ISSN 2348-6201

Reactive Oxygen Species: Its Effects on various Diseases

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ABSTRACT

A free radical is any molecule capable of independent existence that contains one or more free electrons. These free radicals fall under the broader category of reactive oxygen species (ROS). ROS such as O_2^- , H_2O_2, NO^-, OH^-, HOCl, $ONOO^-$ are toxic to cells. ROS act largely by driving several important molecular pathways that play important roles in pathologic processes including neurodegeneration. injury, atherosclerosis, and inflammatory responses and ischemia-reperfusion. ROS, as in various radicals ions leads to mitochondrial dysfunction and consequently other cell organelles damage either through environmental effect or through genetic or metabolic disorders. Reactive molecular species also disturbs other metabolic pathways in a manner that cell's normal functionality gets disrupted. Though diseases caused by reactive oxygen species are many, this review has covered its effect on major diseases. The present review paper will provide the detail of mechanism of ROS and its effect on different pathological states.

Indexing terms/Keywords

Oxidative stress; Reactive Oxygen Species; Free radicals; Pathogenesis.

Academic Discipline And Sub-Disciplines

Molecular Biology

SUBJECT CLASSIFICATION

Biotechnology

TYPE (METHOD/APPROACH)

Review Article

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Biotechnology

Vol 3, No. 1

editor@cirjbt.com

www.jbt.cirworld.com, www.cirworld.com

ISSN 2348-6201

INTRODUCTION

Oxygen is the vital element used for the aerobic life processes. Nearly about 5% and more of the inhaled O_2 is converted into reactive oxygen species (ROS) (1), such as O_2^-, H_2O_2, NO, by the univalent reduction of O_2 by the electron transfer system in mitochondria. The increase in ROS production threatens the cells under the aerobic conditions which derive their energy from the reduction of oxygen, and thus are protected by the antioxidant system of the cells. The imbalance between the ROS production and antioxidant system of the cell causes Oxidative Stress which leads to the cellular dysfunction causing various diseases. Free radicals, superoxide ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), and nitric oxide (NO) are three free radical reactive oxygen species (ROS) that are essential for normal physiology, but also accelerating a cell death through necrotic or apoptotic mechanism (Figure. 1).

