بسم الله الرحمن الرحيم

Oxidative Stress and Atherosclerosis

By

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Lecture's Objectives

By the end of this lecture, students are expected to:

- define "Oxidative Stress"
- determine the molecular effects of oxidative stress
- list some of the diseases related to oxidative stress
- recall the types and sources of Reactive Oxidative Species
- recognize the mechanisms of various anti-oxidants
- identify the components and role of glutathione peroxidase/reductase system
- determine the biochemical basis of G6PD deficiency and to hemolytic anemia
- determine molecular & vascular oof ROS
- recall NO synthesis requirements
- determine the effects of NO, and its roles in oxidative stress
- relate the oxidative stress to the pathogenesis of atherosclerosis

Oxidative stress

- **A condition in which cells are subjected to excessive levels of Reactive Species (Oxygen or Nitrative species) & they are unable to counterbalance their deleterious effects with antioxidants.**

- **It has been implicated in the ageing process & in many diseases (e.g., atherosclerosis and coronary heart diseases).**

Oxidative Stress

Imbalance between oxidant production and antioxidant mechanisms

Oxidative damage to:

DNA

Proteins

Lipids (unsaturated fatty acids)

Oxidative stress and diseases:

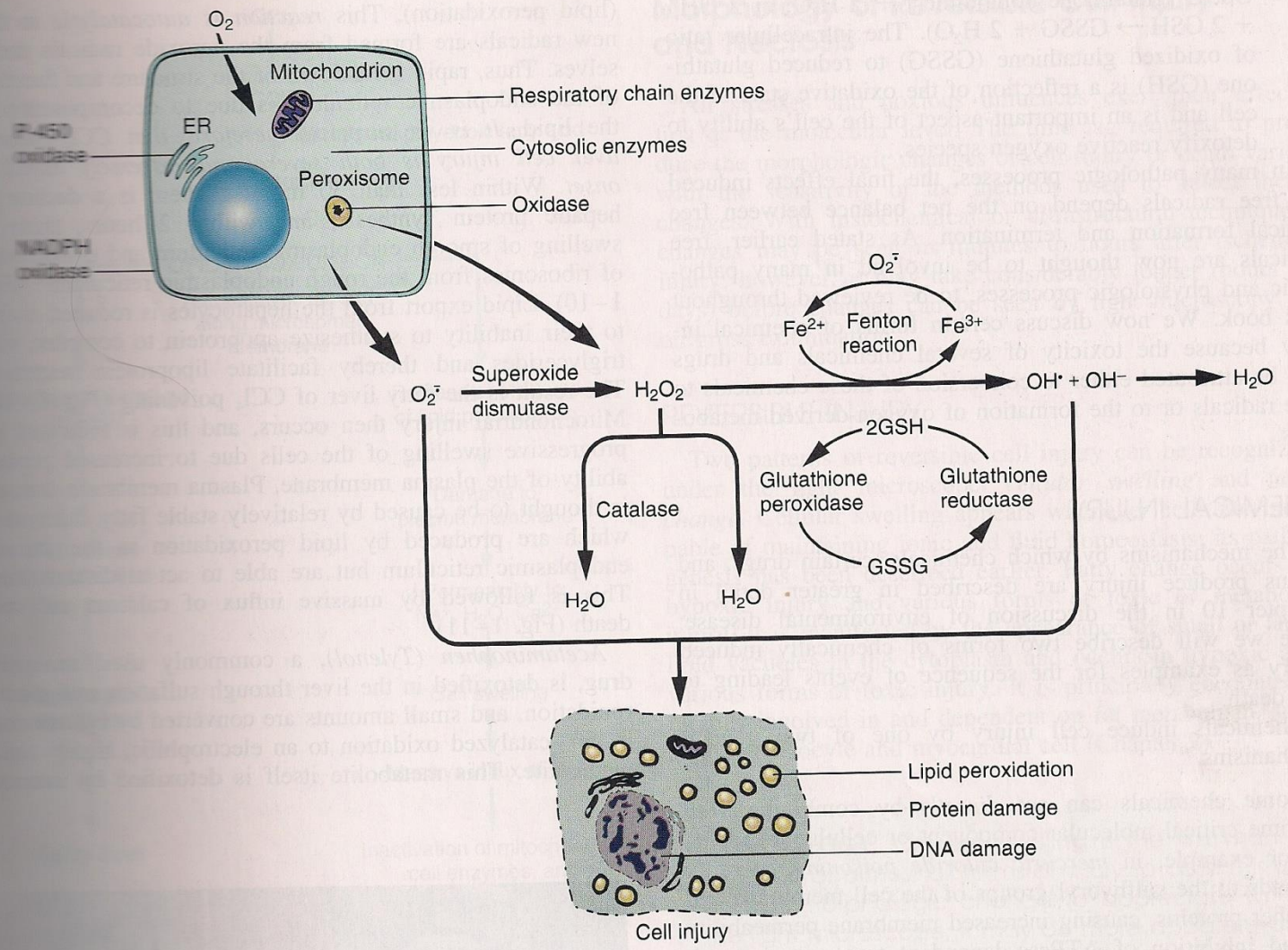
Inflammatory conditions e.g., Rheumatoid arthritis

