Biochemistry – Oxidative Stress and Atherosclerosis

CVS Block

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- Introduction:-

In normal state the cells of our body produce Reactive Oxygen Species (O2- , H2O2, OH) and Nitric Oxide. Also, they produce anti-oxidants to clear out these free radicals. So, finally we could say there is a normal balance of making free radicals and clearing them out.

If there is imbalance, then (Oxidative stress) would be the result.

- What is Oxidative Stress?

- A condition in which cells are faced with excessive levels of Reactive Species (Oxygen or Nitrative species) & they are unable to clear them all out because of the insufficient amount of antioxidants.
- **In Other words:- Imbalance Between oxidant production and antioxidant mechanisms.**

- Types of Reactive Oxygen Species (ROS):-

1- **Oxygen derived Free Radicals:**

Superoxide (O2)

Hydroxyl radical (OH)

Peroxyl radical (ROO) << Produced from poly unsaturdated fatty acids

2- **Non free Radicals:**

Hydrogen Peroxide (H2O2)

- Source of Reactive Oxygen Species:-

1- During course of metabolism:-

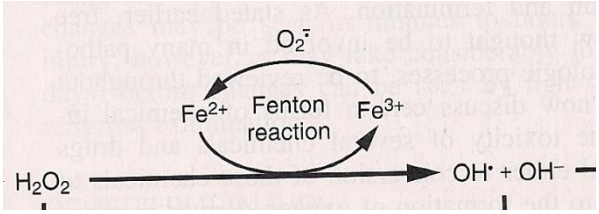
O2 - "Superoxide" , can be produced by :-

a- Auto-oxidation of hemoglobin (which means that Normally 3% of hemoglobin is turned into Methemoglobin (Fe ++ in hemoglobin is oxidized to Fe +++) from this reaction O2-is produced)

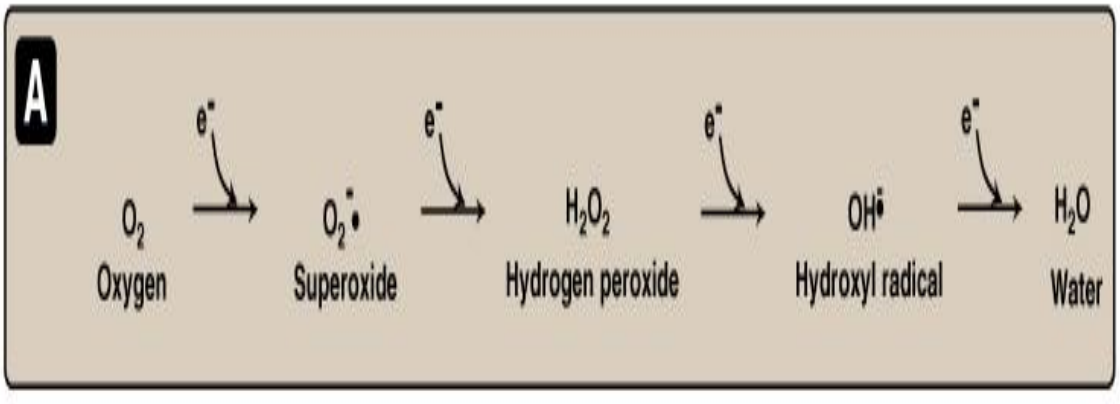
b- Xanthine Oxidase (it is an enzyme used to produce Uric acid and with its production O2- is formed)

OH "Hydroxyl radicals" , can be produced :-

Fenton reaction



O2- , H2O2, OH , by partial reduction of molecular Oxygen in electron transport chain in mitochondria



This is the normal process of electron transport chain ,, if the chain is disturbed at any position ,, it would lead to the production of radicals

