Oxidative Stress

Cardiovascular System Block

Objectives

By the end of this lecture, the First Year students will be able to:

- Define oxidative stress
- Understand the harmful effects of oxidative stress to the cell and its diseases
- List the types, sources and effects of Reactive Oxygen Species (ROS)
- List various antioxidants in the body
- Understand the role of glutathione system in detoxifying oxidants in the body
- Discuss how G6PD deficiency leads to oxidative stress
- Understand the role of Reactive Nitrogen Species (RNS) in contributing to oxidative stress
- Correlate the role of oxidative stress to pathogenesis of atherosclerosis

Overview

- Oxidative stress
- Reactive Oxygen Species (ROS): types, sources, effects
- Antioxidants
- Glutathione system
- G6PD deficiency
- Nitric oxide (NO): Reactive Nitrogen Species (RNS)
- Oxidative stress and atherosclerosis

Oxidative stress

- A condition in which cells are exposed to excessive levels of:
  - Reactive Oxygen Species (ROS) or
  - Reactive Nitrogen Species (RNS)
- Cells are unable to neutralize their deleterious effects with antioxidants
- Oxidative stress is implicated in atherosclerosis, CAD, ageing

Oxidative stress

- Cellular imbalance of oxidants and antioxidants damages:
  - DNA, proteins, lipids
- Diseases due to oxidative stress:
  - Inflammatory diseases (rheumatoid arthritis), atherosclerosis, CAD, obesity, cancer, G6PD deficiency hemolytic anemia

Reactive Oxygen Species (ROS)

- Incomplete reduction of oxygen to water produces ROS
- ROS are continuously formed:
  - As byproducts of aerobic metabolism
  - Thru reactions with drugs and toxins
  - When cellular antioxidant level is low
  - Creating oxidative stress in cell
- ROS can damage DNA, proteins, unsaturated lipids → cell death
- Cells have protective antioxidant mechanisms that neutralize ROS

Reactive Oxygen Species (ROS)

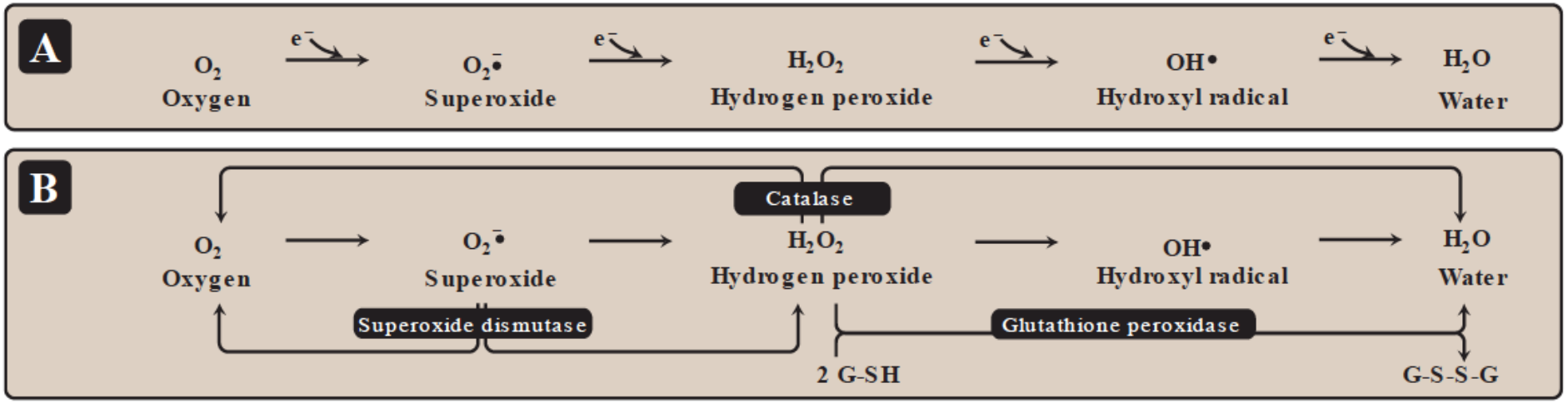


Figure 13.5

A. Formation of reactive intermediates from molecular oxygen. e⁻ = electrons. B. Actions of antioxidant enzymes. G-SH = reduced glutathione; G-S-S-G = oxidized glutathione. (See Figure 13.6B for the regeneration of G-SH.)

