***♥As a refreshment:***

* 3-5% of O2 we breathe in goes for the formation of reactive oxygen species.
* ROS could be generated normally by the body but there can be an excess of them due to environmental factors, radiations, chemicals, infection, inflammatory diseases & others.
* Cellular reactions that normally produce ROS are: 1)oxidases 2)cytochrome p450 (cytochrome p450 control the transfer of electrons to O2 however electrons might escape forming superoxide ion O2- this is an accidental release of O2).
* And we said that complex 4 in respiratory chain is well protected even if free radical intermediates were formed they won't escape.
* Since we have production of ROS, the body should develop a defense system against ROS that are damaging all molecules & causing several diseases, disorders & cancers.

***♥Defense system***: composed of primary & secondary defense systems.

***A)Primary defense system:***

-it's composed of enzymes that neutralize ROS, & these enzymes are: (superoxide dismutase – catalase – GSH peroxidase), these enzymes are called: **Antioxidant Enzymes** (AOE).

-Antioxidant enzymes were studied in many aspects one of them includes high atmospheric pressure e.g.: in Jordan valley eventhough the increase of atmospheric pressure is mild, and another aspect is in diseases.

-AOE are usually found in high concentrations especially in liver and kidney these organs contain alot of organelles that are of high susceptibility to produce ROS such as mitochondria,smooth ER, peroxisomes.

 

-these reactions occur in complex 4, & none of them leak.

-superoxide ion is neutralized by superoxide dismutase, because this superoxide ion is a free radical it must be neutralized otherwise it's going to attack macromolecules and variety of compounds & produce free radical chain reactions.

-By the superoxide dismutase enzyme, O2- is converted to O2 atom & **H2O2**.

- **H2O2** is a weak oxidizing reagent, has the power of penetration and can be a source of the deadly hydroxyl free radical by fenton reaction.



***♥Hydrogen peroxide can be neutralized by:***

***1-catalase*:** this enzyme is not widely spread; it's mostly located in peroxisomes. It converts hydrogen peroxide to water & oxygen atom (that’s why when we put hydrogen peroxide on a wound, we see bubbles getting out).

***2- GSH peroxidase:*** this enzyme is found in mitochondria and cytosol and has different isozymes, it not only neutralizes H2O2 but also organic peroxide:

 a) requires Selenium (Se) metal as a cofactor.

 b) neutralizes hydrogen peroxide by using 2 Glutathione (GSH is known as the most important antioxidant compound in the body, especially in blood, it's an antioxidant scavenger compound). It reduces hydrogen peroxide and itself is oxidized.

c) Glutathione must be regenerated (to reduce it back) by GSH reductase (this enzyme contains a cofactor FAD it takes an electron from NADPH and regenerates reduced Glutathione.

***♥Glutathione***:

* It’s a tripeptide composed of Glutamate, Cystine, and Glycine.
* Glutamate makes a peptide bond with cystine by Gama carboxylate not alpha, & the SH group in cystine is the projecting group that undergoes oxidation & protect neighboring molecules. When Glutathione undergoes oxidation, 2 molecules of glutathione attach forming disulfide bond.

🡪GSSG is one of the compounds that can be calculated to know if we have oxidative stress.

We talked about the three AOE that are considered as the primary defense mechanisms; now we will talk about the secondary defense mechanism.

***♥Secondary defense mechanisms:***

1-Dietary : antioxidant vitamins ( vitamin E & C) & βcarotene.

2-Endogenous compunds with an antioxidant activity.

3- Repair mechanism of DNA.

4- Compartmentization .

***♥Compartmentization :***

-using different compartments in the cell, or compartmentization of molecules within defined organelle, this protects oxidant to diffuse everywhere.

- we notice that in specific places in the cell ,there is high production of ROS, such as in mitochondria, peroxisomes, cytochromeP450enzymes in smooth ER… , & at the same place ,there is high production of antioxidant enzymes , so, ROS are produced & neutralized at the same place or compartment.

 -these enzymes are rich in tissues of (liver, adrenal gland, and kidney) that have high concentration of mitochondria, peroxisomes …

-Ferritin is considered to have an indirect antioxidant activity because it has high affinity for iron, so, it traps iron in the cell & not letting it to float around.

🡪Because iron is a catalyst in fenton reaction that converts hydrogen peroxide to hydroxyl free radical.

🡪When ferritin binds too much iron, it will become Hemosiderin , & this is the first step of iron overload.

***♥Vitamin C & E:***

-vitamin E is the most powerful antioxidant & it's good for heart problems.

-alpha tocopherol is the most famous and widely spread type of vitamin E.

-alpha tocopherol has an antioxidant action by termination free radical lipid peroxidation , it does so, by donating single e- to this lipid radical , so the vitamin will be oxidized.

-the oxidized vitamin can be reduced by vitamin C, so, vitamin C preserve the level of vitamin E.

- vitamin C & beta carotene are also antioxidant , but they act by accepting e- from lipid radical, unlike vitamin e- which donates e-.

-vitamin C also can regenerate reduced vitamin E from the oxidized one.

***♥Other dietary antioxidant:***

***♥Flavonoids:*** They are polyphenolic compounds connected together.

🡪Functions:

1-they can inhibit superoxide ion production.

2-Chelate Fe & Cu.

3-Free radical scavenger.

4- Preserve vitamin E.

-it could exist in: green tea, chocolate, red wine, fruits.

-other flavenoids in other names (not that important): catechins – kaempherol – quercetin) they exist more in colored vegetables & red fruits.

***♥endogenous compounds that have an antioxidant activity:***

1- uric acid (the end product of purine metabolism).

2-bilirubin (the end product of heme metabolism).

3-GSH.

4-lipoic acid.

5-ubiquinone.

6-melatonin(hormone like substance).

***♥Chapter 14 >> Glycoseaminoglycan – glycoprotein***

-in synthesis of GAGs , glycoprotein or glycolipid, we always have a donor sugar. ( the sugar should be activated by forming UDP sugar, which can then be donated to protein, lipid, or, polysaccharide to form glycoprotein , glycolipid, or glycosaminoglycan).

-There are specific transferase enzymes for transferring sugar from donor sugar to acceptor, and to each acceptor we have different enzyme.

-for example→ formation of UDP glucose from glucose 1 phosphate & UDP, then using this UDP Glucose in producing proteoglycan , glycoprotein , UDP glucoronate & UDP galactose(that has a role in making lactose).

-when the donated sugar binds a protein, it will make a glycosedic bond with serine (o-glycosedic bond) or asparagines (N-glycosedic bond).

***♥Formation of Glucornic acid:***

-its formed by UDP Glucose dehydrogenase from UDP glucose , resulting UDP glucornate ( it’s a precursor for several glycosaminoglycan, & also important to drugs and other compounds to make them soluble therefore they can be transported to tissues.

-the best example for the usage of glucornic acid is bilirubin. Bilirubin is not soluble, & in order to be secreted in the bile & reach the feces, this bilirubin in the liver undergoes conjugation with 2 glucornic acid , & this compound then will be called: bilirubin diglucuronide ( the soluble bilirubin).

- Glucornic acid can be metabolized, and it will be converted to xylulose-5-phosphate that enters pentose phosphate pathway (knowing the details of this pathway are not important).

-Other animals(except primates and ginny pigs) & plants contain enzymes that converts glucornic acid to vitamin C (ascorbic acid) , that’s why we have to take vitamin C , unlike plants which produces it.