Athersclerosis and coronary heart diseases

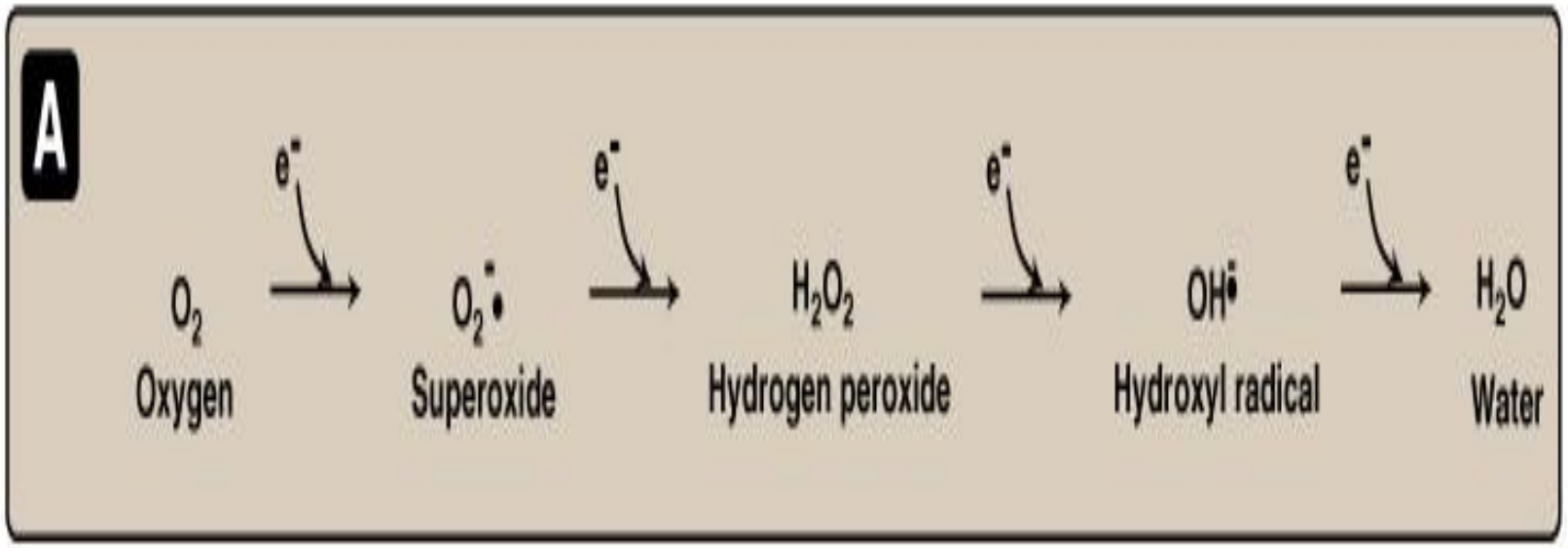
Obesity

Cancers

G6PD deficiency hemolytic anemia


O_2
Mitochondrion
Respiratory chain enzymes
ER
P-450 oxidase
Cytosolic enzymes
Peroxisome
Oxidase
NADPH oxidase
$O_2^{\cdot-}$
Fe^{2+}
Fenton reaction
Fe^{3+}
$O_2^{\cdot-}$
Superoxide dismutase
H_2O_2
$OH^{\cdot} + OH^-$
H_2O
2GSH
Glutathione peroxidase
Glutathione reductase
Catalase
GSSG
H_2O
H_2O
Lipid peroxidation
Protein damage
DNA damage
Cell injury