Types and sources of ROS

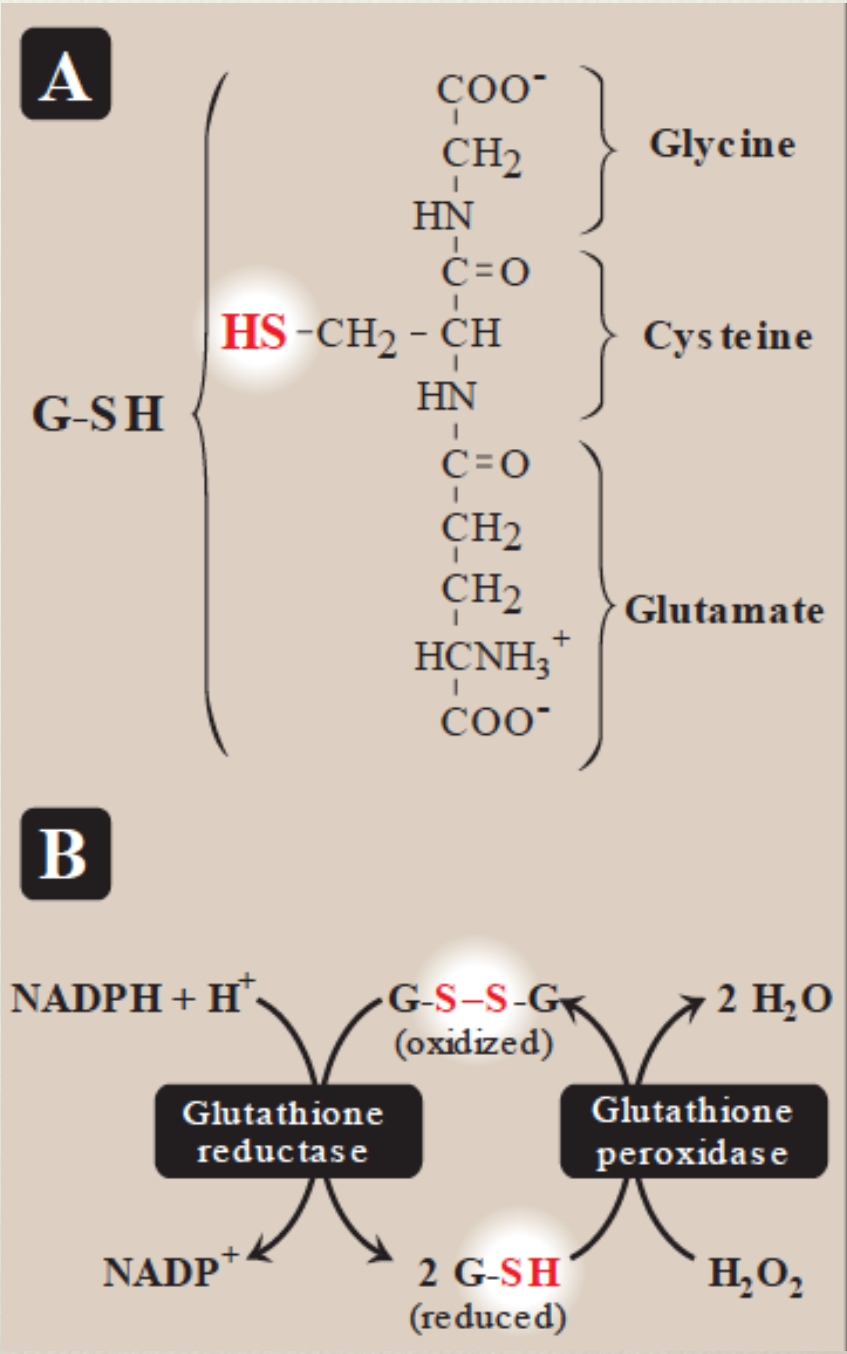
- Free radicals:
  - Superoxide ($O_2^{\bullet -}$)
  - Hydroxyl radical ($OH^{\bullet}$)
- Non-free radical:
  - Hydrogen peroxide (H_2O_2)
- Sources:
  - Aerobic metabolism
  - Partial reduction of molecular oxygen in ETC
  - Ingestion of drugs, toxins, chemicals