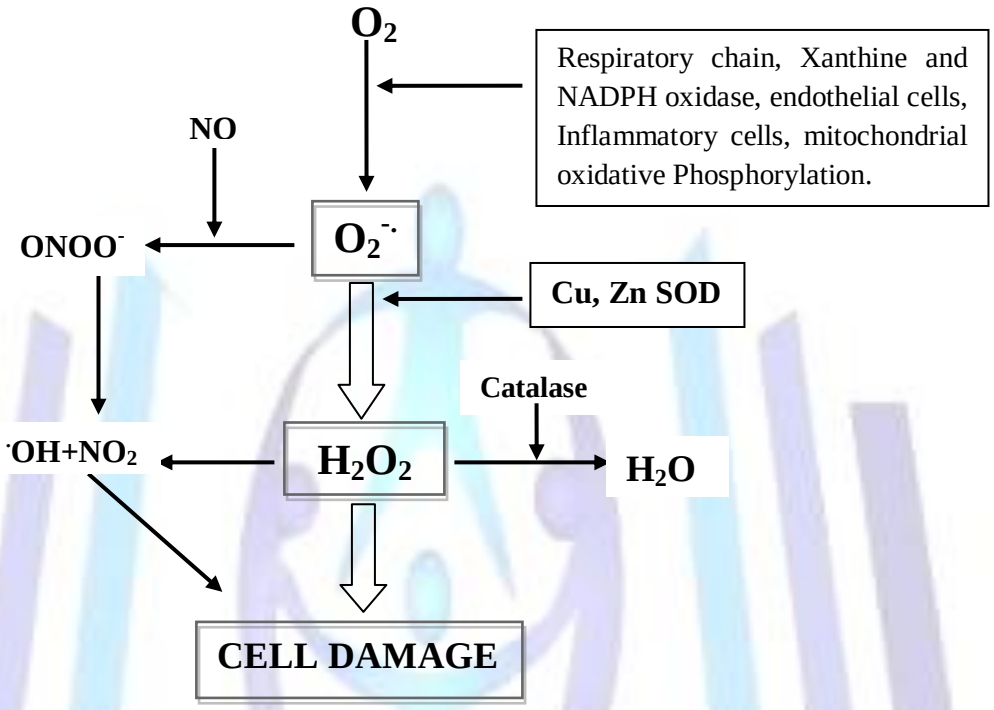

Figure.1. Oxidative stress and Reactive Oxygen Species

Harmful effects of ROS on the cell can be described as DNA damage, Lipid peroxidation and Oxidations of amino acids in proteins, Inactivation of specific enzymes by oxidation of co-factors. In diseases such as Alzheimer's disease, rheumatoid arthritis, multistage carcinogenesis, cerebral and cardiac ischemia, inflammatory bowel disease, and aging which are mostly caused by ROS (Figure. 2) has been extensively studied.with specific emphasis on their molecular characterization.

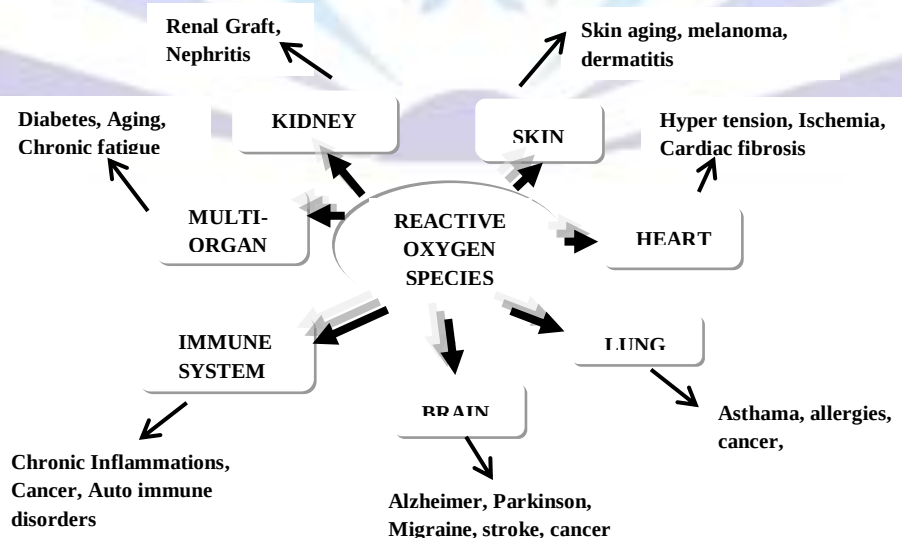

Figure.2. Effect of Reactive Oxygen Species on various Organs

Superoxide (O_2^-)

Superoxide (O_2^-) is generated by the mitochondrial electron transfer chain during the oxidation of reduced nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide (NAD^-), and also as a by-product of many enzymes that act as oxidases(2). The beneficial effects of O_2^- include regulation of vascular function, cell division, inflammation, apoptosis, and bactericidal activity of neutrophils (3) whereas, decreased levels of O_2^- can lead to an increased susceptibility to bacterial infections.

Hydrogen peroxide (H_2O_2)

superoxide dismutase catalyzed dismutation of O_2 as well as many other enzymatic reactions causes production of Hydrogen peroxide (H_2O_2). H_2O_2 can diffuse across membranes and through the cytosol unlike O_2^-, which remains at the site of production (4). Since H_2O_2 is a powerful oxidizing agent, cells express abundant catalase, glutathione (GSH), and thioredoxin (Trx) that convert H_2O_2 to water. Reaction of H_2O_2 with free Fe^{2-}causes oxidation of iron and production of hydroxyl radicals. Hydroxyl radical production has many severe cocsequences, including loss of vasodilation which can lead to tissue hypoxia and endothelial injury (5).