Reactive Oxygen Species (ROS)

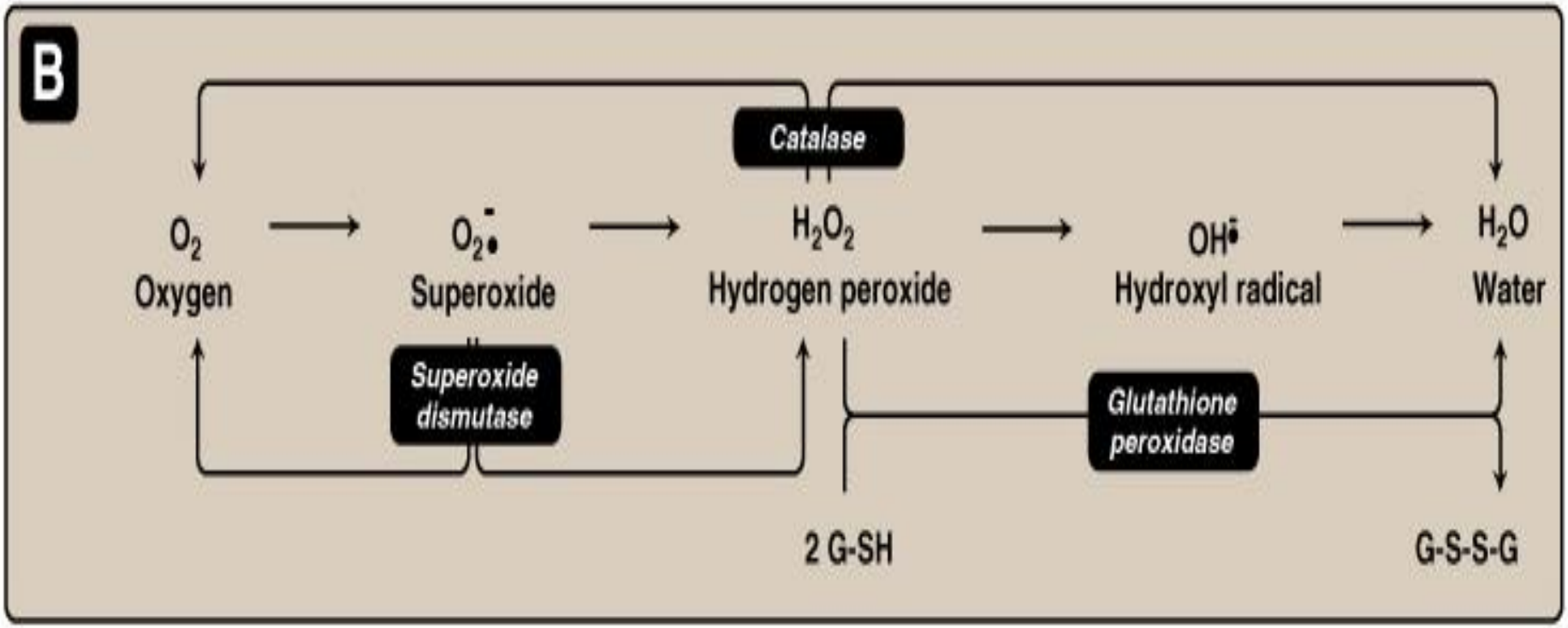


Oxygen-derived free radicals :