Antioxidants

- Enzymes:
  - Superoxide dismutase
  - Catalase
  - Glutathione system
- Vitamins:
  - Vitamins A, C, E
  - β-Carotene

Glutathione system

- Present in most cells
- Chemically detoxifies H_2O_2
- Catalyzed by glutathione reductase
- Uses NADPH that reduces glutathione which reduces H_2O_2



G6PD deficiency

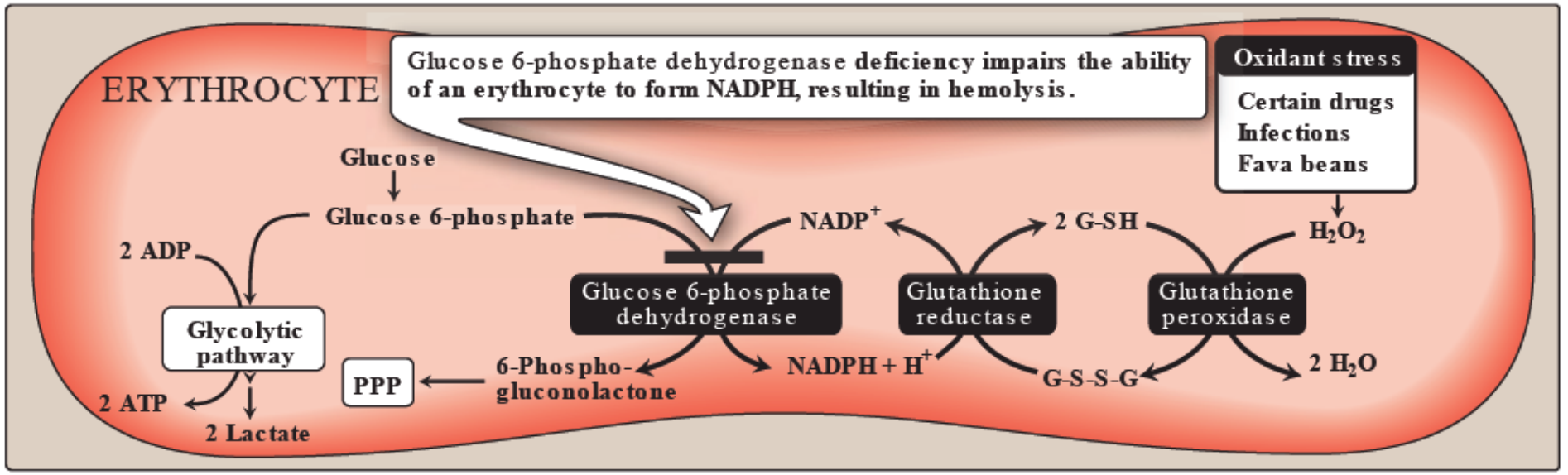


Figure 13.10

Pathways of glucose 6-phosphate metabolism in the erythrocyte. NADP(H) = nicotinamide adenine dinucleotide phosphate; G-SH = reduced glutathionine; G-S-S-G = oxidized glutathionine; PPP = pentose phosphate pathway.