2- Ingestion of toxins, chemicals, drugs

- Effect of oxidative Stress (Oxidative stress Damage):-

1- It plays a role in the process of ageing (that's why many anti-aging creams have anti-oxidants in them ,,, ladies ;P)
2- It plays a role in many diseases
   - Atherosclerosis , coronary heart diseases
   - Obesity
   - Cancers
   - G6PD Deficiency Hemolytic Anemia (going to take this in brief later☺ AFTER the explanation of the Glutathione System)
3- Molecular effects:
   - Lipids > Lipid Peroxidation (Especially Poly unsaturated fatty acids , it has no effect on saturated fatty acids)
   - Protein and Enzymes > Protein denaturation and Inactivation of enzymes
   - DNA > DNA damage
   - Cytoskeletal damage (they are function proteins)
   - Cell Signaling effects (e.g. release of Ca++ from intracellular stores)
   - Chemotaxis (attraction of neutrophils and macrophages to the site of infection by inflammatory mediators)
4- Vascular effects:
   - Altered vascular tone (Vasodailation)
   - Increase endothelial cell permeability (chemotaxis and leading to edema)

- Anti-Oxidants (divided by type)

1- Enzymes:

- **Superoxide Dismutase** (Changes O2- into H2O2 ,,, You might say “what the hell! I thought antioxidants get rid of free radicals! How come it turned it to another radical!” well I say to you ,,, that is true little one ☺ but H2O2 is considered to be less reactive than O2- therefore less dangerous !)
- **Catalase** (Changes H2O2 into H2O and O2)
- **Gutathione system** “this system has many elements that work together ”

  1- Glutathione (reduced and oxidized forms)

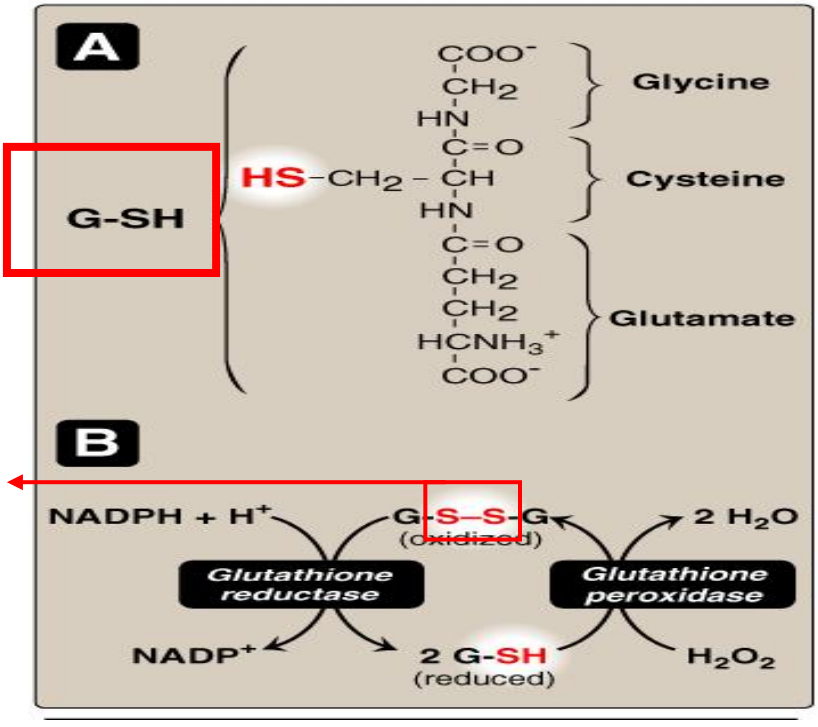
  2- NADPH

  3- Selenium “Trace element”

  (this system changes H2O2 into H2O)

Explanation of the system

It is written like that to donate that the SH group is the active group … that’s all ☺ nothing fancy!



