

Oxidative Stress

Cardiovascular System Block

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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)

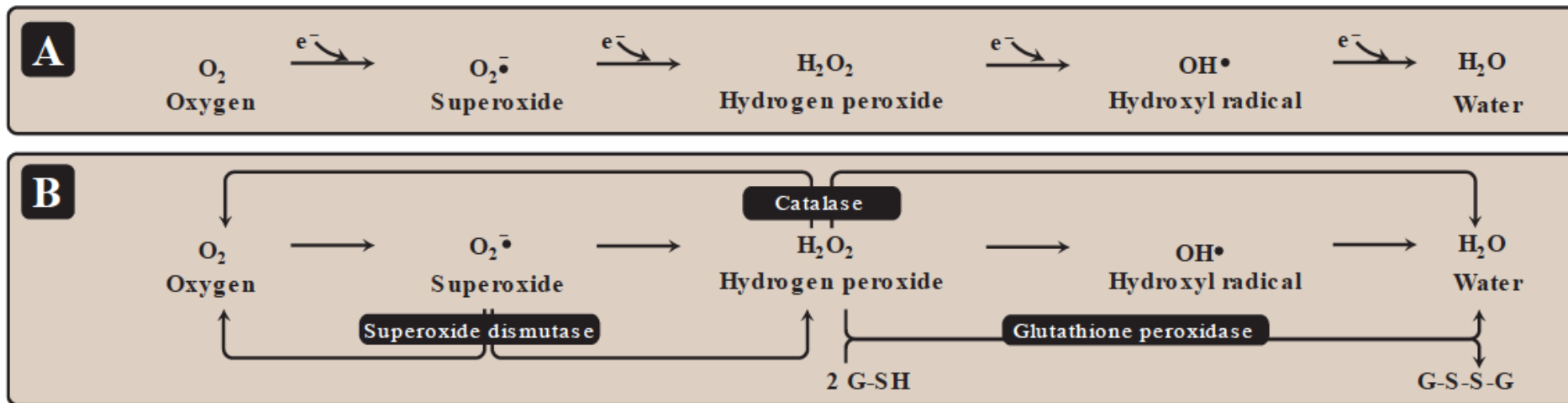


Figure 13.5

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:

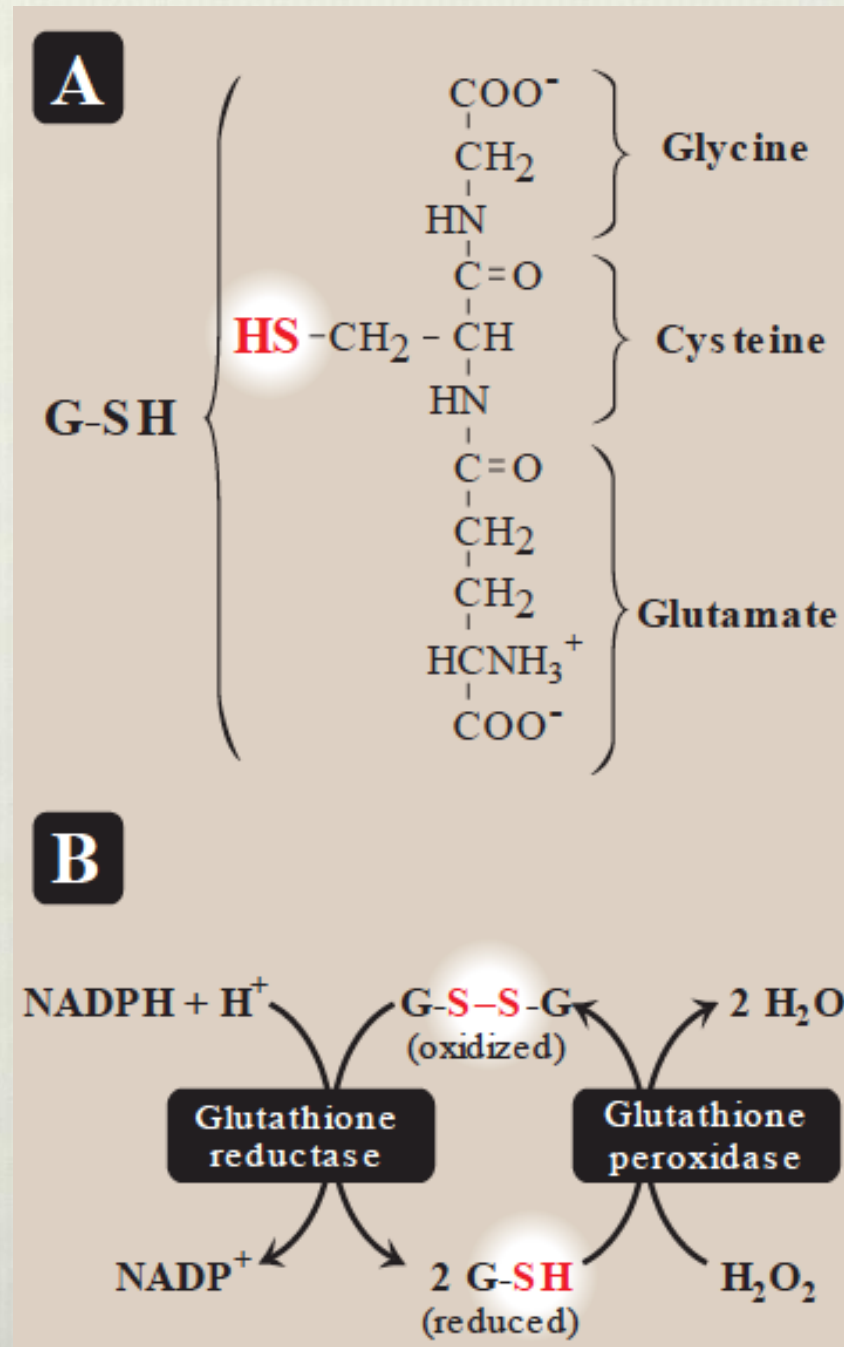
- ❖ Superoxide dismutase
- ❖ Catalase
- ❖ Glutathione system