- Leads to NADPH deficiency
- Cells are unable to reduce free radicals
- Oxidation of cellular proteins is increased causing impaired cell functions

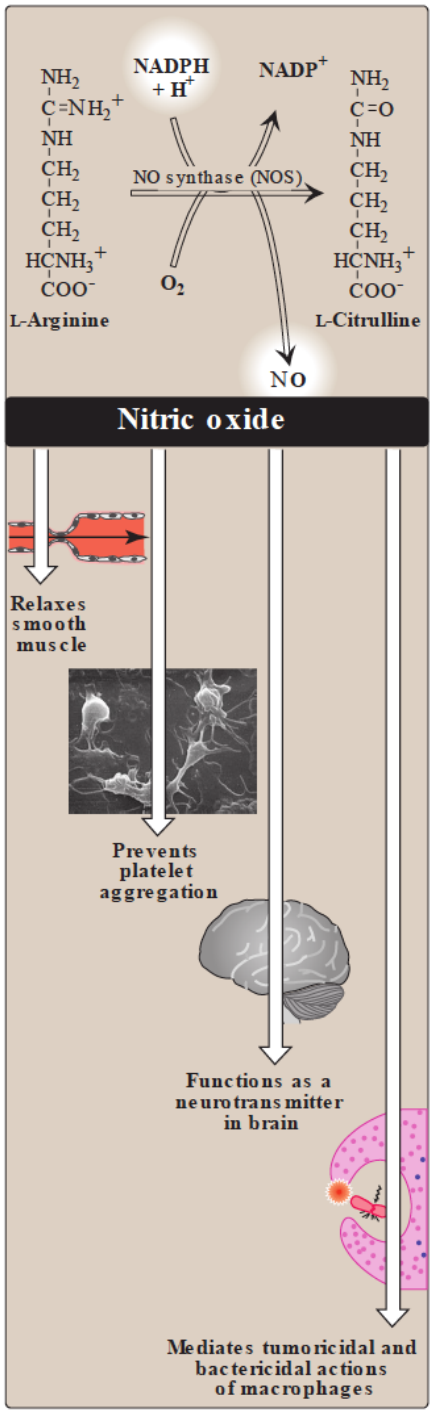
Effects of ROS

- Lipid peroxidation (polyunsaturated fatty acids)
- DNA damage
- Protein denaturation
- Cytoskeletal damage
- Chemotaxis
- Cell signaling effects
  - Release of Ca^{2+} from intracellular stores
- Altered vascular tone
- Increased endothelial cell permeability

Nitric oxide (NO)

- Endothelial-derived relaxing factor
- Causes vasodilation by relaxing vascular smooth muscle
- NO is a gas with short half-life (3-10 sec)
- NO + Oxygen/Superoxide → Nitrates, Nitrites, Peroxynitrite ($O{=}NOO^-$)
- Peroxynitrite is a Reactive Nitrogen Species (RNS)

Synthesis and some of the actions of nitric oxide (NO). NADPH = reduced nicotinamide adenine dinucleotide phosphate. [Note: Flavin mononucleotide, flavin adenine dinucleotide, heme, and tetrahydrobiopterin are additional coenzymes required by NOS.]



Nitric oxide (NO)

- NO is produced by nitric oxide synthase:
  - eNOS in the endothelium (vaso-relaxation)
  - nNOS in the neural tissue (neurotransmission)
  - iNOS in macrophages, neutrophils (infection)
  - bNOS (bacterial)
- iNOS activity (normally low) increased by infection and pro-inflammatory cytokines
- Activated macrophages produce $O_2\bullet^-$ radical + NO → OH• radical → highly bactericidal
- Increased iNOS activity → free radicals → oxidative stress