e.g., Superoxide and hydroxyl radicals

Non-free radical: Hydrogen peroxide

Antioxidant Mechanisms



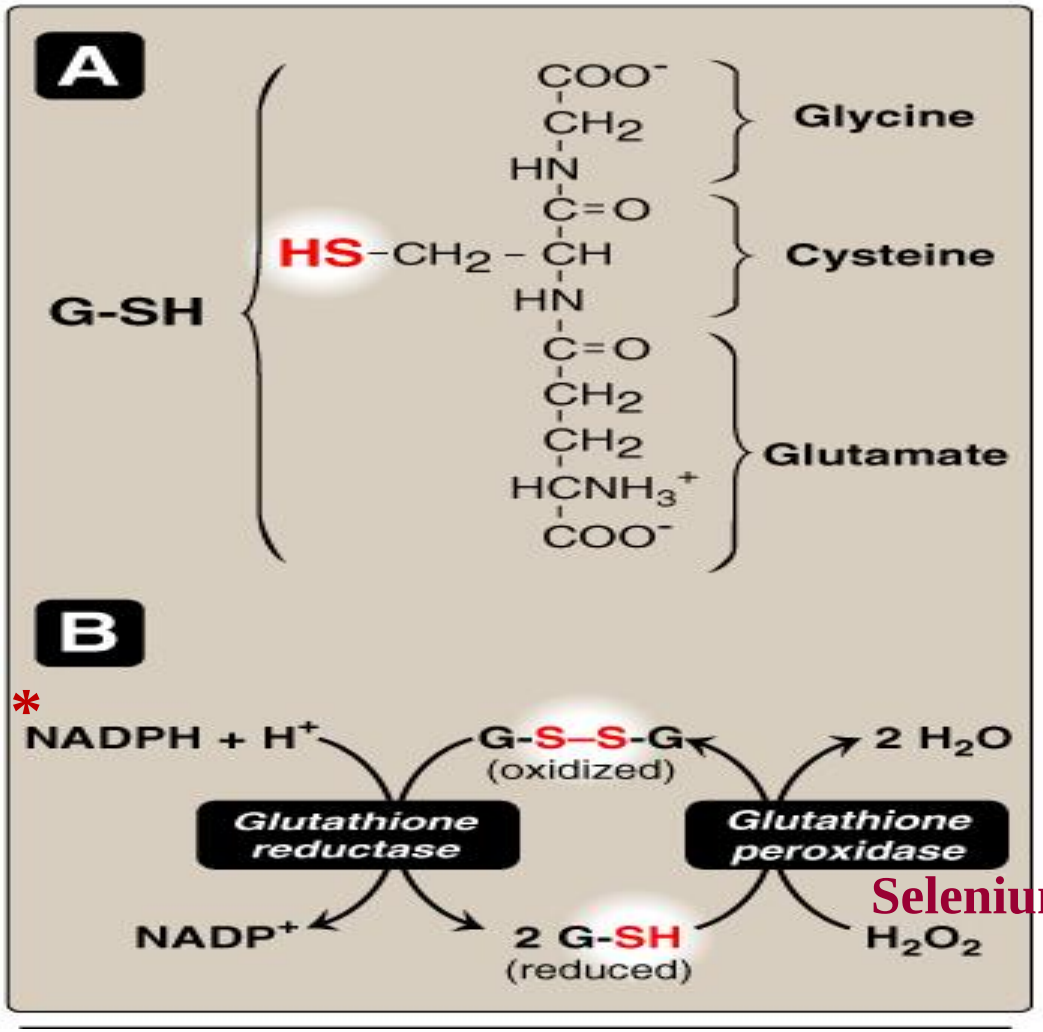
ROS: Types and Sources

- **Types:**
  - **Free radical:**
    Superoxide ($O_2^{\cdot}$) –
    Hydroxyl radical ($OH^{\cdot}$)
    Peroxyl radical ($ROO^{\cdot}$)
  - **Non free radical:**
    Hydrogen peroxide (H_2O_2)
- **Sources:**
  - **During course of metabolism**
    e.g., $O_2^{\cdot -}$ **by auto-oxidation of hemoglobin and xanthine oxidase**
    $OH^{\cdot}$ **by Fenton reaction**
    $O_2^{\cdot -}$ **,** H_2O_2 **,** $OH^{\cdot}$ **By partial reduction of molecular oxygen in electron transport chain in mitochondria**
  - **Ingestion of toxins, chemicals or drugs**