Nitric oxide (NO)

Cytosolic activity of enzyme known as NO synthase (NOS) causes generation of NO which plays a major role by activating the soluble guanylate cyclases that regulates the ion channels and thus regulating vascular tone. Apart from it through direct inhibition of cytochrome oxidase NO modulates cellular respiration by competitively occupying the oxygen binding site of enzyme (6). Recovery from neuronal injury is promoted by NOS inhibitors (7). It is also believed to act as a neurotransmitter regulating neuronal channel (8). Endothelial NO produces vasodilation that can improve blood flow under ischemic insult,, but neuronal NO is produced during downstream of calcium dysregulation and can prevent energy generation in the mitochondria (9). Apart from it most importantly, in certain environments NO acts as an antioxidant and prevents the lipid peroxidation (10).

PATHOLOGICAL EFFECTS

Cancer

Instead of the fact that they are opposite ROS plays a key role in both Apoptosis and Cancer (11). In addition, oxidative DNA damage has been clearly linked to induction of carcinogenesis (12) and, 8-oxo-2'-deoxyguanosine, the DNA oxidative product has been reported to be highly mutagenic (13). Contribution to carcinogenesis of ROS is through interference with signal cascade systems, which among others included, the nuclear transcription factor kappa B (NFkB), activated protein-1 (AP-1), phospholipase A2, mitogen-activated protein kinases (MAPKs) and c-Jun kinase (14-18). Rapid reaction of cells to redox imbalance is through a plethora of biological responses, including cell cycle-specific growth arrest, gene transcription, and initiation of signal transduction pathways and repair of damaged DNA. These early events are likely to determine whether a cell will necrose, senesce, apoptose or survive and proliferate (19). Inhibition of apoptosis, follicular lymphomas, and carcinomas with p53 mutations causes tumors such as: lung cancer, colorectal cancer, medullary breast carcinoma; and hormone-dependent tumours: such as breast, prostate and ovarian cancer (20-22).

Apoptosis can be initiated by a variety of stimuli, oxidants, including, glucocorticoids, hyperthermia growth-factor or hormone withdrawal, ionizing radiation and multiple classes of chemotherapeutic agents (23-24). The stress exerted on the cell provides its viability. Following an apoptotic signal, progression in lipid peroxidation due to cells sustains. leads ROS and oxidative damage in the induction of apoptosis (25-28). The protein Bcl-2 protects against apoptosis by blocking cytochrome c release hence this protein may have an antioxidant function (29-34). It is suggested that oxygen inhibits the proliferation of human lymphocytes and fibroblasts (35-37). ROS as a mediator of apoptosis acts by decreasing intracellular glutathione, the major buffer of the cellular redox status and/or by increasing cellular reactive species (37-41). H_2O_2 at low doses induces apoptosis via production of OH^- radicals and alteration of the oxidant/antioxidant pathway (42-43). a proton gradient and superoxide radicals is generated by Mitochondrial respiration, causing alkaline-induced cell death, mitochondrial integrity and oxidative stress (44).

Diabetes

Diabetes mellitus is a group of metabolic diseases. It is characterized by hyperglycemia resulting from defects in secreation of insulin or insulin action, sometimes both (45). Several other factors like hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis besides hyperglycemia. At this level the progression of disease will be at high risk (46-47).

Chronic diseases, such as atherosclerosis, diabetes and rheumatoid arthritis are common end points of oxidative stress and oxidative damage to the tissue (48). Oxidative stress is currently suggested as mechanism underlying diabetes and diabetic complic ations (49) as persistent hyperglycemia causes increased production of reactive oxygen species (ROS). Increasing production and/ or decreased destruction of nonenzymic and enzymic catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) (highly reactive) antioxidants of aerobic respiration that is where O_2 is commonly produced. SOD which is primarily produced is the front line of defense against ROS-mediated injury (51).

Lipids when react with free radicals, they undergo peroxidation to form lipid peroxides decomposing to form numerous products including malondialdehyde. In nervous system injury in diabetes,a one unifying mechanism causes both

metabolic and vascular insults to be increased by cellular oxidative stress and impairing the function of mitochondria (53, 54). Through *in vivo* and *in vitro* measurement of oxidative stress in sensory neurons as well as neuronal protection by antioxidants this hypothesis have been supported. *In vitro*, O_2 and H_2O_2 is produced by application of 10–20 mm glucose to dorsal root ganglia neurons that leads to lipid oxidation and neuronal death. IGF-I prevents this glucose-induced death, in part through decreased ROS production (55-56). Oxidative stress in diabetes and the development of complications is closely correlated. As the disease progresses, depending upon the level of glycemic control, plasma lipid peroxidation products increases and antioxidant potential decreases (57). Similarly, oxidative stress is linked to preclinical features of disease, such as vascular endothelial activation that can lead to atherosclerosis (58). In women, due to the early increment of oxidative stress in diabetes is more pronounced and this may cause increased cardiovascular disease patients (59).

