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Free Radical Pharmacology and its role in various diseases

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ABSTRACT

Free Radicals are molecules with an unpaired electron and are important intermediates in natural processes. Free radicals are very unstable and react quickly with other compounds, and try to capture the needed electron to gain stability. Once the process is started, it can cascade, and finally results in the disruption of a living cell. Generally, harmful effects of reactive oxygen species on the cell are most often like damage of DNA, oxidations of polydesaturated fatty acids in lipids, oxidations of amino acids in proteins, oxidatively inactivate specific enzymes by oxidation of co-factors. Free radicals cause many human diseases like cancer Alzheimer's disease, cardiac reperfusion abnormalities, kidney disease, fibrosis, etc. The free radicals formed in our body are combated by antioxidants that safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Excessive exercise has been found to increase the free radical level in the body and causes intense damage to the Regular physical exercise enhances the antioxidant defense system and protects against exercise induced free radical damage.

Keywords: Radicals, Free Radicals, Reactive oxygen species, Anti-oxidant, Redox signaling.

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Introduction

Free Radicals are molecules with an unpaired electron. Due to the presence of a free electron, these molecules are highly reactive. They are important intermediates in natural processes involved in cytotoxicity, control of vascular tone, and neurotransmission. Radiolysis is a powerful method to generate specific free radicals and measure their reactivity.[1]

Types of free radicals:

1. Super oxide
2. Hydrogen oxide
3. Hydroxyl radical
4. Singlet Oxygen
5. Hydroperoxy Radical.
6. Lipid peroxide Radical.
7. Nitric Oxide.

Generation of Free Radical:

The generation can be endogenous (within the body) or exogenous (outside the body). The exogenous source of free radical is from the environment. These include oxidizing agent i.e. Ionizing radiations (from industry, sun exposure, cosmic rays, medical x-ray); Ozone and nitrous oxide (primarily from automobile exhaust); Heavy metals (such as mercury, cadmium and lead); Cigarette smoking (both active and passive); Alcohol; Unsaturated fat (this may create a strain on the natural antioxidants of the body) and other chemicals (pesticides) and compounds from food, water, drugs and air. Endogenous free radical formation occurs continuously in the cells as a consequence of both enzymatic and non-enzymatic reactions. Endogenous free radicals are produced in the body by four different mechanisms:

- The normal metabolism of oxygen requiring nutrients.
- White blood cells destroy parasites, bacteria and viruses by using oxidants (free radicals) such as nitric oxide, super oxide and hydrogen peroxide.

1. Other cellular components called peroxisomes produce hydrogen peroxide as a by-product of the degradation of fatty acids and other molecules.
2. An enzyme in the cells called cytochrome P450 is one of the body's primary defenses against toxic chemicals ingested with food. [2,3,4]

Sources of Free Radical:

1. **Enodogeneous:**

- Mitochondria
- Xanthene oxidase
- Phagocytes
- Peroxisomes
- Arachidonate Pathways
- Ischemia/Reperfusion
- Inflammation

2. **Exogeneous:**

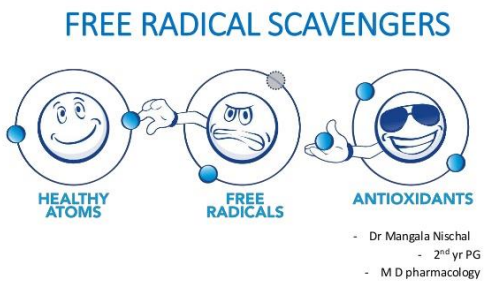
- Cigarette Smoking
- Environmental Pollutants
- Radiation
- Ozone
- Industrial Solvents

3. **Physiological Factor:**

- Mental Status
- Disease Condition

Free Radical Scavengers (Antioxidant)

Antioxidant: Those substances when present at low concentration, compared to those of an oxidizable substrate, will significantly delay or inhibit oxidation of that substrate.



Sources of Antioxidant:

Endogenous: Superoxide dismutase, Catalase, Glutathione Peroxidase

Food: Vitamin A, C, E, beta, Carotine, Selenium, Lycopene.

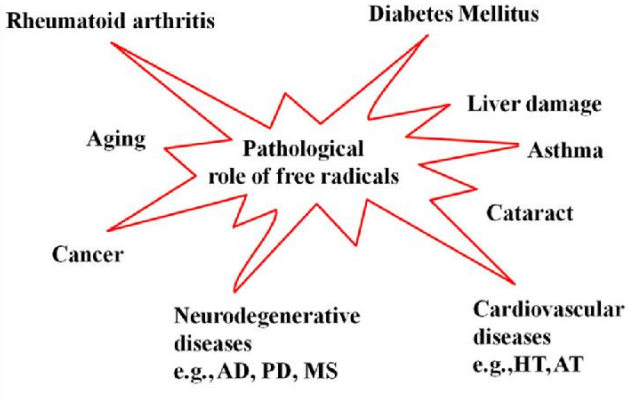
Targets:

1. Lipids: Peroxidationof lipids in cell membrane can damage cell membrane by disrupting fluidity and permeability .Lipid peroxidation can also adversely affect the function of membrane bound protein such as enzyme and receptor.