❖ Vitamins:

- ❖ Vitamins A, C, E
- ❖ β -Carotene

Glutathione system

- ❖ Present in most cells
- ❖ Chemically detoxifies H_2O_2
- ❖ Catalyzed by glutathione reductase
- ❖ Produces **NADPH** that reduces H_2O_2



G6PD deficiency

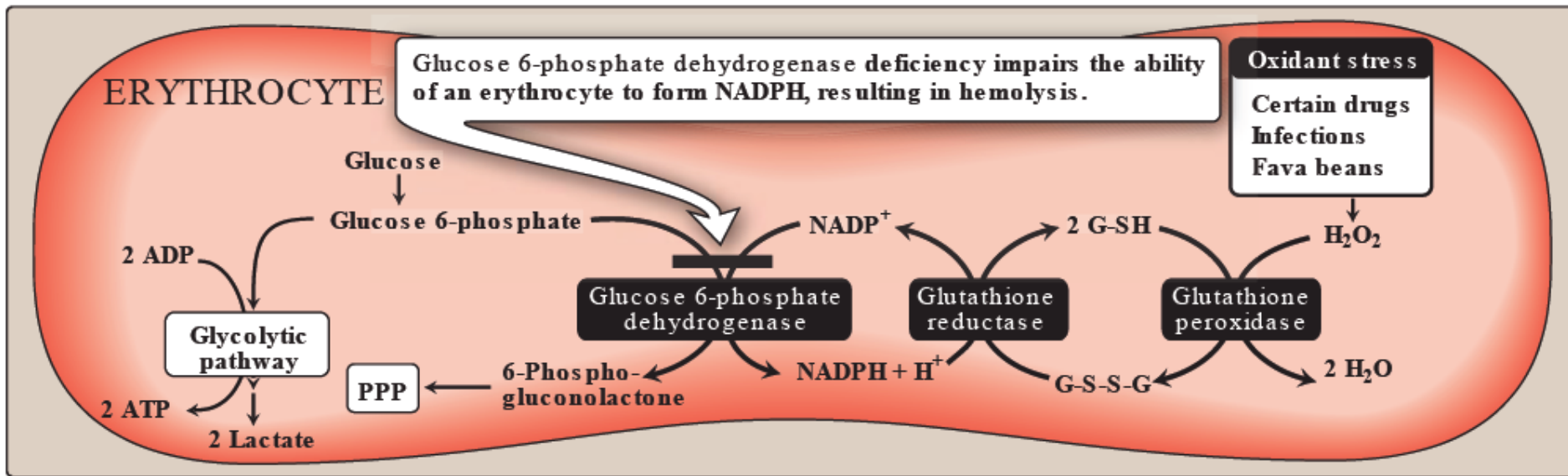


Figure 13.10

