Biochemistry Teamwork

Oxidative stress

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OXIDATIVE STRESS

Oxidative stress is a condition in which cells are subjected to excessive levels of Reactive Species (Oxygen or Nitrative species) & are unable to counterbalance their deleterious effects with antioxidants.

When does this happen?

With ageing

In many diseases Ex: atherosclerosis, coronary heart disease, obesity, cancers, inflammatory conditions (rheumatoid arthritis) and G6PD deficiency leading to hemolytic anemia. Apoptosis

The cells are under high oxidation pressure in which they pass by the oxidative agents to the adjacent cell.

Oxidants increase oxidative stress

Antioxidants relieve it.

So, oxidative stress occurs when there is more oxidant production than antioxidant [imbalance]

-Oxidative stress causes damage to:
DNA, Proteins and unsaturated*** Lipids

- Oxidants will
- convert unsaturated Lipid to free radical fatty acids
- impair proteins function
- may cause mutation In DNA

Reactive oxygen species[ROS]**:**

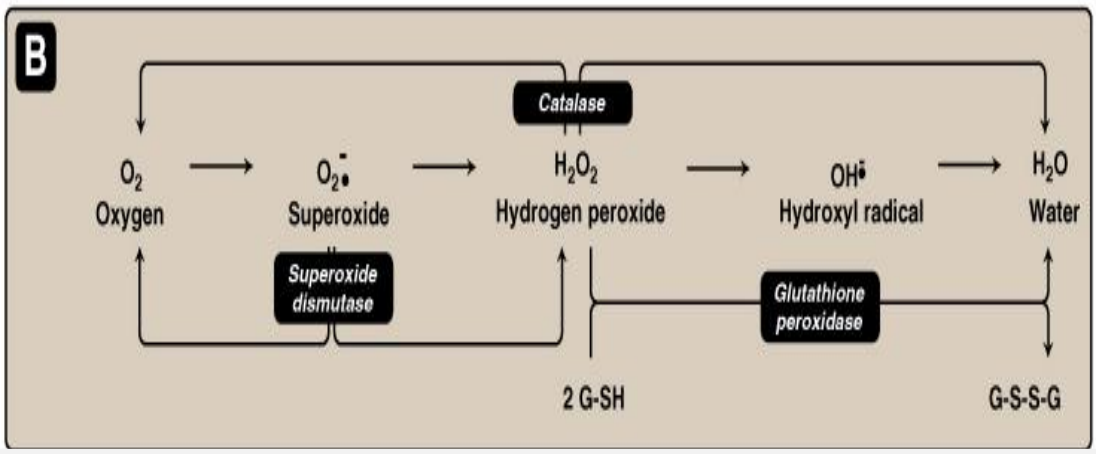
Free radicals
Superoxide (O_2^{-*})
Hydroxyl radicals (OH^{-*}) ←
Peroxyl radical (ROO^{-*})

non-free radicals
hydrogen peroxide (H_2O_2)

-Hydroxyl radicals is the most toxic form of Reactive oxygen species
-Peroxyl radical is a free radical derivative from fatty acids

Sources:

1. during course of metabolism:
    a. O_2 by auto-oxidation of hemoglobin and xanthine oxidase.
    b. OH by fenton reaction
    c. O_2, H_2O_2, OH by partial reduction of molecular oxygen in ETC (electron transport chain) in the mitochondria
2. Ingestion of toxins, chemicals or drugs



-Hydroxyl radicals is formed in presence of h2o2 and Fe+2
-Catalase convert H2O2 water , so the body get rid of it

-Superoxide dismutase convert O2 to h2o2 which is less toxic ,because it's not a pure free radical and can be eradicated easily
-Superoxide dismutase is antioxidants even if it does not eradicate O2 completely
This process has to be gradual or it will cause a burst , and it takes place in mitochondria in respiratory chain

Anti-oxidants:

Any defect in these enzyme , Oxidants will cause damage
Catalase is present only in Peroxisomes which is not found in RBCs

