxidation of the relevant cysteine thiols in atherosclerosis [67]. An imbalance of reduced production of NO or increased production of superoxide results in the endothelial dysfunction [68].

The dual role is performed by the nitric oxide NO in the cells, and at low concentrations, it regulates normal protective functions, but at high concentration may contribute to the pathogenesis [69]. Oxidative stress, mitochondrial dysfunction, and stress-related cell death pathways (apoptosis and necrosis) are related to the improper functioning of cardiovascular system [70]. Most ROS that are generated as by-products during mitochondrial electron transport and reactive nitrogen species (RNS) are peroxynitrites and nitric oxide, contributing to the role in the development of cardiovascular disease [71]. The specific markers of ROS are altered to inflammation that enhanced the risk of atherosclerosis by diabetes [72]. The vasodilator activity of NO may be unique among therapeutic options for management of hypertension, renal disease, and left ventricular hypertrophy [73].

4.2 Free radical cause peroxynitrites

Nitric oxide is important physiological signaling molecule also known as the endothelial-derived-relaxing factor (EDRF), and can form free radicals like peroxynitrites capable of peroxidizing the LDL and proteins [74]. Formation of peroxynitrite is augmented in inflammatory-like conditions such as ischemia-reperfusion injury in the high dose manner [75]. Proinflammatory cytokines stimulate the concerted enhancement in superoxide and NO-generating activities in the heart and causes myocardial contractile failure [76]. The protein nitration and inactivation of creatine kinase during heart failure in cardiac muscles are performed by peroxynitrites [77].

Peroxynitrite depresses myocardial contractility by decreasing the ability of Ca^{2+} to trigger contraction through cGMP/cGMP-dependent protein kinase pathway [78]. The peroxynitrite exposure results in reduced sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA2a isoform) activity is a major determinant of reduced

contractility in heart failure [79]. Peroxynitrites that are present in higher concentrations depicts a crucial pathogenic mechanism of stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, and neurodegenerative disorders [12]. The synergistic performance of nitric oxide, superoxides, peroxynitrites are effect on mitochondrial function and cell death [80].

4.3 Free radical cause lipid peroxidation

Abnormalities in levels of antioxidants like GSH are associated to accumulation of lipid peroxidation in chronic heart failure [81]. Increased formation of lipid peroxides and aldehydes has been observed in atherosclerosis, ischemia-reperfusion, and heart failure [82]. Atherosclerosis, the hardening of arteries under oxidative stress is related to oxidative changes of low density lipoproteins (LDL) which is an early prediction of development of cardiovascular disease [83]. The proinflammatory effects that result from the peroxidation of lipids, which provide critical structure and function in cellular membranes, are the main sites of pollutant attack in cardiovascular diseases of atherosclerosis, arrhythmia, hypertension, and stroke [84].

5. Immunological disorders

5.1 Free radical cause nitric oxide

Peroxynitrite converts low density lipoprotein to a form recognized by the macrophage scavenger receptor and that this process is associated with modification of the protein and lipid, and with the oxidation of alpha-tocopherol to alpha-tocopherol quinine [85]. The activated macrophages are involved in the production of large amounts of nitric oxide and indirectly diminish lymphocyte proliferation [86]. Tyrosine nitration is recognized as a prevalent and significant post-translational protein modification that serves as an indicator of nitric oxide-mediated oxidative inflammatory reactions [87]. Prolonged iNOS expression peroxynitrite may exacerbate inflammatory responses mediated by NF-kappaB due to prolonged inducible nitric oxide synthase [88].

NO regulates the structural and functional activity of many immune and inflammatory cells like macrophages, T lymphocytes, antigen-presenting cells, mast cells, neutrophils, and natural killer cells [89]. The proinflammatory nature of NO is actively involved in the process of inflammation only at higher concentrations [90]. The macrophages in active state are actively engaged in the production of not only NO production but also TNFα production [91]. Stimulatory effects of NO on integrin β1 expression and Talin phosphorylation were mediated by the cGMP signaling pathway, which is likely involved in wound healing [92].

