PASSION ACADEMIC TEAM YU - MEDICINE

Sheet#

Lec. Date : 17-2-2020

Lec. Title : Oxygen toxicity

Written By :

If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

RESPIRATORY SYSTEM

*acidosis happens due to many reasons, even the metabolic acidosis itself can be caused by many conditions,,,

→one of them lactate, … and so on.

Also, renal function cause acidosis, (kidney may be the cause of acidosis)

*If you have acidosis in the blood, the hydrogen ions are supposed to transported through this system, but not freely ,it transport as H_2CO_3, unless in the tubular cell, we have a mechanism of Na-ATPase transporter as well as K-ATPase transporter and symport and antiport transportation.

Renal tubular acidosis. (is more than 5 types)
**If we have deficiency in one of these transporters, which is 2 types:
1-type one deficiency: in the membrane of tubular cells towards the lumen.
2- type 2 renal tubular acidosis.
*carbon dehydrase enzyme, Is 2 types (one of them inside the cell and another one in the surface)
Why it is availabe in the cell?
It is to convert the H2Oand CO2 into H2CO3, and also in the surface, because we have also H2D and CO2.

Once you want to be reabsorb the bicarbonate, it will go through this system.Once you want to release it, it will go backwards.
But usually we reabsorb it, in order to prevent acidosis.
** If there is any defection in these transporters, and we cannot convert the bicarbonate back into hydrogen it will remain in the plasma→ so we will have acidosis.
The cause of all of the above is renal tubular cells, that why we call it renal tubular acidosis.
Why we have hypokalemia with it? (ايش العلاقة بينهم؟)
Because of the deficiency of the transporters or the symport mechanism of hydrogen ions, we are not releasing potassium ions, that's why we have hypokalemia.
So the presence of cations (which is hydrogen ions) preventing the reabsorption of potassium ions→ hypokalemia.

Biochemistry of Oxygen Toxicity

Dr. Mazhar Al Zoubi

*During the oxidation of glucose, there is releasing hydrogen (which is electron in this case), in the reaction.
*There is no problem for now,,,
*But at the end of the day, these electrons (some of them) will be toxic to the body, because it will cause electrical shock as it interact with radicals inside the cell.
*So this electrons should be transported to new molecules (this is oxygen and hydrogen to form water),,,
#That's why we need oxygen.
One of the things that caused toxicity is that this electrons will affect another molecule like DNA→ mutation, they may also cause destruction of protein lipids,,,
So oxidation is type of toxic, when it excess.
We should have antioxidant

•The term “oxidative stress” began to be used frequently in the 1970s.

•**Toxic** effects of molecular oxygen (Gerschman et al., 1954)

•Potential contribution of such processes to the phenomenon of aging (Harman, 1956).

•The recognition in 1968 that biological systems could produce substantial quantities of the superoxide free radical, O_2^-, through normal metabolic pathways (McCord and Fridovich, 1968) and that enzymes, the superoxide dismutases (SOD),(resistant of superoxide molecule), had evolved with the apparent sole purpose of protecting aerobic organisms from the presumed toxicity of this free radical (McCord et al., 1969 and McCord et al., 1971) spurred much interest.

Reactive Oxygen Species (ROS)

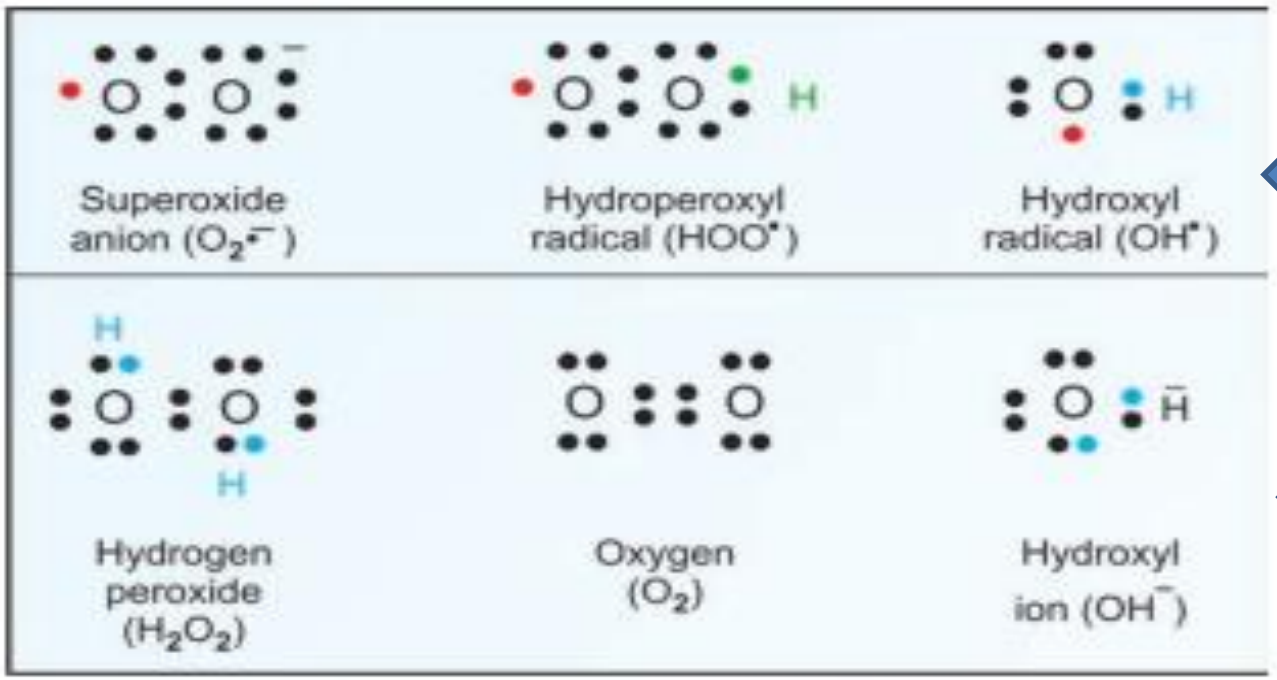


Fig. 20.2. Some free radicals. Please compare hydroxyl radical (free radical) with hydroxyl ion, which is not a free radical. Also compare oxygen with superoxide anion

Free radical.
The red dot means that this O accept extra e- from somewhere.

ROS

In general, we call all of them ROS because it have O , but in fact there is differences between them.

•The terms "oxidative stress" and "free radical damage" are NOT synonymous and may not always be interchangeable.

• Free radical is generally represented by a superscript dot, (R•)

•**e.g. Oxygen can accept single electrons, up to 2 unpaired electrons (O_2 ↑↑)**

•Therefore, "Free radicals (**one or more unpaired electrons**)" and "reactive oxygen species" (ROS) are also NOT synonymous, as many ROS (singlet oxygen $^1O_2$, hydrogen peroxide H_2O_2)are NOT free radicals).

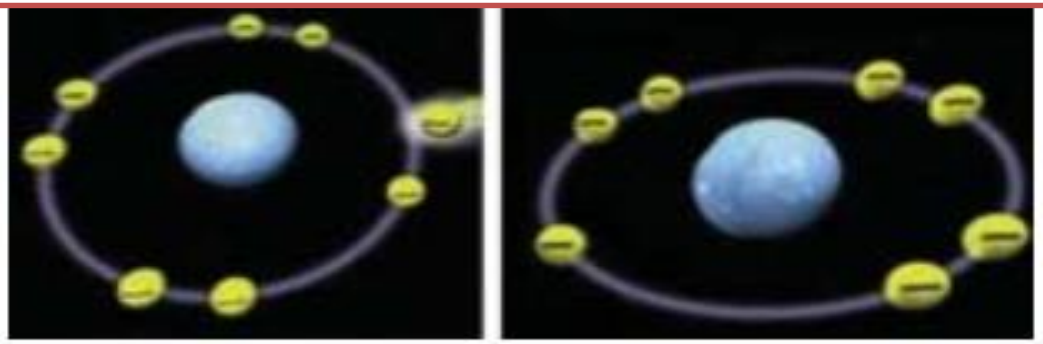


Fig. 20.1. Left side = normal oxygen atom with all paired electrons; one electron is in the process of jumping out. Right side = free radical, with an unpaired electron

ROS members

i. Superoxide anion radical ($O2^{-\bullet}$)

ii. Hydroperoxyl radical ($HOO^{\bullet}$)

ii. Hydrogen peroxide (H_2O_2). One of the important molecule in our bodies, we generate it in WBCs in order to resist M.O.

iv. Hydroxyl radical ($OH^{\bullet}$)

v. Lipid peroxide radical ($ROO^{\bullet}$)

vi. Singlet oxygen ($^1O_2$)

vii. Nitric oxide ($NO^{\bullet}$)

viii. Peroxy nitrite ($ONOO^{-\bullet}$).