Skin Diseases

Skin, which is the largest human body organ, is constantly exposed to an array of chemical and physical environmental pollutants and thus provides a major interface between the environment and the body (60). Exposure of skin in UV radiation or xenobiotics drugs generates ROS in excessive quantities that quickly swamp tissue antioxidants and their pathways (61). Infiltrating activated leukocytes that possess abundant systems capable of generating these species, are an additional source of oxygen radicals in skin as well as in other organs, among which are O_2 and hypochlorite an important sources of ROS in situ. Many of these agents are capable to generate ROS intrinsically or their metabolites such as redox active quinines. Many of them are involved in the pathogenesis of multiple skin disorders/allergic reactions/neoplasms (63, 64). eicosanoids driving cutaneous inflammation is another important pathway, which are generated from arachidonic acid (AA) by the enzyme prostaglandin H synthetase that generates hydroxyl-endoperoxides. The eicosanoids including the leukotrienes and the prostaglandins are an important inflammatory mediators. Inducible nitric oxide synthase is another pro-oxidant enzyme present in skin, which is induced in infiltrating leukocytes and other phagocytic cells, and produces NO. NO interacts with respiratory burst generated OS to form a highly unstable reactive species $ONOO^-$, that can damage DNA thereby producing point mutations, deletions, or rearrangements (65, 66). Following UVB exposure Urocanic acid is another molecule in skin that undergoes cis–trans isomerization and is likely involved in the immunosuppressive as well as photo aging effects of sunlight and is also known to prolong skin-graft survival time, and affect natural killer cell activity (67). UVA irradiation of trans-urocanic acid generates O_2 radical ion that after initiating c-jun N-terminal kinase (JNK) signaling, leads to interstitial collagenase induction as well as the synthesis of IL-1 and IL-6 a proinflammatory cytokines, in UVA-irradiated fibroblasts and this revelation is determined by enhanced production of 5a-cholesterol hydroperoxide, a marker of O_2 generation. However, endogenously generated chromophores like nicotinamide adenine dinucleotide (reduced form)/nicotinamide adenine dinucleotide phosphate (reduced form), tryptophan, riboflavin, etc. modulates this response (68).

The Ageing process

It has been proposed that the although mitochondria express a variety of protective defenses (antioxidant and repair enzymes as well as low molecular weight antioxidants), oxidation of proteins and the slow accumulation of DNA lesions resulting from the continuous formation of ROS may contribute to the ageing process (69). increased formation of ROS is caused due to effect in rate of electron flow through some these lesions, which supports the observed correlation between the rate of mitochondrial O2−• and H2O2 formation and at the same time lifespan among several species (70). Deficiencies in the mitochondrial DNA repair system directly correlates to ageing process. Since mitochondrial DNA does not contain histones, and therefore it is less protected against oxidative stress than the nuclear DNA. Consequently, the a 10- to 20-fold increase in the content of 8-hydroxyguanine, the product of guanine oxidation is shown by mitochondrial DNA (71). Because of this mtDNA damage may indirectly inhibit respiration and stimulate ROS formation, since the mitochondrial chromosome codes for some electron carriers. A human condition that causes premature ageing, Cockayne syndrome, has been associated with a deficiency in the mitochondrial enzyme required for DNA repair that catalyses the removal of 8-hydroxyguanine (72). A more direct correlation between oxidative stress and ageing are shown by other studies. First, further linking oxidative stress with ageing, there is a correlation between accumulation of oxidized proteins and lifespan (69). Overexpression of catalase and SOD results in a 25 % increase in the lifespan of Drosophila melanogaster is shown by another study in a more direct approach (73-75).