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

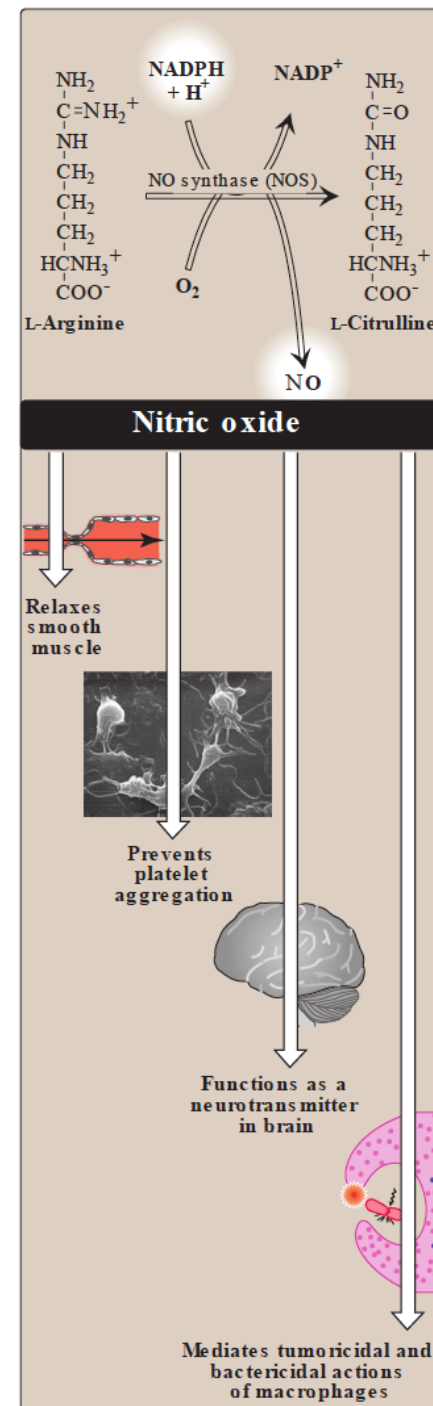
Effects of ROS

- ❖ 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

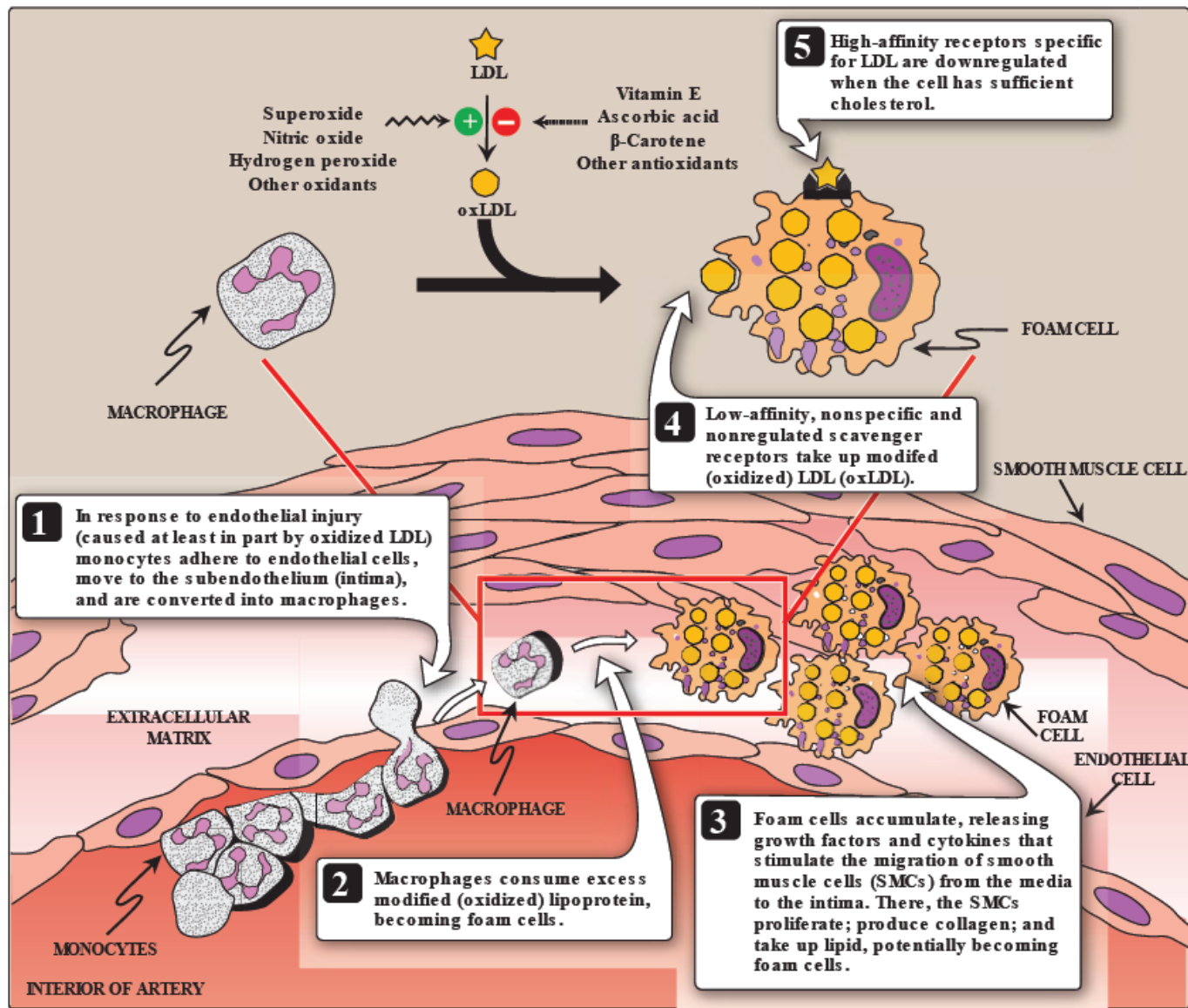


Figure 18.22

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.