**Even they are ROS or free radicals, the important thing is that these molecules are active,(they are doing oxidation or oxidative stress).

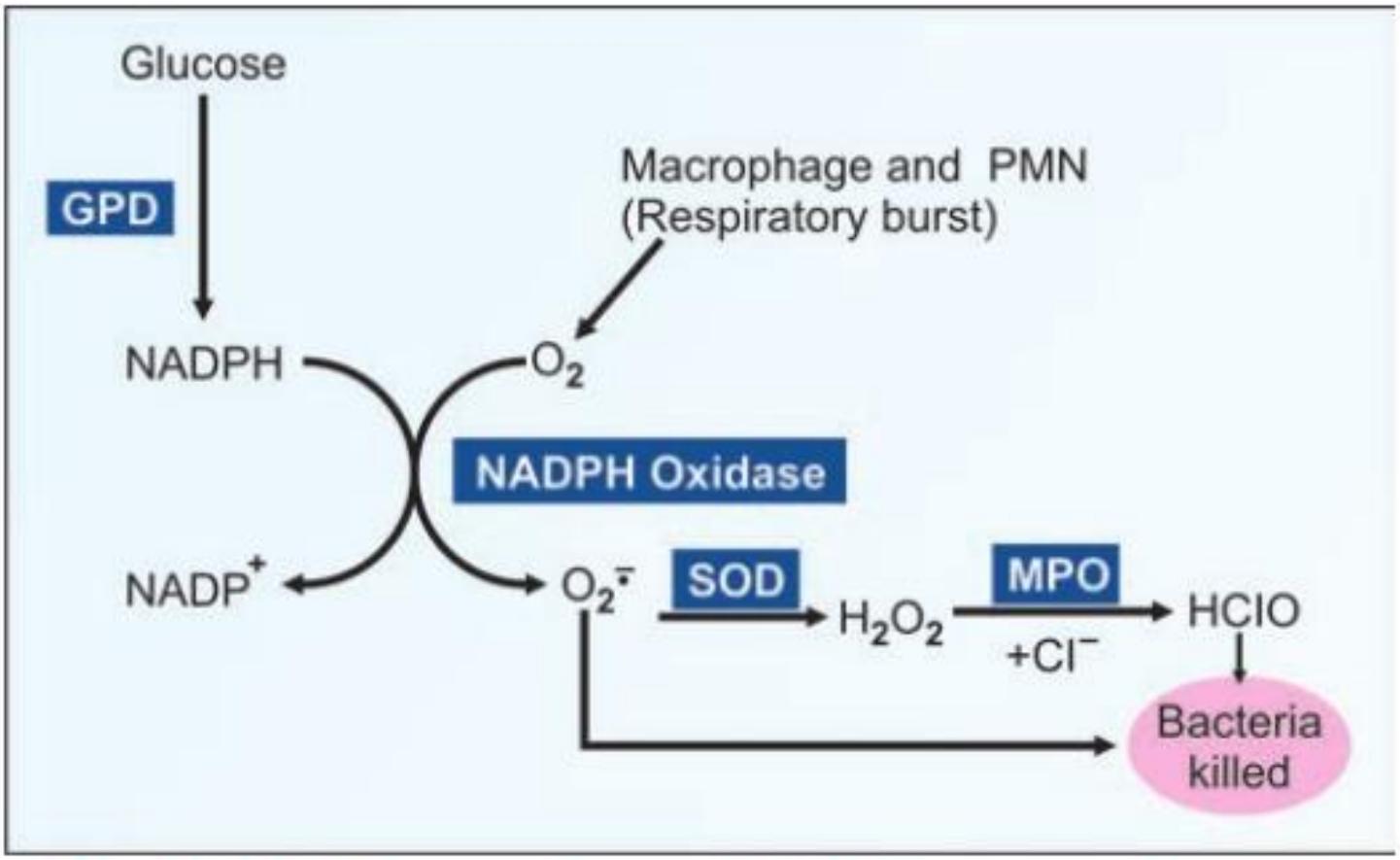
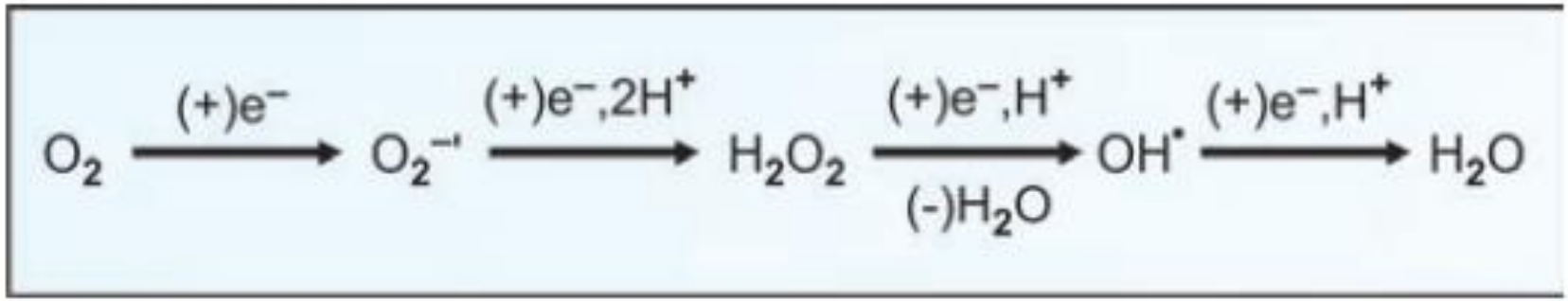


Fig. 20.3. Generation of ROS in macrophages

we do glucose oxidation through non glycolysis for 2 purposes, one of them is to generate NADPH, which is reducing agents (going to be antioxidants) but not directly work against oxidative stress, it is helper for NADPH oxidase, which is responsible for production of free radical→ H2O2→ formation of HCLO (toxic molecule),,,, all of this happen in WBCs.

reduction steps of oxygen



Characteristics of the ROS are:

a. Extreme reactivity.

b. Short life span, as they are active.

c. Generation of new ROS by chain reaction.

d. Damage to various tissues. →mainly the are damaging DNA as a major site of risk.

Generation of ROS

About 1-4% of oxygen taken up in the body is converted to free radicals.

- Mitochondrial ROS production is modulated largely by the rate of ETC.
- **xanthine oxidase** and **aldehyde oxidase** form superoxide anion radical or hydrogen peroxide. In nucleotide metabolism, when the body want to synthesis purine and pyrimidine , it use xanthine oxidase .
- **NADPH oxidase.** In macrophages
- **nitric oxide synthase (NO**), as neurotransmitter (signaling molecule) that is important to vasodilation.

Generation of ROS

- **Lipooxygenase** in platelets and leukocytes, enzyme responsible of oxygenation of fatty acids →free radical of fatty acids.
- Ionizing radiation

$$H_2O \xrightarrow{\text{(gamma, UV radiation)}} H^{\bullet} + OH^{\bullet}$$

- Light of appropriate λ can produce singlet oxygen. (wave length)
- Cigarette smoke and air pollutants
- Under hypoxic conditions, the mitochondrial respiratory chain also produce NO

A lot of sources targeting one molecule(DNA), once you have one of them → mutagen.