NEURODEGENERATIVE DISEASES

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a neurological disease that has been associated with oxidative stress. About 10 % of the cases of familial ALS have been linked to a mutation in the gene coding for CuZn SOD (76). Misfolding will be occur due to this mutation, and the effective import of this enzyme to the inter-membrane space will be prevented, thus increasing the steady-state concentration of O2−• in this compartment, a process that may lead to apoptosis (77).

Leber Hereditary Optic Neuropathy

Another genetic mutation indirectly associated with increased formation of ROS is the mutation in one of the subunits of Complex I responsible for Leber hereditary optic neuropathy that causes neuronal apoptosis. In a recent article, the investigators manipulated the expression of MnSOD in order to increase the intramitochondrial steady state of O2−• in normal cells, resulting in the same histopathological changes observed in Leber's disease (78).

Alzheimer's Disease & Parkinson's disease (Mechanisms of Oxidative Stress: ROS Production by Mitochondrial Dysfunction and NADPH Oxidase)

In many neurodegenerative diseases including AD, PD, Huntington's disease, ALS, PSP, Friedreich's ataxia, Neurodegeneration with brain iron accumulation, and optic atrophy, mitochondrial pathology is evident (Figure 3). The respiratory chain dysfunction and oxidative stress, reduced ATP production, calcium dysregulation, mitochondrial permeability transition pore opening, peturbation in mitochondrial dynamics, and deregulated mitochondrial clearance shows whole spectrum of mitochondrial dysfunction. From the hippocampus and platelets of AD patients, as well as in AD animal models and AD cybrid cells, in mitochondria the complex IV activity is reduce (79).

