

Free Radicals & Antioxidants

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OBJECTIVES

- ❖ What Is Meant By A Free Radical?
- ❖ knowledge of reactive oxygen species (ROS) and reactive nitrogen species (RNOS)
- ❖ Effects on different body biomolecules
- ❖ Associated diseases

- ◎ **A free radical** is a molecule or molecular fragment that contains one or more unpaired electrons in its outer orbital.
- ◎ **Represented by a superscript dot, (R•).**
- ◎ **Oxidation reactions** ensure that molecular oxygen is completely reduced to water.
- ◎ **The products of partial reduction of oxygen are highly reactive, called Reactive oxygen species or ROS**

Free Radicals

- ⊙ Superoxide anion radical ($\text{O}_2^{\cdot-}$)
- ⊙ Hydroperoxyl radical ($\text{HOO}^{\cdot}$)
- ⊙ Hydrogen peroxide (H_2O_2)
- ⊙ Hydroxyl radical ($\text{OH}^{\cdot}$)
- ⊙ Lipid peroxide radical ($\text{ROO}^{\cdot}$)
- ⊙ Singlet oxygen ($^1\text{O}_2$)
- ⊙ Nitric oxide ($\text{NO}^{\cdot}$)
- ⊙ Peroxy nitrite ($\text{ONOO}^{\cdot-}$).

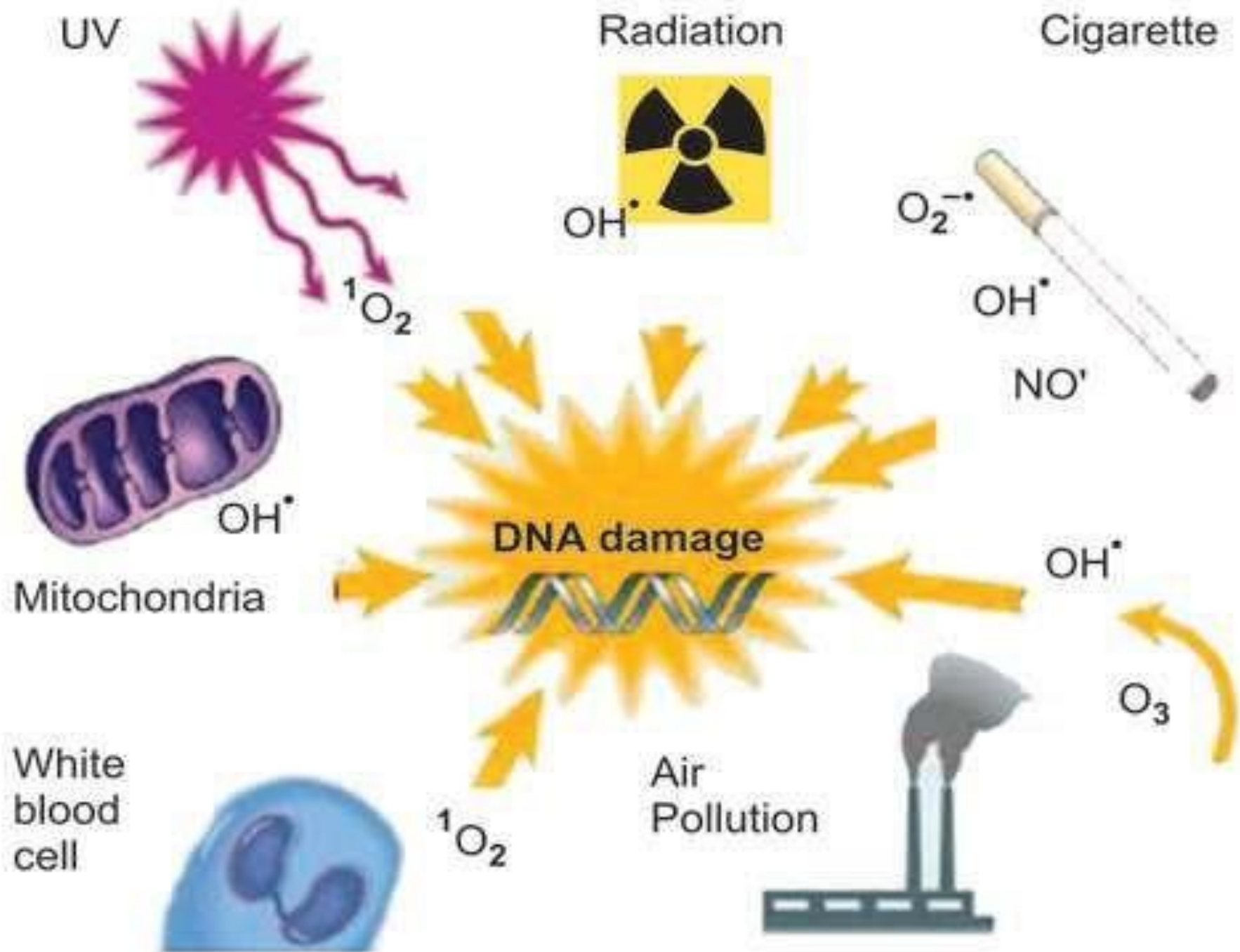
- ◎ **H₂O₂ & singlet oxygen are not free radicals**
- ◎ **Because of their extreme reactivity, they are included in the group of ROS.**