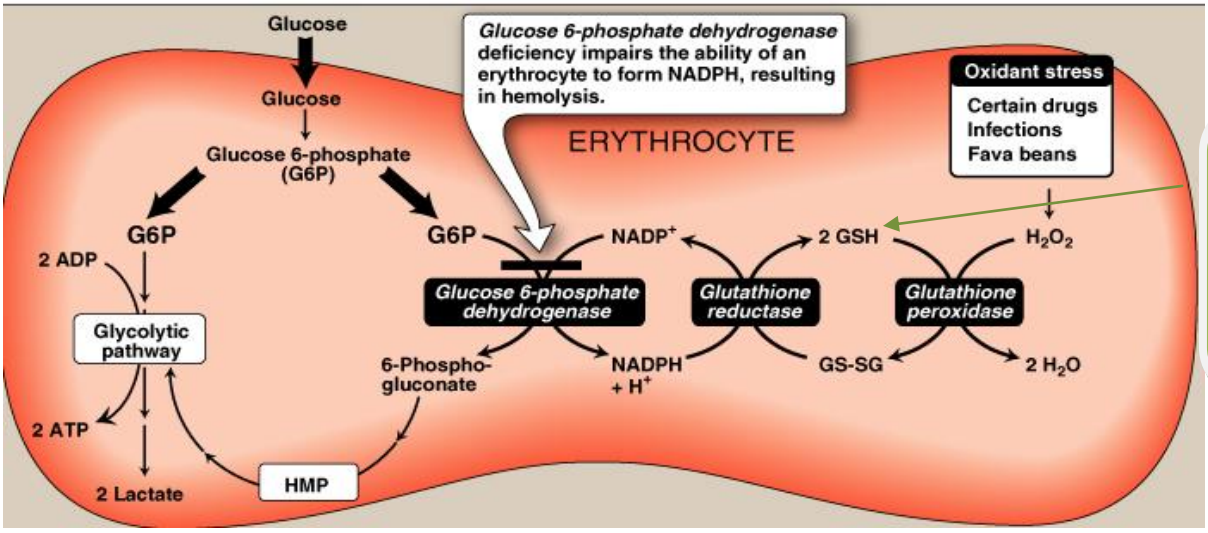
<u>Enzymes:</u>
–Superoxide dismutase
–Catalase
–Glutathione system (glutathione, NADPH, reductase, peroxidase & selenium)

<u>Vitamins:</u>
–Vitamin C (ascorbic acid)
–Vitamin A and β-carotenes
–Vitamin E

-Vitamin C is water soluble
–Vitamin A and Vitamin E are fat soluble

<u>Trace elements:</u>
–Selenium

Glutathione System



The 2H ions from 2G-SH are added to H2O2 by glutathione Peroxidase to convert it into 2H2O

-In the reduced form 2(G-SH) are oxidized by GP (glutathione peroxidase) to form 1(GS-SG). GP is an enzyme that requires selenium to function.

-The oxidized form (GS-SG) can be reduced to (G-SH) by the enzymeGR (glutathione reductase) with the help of an electron donor (NADPH + H^+).

-The electron donors are supplied by the HMP shunt in glycolysis. G-6-PD (glucose-6-phosphate dehydrogenase) is the main source of NADPH +H^-. Any defect will lead to oxidative stress in the form of hemolytic anemia. RBCs don't have Catalse which may help in H2O2 eradication

-Effects of oxidants:

Molecular effects:
–Lipid peroxidation (polyunsaturated fatty acids)
–Protein denaturation
–Inactivation of enzymes
–DNA damage
–Cell signaling effects
(e.g., release of Ca^{2+} from intracellular stores)
–Cytoskeletal damage
–Chemotaxis

Vascular effects:
–Altered vascular tone
–Increased endothelial cell permeability
RBCS don't have Catalse which may help in H2O2 eradication

Nitric oxide:

Free radical gas
Very short half-life (seconds)
Metabolized into nitrates & nitrites

Synthesis:
Enzyme: NO synthase (NOS)
Precursor: L-Arginine

Effects:
-Relaxes vascular smooth muscle
-Prevents platelet aggregation
-Bactricidal & Tumoricidal effects
-Neurotransmitter in brain