Notice that the H+ is gone wich means that Glutathione has been Oxidized

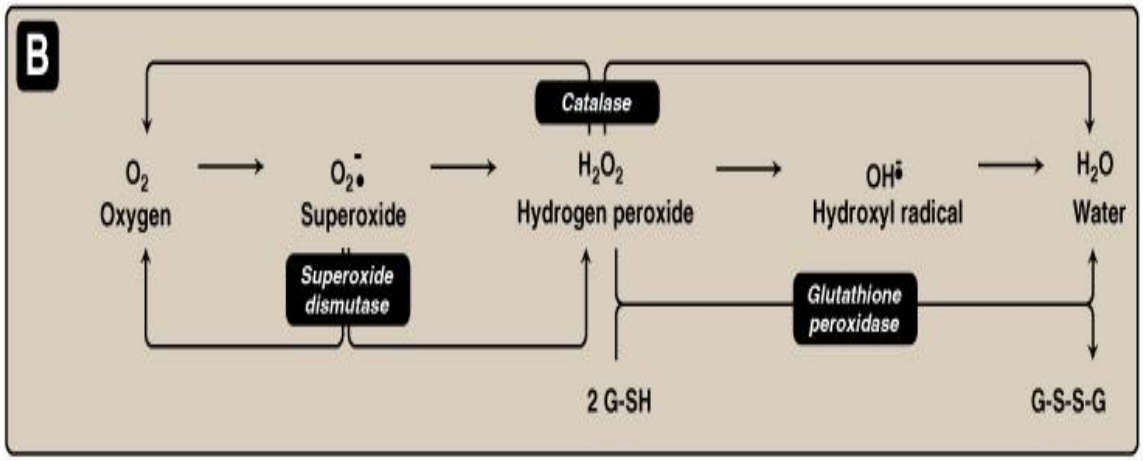
So , basically Glutathione is made up from three amino acids Glycine , Cysteine , Glutamate

Note that every Oxidation (removal of H+) reaction has to be Accompanied by a Reduction (addition of H+) reaction

Steps :-

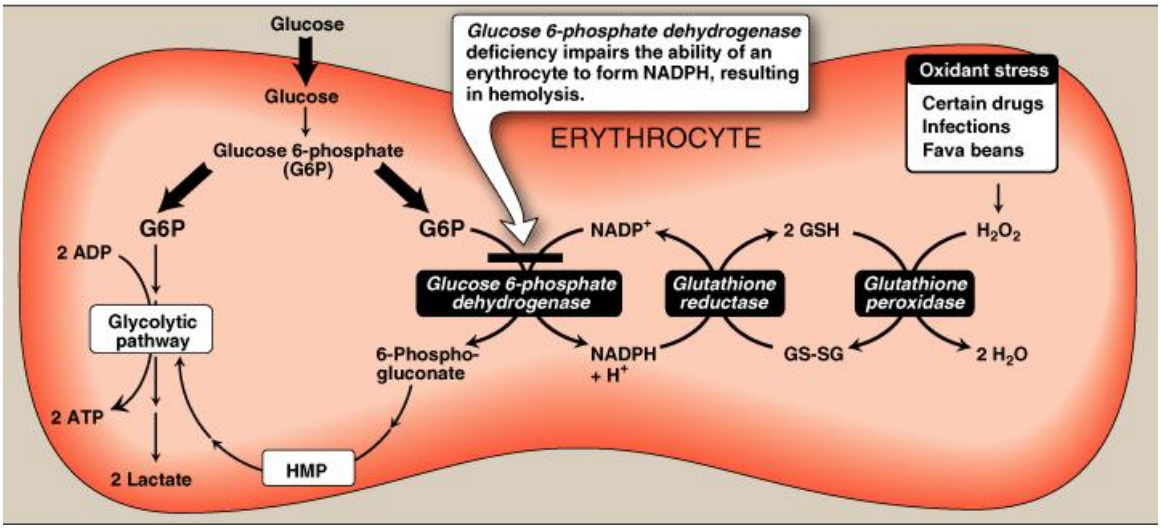
1- 2 G- SH gets Oxidized to G-S-SG and H2O2 is reduced and turns to 2H2O with the help of Glutahione Peroxidase
2- G-S-S-G gets Reduced to 2G-SH and NADPH gets Oxidized to NADP+ with the help of Glutathone reductase

And so on ,,



This picture only shows the work of the anti-oxidant enzymes on the different radicals . (summery of what is written previously)