2. Protein: Direct damage to protein can be caused by free radical; it affects many proteins interfering with enzyme activity and that of structural proteins.

3. DNA: Fragmentation of DNA is caused by free radical attack which causes activation of **polysynthetase** enzyme; it splits NAD^+ to aid the repair of DNA .[5]

Role of free radical in various diseases:



Diabetes Mellitus:

Diabetes mellitus is heterogeneous group of chronic disorders characterized by enhanced blood glucose levels (hyperglycemia) resulting from defective insulin secretion (in type I diabetes), resistance to insulin action (in type II diabetes) or both. The major symptoms are thirst, hunger, emaciation, and weakness, eventually lead to coma. DM is associated with the increased production of free radicals or decreased activity of the antioxidant systems, which leads to development of oxidative stress.

The hyperglycemic condition induces increased free radical production via four different routes namely:

1. Increased glycolysis, results in increased ratio between the rate of oxidation of G3P to 1, 3-DPG, following increased NADH/NAD^+ ratio (redox imbalance).
2. Activated sorbitol (or polyol) pathway,c auses the accumulation of both sorbitol and fructose, results in decreased reduced GSH and increased NADH/NAD^+ ratio.
3. Autoxidation of glucose, results in the generation of different free radicals such as H2O2, $OH^•$, $O_2^{•-}$ and keto aldehydes.
4. Non enzymatic protein glycation, results in the formation of AGEs which upon interacting with RAGEs generate oxidative stress .[6,7,8,9.]

Neurodegenerative Diseases

The central nervous system (CNS) is mainly susceptible to the oxidants due to the presence of high lipid content, high consumption of oxygen, and low levels of antioxidant enzymes, for example, SOD is localized primarily in neurons, and GSH and GPx are restricted in astrocytes. The lipid peroxidation by ROS leads to progressive loss of membrane fluidity, decreases membrane potential, and increases permeability to ions such as Ca^{2+}. The region of the brain such as hippocampus nigr and the striatum are particularly susceptible to attack by free radicle .[10,11,12]

Alzheimer's Disease:

AD is characterized by the accumulation of amyloid protein plaques (formed from the improper folding and processing of amyloid β pr……P-0-P-ecursor protein and intracellular neurofibrillary tangles made up of abnormal and hyper phosphorylated tau protein. The hyper phosphorylated tau protein aggregates binds to Fe^{3+}, results in the production of neurofibrillary tangles. The Amyloid-β peptide (Aβ) can chelate with transition metal ions (Cu^{2+}, Zn^{2+} and Fe^{3+}),. The lipid peroxidation is also extensive in AD patients, which can induce neuronal death by multiple mechanisms such as impairment of function of ion pumps (both Na^+/K^+-ATPase

and Ca^{+2}-ATPase), glucose transporters and glutamate transporters. The other oxidative NN B888666markers of protein damage such as protein carbonyls and 3-nitrotyrosine have been also observed in AD patients .[17,18,19]

Cancer

It is one of the leading causes of death in humans. Free radicals cause different types of chemical changes in DNA,. Cancer cells in particular, in comparison to normal cells, have higher levels of ROS and are more susceptible to mitochondrial dysfunction due to their higher metabolic rate. Cancer cells display elevated levels of oxidative stress due to activation of oncogenes and loss of tumor suppressors. ROS by altering the growth signals and gene expression cause continuous proliferation of cancer cells. ROS can …damage DNA by inducing base modifications, deletions, strand breakage, chromosomal rearrangements and hyper- and hypo-methylation of DNA .[20,21,22,23,24,25]

Breast Cancer

In majority of breast carcinomas the oxidative stress can be induced by the over expression of thymidine phosphorylase enzyme which catabolizes thymidine to thymine and 2-deoxy-D-ribose-1-phosphate; the latter is a powerful reducing sugar that rapidly glycates proteins, generating oxygen radicals within the carcinoma cell. Another breast specific mechanism of oxidative stress induction involves a mammary gland specific lactoperoxidase enzyme catalyzed one electron oxidation of 17-β-oestradiol to a reactive phenoxyl radical [26,27].