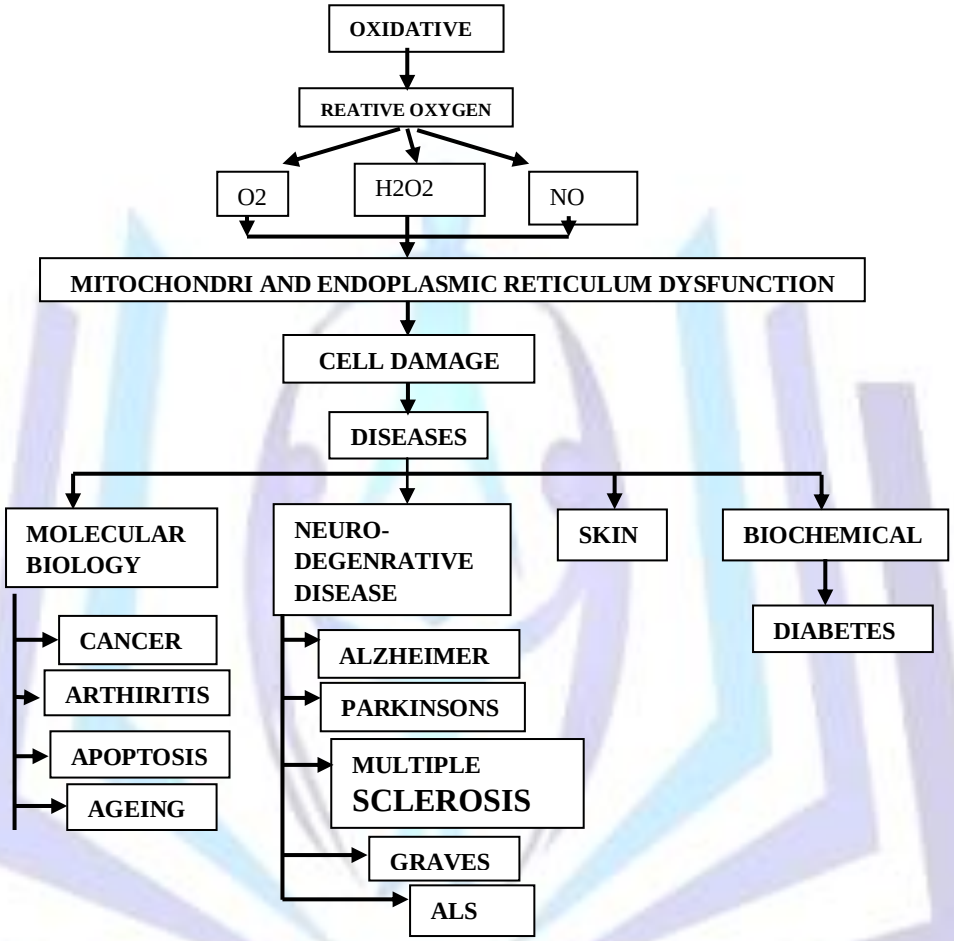

Figure.3. Work flow chart of Effect of Oxidative Species in causing Diseases.

Consequent increase in ROS production and opening of the PTP due to deregulation of calcium homeostasis has been demonstrated in AD, with βA causing increased cytoplasmic calcium levels and mitochondrial calcium overload. βA is responsible for induced opening of PTP in isolated mitochondria and primary astrocytes (80, 81). In brains of AD patients, activation of NOX2 has been demonstrated (82), which shows an upregulation of NOX1 and NOX3 in early stage postmortem AD brain (83). The role of NADPH oxidase in AD has also been suggested at a cellular level. Direct activation of NADPH oxidase in rat primary culture of microglial cells and human phagocytes is induced by Amyloid-beta (βA) (84-86). Through B-class scavenger receptor CD36, βA activates microglial NOX (87). Active NADPH oxidase transfers protons across the membrane and for normal functioning, requires opening of an ion/anion channel for charge compensation (88). In βA activated microglia, by blocking the charge compensatory mechanism of NADPH oxidase, inhibition of CLIC1 channel, inhibited superoxide production and protect cells (89). By its antioxidant properties, Neuroprotective effect of some endogenous compounds, such as hormone melatonin is induced (90). βA also activates NADPH oxidase by massive NO production and the generation of peroxynitrate and inducing calcium entry into astrocytes but not neurons (91) resulting in the generation of oxidative stress, which depolarises the mitochondrial membrane and, in combination with calcium, induces opening of the mitochondrial permeability transition pore (mPTP) as well as changing membrane structure through activation of phospholipase C (92). This oxidative stress signal is passed to more vulnerable neighboring neurons than astrocytes. It has therefore been suggested that due to increased oxidant production by NADPH oxidase, depletion of GSH in astrocytes could diminish GSH release from astrocytes and consequently deplete GSH in

neurons. Although, in some studies it is evident that *β*A and the presenilins exhibit the ability to activate NADPH oxidase in primary neurons (91). In Parkinson's disease (PD), oxidative stress has been demonstrated in both the rotenone and MPTP-induced toxin models showing further activation of NADPH oxidase (NOX2) in microglia (193). Furthermore, pharmacological inhibition of NADPH oxidase is able to protect mesencephalic dopaminergic neuronal (N27) cells against MPP+-mediated dopaminergic degeneration (94). Interestingly, the NADPH oxidase is activated by Oxidative Medicine and high cytosolic calcium concentration, leading to overproduction of superoxide inhibitingt the plasmalemmal glucose transporter resulting in deregulation of mitochondrial metabolism (95). In cytosol of neocortical neurons the *β*A is able to activate production of H2O2 (96). Inhibitor of XO allopurinol significantly suppressed $OH^{\cdot}$ suggesting a potential role for XO in the oxidative stress associated with PD and AD (97). In different neuronal populations neurodegenerative disease is the selective vulnerability that may affected in a progressive and often stereotyped manner. However, the susceptible neuronal population varies between diseases, despite oxidative stress being implicated as the major pathogenic process in all of them and neurons were affected, there must be additional factors that determine the selective cell death in each disease. Certain neuronal groups have high intrinsic levels of oxidative stress and are therefore more vulnerable to additional disease-related oxidative stress. Neurons that have long axons and multiple synapses have high bioenergetic requirements for axonal transport or long-term plasticity and will render these groups of neurons far more sensitive to degeneration than other neuronal groups. Different neuronal groups exhibit different degrees of oxidative stress. The exposure of neurons at higher levels of cytosolic dopamine; that is, dopaminergic neurons are also exposed to additional oxidative stress produced by the metabolism of dopamine by MAO (which generates hydrogen peroxide) as well as the autooxidation of dopamine (which generates superoxide). Thus endogenous dopamine, as well as exogenous treatment with levodopa (used in PD) may be a further source of oxidative stress that may worsen pathogenesis (98, 99). However, it should be noted that the MAO-induced metabolism of dopamine and production of hydrogen peroxide have an important role in physiological calcium signaling in astrocytes and is not solely a pathological process (100). One interesting hypothesis has emerged from the discovery that adult substantia nigra pars compacta dopaminergic neurons have an autonomous pacemaker mechanism that utilizes L-type calcium channels resulting in intracellular calcium oscillations showing for the vulnerability of specific neuronal groups in Parkinson's disease. As the repeated and persistent entry of calcium into cells needs to be counterbalanced by ATP demanding pumps to restore the calcium concentration creates a metabolic stress for such neurons. In fact it has been demonstrated that the opening of these kinds of ion channels results in higher levels of OS in the mitochondria of such neurons (101).