Oxidative stress and atherosclerosis

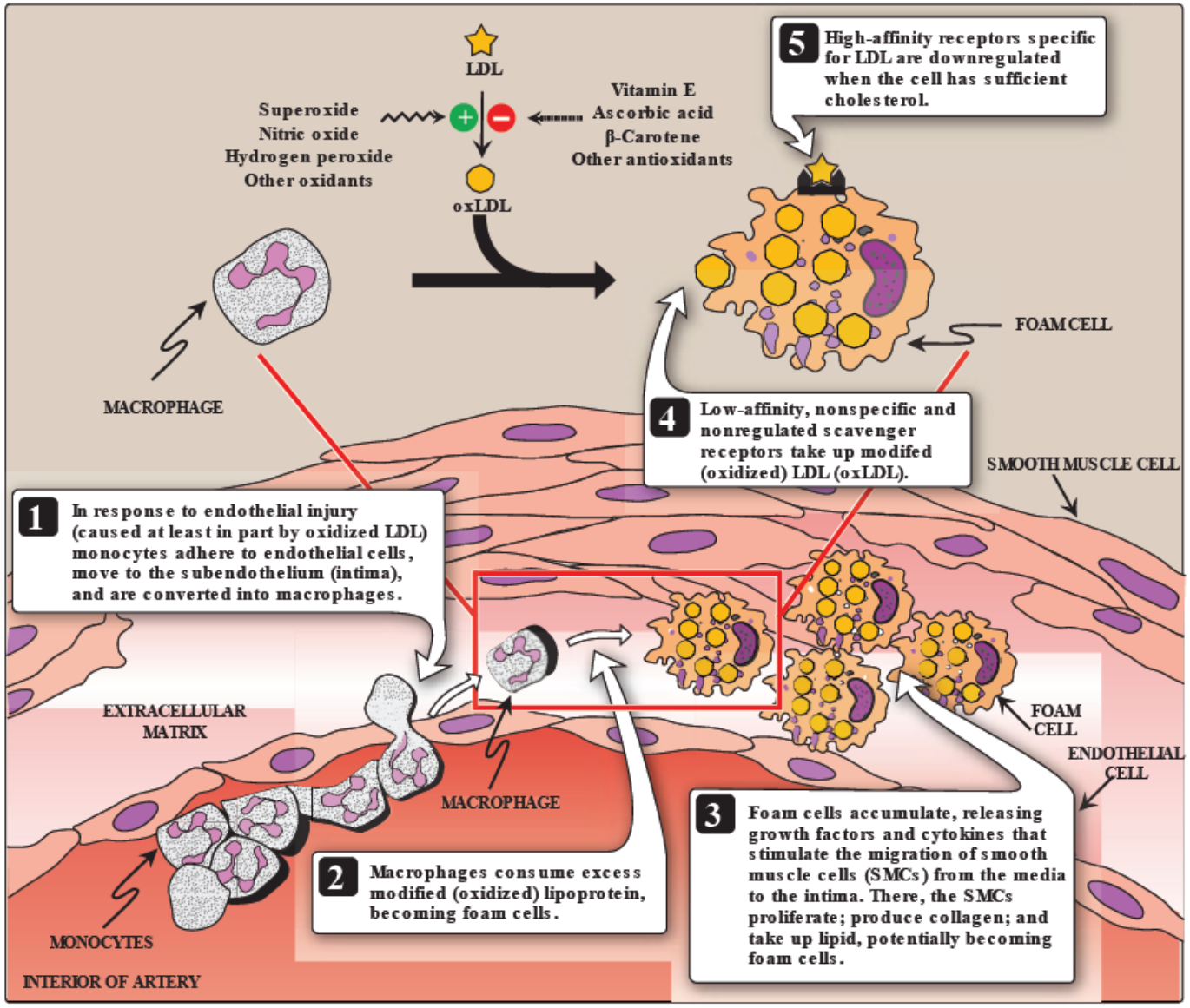


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Take home message

- Oxidative stress is due to excessive production of ROS and NOS in the cells.
- Cells neutralize these oxidants by a number of antioxidant processes.
- Imbalance between oxidants and antioxidants in the cells can result in the development of many diseases including atherosclerosis.

References

- Lippincott's Biochemistry, 6th Edition, Chapter 13, pp. 148-152. Lippincott Williams & Wilkins, New York, USA.