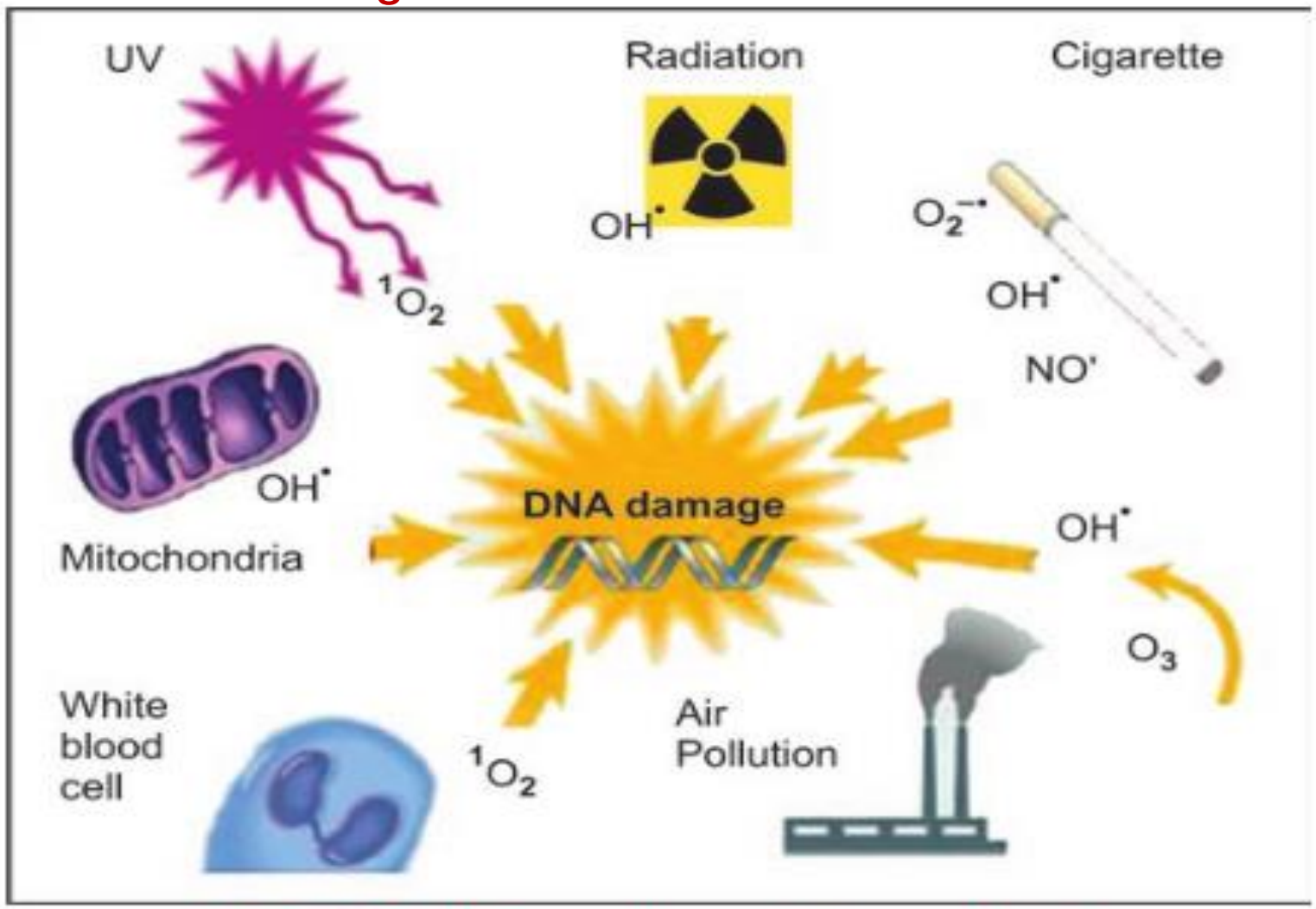
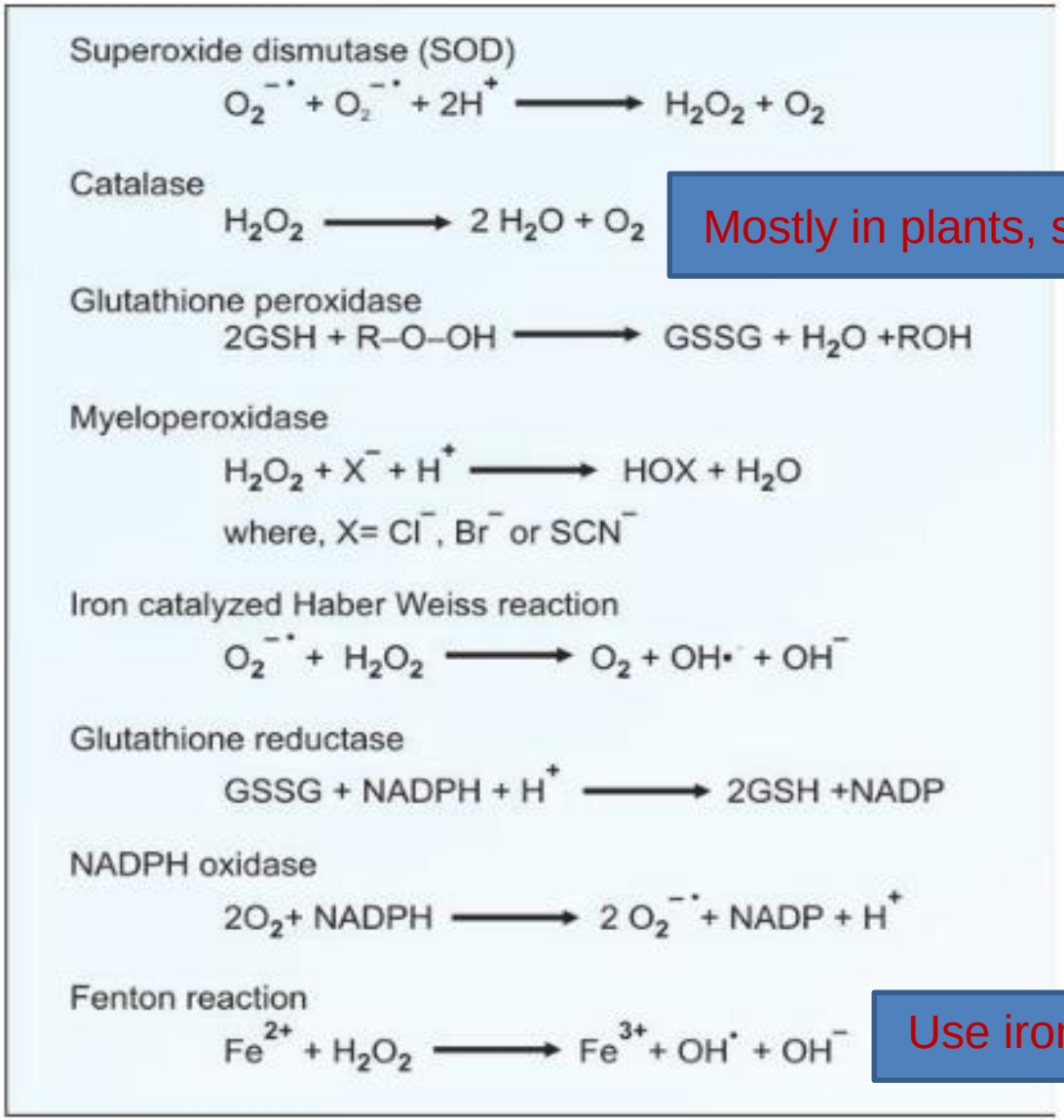


Fig. 20.4. Formation of free radicals

Defense mechanism that we should have in our bodies.



Mostly in plants, sometimes in bacteria.

Use iron as a source of e-

Fig. 20.5. Reactions involved in ROS. Note: Fenton reaction and Haber-Weiss reactions are dependent on iron