Antioxidants

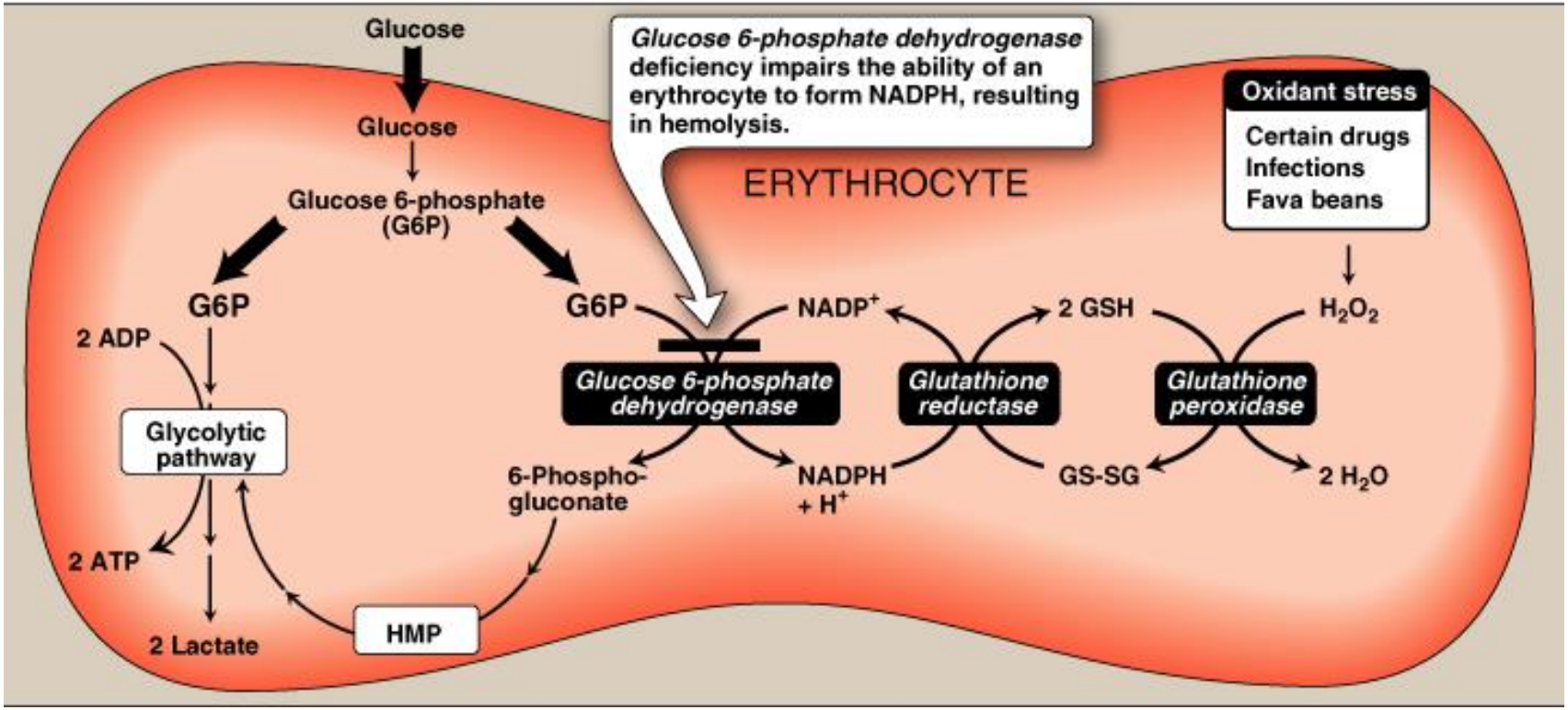
- **Enzymes:**
  - **Superoxide dismutase**
  - **Catalase**
  - **Glutathione system (glutathione, NADPH, reductase, peroxidase & selenium)**
- **Vitamins:**
  - **Vitamin C (ascorbic acid)**
  - **Vitamin A and β-carotenes**
  - **Vitamin E**
- **Trace elements:**
  - **Selenium**