5.2 Free radical cause peroxynitrites

Physiological role for $ONOO^-$ as a down-modulator of immune responses and also as key mediator in cellular and tissue injury is associated with chronic activation of the immune system [93]. In chronic inflammatory diseases, peroxynitrite formed by phagocytic cells may cause damage to DNA which acts as epitopes for the production of autoantibodies [94]. The central role of peroxynitrite is performed in the control of infections in macrophages [95]. They are produced throughout the vascular system, regulate differentiation and contractility of vascular smooth muscle cells, control vascular endothelial cell proliferation and migration, mediate

platelet activation and hemostasis, and significantly contribute to the immune response [96]. Elevated reactive oxygen and nitrogen species are reduced levels of glutathione with chronic systemic inflammation with elevated levels of pro-inflammatory cytokines [97]. The ONOO— could be modified by the histone proteins that lead to formation of oxidatively nitrated histones in the initiation and progression of autoimmune inflammatory diseases [98]. Peroxynitrite represents both a pathophysiologically relevant endogenous cytotoxin and a cytotoxic effector against invading pathogens [99]. Being a mediator of protein oxidation and nitration, lipid peroxidation, mitochondrial dysfunction, and cell death, peroxynitrite represents both a pathophysiologically relevant endogenous cytotoxin and a cytotoxic effector against invading pathogens [99].

5.3 Free radical cause lipid peroxidation

Plasma malondialdehyde and glutathione levels have been used as a determinate of oxidative status in the chronic immunological disorders; systemic lupus erythematosus (SLE) is a complex [100]. 4-Oxo-2-nonenal (ONE) is a highly reactive aldehyde originating from the peroxidation of polyunsaturated fatty acids involved in the pathogenesis of autoimmune disorders [101]. The product of lipid peroxidation is 4-hydroxynonenal (HNE) that acts as specific marker of immunosenescence and aging-related disorders [102].

6. Renal diseases

6.1 Free radical cause peroxynitrites

Ischemia-reperfusion injury showed decreased levels of 3-nitrotyrosine-protein adducts. The iNOS-generated NO mediates damage in I-R injury possibly through ONOO— formation [103]. Patients with chronic renal failure (CRF) showed decreased endothelium-dependent vasodilatation to acetylcholine, have increased markers of oxidative stress, and diminished antioxidant activity [104]. ONOO— could induce entire mitochondrial protein nitration, responsible for the damage of renal mitochondria in diabetes [105]. Nitrosative stress is involved in cisplatin-induced nephrotoxicity in rats through peroxynitrite-induced nephrotoxicity and protein nitration [106]. Renal hypoxia and ischemia promotes the formation of reactive oxygen species (ROS) such as superoxide radical anions, peroxides, and hydroxyl radicals, that can oxidatively damage biomolecules and membranes, and affect organelle function and induce renal tubule cell injury, inflammation, and vascular dysfunction [107].

6.2 Free radical cause nitric oxide

The rate of whole body NO synthesis was increased in the end stage renal disease (ESRD) patients [108]. In several animal models of renal disease, the increase in NO synthesis is associated with reduced degree of glomerulosclerosis, infiltration of the kidney by invading macrophages [109]. The relations between endothelial and inducible nitric oxide synthases are perturbed in renal ischemia primarily as a result of endothelial dysfunction [110]. The nitric oxide is highly reactive and exerts its chronic effects only at high concentrations which are responsible for the complications of dialysis of patients with chronic kidney disease [111]. Patients with chronic kidney disease (CKD) have been found the decreased levels in all stages of CKD [112]. Intracellular nitric oxide (iNO) substantially increased the risk of renal

dysfunction in patients with acute respiratory distress syndrome (ARDS) [113]. The process of oxidative stress affects kidney function by elevated the damage in renal vessels, glomeruli, and tubules [114]. In patients with multiple valve replacement and prolonged cardiopulmonary bypass, administration of nitric oxide decreased the incidence of acute kidney injury [115].