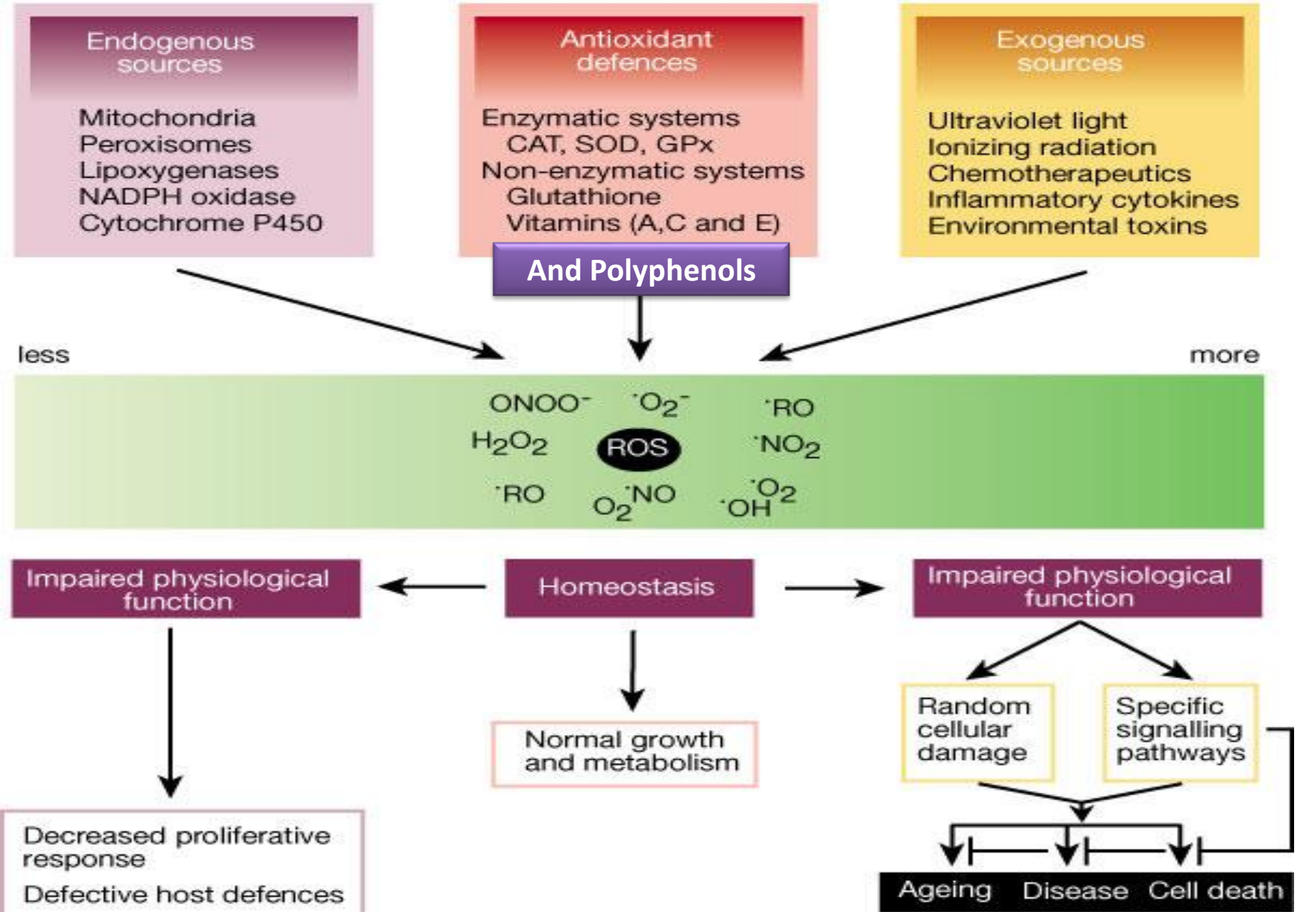
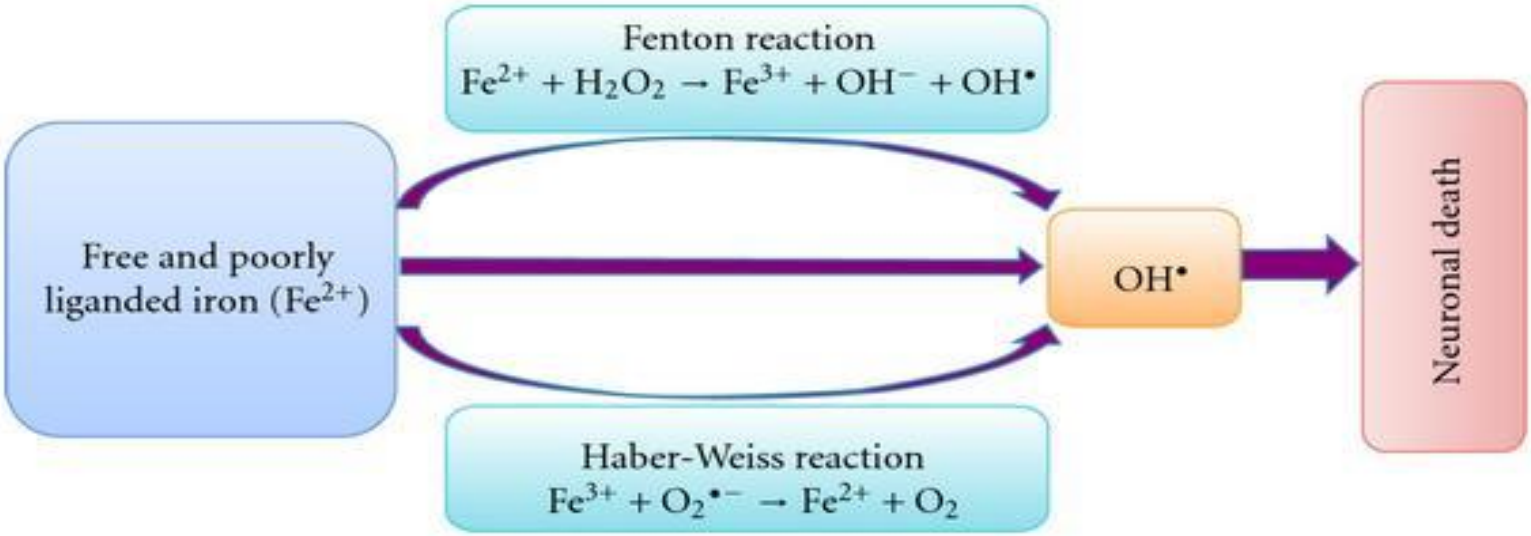


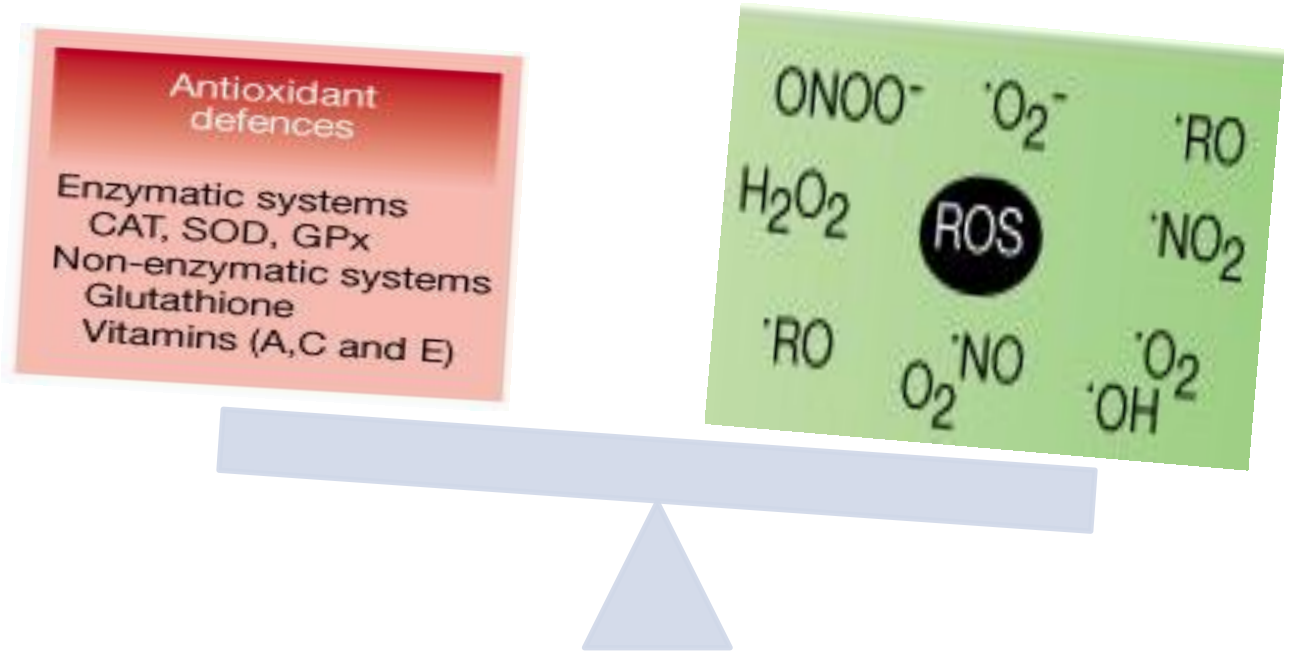
FIGURE 1. The sources and cellular responses to reactive oxygen species (ROS).

