

GENERAL PATHOLOGY

L-7 PATHWAYS:

MEMBRANE DAMAGE

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CELL INJURY

2. MEMBRANE DAMAGE

■ Direct Damage

- Bacterial toxins. Clostridium –phospholipase
- Viral proteins.
- Cytolytic lymphocytes.
- Physical agents.
- Irradiation
- Chemical toxins or drugs
- Complement Components

■ Lipid peroxidation

Free Radicals

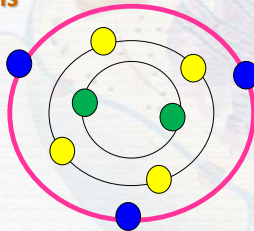
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Membrane Damage

□ Lipid peroxidation

□ Free Radicals

- F.R. Chemical has unpaired electron in outer orbit -- oxidation reduction reactions



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Membrane Damage

□ Free Radicals

■ can react with

- Organic and
- Inorganic substances
 - Proteins
 - Lipids
 - Nucleoproteins

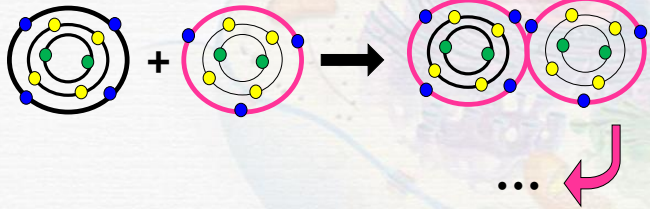
Making them useless or unstable

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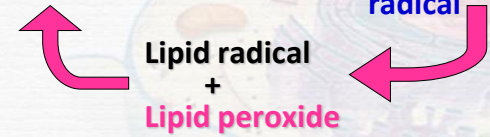
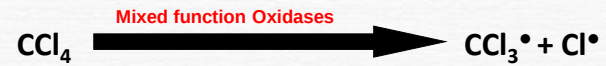
Membrane Damage

Free Radicals

- Once this reaction is started – it continues...

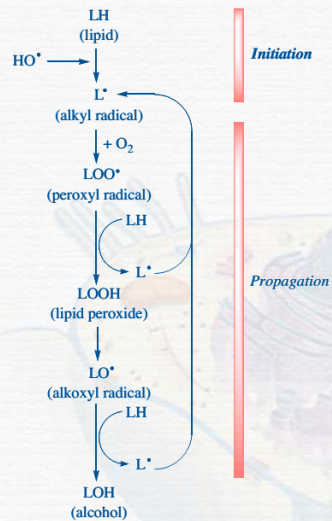


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Lipid peroxide -- highly unstable -- break down $\longrightarrow$ aldehydes

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Free Radicals

- Also degrade enzymes

- Fragmentation of polypeptide chains
- Cross-linking sulfhydryl (-SH) groups

- DNA

- Strands break
- Abnormal cross linking

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□ Lipid peroxidation

- Main attack is membrane (especially of organelles)

- Cu and Fe -- catalyst

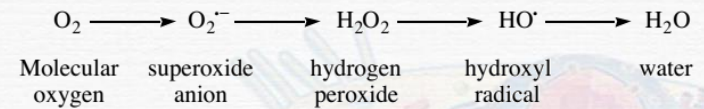
□ Mitochondria -- cytochromes

□ ER

Lysosomal membranes – slightly resistant

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Normal Oxygen conversion to water

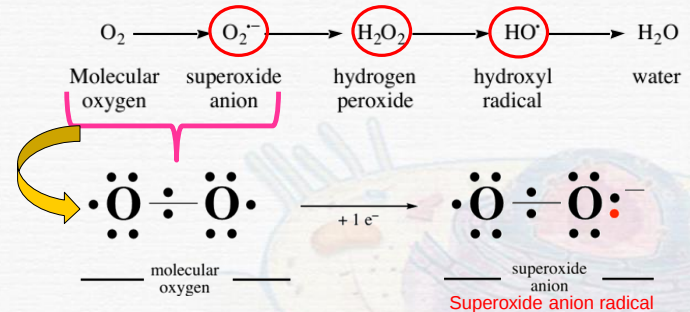


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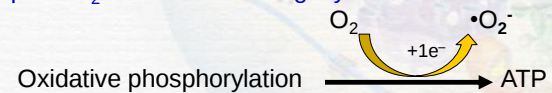
SOURCES OF FREE RADICALS

