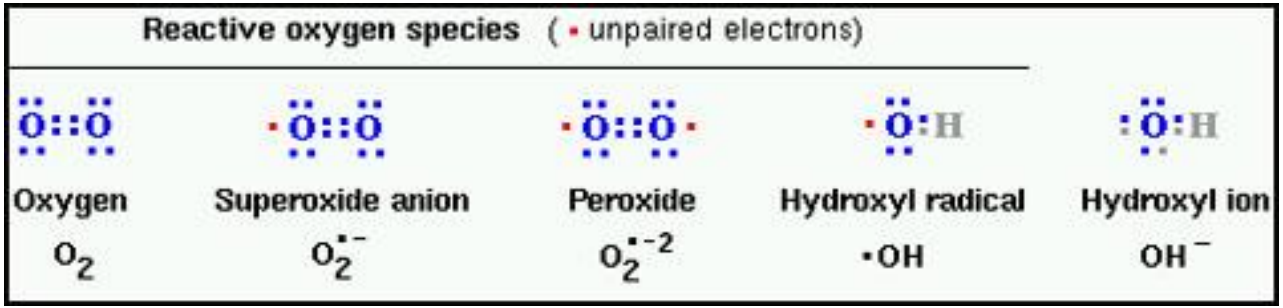
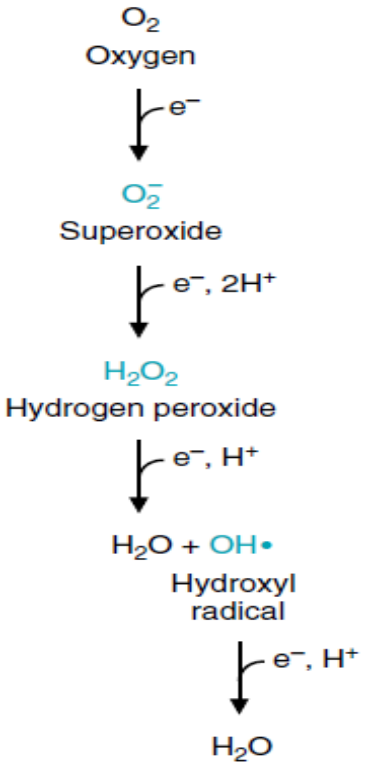
Oxygen Toxicity

What are Radicals ?

- **A radical :** is a molecule that has a single unpaired electron in an orbit.;
  - **Free Radicals :** are highly reactive and unstable that create a chain reaction
- Oxygen single electrons cannot react rapidly with the paired electrons found in the covalent bonds of organic molecules



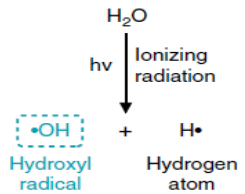


Reactive Oxygen Species

- Free radicals initiate chain reactions by extracting an electron from a neighbouring molecule to complete their own orbit
- **The superoxide anion:** a highly reactive free radical, but has limited lipid solubility and cannot diffuse far
- **Hydrogen peroxide:** is a weak oxidizing agent that is classified as a ROS because it can generate the hydroxyl radical (OH•)
  - is also the precursor of hypochlorous acid (HOCl), a powerful oxidizing agent that is produced by neutrophils
- **The hydroxyl radical:** is probably the most powerful of the ROS , because its lipid solubility

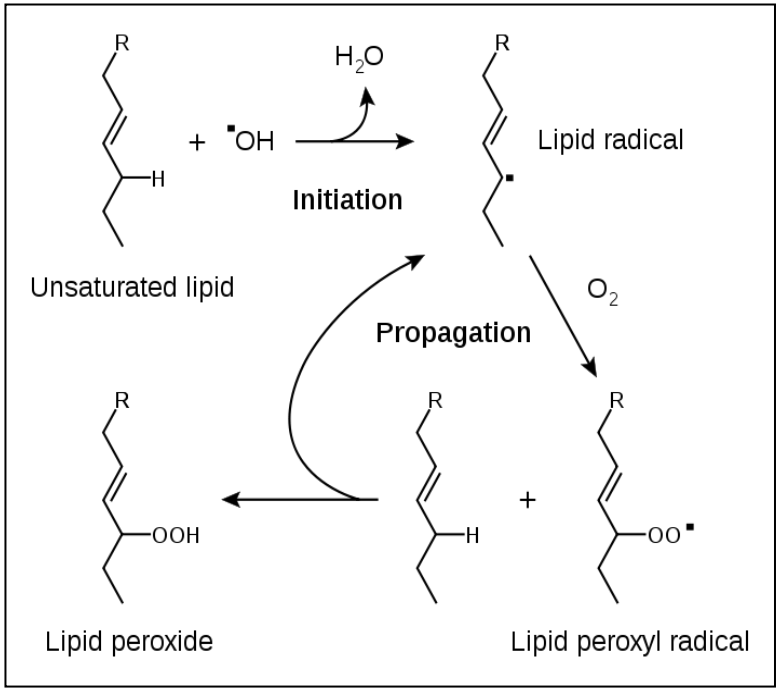
Major sources of ROS

- **Coenzyme Q :** is the only component of the electron transport chain that is not protein bound
  - When CoQ accepts a single electron it can accidentally transfer an electron to dissolved O_2, thereby forming superoxide
    - the major site for generation of toxic oxygen free radicals in the body
- **Oxidases, Oxygenases, and Peroxidases**
  - Free radical intermediates of these reactions may be accidentally released before the reduction is complete.
- **Ionizing Radiation**
  - has a high energy level that it can split water into hydrogen and hydroxyl radicals, thus leading to radicals formations