Nature **408**, 239-247


Fenton reaction
$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^\bullet$
Free and poorly liganded iron (Fe^{2+})
$OH^\bullet$
Neuronal death
Haber-Weiss reaction
$Fe^{3+} + O_2^{\bullet-} \rightarrow Fe^{2+} + O_2$

Anti oxidants

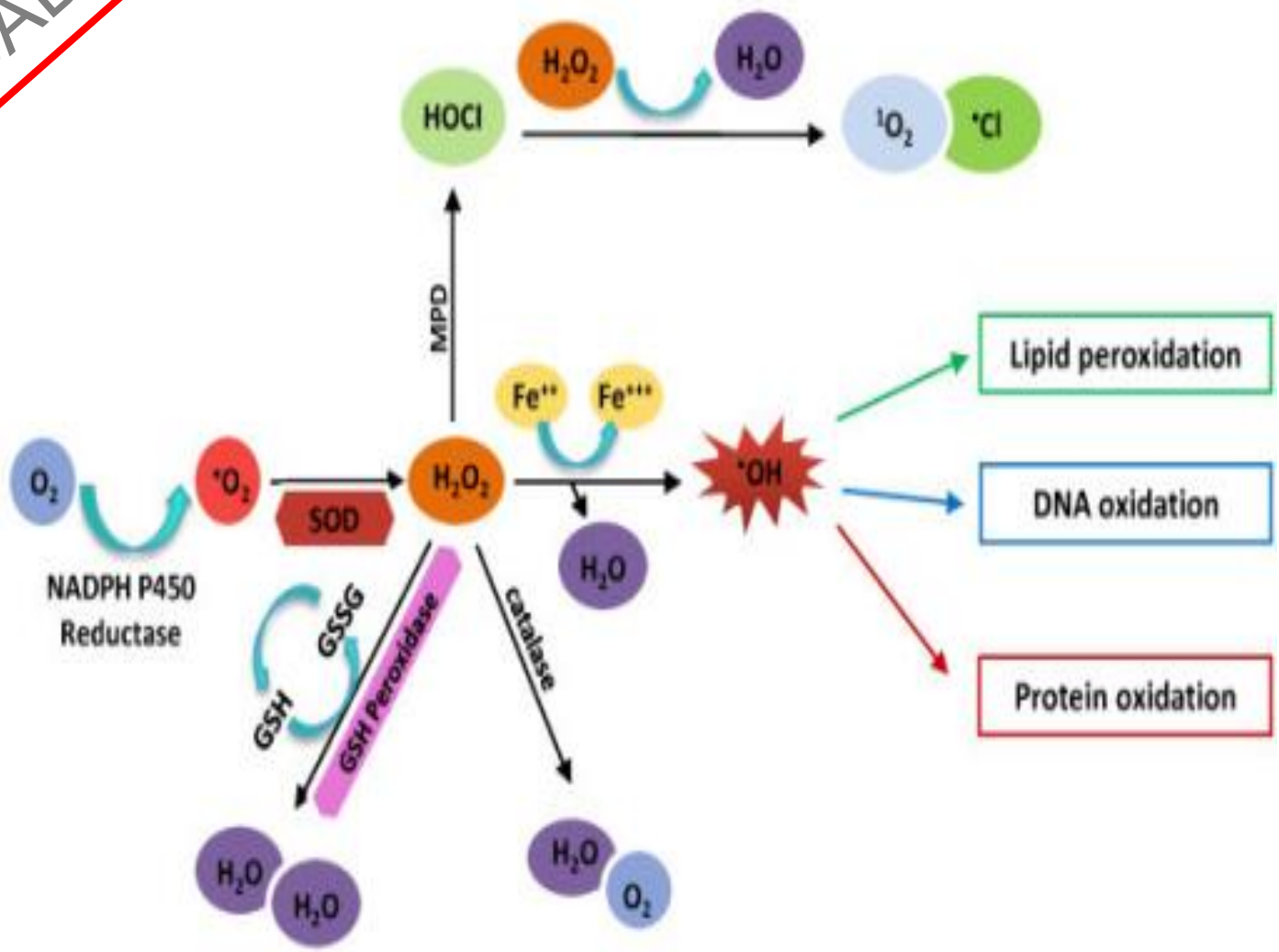
Oxidants



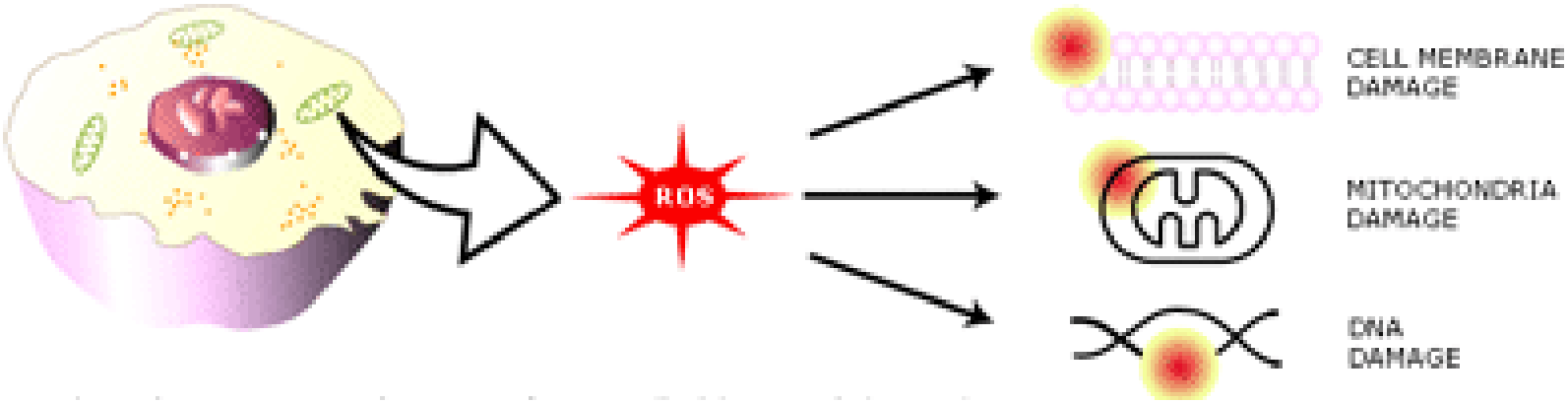
What that has to do with Oxygen ?!

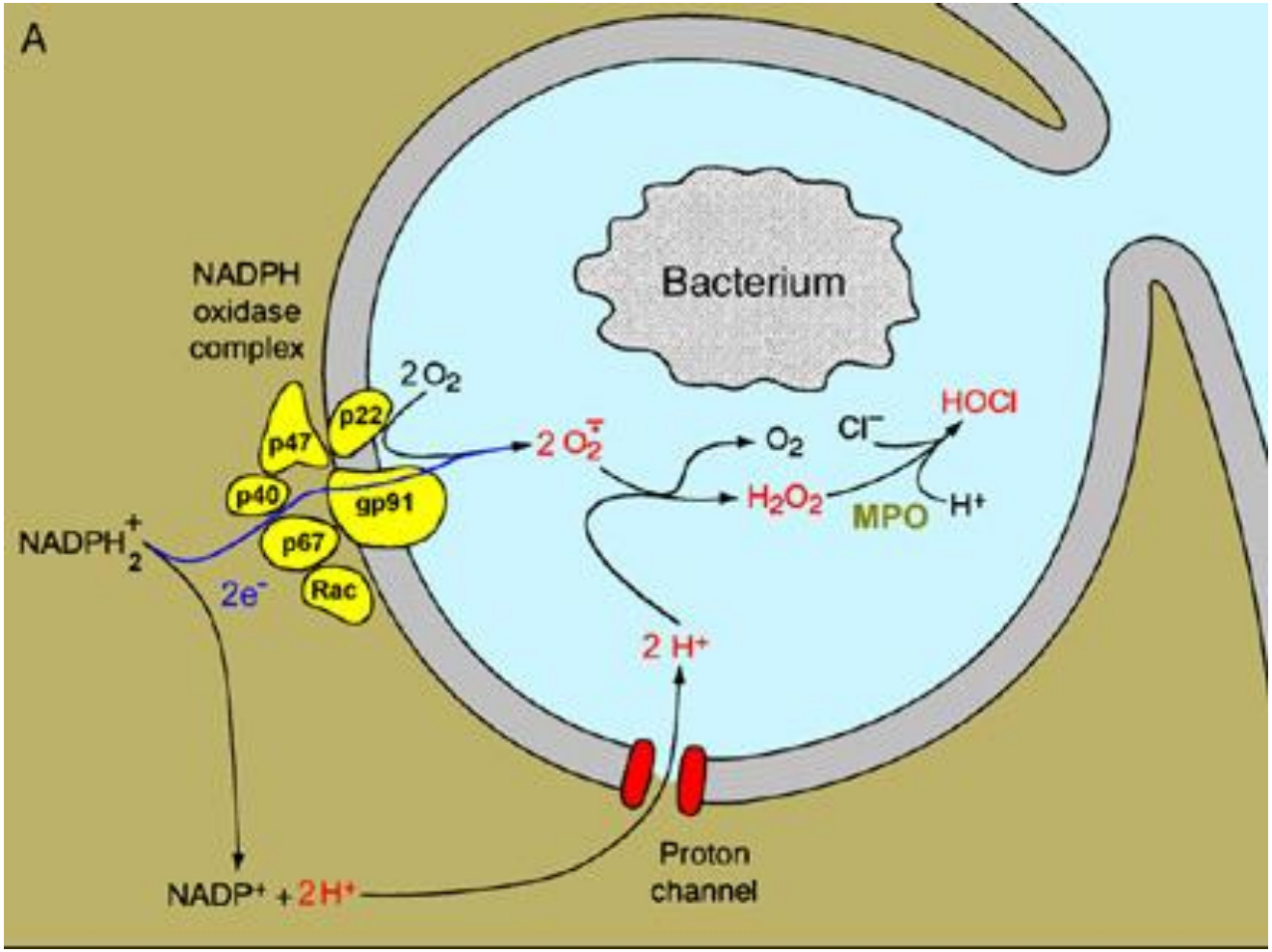
- O2 is an abundant element on the earth (49 %).
- 20 % of the atmosphere.
- 65 of Human body !
  - Cellular respiration.
  - Other metabolic reactions and defenses.
  - Drug metabolism