Like it was said previously that the brief explanation G6PD Deficiency Hemolytic Anemia will be explained after the Glutathione System,,, well the time has come! ☺



G6PD stands for (Glucose 6-Phosphate dehydrogenase)
And it is very important in the RE-reduction of NADP+ to NADPH
So that NADPH can do its job which is the (reduction of G-S-S-G to turn it back to 2 G-SH)

So, What happens is :-

If there is a deficiency in this enzyme (G6PD) then NADP+ will not get reduced therefore (G-S-S-G) will not get reduced either and then this will lead to the accumulation of H2O2 in the RBC ,,, and leading to Red Blood Cell hemolysis

Cool? ☺

2- Vitamins:

- Vitamen C (ascorbic Acid) “water soluble”
- Vitamin A and Beta-cartoenes “Fat soluble”
- Vitamin E

3- Trace elements:

- Selenium

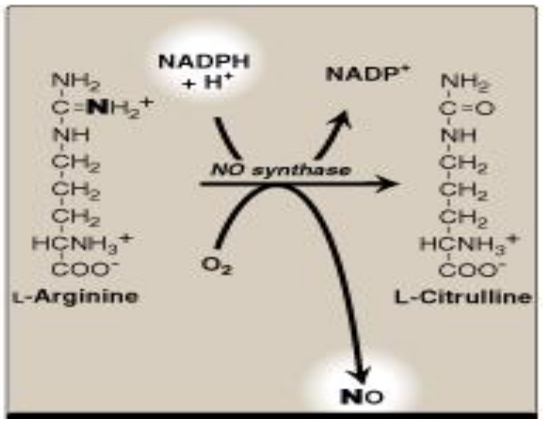
- Nitric oxide (NO):-

- **Characteristics :-**

1- Free Radical gas
2- Very short half-life
3- Metabolized into Nitrates and Nitrites

- **Synthesis:-**

1- Enzyme :- NO Synthase
2- Precursor: L-Arginine

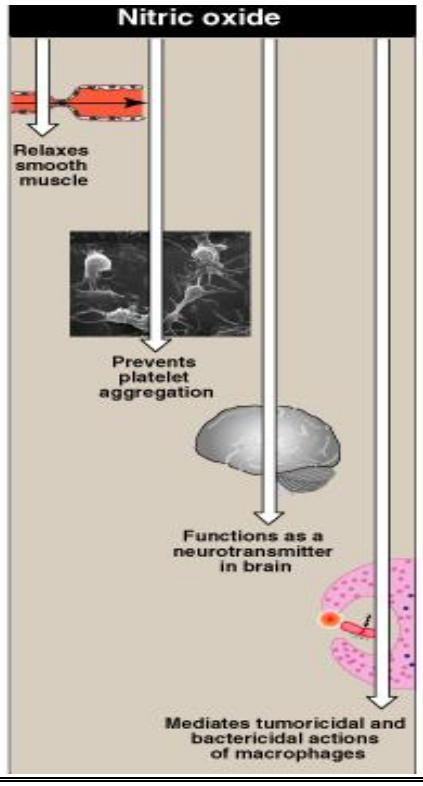


Explination of the Synthesis "the picture":-

L- Arginine is turned in to L- citruline with the help of NO Synthase this leading to the production of Nitric Oxide

