MUNI
PHARM

Reactive oxygen and nitrogen species

Biophysics

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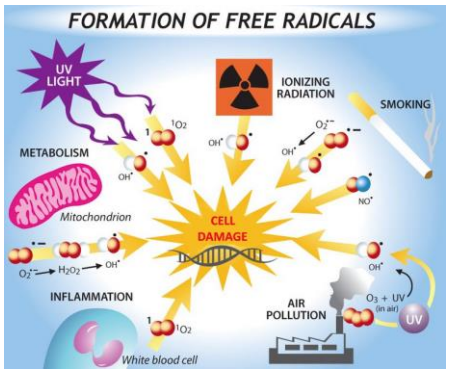

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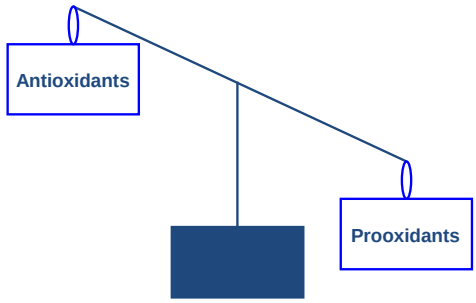
Oxidative Stress



"An imbalance favoring prooxidants and/or disfavoring antioxidants, potentially leading to damage"

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Reactive oxygen species (ROS) and reactive nitrogen species (RNS)

- ROS and RNS are substances with strong oxidizing effects.
- Free radicals are substances which contain unpaired electron.

Radicals:	
$O_2^{\cdot -}$	Superoxide
$^{\cdot}OH$	Hydroxyl
$RO_2^{\cdot}$	Peroxyl
$RO^{\cdot}$	Alkoxyl
$HO_2^{\cdot}$	Hydroperoxyl
$NO^{\cdot}$	Nitric Oxide
$NO_2^{\cdot}$	Nitrogen dioxide

Non-Radicals:	
H_2O_2	Hydrogen peroxide
$HOCl^{-}$	Hypochlorous acid
O_3	Ozone
$^1O_2$	Singlet oxygen
$ONOO^{-}$	Peroxynitrite

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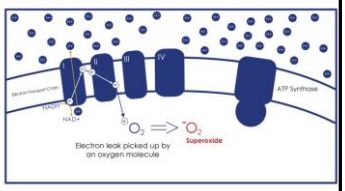
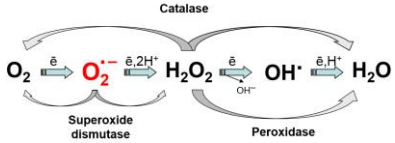
Physiological functions of RONS

1. **Cellular Respiration (Electron Transport Chain)**

1-4 % of the oxygen molecule is reduced into a free radical called superoxide.





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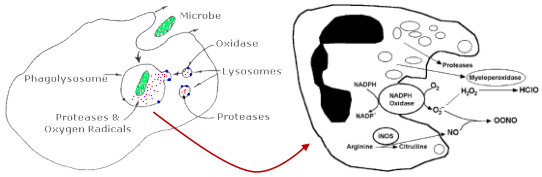
Physiological functions of RONS

2. Phagocytosis

- is the process by which a cell engulfs a solid particle to form an internal compartment known as a phagosome. In an organism's immune system, phagocytosis is a major mechanism used to remove pathogens and cell debris.
- the pathogen becomes trapped in a phagosome which then fuses with a lysosome to form a phagolysosome. Within the phagolysosome, enzymes and toxic peroxides digest the pathogen.



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Physiological functions of RONS

3. Oxidation and hydroxylation reactions
Metabolism of xenobiotics (hydroxylation), synthesis of cholesterol and bile acids by oxygenases.

4. Signaling molecules
Nitric oxide (NO):
- relaxation of the smooth muscle cell
- signaling molecule in the nervous system

Singlet oxygen:
-activation of protein kinases and phosphatases (catalyze binding of phosphate groups (phosphorylation) to amino acid residues in proteins)
-modulation of transcription factors (modulating transcription of genetic information from DNA to RNA)
-activation of metalloproteinases (meaning e.g. in regeneration of tissue, inflammation)

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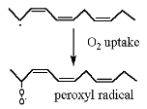
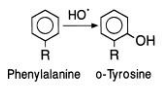
Pathological states associated with oxidative stress

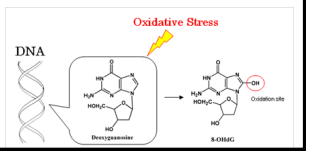
1. Lipid peroxidation
- is the oxidative degradation of lipids. It most often affects polyunsaturated fatty acids in the lipids in cell membranes, resulting in cell damage.



2. Protein oxidation
- is the modification of amino acids and the subsequent change in conformation of the proteins and loss of their biological activity.



3. DNA damage
- oxidation of purine and pyrimidine bases and subsequent mutations.



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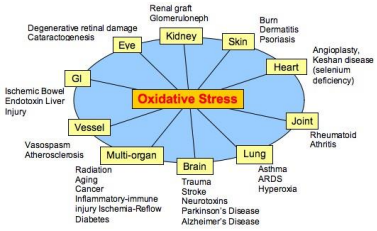
Pathological conditions that involve oxidative stress

- **Inflammation**
- **Atherosclerosis**
- **Ischemia/reperfusion injury**
- **Cancer**
- **Neurodegenerative disease**
- **Diabetes**
- **Asthma**
- **Aging**



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Defenses against prooxidants

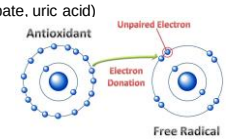
1. **Prevention of prooxidant formation (e.g. NOS or NADPH oxidase inhibitors, metal-chelating proteins - transferrin, lactoferrin)**
2. **Scavenging of prooxidants**
3. **Breaking the chain of radical reactions**

"Donor" antioxidants (eg. tocopherol, ascorbate, uric acid)

$LOO\bullet + TOH \longrightarrow LOOH + TO\bullet$

"Sacrificial" antioxidants (eg. nitric oxide):

$LOO\bullet + NO\bullet \longrightarrow LOONO$



4. **Repair of damage caused by prooxidants (phospholipases, proteases, enzymes repairing DNA)**

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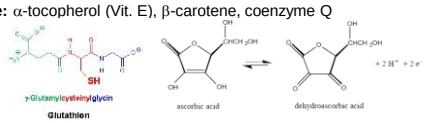
Defenses against prooxidants

ANTIOXIDANT: a substance that is able, at relatively low concentrations, to compete with other oxidizable substrates and, thus, to significantly delay or inhibit the oxidation of other substrates

Small Molecules

-Water soluble: glutathione, uric acid, ascorbate (Vit. C)

-Lipid soluble: α-tocopherol (Vit. E), β-carotene, coenzyme Q



Proteins

-Intracellular: SOD (I and II), glutathione peroxidase, catalase

-Extracellular: SOD (III), plasma proteins (e.g. albumin)

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