O2 is BAD


HOCl
H_2O_2
H_2O
$^1O_2$
$^{\bullet}Cl$
MPD
Fe++
Fe+++
O_2
$^{\bullet}O_2$
SOD
H_2O_2
$^{\bullet}OH$
H_2O
NADPH P450
Reductase
GSSG
GSH
GSH Peroxidase
catalase
Lipid peroxidation
DNA oxidation
Protein oxidation
H_2O
H_2O
H_2O
O_2

ROS (Type of Free Radicals) Damage





myeloperoxidase (MPO)

Cellular injury occurs through the production of ROS:

1. Superoxide Anion
2. Hydoxyl Radicals
3. Hydrogen Peroxide

There are antioxidant defenses within cells that reduce these species

Free Radical Scavenger Systems

1. Superoxide dismutase (SOD)
2. Glutathione peroxidase
3. Glutathione reductase
4. Catalase
5. Polyphenols

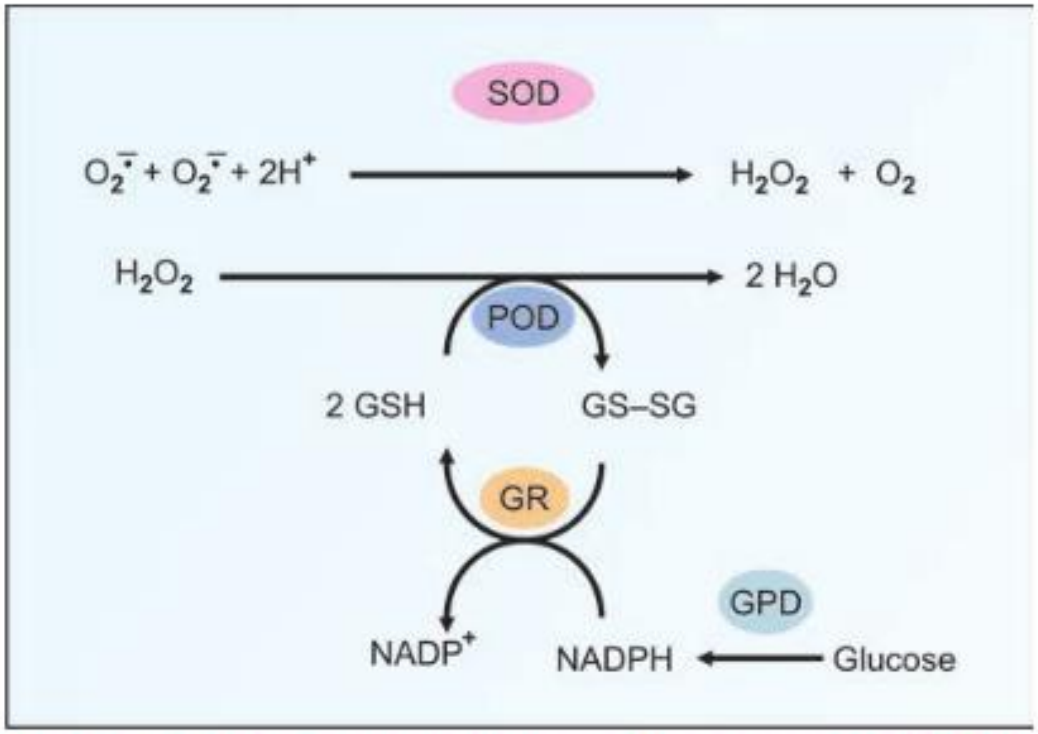


Fig. 20.6. Free radical scavenging enzymes. SOD = super oxide dismutase. POD =peroxidase. GSH = glutathione. GR= glutathione reductase. GPD= glucose-6-phosphate dehydrogenase