Multiple Sclerosis Lesions

Production of ROS is accomplished by two principally different mechanisms: activation of free radical producing those enzymes which are involved in oxidative burst, and by mitochondrial dysfunction (102-104). The result through microarray studies shows a deterioration of mitochondrial function in active multiple sclerosis lesions, which appears to be related to active degeneration of myelin, oligodendrocytes, neurons and axon (105-107). After formation of bruise the mitochondrial numbers and activity of enzyme is increase, apparently reflecting the increased metabolic demand of demyelinated axons in the lesions or a reaction to chronic mitochondrial insult (107-108). Furthermore, cells containing oxidized lipids and oxidized DNA are mainly concentrated at these sites (109) and the clearest damage to mitochondria in oligodendrocytes and axons is seen in this area (105-107). Experimental studies suggest that oxidative tissue damage under these conditions is most likely mediated by peroxynitrite (110). ROS is produced by activated microglia through classical Nox2-dependent oxidative burst. This view is supported by several observations. *First*, p22phox and gp91phox are more abundantly expressed in active multiple sclerosis lesions compared with other oxidases, such as MPO (111-113). *Secondly*, the co-expression of different components of the Nox2 complex in the same microglia cells indicates that these complexes are functionally active. *Thirdly*, the expression of p22phox and gp91phox are less intense in macrophages. Potential functional importance of Nox2 complexes in inflammatory demyelinating brain lesions are shown by the protective effect of gp91phox gene deletion in animals with autoimmune encephalomyelitis (114, 115). In vitro, microglia toxicity is, in part, mediated through ROS production by the Nox1 complex (116).

Oxidative Stress and the Thyroid Gland

Synthesis of thyroid hormones requires formation of the hydrogen peroxide; a highly reactive oxidant.H_2O_2 and $I^{\cdot}$ are immediately used in peroxidation reaction that is catalysed by thyroid peroxidase (117). In a healthy thyroid, ROSs are produced in an area that is located at the apical pole of the cell in microvilli, where H2O2 is consumed either during the hormone synthesis or by antioxidant systems (118). However, Th1- induced ROS production causes ROS accumulation both in the cytoplasm and in nuclei, where it can become toxic. As hydrogen peroxide and iodine are cosubstrates in thyroid hormone production, iodine inhibits hydrogen peroxide production. Tobacco smoke contains thyocyanate that blocks iodine transport into thyrocite. This could increase H2O2 production and oxidative load, especially when associated with other environmental factors. Increase in ROS balanced by the increase in AOD would lead to minimal inflammation, but unopposed increase in ROS would lead to strong inflammation and cell necrosis. Reducing ROS would lead to inflammation reduction and vice versa (119, 120).