Glutathione System



* Glucose-6-phosphate dehydrogenase (G-6-PD) is the main source for NADPH generation and is, therefore, essential for proper function of glutathione system

Biochemical Basis of G6PD Deficiency Hemolytic Anemia



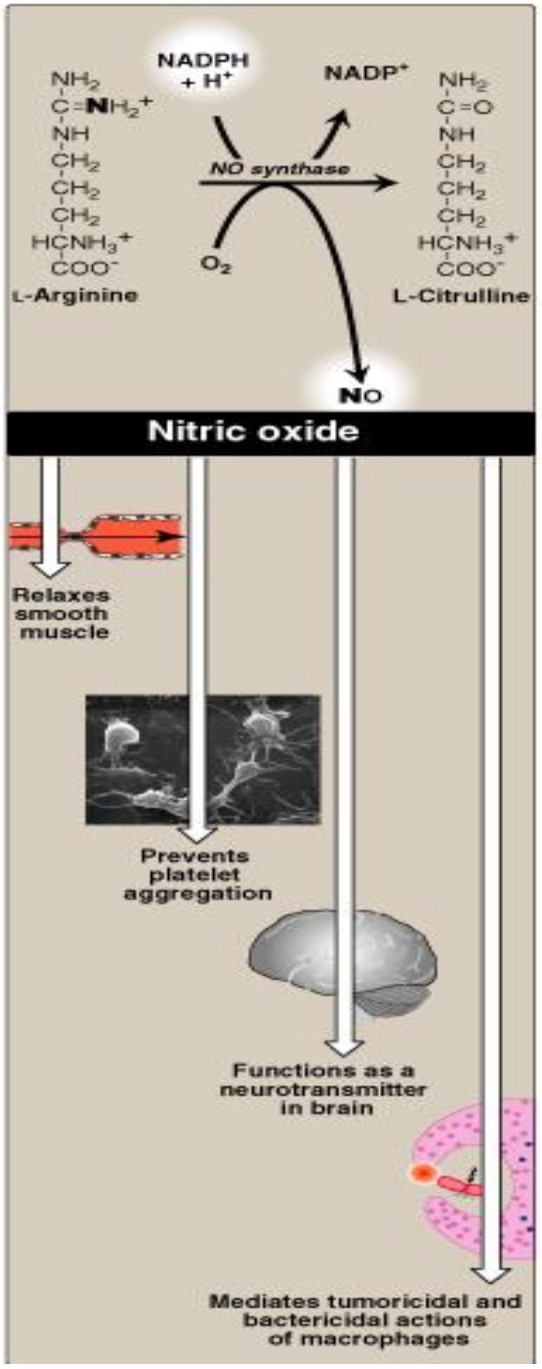
Molecular & Vascular Effects of ROS

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

- **Vascular effects:**
  - **Altered vascular tone**
  - **Increased endothelial cell permeability**

Nitric Oxide (NO)

- **NO:**
  - 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
  - Neurotransmitter in brain
  - Bactricidal & Tumoricidal effects