Prostate Cancer

The ROS produced are responsible for the cellular proliferation of prostate cancer cells. Overexpression of NADPH oxidase 1 (Nox1) protein is an early event in the development of prostate cancer. The superoxide produced (by NOX) in prostate cancer cells facilitates cellular immortality through resistance to programmed cell death which results in cancer-promoting effect .[28,29,30]

Lung Cancer

Lung cancer has been the most commonly diagnosed cancer and is the central cause of cancer death in men worldwide. Lung cancer mortality account 30 % of all cancer related deaths. Cigarette Smoking is the most crucial environmental risk factor in lung cancer etiology. It is estimated that smoking accounts for ~80 % of global lung cancer burden in males and 50 % in females. Cigarette smoke particulate matter contains complex mixture of numerous carcinogens and stable ROS with very long half-lives. These ROS can damage the tissues resulting in progressive transformation of cells into the malignant form, which leads to increased frequency of mutations by the oxidative damage to DNA and, eventually leading to lung cancer . Smokers develop lung cancer a 10-fold higher than non-smokers. Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) commonly coexist in smokers, and the presence of COPD increases the risk of developing LC .[31,32,33.34,35]

Bladder Cancer

The most common risk factors for bladder cancer are cigarette smoking, exposure to industrial carcinogens (aromatic amines), high levels of arsenic intake and diet. Oxidative stress critically contributes to the development of bladder cancer. Various lines of evidence reported an increased oxidative stress in patients with breast cancer. Increased NO levels have been reported in bladder cancer patients. This NO stimulates matrix metalloproteinase (MMPs), especially prolidase activity, which is involved in the terminal step of collagen degradation. Significantly higher serum prolidase activities were reported in patients with bladder cancer than healthy controls .[36,37,38,39,40,41]

Cardiovascular Diseases (CVDs)

Cardiovascular diseases are a class of pathologies involving the heart and blood vessels (arteries, capillaries, and veins). They include cardiac diseases, vascular diseases of the brain and kidney, and peripheral arterial disease. Most of the people are dying due to CVDs compared to other diseases [42].

Hypertension (HT)

Hypertension (HT) is a major health problem. Persons with hypertension are at an increased risk for stroke, heart disease, kidney failure, and premature mortality. Increased ROS generation eliminates $NO^{\bullet}$ by forming $ONOO^{-}$, thus reducing $NO^{\bullet}$ bioavailability which leads to decreased endothelium-dependent vasodilation subsequent in hypertension. A decrease in NO bioavailability and an increase in oxidative stress are present in human hypertension. Oxidation-induced impairment of NO also results in reduced opposition to the vasoconstrictive and hypertensive effects of angiotensin II. Angiotensin II decreases NO bioavailability by promoting oxidative stress [43,44,45,46].

Rheumatoid Arthritis (RA)

RA is a chronic disease. The disease is characterized by synovial and systemic inflammation with joint swelling, morning stiffness, destruction of articular tissues, joint deformities, fatigue, loss of appetite and weakness. It is believed to be a T-lymphocyte. This cytokine release and subsequent migration is thought to be responsible for the chronic inflammation and characteristic changes in RA.

Both ROS and RNS damage cartilage. Tissue injury in inflammation results in $NO^{\cdot}$ production by articular chondrocytes and synovial fibroblasts and elevated levels of $NO^{\cdot}$ are observed in the serum and synovial fluid of RA patients The free radicals, particularly $NO^{\cdot}$ and $O_2^{\bullet -}$, inhibit the synthesis of matrix components like proteoglycans by chondrocytes and also damage the extracellular matrix through activation and up regulation of matrix metalloproteinase. The HOCl, produced by myeloperoxidase (MPO) in neutrophils, chlorinate the tyrosine residues to form 3-chlorotyrosine and damage the collagen, thus implicated in arthritogensis. RA patients have increased plasma MPO concentrations [47,48]

Asthma

Asthma is the most common disorders of the airways of the lungs and is one of the major global health problems. It is characterized by chronic inflammation of the airways involving variable and recurrent airflow obstruction and bronchial hyper reactivity associated with airway remodeling Airway remodeling is a dynamic process involving mucous hyper secretion, collagen deposition, wall thickening, myocyte hypertrophy and hyperplasia, myofibroblast hyperplasia, vascular proliferation and alterations in airway elastic fibers, all of which culminate in persistent structural alterations of the airway. NO is endogenously produced in mammalian airways by NOS and is known to regulate many aspects of human asthma, including modulation of airway and vascular smooth muscle tone and the inflammation.

The Benefits of Free Radicals

- In body they control the flow of blood through our arteries, to fight infection, to keep our brain alert and focus.
- Similar to antioxidants, some free radicals are involved as signaling molecules, i.e, they are responsible for turning on and off genes.
- Some free radicals like NO and superoxide produced in a very high amount by immune cells to poison viruses and bacteria.
- Some free radicals kill cancer cells, in fact certain cancer drugs aim in increasing the free radical amount in the body.[49]

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