7. Some other type of free radicals

7.1 Hydroxyl radicals

It is the most reactive of the free radical molecules. It damages cell membranes and lipoproteins by lipid peroxidation. Damage to lipoproteins in low density lipoprotein plays an important role in atherosclerosis. •OH is formed by radiolysis of water and by reaction of H2O2 with ferrous (Fe^{2+}) ions; the latter process is termed as Fenton reaction [116, 117]. The reactive oxygen species, hydroxyl (•OH) radical is one of the potential inducers of DNA damage. A variety of adducts are formed on reaction of •OH radical with DNA. The •OH radical can attack purine and pyrimidine bases to form •OH radical adducts, which are both oxidizing and reducing in nature which in turn can induce base modifications and sometimes release of bases. Some of the important base modifications include 8-hydroxydeoxyguanosine (8-OHdG), 8 (or 4-,5-)-hydroxyadenine, thymine peroxide, thymine glycols, and 5-(hydroxymethyl) uracil [118].

7.2 Free radical cause lipid peroxidation

Lipids that contain phosphate groups (i.e., phospholipids) are essential components of the membranes that surround the cells and cell structures. Free radicals in the presence of oxygen may cause degradation (peroxidation) of lipids within plasma and organellar membranes. Oxidative damage is initiated when the double bonds in unsaturated fatty acids of membrane lipids are attacked by oxygen derived free radicals particularly by OH. The lipid free radical interactions yield peroxides, which are themselves unstable and reactive, and an autocatalytic chain reaction called propagation ensues which can result in extensive membrane, organellar, and cellular damage [116, 119]. Oxidative destruction of polyunsaturated fatty acids by lipid peroxidation is damaging because it may alter the integrity of cell membranes. [120].

7.3 Superoxide oxygen (O_2•—one electron)

It is generated by direct auto-oxidation of O2 during mitochondrial electron transport reaction. Alternatively, O2• is produced enzymatically by xanthine oxidase and cytochrome P450 in the mitochondria or cytosol [121]. O2• so formed is catabolized to produce H2O2 by superoxide dismutase (SOD), a metalloprotein. It is considered to be the least reactive type of ROS and the most commonly produced free radical in humans. Once it is produced, it triggers a rapid cascade of events that creates other free radicals.

7.4 Singlet oxygen

Singlet oxygen ($^1O_2$) is an electronically excited form of oxygen which is well known to be formed when photosensitizers such as chlorophyll or the aromatic dye rose Bengal absorb light energy and transfer some of that energy to molecular oxygen

[122, 123]. Various nonphotosensitized mechanisms for its formation have also been reported and suggested to occur in biological systems, but the importance of such endogenous singlet oxygen formation has had a controversial history [122, 124]. Ozone (O3) is best known as occurring in the stratosphere where it shields organisms on earth from ultraviolet C and much of ultraviolet B radiations, which are the most damaging UV components of solar radiations because they are readily absorbed by DNA [125, 126]. It is also known as a respiratory system-damaging pollutant in the troposphere and ironically as a therapeutic agent in alternative medicine [127]. More recently, it was shown that antibodies or amino acids catalyze the conversion of singlet oxygen ($^1O_2$) to ozone (O_3) and that this reaction occurs during the killing of bacteria by activated neutrophils [128, 129]. Since both singlet oxygen and ozone are highly reactive oxygen species, a full understanding of their mechanisms of formation and action *in vivo* is necessary. Hence, various reported mechanisms of the endogenous formation of these reactive oxygen species (ROS), the potential relevance of such pathways in human physiology, diseases and activity of these oxidants.

8. Conclusions

The free radicals are normally synthesized during metabolic reactions in the cells and disease. These free radicals are removed by various scavenging activities of cellular and noncellular antioxidants. The imbalance of excess ROS formation and diminished activity of antioxidants results in the formation of oxidative stress which is linked with various pathological chronic conditions like cardiovascular, neurodegenerative, and renal disorders.

Conflict of interest

The authors report no declarations of interest.

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