$$2\ H_2O_2 \xrightarrow{\text{Catalase}} O_2 + 2\ H_2O$$

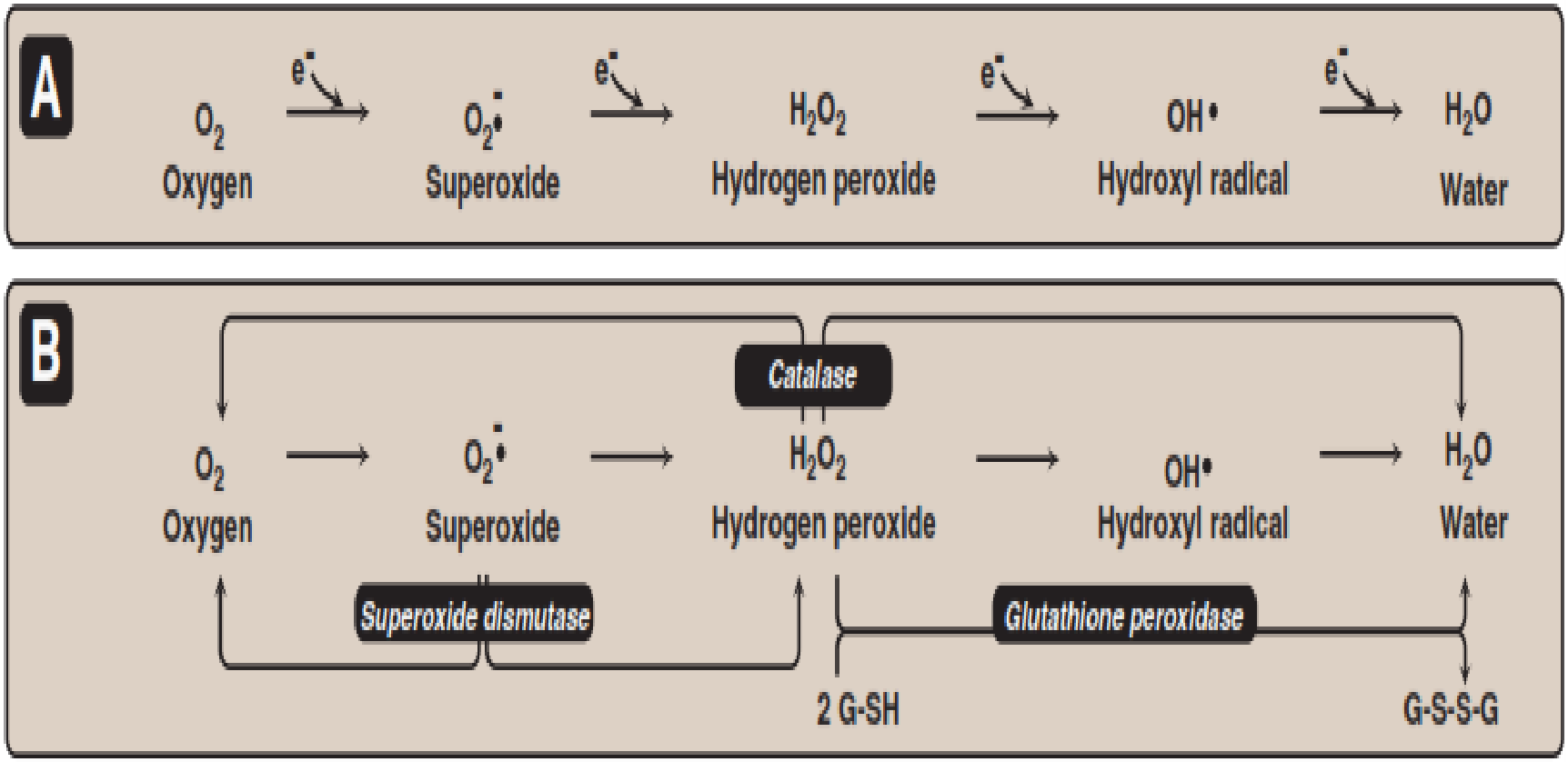


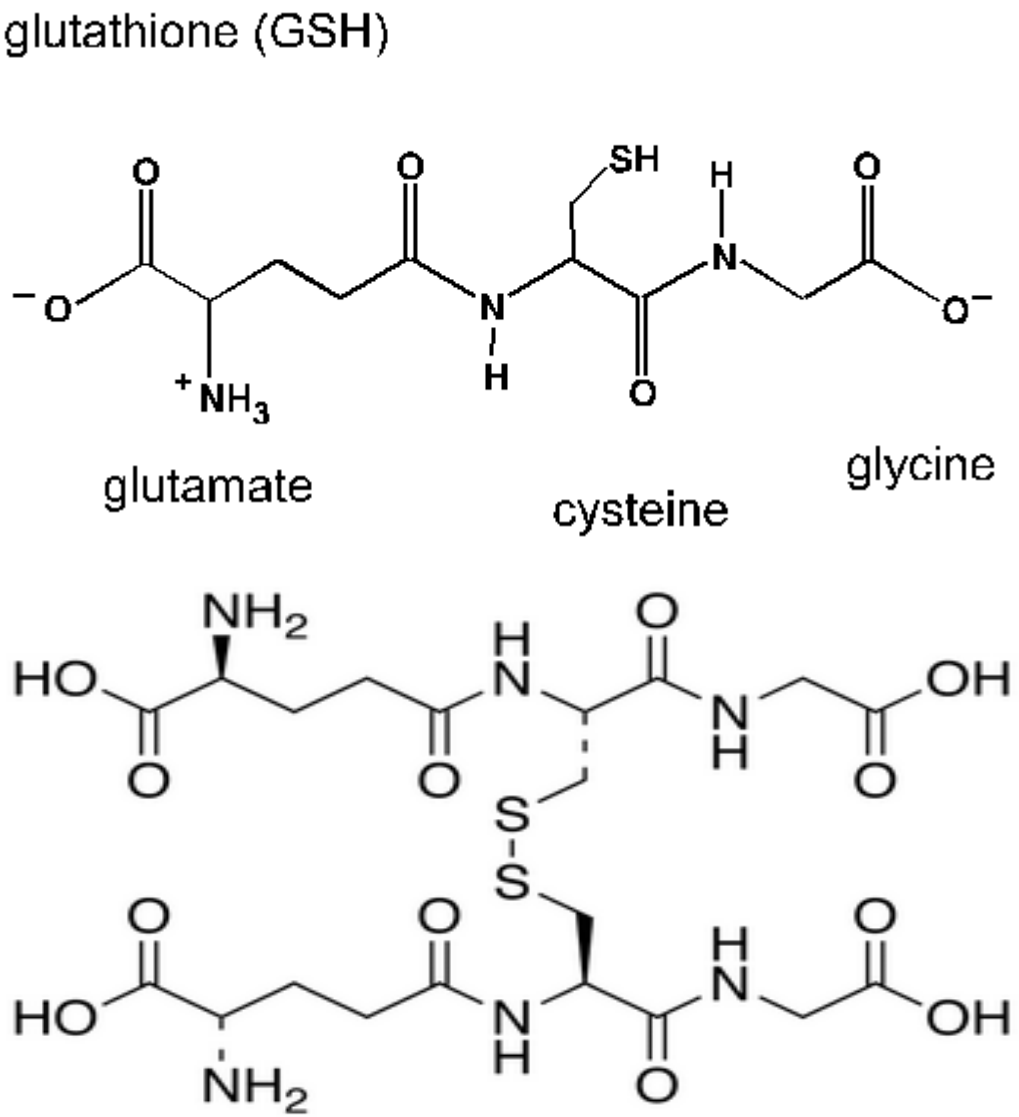
Figure 13.5

A. Formation of reactive intermediates from molecular oxygen. B. Actions of antioxidant enzymes. G-SH = reduced glutathione; G-S-S-G = oxidized glutathione.

Glutathione

*Glutathione is consist of : glutamate, cycteine and glycine. (it is tripeptide).

*Once it conjugated by oxidative process it will form the oxidized form (the below), which is hexyl peptide.



Non-enzymatic Antioxidant compounds:

Glutathione
Vitamin C
Vitamin E
Vitamin A
Uric acid

Damage Produced by Reactive Oxygen Species

- Peroxidation of PUFA (poly unsaturated fatty acids)
- All biological macromolecules are damaged

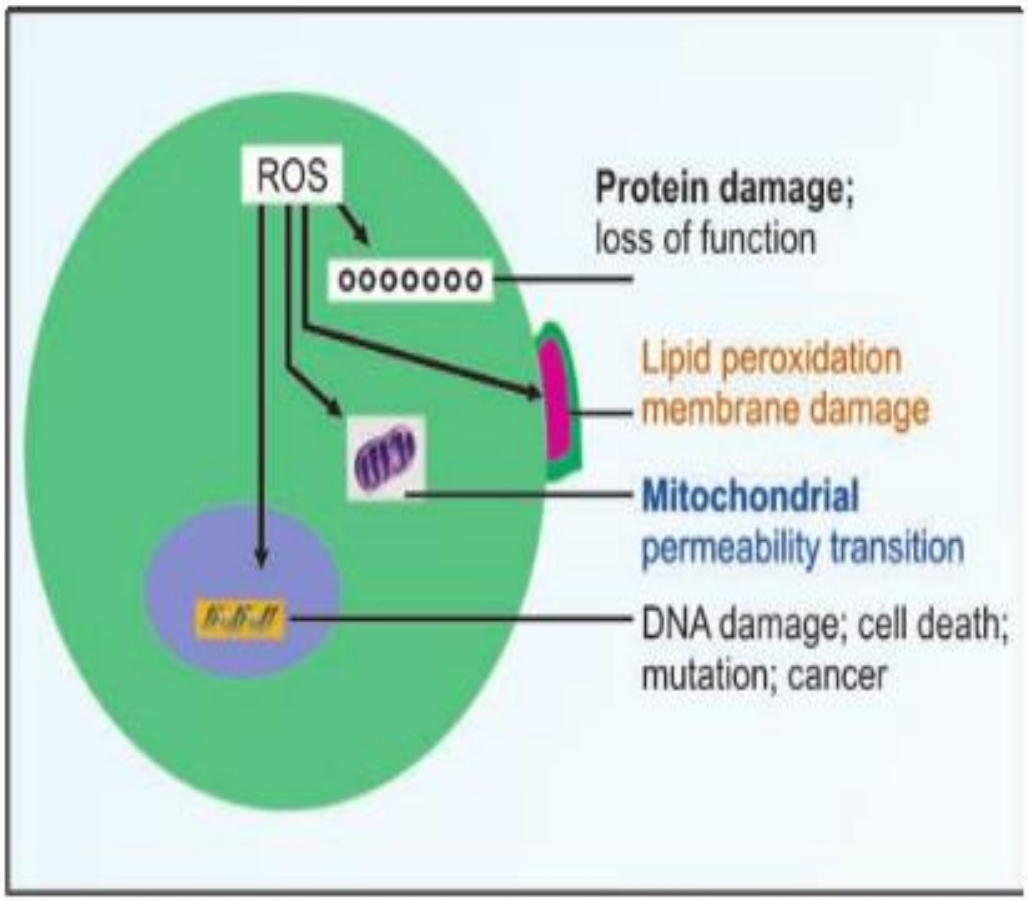


Fig. 20.7. Damages by reactive oxygen species

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CLINICAL SIGNIFICANCE

1. **Chronic Inflammation (rheumatoid Arthritis, chronic glomerulonephritis)**
2. **Acute Inflammation**
3. **Respiratory Diseases**
    1. **bronchopulmonary dysplasia. Newborn O2 exposure**
    2. Adult **respiratory distress syndrome (ARDS), Neutrophils recruitment**

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4. Diseases of the Eye

1. Retrolental fibroplasia (retinopathy of prematurity), high O2
2. Cataract

5. Reperfusion Injury

– During ischemia, the activity of xanthine oxidase is increased

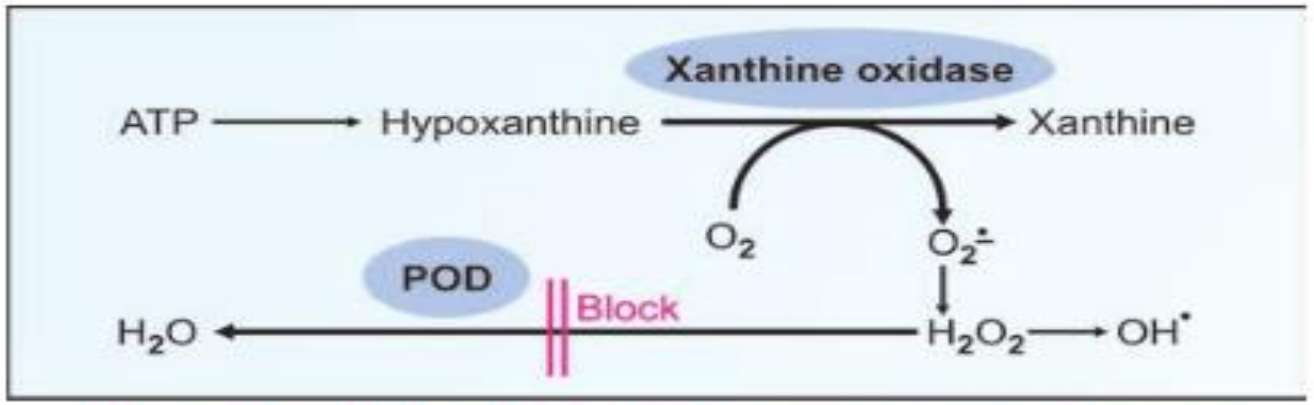

Fig. 20.8. Explanation for reperfusion injury

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6. Atherosclerosis and Myocardial Infarction