ROS reactions that damage body

- **Membrane Attack:**
  - a hydroxyl radical begins the chain reaction by extracting a hydrogen atom from lipids.
  - The chain reaction is propagated when O_2 adds to form lipid peroxyl radicals (ROO•) and lipid peroxides (ROOH)
  - 3- Eventually lipid degradation occurs, forming such products as malondialdehyde



ROS reactions that damage body

- **Proteins and Peptides:**
  - Radicals may cause protein fragmentation and amino acids cross-link with other amino acids
    - Free radical attack on protein cysteine residues can result in cross-linking and formation of aggregates that prevents their degradation
- **DNA:**
  - The hydroxyl radical can cause base alterations
  - it also can attack the deoxyribose backbone

Nitric Oxide and Reactive Nitrogen oxygen species

- NO is produced by the lining of the blood vessels known as endothelium
- At low concentrations, it functions physiologically as a neurotransmitter that causes vasodilation
- At high concentrations, it combines with O_2 or with superoxide to form additional reactive and toxic species containing both nitrogen and oxygen
  - involved in neurodegenerative diseases, such as Parkinson's disease, and in chronic inflammatory diseases, such as rheumatoid arthritis

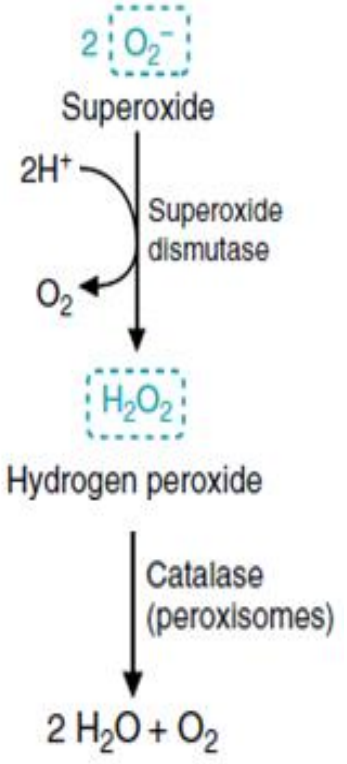
Cellular defence against Oxygen Toxicity

- **Cellular compartmentation :**
  - separation of species and sites involved in ROS generation from the rest of the cell
    - many of the enzymes that produce hydrogen peroxide are found in peroxisomes with a high content of antioxidant enzymes
- **Metal sequestration :**
  - Metals are bound to a wide range of proteins within the blood and in cells, preventing their participation in free radical production
    - Iron, for example, is tightly bound to its storage protein, ferritin and cannot react with hydrogen peroxide
- **Repair of damaged cellular components :**
  - Oxidized amino acids on proteins are continuously repaired through protein degradation and resynthesis of new proteins

Cellular defence against Oxygen Toxicity

❖ **Antioxidant Enzymes :**

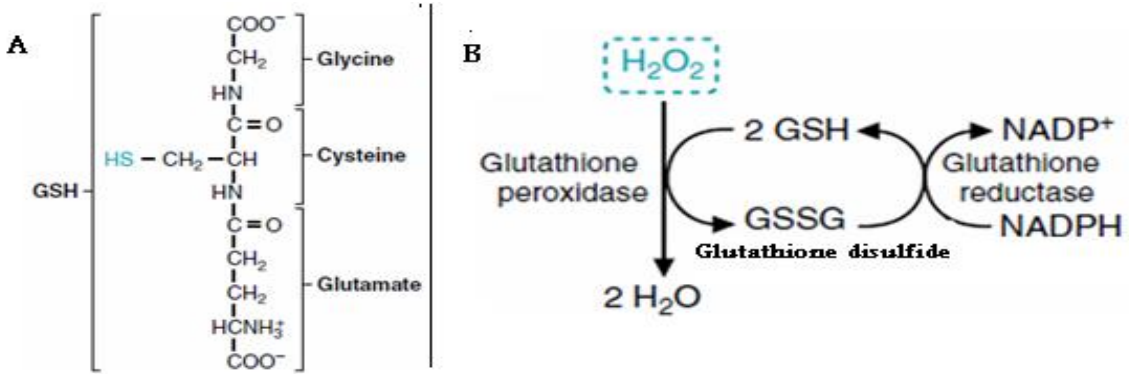
1. **Superoxide Dismutase :**
   - Found in nucleus and mitochondria and also found extracellularly
   - conversion of **superoxide anion to hydrogen peroxide**
   - the primary defence against oxidative stress
   - utilizes different positively charged metal ions
2. **Catalase :**
   - found principally in peroxisomes, and to a lesser extent in the cytosol
   - **Reduce H2O2 to water**
   - The highest activities are found in tissues with a high peroxisomal content (kidney and liver



Cellular defence against Oxygen Toxicity

3. Glutathione Peroxidase and Glutathione Reductase :

- Glutathione is a tripeptide composed of glutamate, cysteine, and glycine
- The cysteine provides an exposed free sulphydryl group (SH) that is very reactive
- **Glutathione peroxidases** are the major means for removing H_2O_2 produced outside of peroxisomes
- In these reactions, two glutathione molecules are oxidized to form a single oxidized glutathione molecule the glutathione disulfide (GSSG)
- **Glutathione reductase** reduces GSSG to glutathione form by transferring electrons from NADPH



Cellular defence against Oxygen Toxicity

❖ **Dietary antioxidants :**

- by donating a hydrogen atom (with its one electron) to the radical. And it becomes oxidized

1. **VITAMIN E :**
   - Is also known as α-tocopherol
   - Is a lipid-soluble antioxidant that functions principally to protect against lipid peroxidation in membranes
   - remove the free radical intermediates and prevent the oxidation reaction from continuing
2. **ASCORBIC ACID :**
   - regenerate the reduced form of vitamin E through donating electrons to the oxidised vitamin E
3. **CAROTENOIDS**