Characteristics of ROS:

- ◎ **Extreme reactivity.**
- ◎ **Short life span.**
- ◎ **Generation of new ROS by chain reaction.**
- ◎ **Damage to various tissues.**

ENVIRONMENTAL EFFECTS

- **Result of drug metabolism. Cytochrome P450 related reactions.**
- **Due to damage caused by ionizing radiations on tissues (X-rays) Photolysis of O₂ by light**
- **Photoexcitation of organic molecules**
- **Cigarette smoke Alcohol promotes lipid peroxidation.**



Lipid peroxidation

Lipid peroxidation occurs in 3 stages- initiation,
propagation & termination

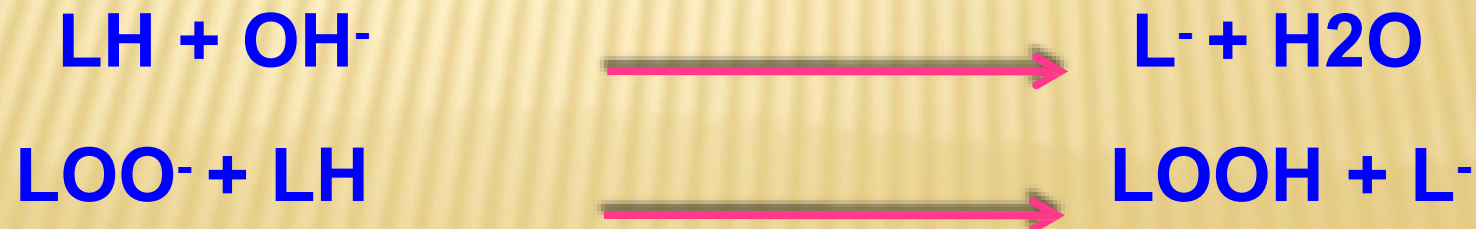
Initiation phase:

- ⊙ This step involves the removal of hydrogen atom (H) from polyunsaturated fatty acids (LH), caused by hydroxyl radical.



Propagation phase:

- Under aerobic conditions, the fatty acid radical ($L^\cdot$) takes up oxygen to form peroxy radical ($LOO^\cdot$).
- The latter, in turn, can remove H-atom from another PUFA (LH) to form lipid hydroperoxide ($LOOH$).



- ⊙ The hydroperoxides are capable of further stimulating lipid peroxidation as they can form alkoxy ($\text{LO}^\cdot$) & peroxy ($\text{LOO}^\cdot$) radicals.



Termination Phase:

- ⊙ Lipid peroxidation proceeds as a chain reaction until the PUFA gets oxidized.

- ◎ **The beneficial affects of the free radicals generated by the body.**
- ◎ **A large amount of O₂ is consumed by macrophages during their bactericidal function, a phenomenon referred to as respiratory burst.**

Harmful effects of free radicals

- ⊙ **Proteins:** Free radicals cause oxidation of sulfhydryl groups & modification of certain amino acids (e.g. methionine, cysteine, histidine, tryptophan).
- ⊙ **ROS** may damage proteins by fragmentation, cross-linking & aggregation.
- ⊙ **Lipids:** PUFA are susceptible to damage by free radicals.