- Low density lipoproteins (LDL)

7. Shock-related Injury

8. Skin Diseases

9. Carcinogenesis and Treatment

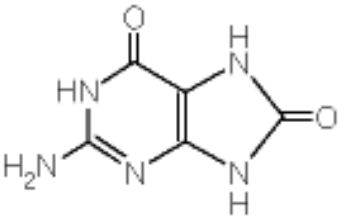
10. Aging Process

DNA

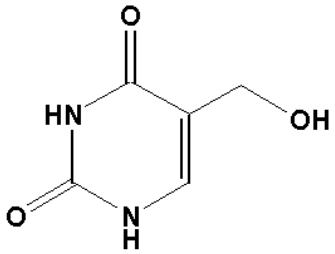
Generation of altered oxidized bases such as:

1. 8-oxoguanine.
2. 5-hydroxyuracil.
3. Thymine glycol.

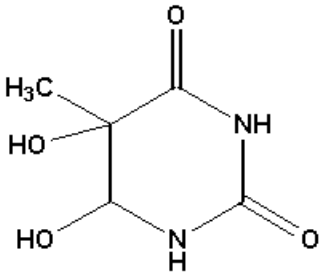
Relieved by nucleotide hydrolase



8-Oxoguanine



5-Hydroxymethyluracil



Thymine glycol

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What will happen during pregnancy and birth

Higher activity of antioxidant enzymes

Preterm babies have to face ROS stress

Table 3. *Comparison of infants by gestational age at birth**

Gestational age (wks)	FiO_2	PAO_2 (kPa)	PaO_2 (kPa)	GSSG (μM)	GSH (μM)	GSH/GSSG
23–33	0.39 ± 0.26	30.1 ± 23.4	9.1 ± 2.3	0.71 ± 0.52	2.40 ± 1.38	6.38 ± 0.058
34–42	0.69 ± 0.32	59.1 ± 29.1	8.6 ± 3.7	0.48 ± 0.33	3.44 ± 2.12	12.17 ± 2.08
Unpaired *t* test	6.776	7.009	1.182	2.696	3.930	3.750
p	< 0.001	< 0.001	NS	0.008	< 0.001	< 0.001

* Data are mean ± SD, with *t* and *p* (two tailed). There were 165 samples from 55 infants in the 23 to 33 wk group and 46 samples from 14 infants in the 34 to 42 wk group.

We want to notice here that there is a difference in the glutathione concentration between the 23-33 week of gestation and the final weeks.

This mean that infant is exposed to more oxidants and the difference in the value is very significant.

Proteins, DNA and Lipids will be affected by ROS

e.g. Protein-SH, Oxo8dG and lipid peroxidation.

هاد اخر سلايد حكاه الدكتور ما بعرف شو وضع باقي السلايدات

Oxygen toxicity can cause damage at multiple levels

1. System wide cellular injury
2. Airway injury
3. Lung parenchymal injury

Airway Injury:

Many healthy volunteers will experience substernal heaviness, pleuritic chest pain, cough and dyspnea within 24 hours of breathing pure oxygen.

This is a result of tracheobronchitis and absorptive atelectasis.

Erythema and edema can be observed on bronchoscopy in patients treated with 90% FiO_2 for 6 hours.

Concentration of reactive oxygen species in exhaled gas increases after only 1 hour of breathing 28% oxygen, regardless of the presence of underlying lung disease

Bronchopulmonary dysplasia or BPD

- A disease in neonates following recovery from neonatal RDS.

- Characterized by epithelial hyperplasia and squamous metaplasia in the large airways, thickened alveolar walls, and peribronchial and interstitial fibrosis.

Lipid Peroxidation

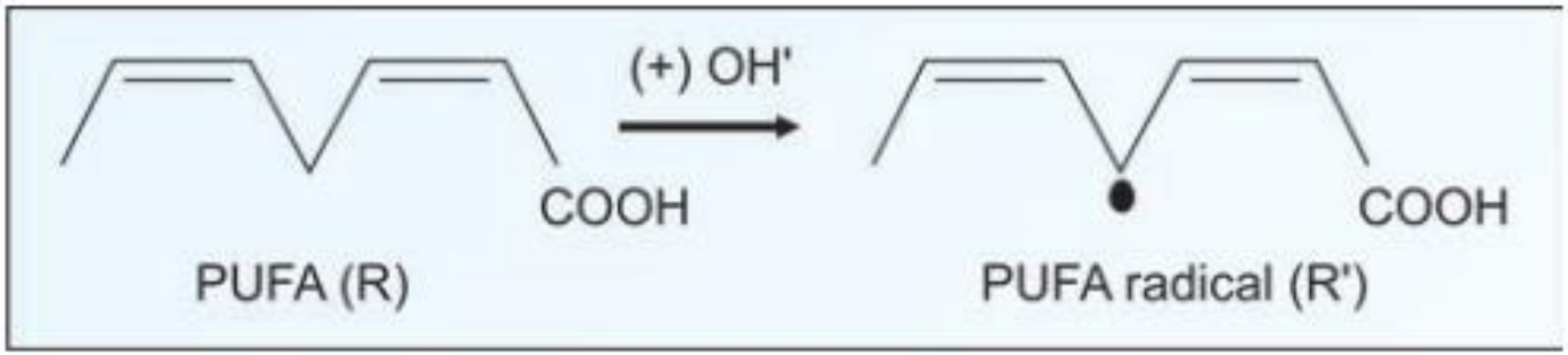

Fig. 20.9. Peroxidation of poly unsaturated fatty acids

Lipid Peroxidation

1. **Initiation Phase**

$$RH + OH^{\bullet} \xrightarrow[\text{metal ion}]{} R^{\bullet} + H_2O \quad \text{(Reaction 1-A)}$$

$$ROOH \longrightarrow ROO^{\bullet} + H^{+} \quad \text{(Reaction 1-B)}$$

2. **Propagation Phase**

$$R^{\bullet} + O_2 \rightarrow ROO^{\bullet} \quad \text{(Reaction No.2)}$$

$$ROO^{\bullet} + RH \rightarrow ROOH + R^{\bullet} \quad \text{(Reaction No.3)}$$

3. **Termination Phase**

$$ROO^{\bullet} + ROO^{\bullet} \rightarrow RO\text{--}OR + O_2 \quad \text{(Reaction 4-A)}$$

$$R^{\bullet} + R^{\bullet} \rightarrow R\text{--}R \quad \text{(Reaction 4-B)}$$

$$ROO^{\bullet} + R^{\bullet} \rightarrow RO\text{--}OR \quad \text{(Reaction 4-C)}$$

Role of Anti-Oxidants

- There are two types of anti-oxidants:
  1. **Preventive anti-oxidants:**
     - Catalase
     - Glutathione peroxidase,
     - Ethylene diamine tetra-acetate (EDTA).
  2. **Chain breaking anti-oxidants**
     - Superoxide dismutase
     - uric acid
     - vitamin E. **Alpha tocopherol**

Anti-oxidants

1. **Vitamin E** is the lipid phase antioxidant.
2. **Vitamin C** is the aqueous phase antioxidant.
3. **Ceruloplasmin** can act as an antioxidant in extracellular fluid (Chapter 28).
4. **Caffeine** is another effective anti-oxidant.
5. Cysteine, glutathione and **vitamin A** are minor anti-oxidants. **Beta carotene** can act as a chain breaking antioxidant, but is less effective than alpha tocopherol.

Anti-oxidants used as therapeutic agents

1. **Vitamin E**
2. **Vitamin C**
3. Dimethyl thio urea
4. Dimethyl sulfoxide
5. Allopurinol