Bactricidal & Tumoricidal effects is a defensive mechanism against infections

Nitric Oxide

Beneficial
eNOS
produced by endothelial NOS
➔dilation and perfusion

Detrimental
iNOS, nNOS
produced by neuronal nNOS
or by inucible form of iNOS
➔iNOS is associated with inflammation

* Vasodilator drugs such as nitroglycerin are metabolized into NO ➔ vasodilation

Pathological Uptake of LDL Causing Atherosclerosis:

Modified (oxidized) LDL cause oxidative stress

injuring the endothelium of the arterial wall

Monocytes adhere to the endothelial cells to become macrophages in the intiam

Macrophages scavenger receptors uptake oxLDL

Accumulation of lipids inside the cell

RESULTS IN ATHEROSCLEROTIC PLAQUE FORMATION

The oxidized part could be the Abo-proteins or fat acids in LDL

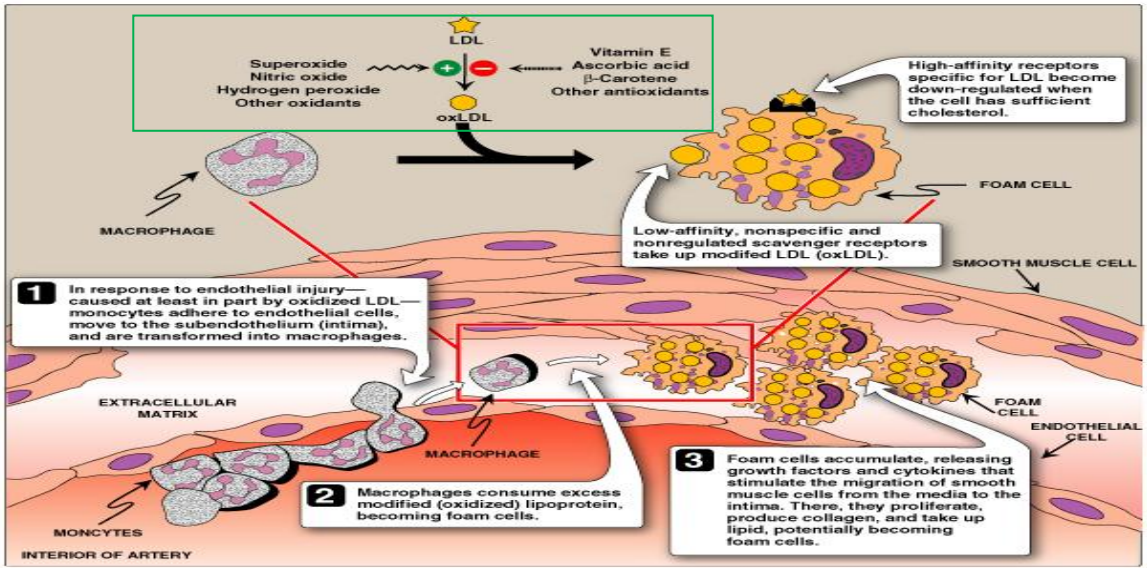
Scavenger receptor class A that regulate this pathological process are different than LDL-R in that they:

- are non-specific
- have low affinity
- are unregulated

The unregulated receptors continue taking up oxidized LDL even if its level is high inside the cell

Normal physiological uptake of LDL:
Unmodified LDLs bind to LDL-R:

- are specific
- have high affinity
- are tightly regulated by receptor-mediated endocytosis



Athersclerotic plaque Formation

Review Question

1. which one of the followings is an Antioxidant:
A- Superoxide
B- G6PD
C- Vitamin E
D- Vitamin b3

2-What is the most virulent to be damaged by free radicals:
A- G6PD
B-RNA
C- DNA
D- Catalase

3-which form of Nitric Oxide is Detrimental ??
A- eNOS
B- nNOS
C- iNOS
D-B and C

4. which of the following receptors are responsible for forming the foam-cell macrophages:
A-Scavenger A
B- Scavenger B
C-there no specific receptors
D- all above

Which of the following enzyme needs selenium to function ?
A- Superoxide dismutase
B- glutathione reductase
C- glutathione peroxidase
D-Catalase

Answers
1-C
2-C
3-D
4-A
5-C