Graves' disease (Peripheral Tissues and Retro-orbital Tissues)

Graves' disease is characterized by increased oxidative stress. However, thyroid hormones, per se, induce OS, which is tissue and species specific. Even in subclinical hyperthyroidism, oxidative stress and antioxidative response seem to be increased (121, 122). It seems that the oxidative stress-induced activation of the NF-kappaB pathway might play a role in the autoimmune response in hyperthyroidism (123). Therefore, when antioxidant supplementation is added to methimazole, euthyroidism is more rapidly achieved (124,125). Hyperthyroidism is associated with increased lipid

peroxidation products in rat liver and with increased activities of glutathione peroxidase, superoxide dismutase, and catalase in the liver (126). Liver oxidative stress increases quickly after increase of thyroid hormones (127). In rat kidney and testis, hyperthyroidism is associated with increased oxidative stress and lipid peroxidation (128-130). Hyperthyroidism is also associated with increased oxidative stress and oxidative damage to lipids and genomic DNA in the aortic wall (131). During hyperthyroidism, there is an increase in myocardial oxidative stress that is associated with lipid peroxidation and protein oxidation. Myocardial antioxidant enzyme activities elevation accompanied by protein expression induction occurs after four weeks of hyperthyroidism (132). It seems that oxidative stress plays an important role in cardiac hypertrophy, by the redox activation of AKT1 and JUN/FOS signaling pathways (133). Redox imbalance due to hyperthyroidism induces adaptation of antioxidant systems, also inducing ERK1/2 activation and leading to development of cardiac hypertrophy (134). This response may involve the thyroid hormone-induced upregulation of HSP70 (135). In skeletal muscle, hyperthyroidism causes increased oxidative stress associated with oxidative modification in myosin heavy chain causing the decrease in force production (136). Enhanced adipogenesis and overproduction of glycosaminoglycans causes an increase in orbital volume and fibrosis of the extraocular muscles (137) causing Grave's disease. In orbital fibroblasts, obtained from subjects with severe grave orbitopathy, superoxide radicals induce a dose dependent cellular proliferation (138). IL-1*β* is produced by activated macrophages and is an important mediator of the inflammatory response. Adding IL-1*β* to cultures of retroorbital fibroblasts causes an increased oxygen-free radical production in a dose-dependent manner. This is observed both in Graves' and in control cultures. Total intracellular superoxide dismutase (SOD) activity was stimulated by IL-1*β*, both in control and in Graves' cultures. HSP72 is a stress inducible form of cytosolic HSP70. Its expression is induced by the environmental stress, such as heat shock, anoxia, and ischemia. Antioxidants, methimazole, and PTU reduced H2O2-induced HSP72 expression, and to a lesser degree heat-induced HSP72 expression (139-141). In patients with Graves' orbitopathy, there was significant correlation between TSH receptor antibody levels and 8-hydroxy-2_-deoxyguanosine (a biomarker of DNA damage) content (142). It should be noted that smoker had higher urinary 8-OhdG level than never-smokers, and that smoking was significant factor in multivariate analysis. Study by Tsai et al. implies that smoking-induced oxidative stress contributes to the pathogenesis of Graves' orbitopathy (143, 144). One of the major forms of DNA damage induced by OS is 7, 8-dihydro-8-oxoguanine, referred in an abbreviated way as 8-oxoguanine (8-oxoG). This type of DNA damage is repaired by the base excision repair pathway.

CONCLUSION

Oxidative stress plays an important role in human pathogenesis. Accumulation and eneration Of (ROS) Reactive Oxygen Species within cells are detrimental and can exacerbate the disease progression. Therefore, several strategies have been studied to prevent or slow down ROS-mediated damages The concept of oxidative stress simply implied that ROS/RNS are toxic species because of their highly reactive nature. The production of ROS is mainly accomplished by two principally different mechanisms: activation of free radicalproducing enzymes, such as those involved in oxidative burst, and by mitochondrial dysfunction an increment in the generation of Reactive Oxygen Species such as superoxide, hydrogen peroxide and hydroxyl radical is the cause of oxidation and modification of structure of membrane lipids, cellular proteins and nucleic acids. In summary, ROS formation is part of normal cellular physiology. Excessive or abnormal free radical production and accumulation result in oxidative stress which responsible for a significant pathology in many diseases, including Cancer, Diabetes and neurodegenerative diseases. Investigations into the specific molecular targets of ROS in different pathway and the specific signaling mechanisms will be important for the understanding of biology and of different diseases for future research purposes.

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ISSN 2348-6201

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