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Superoxide Anion Radical



Incomplete O_2 Reduction in Phagocyte



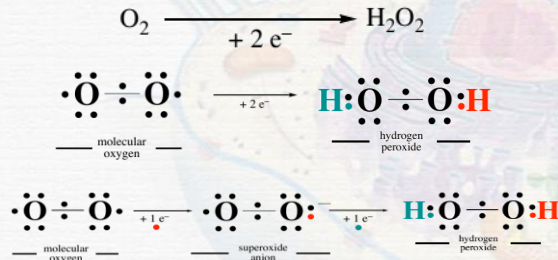
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Hydrogen Peroxide

□ In peroxisomes formation of Hydrogen peroxide (H_2O_2)

Hydrogen peroxide (H_2O_2) can be formed upon two-electron reduction of molecular oxygen or one-electron reduction of superoxide anion (O_2^-):

Two-electron reduction of molecular oxygen

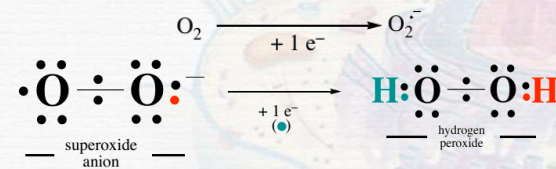


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□ In peroxisomes formation of Hydrogen peroxide (H_2O_2)

Hydrogen peroxide (H_2O_2) can be formed upon two-electron reduction of molecular oxygen or one-electron reduction of superoxide anion (O_2^-):

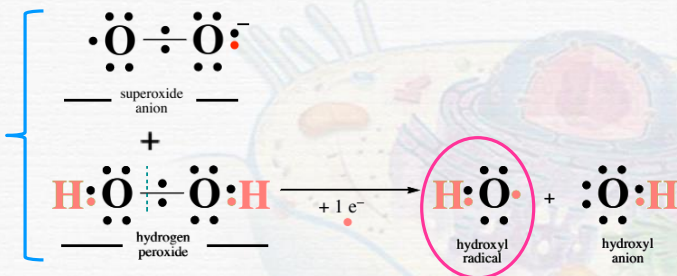
One-electron reduction of superoxide anion



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Hydroxyl Radical

- Hydroxyl radical ($HO^\bullet$) is the most reactive oxygen species originating from a reaction between superoxide anion radical ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2)



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Other source: during excessive exposure to ionizing radiation, originates from the breakdown of hydrogen peroxide (H_2O_2) via a **Fenton reaction**.



- The Fenton reaction entails a metal-dependent reduction of hydrogen peroxide (H_2O_2) to hydroxyl radical ($HO^\bullet$).
- Transition metals, such as copper (Cu), iron (Fe), and cobalt (Co), in their reduced form catalyze this reaction

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- NO is a widespread chemical mediator
 - Can act as a free radical.
 - Can be converted into peroxynitrite.
- Ionizing radiation (UV light, X-rays)
 - H₂O hydrolyzed into •OH and •H (hydrogen) free radicals.
- Breakdown of exogenous chemicals (CCl₄).

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FREE RADICAL CONVERSION TO NON-RADICAL SPECIES/PRODUCTS

REMOVAL OF SUPEROXIDE ANION

spontaneous, nonezymic dismutation



enzymic dismutation



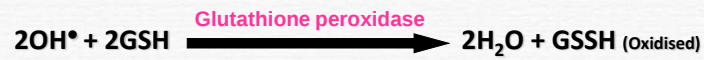
SOD based conversion is 10,000 fold faster

REMOVAL OF HYDROGEN PEROXIDE

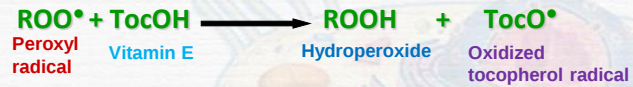


- **Catalase**. This enzyme is located in the peroxisomes
- **Glutathione Peroxidase**. The enzyme occurs in cytosol and the mitochondrial matrix

REMOVAL OF HYDROXYL RADICAL

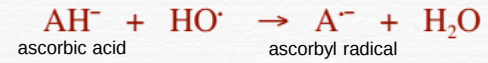


REMOVAL OF PEROXYL RADICAL BY VITAMIN E



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Vitamin C



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QUESTIONS
???

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