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 ($O_2^{-\bullet}$)
- Hydroperoxyl radical ($HOO^{\bullet}$)
- Hydrogen peroxide (H_2O_2)
- Hydroxyl radical ($OH^{\bullet}$)
- Lipid peroxide radical ($ROO^{\bullet}$)
- Singlet oxygen ($^1O_2$)
- Nitric oxide ($NO^{\bullet}$)
- Peroxy nitrite ($ONOO^{-\bullet}$).

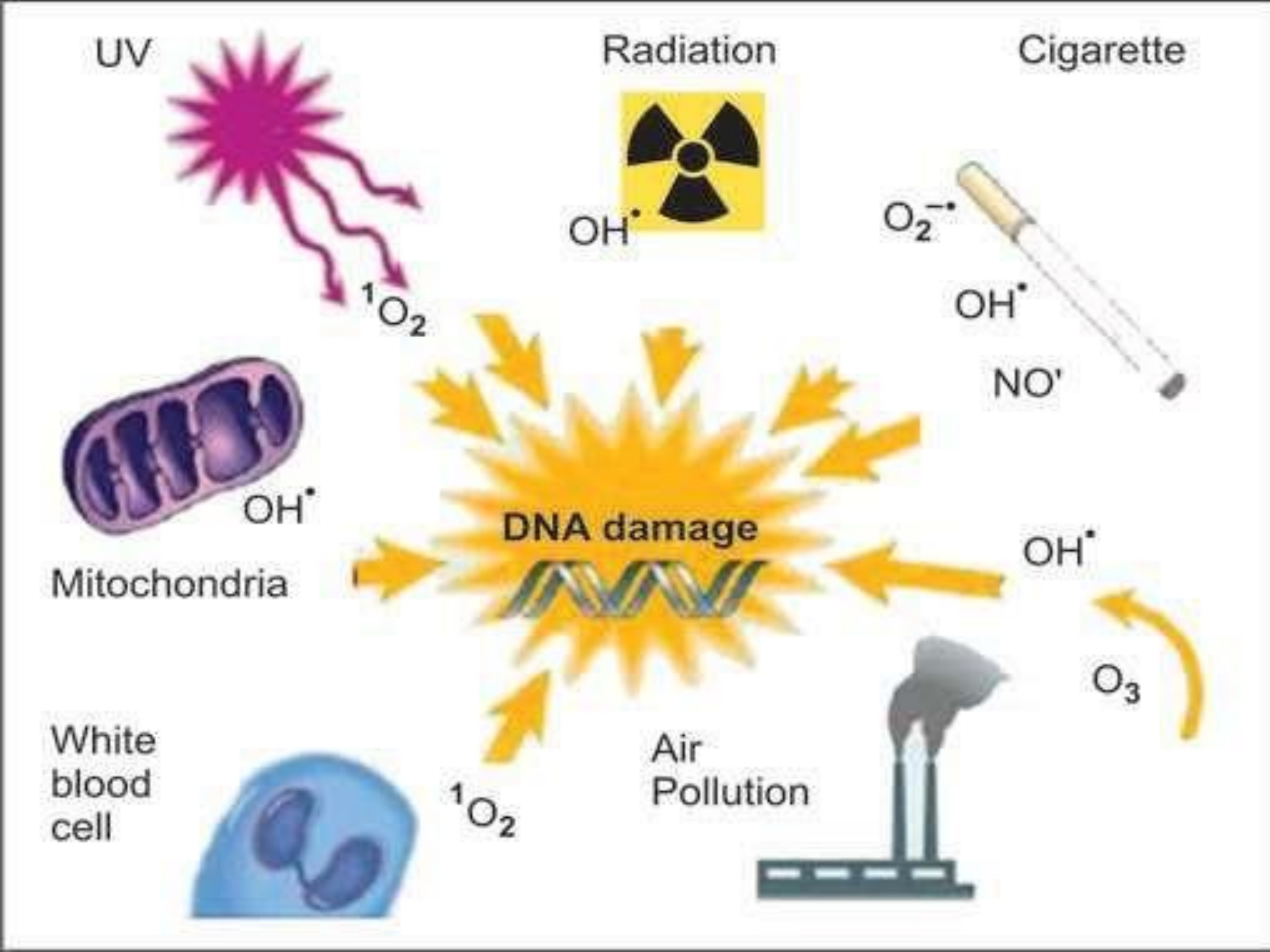
- H_2O_2 & singlet oxygen are not free radicals
- Because of their extreme reactivity, they are included in the group of ROS.

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.


UV
$^1O_2$
Radiation
$OH^{\bullet}$
Cigarette
$O_2^{-\bullet}$
$OH^{\bullet}$
NO'
$OH^{\bullet}$
Mitochondria
DNA damage
$OH^{\bullet}$
O_3
White blood cell
$^1O_2$
Air Pollution

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.

$$LH + OH^- \longrightarrow L^- + H_2O$$

Propagation phase:

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

$$LH + OH^- \longrightarrow L^- + H_2O$$

$$LOO^- + LH \longrightarrow LOOH + L^-$$

- The hydroperoxides are capable of further stimulating lipid peroxidation as they can form alkoxy (LO^-) & peroxyl (LOO^-) radicals.

$$2LOOH \longrightarrow LO^- + LO2^- + H2O$$

$$LOOH \longrightarrow LO^- + LOO^- + \text{aldehydes}$$

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 H2O2 & 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 (O2) to hydrogen peroxide & O2.
- This is the first line of defense to protect cells from the injurious effects of superoxide

Catalase:

- H2O2 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