- **Effects:-**

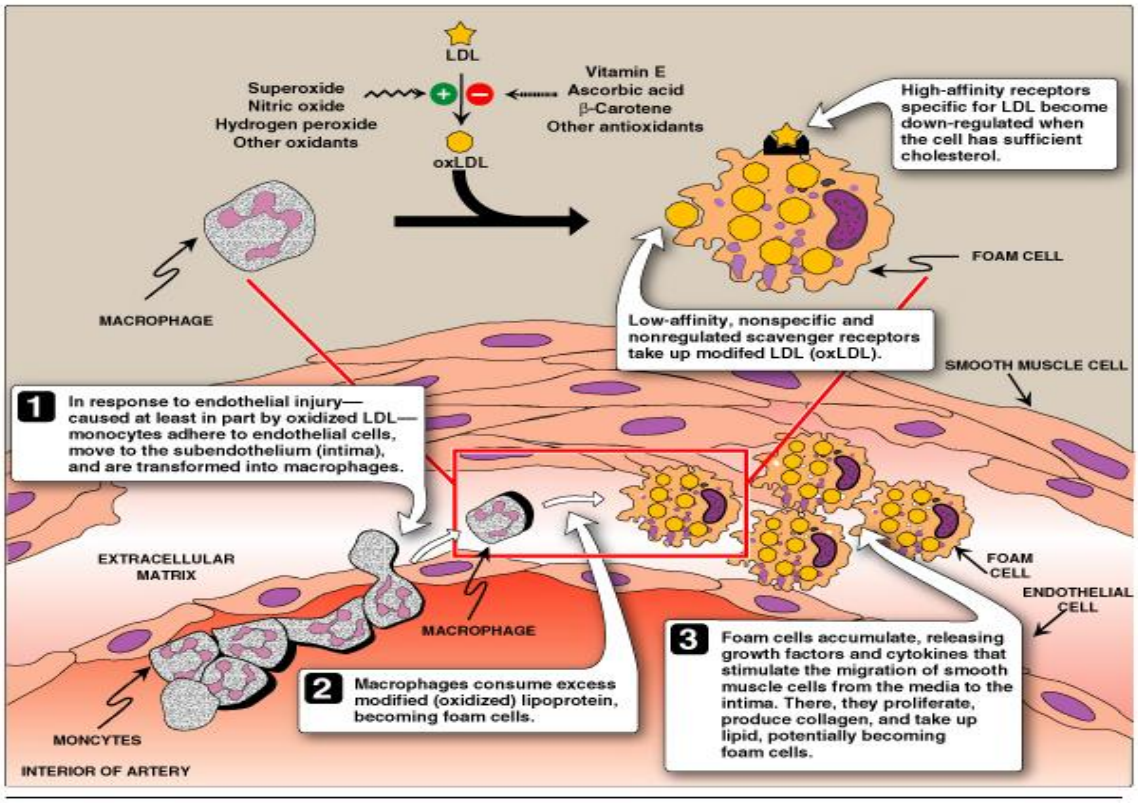
1- Relaxes Vascular smooth muscle
2- Prevents Platelet aggregation
3- Bactericidal and Tumoricial effects
4- Neurotransmitter in the brain



- Oxidative stress : Role Of Nitric Oxide (NO)

- This may be both beneficial and detrimental (dangerous) , depending upon when and where NO is released
- NO produced by endothelial NOS (eNOS) “Endothelial Nitric Oxide Synthase” which is found in the endothelial lining → improving vascular dilation and perfusion (i.e., beneficial).
- Vasodilators such as nitroglycerin (<that’s a drug) is metabolized into NO and causes vasodilatation
- In contrast, NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) has been reported to have dangerous effects.
- Increased iNOS activity is generally associated with inflammatory processes

- Pathogenesis of Atherosclerosis



Steps:

1- LDL gets Oxidized (modified) → this leading to Oxidative Stress (Imbalance between oxidants and antioxidants),, in other words can not get rid of Oxidized form of LDL

2- Endothelial injury of the arterial wall caused at least in part by the oxidized LDL
3- Adherence of Monocytes in the blood to the endothelial cells and then they move into the intima where it turns into macrophages
4- Oxidized LDL is taking in by Macrophage scavenger receptors on the macrophage which leads to the transformation f the macrophages into Foam cells "Accumulation of excess lipids inside the cells
5- In the end atherosclerotic Plaque is formed

NOTE!!! That the Oxidized LDL is not taken up by the normal LDL receptor which is the tightly regulated LDL-Receptor

But it is taken up by Macrophage scavenger receptor, which is a Low affinity, non-specific and unregulated receptor

That's about it for Oxidative Stress ☺

Good luck to all

And

Happy studying ! ☺