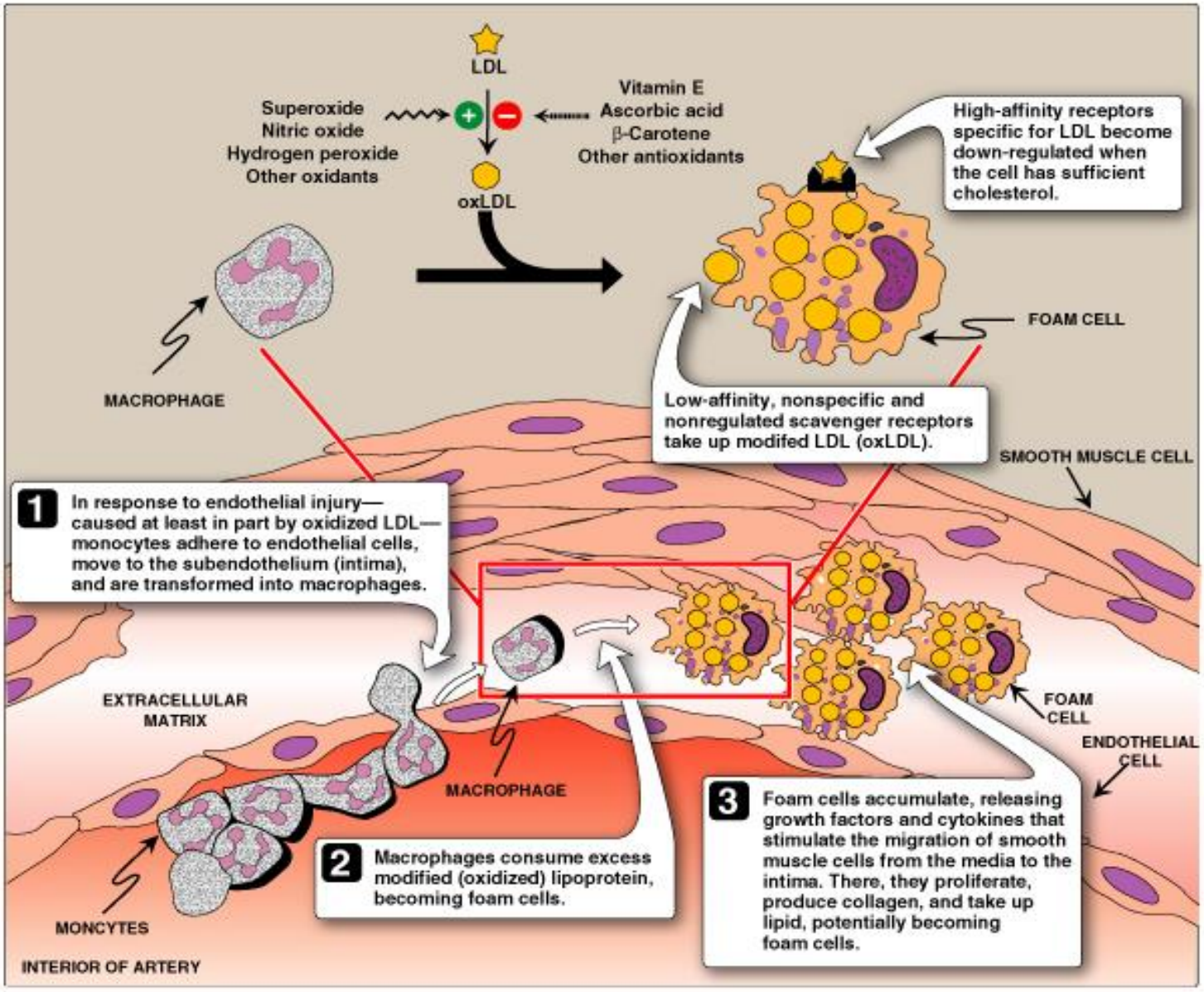
Oxidative Stress: Role of Nitric Oxide (NO)

- **This may be both beneficial and detrimental, depending upon when and where NO is released**
- **NO produced by endothelial NOS (eNOS) → improving vascular dilation and perfusion (i.e., beneficial).**

  Vasodilators such as nitroglycerin 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 detrimental effects.**
- **Increased iNOS activity is generally associated with inflammatory processes**