- ⊙ **Carbohydrates:**
- ⊙ **Oxidation of monosaccharides (e .g. glucose) can produce H_2O_2 & oxoaldehyde.**
- ⊙ **Glycation increases the susceptibility of proteins to the attack by free radicals. E.g. DM.**
- ⊙ **Nucleic acids:**
- ⊙ **Free radicals may cause DNA strand breaks, fragmentation of bases & deoxyribose.**

Clinical significance

- ⊙ **Chronic Inflammation**
- ⊙ **Chronic inflammatory diseases such as rheumatoid arthritis are self-perpetuated by the free radicals released by neutrophils.**
- ⊙ **ROS induced tissue damage appears to be involved in pathogenesis of chronic ulcerative colitis, chronic glomerulonephritis,**

- ⊙ **Cardiovascular diseases (CHD):**
- ⊙ **Oxidized low density lipoproteins (LDL),**
formed by the action of free radicals,
promote atherosclerosis & CHD.
- ⊙ **Cancer:**
- ⊙ **Free radicals can damage DNA & cause**
mutagenicity and cytotoxicity & play a key
role in carcinogenesis.

- ◉ **Respiratory diseases:**
- ◉ **Direct exposure of lungs to 100% oxygen for along period is known to destroy Endothelium & cause lung edema.**
- ◉ **This is mediated by free radicals.**
- ◉ **ROS are also responsible for adult respiratory distress syndrome (ARDS), a disorder characterized by pulmonary edema.**

- ◉ **Diabetes:**
- ◉ **Destruction of islets of pancreas due to the accumulation of free radicals is one of the causes for the pathogenesis of IDDM.**
- ◉ **Cataract:**
- ◉ **Increased exposure to oxidative stress contributes to cataract formation.**
- ◉ **Male infertility:** Free radicals reduce sperm motility & viability & male infertility.

- ⦿ **Aging process:**

- ⦿ **Reactive oxygen metabolites (ROM) play a pivotal role in the degenerative brain disorders such as Parkinsonism, Alzheimer's dementia and multiple sclerosis.**

- ⦿ **Cumulative effects of free radical injury cause gradual deterioration in aging process.**

Antioxidants

Antioxidants in relation to lipid peroxidation:

- ⊙ **Preventive antioxidants** that will block the initial production of free radicals e.g. catalase, glutathione peroxidase.
- ⊙ **Chain breaking antioxidants** that inhibit the propagative phase of lipid peroxidation e.g. Superoxide dismutase, vitamin E, uric acid.

According to location:

- ⊙ **Plasma antioxidants:** e.g. β -carotene, ascorbic acid, bilirubin, uric acid, ceruloplasmin, transferrin.
- ⊙ **Cell membrane antioxidants:** e.g. α -tocopherol.
- ⊙ **Intracellular antioxidants:** e.g. SOD, catalase, glutathione peroxidase.

According to nature & action:

- ⊙ **Enzymatic antioxidants:**
- ⊙ **E.g. SOD, catalase, glutathione peroxidase & glutathione reductase.**
- ⊙ **Non-enzymatic antioxidants:**
- ⊙ **Nutrient: carotenoids, α -tocopherol, selenium & vitamin C.**
- ⊙ **Metabolic: glutathione, ceruloplasmin, albumin, bilirubin, transferrin, ferritin, uric acid.**

Antioxidant enzymes

Superoxide dismutase:

- ⦿ **It converts superoxide (O_2^-) to hydrogen peroxide & O_2 .**
- ⦿ **This is the first line of defense to protect cells from the injurious effects of superoxide**

Catalase:

- ⦿ **H_2O_2 is metabolised by catalase.**

Glutathione peroxidase:

- ⦿ It detoxifies H_2O_2 to H_2O , while reduced glutathione (G-SH) is converted to oxidized glutathione (GS-SG).
- ⦿ The reduced glutathione can be regenerated by **glutathione reductase** utilizing NADPH.
- ⦿ HMP shunt is the major source of NADPH.

Q1: role of free radicals in the body is:

1. Harmful only
2. Benefecial only
3. Both 1&2
4. Non of the above

Q2: glutathione peroxidase is :.

1. Chain braking antioxidant.
2. Preventive antioxidants.
3. Reparative antioxidant.
4. Non of the above.

Q3: Vitamin C Is :

1. Nutrient Antioxidant
2. Enzymatic Antioxidant
3. Metabolic Antioxidant
4. Non Of The Above

Q4: all of th following are antioxidants except :

1. VITAMIN C
2. VITAMIN E
3. SELENIUM
4. GLYCINE

Thank you