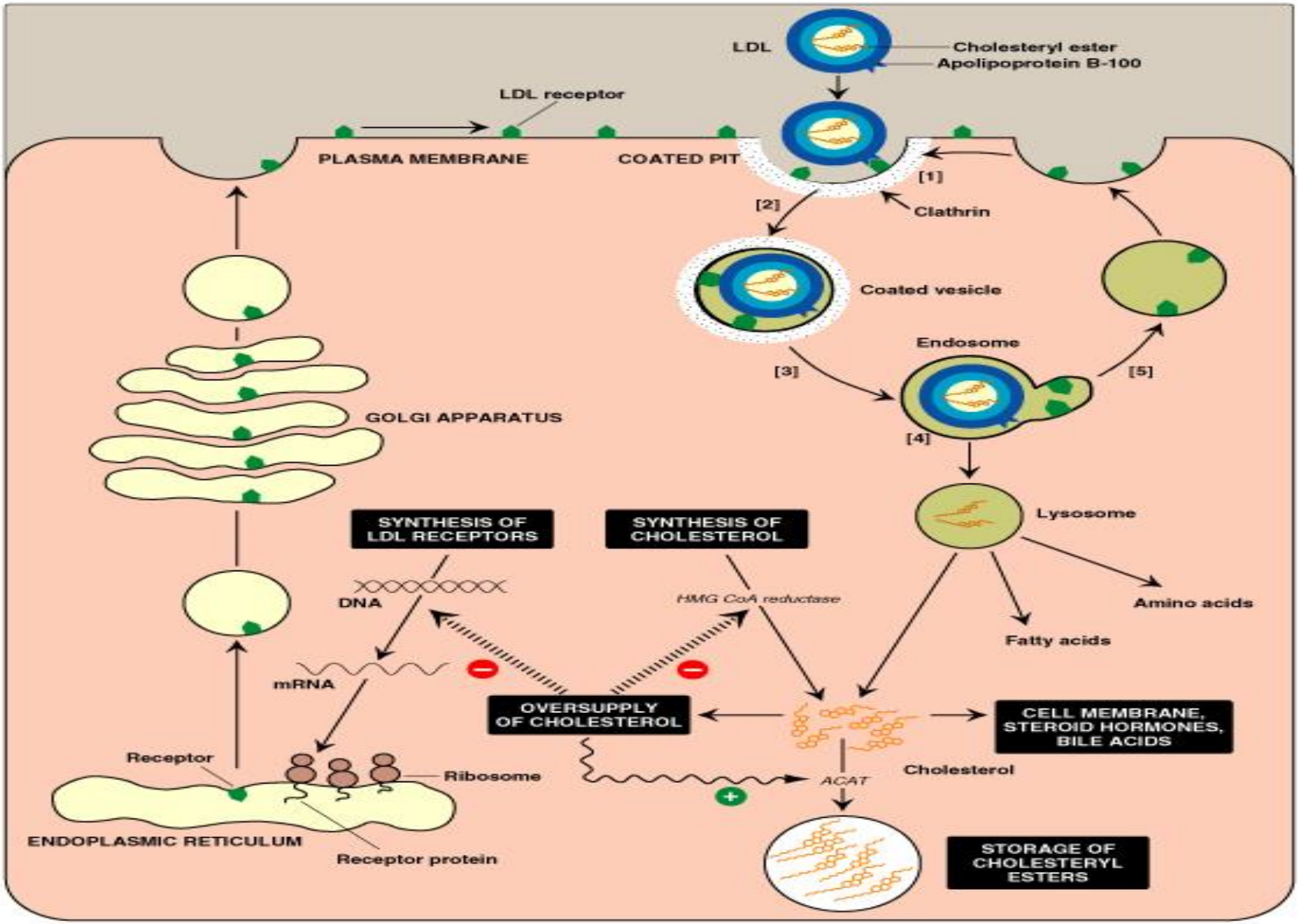
Pathogenesis of Atherosclerosis

- Modified (oxidized) LDL … Oxidative stress
  (imbalance between oxidants and antioxidants)
- Endothelial injury of arterial wall
- Adherence of monocytes to endothelial cells and their movement into intima where it becomes macrophages
- Uptake of oxLDL by macrophage scavenger receptor:
  Scavenger receptor class A (SR-A)
  Low-affinity, non-specific receptor
  Un-regulated receptor
- Foam cell transformation: Accumulation of excess lipids inside the cells (unregulated receptor)
- Atherosclerotic plaque formation



Atherosclerotic plaque Formation

Compare to physiological uptake of LDL (unmodified) by high-affinity, specific & tightly regulated LDL-Receptor



LDL: Receptor-Mediated Endocytosis