SB20

Hypoxia and hyperoxia

- The ME**LA**S syndrome (mitochondrial encephalopathy, **lactic acidosis** and stroke-like episodes)

- is a **mitochondrial disease** with **heart manifestations**
- in which hypertrophic cardiomyopathy is the most outstanding.

- A pregnant 23-year-old female undergoes neurology and cardiology consultations for possible mitochondrial disease

- On **ECG** concentric **ventricular hypertrophy** and normal ventricular function were found, with no other cardiovascular history

- Her **mother** had died at 42 years of age diagnosed with MELAS syndrome, with **hypertrophic cardiomyopathy**, multiple episodes of acute lung oedema, deafness and repeat ictus.

- Her **grandmother** had died in the fourth decade of life due to non-specified **heart causes.**

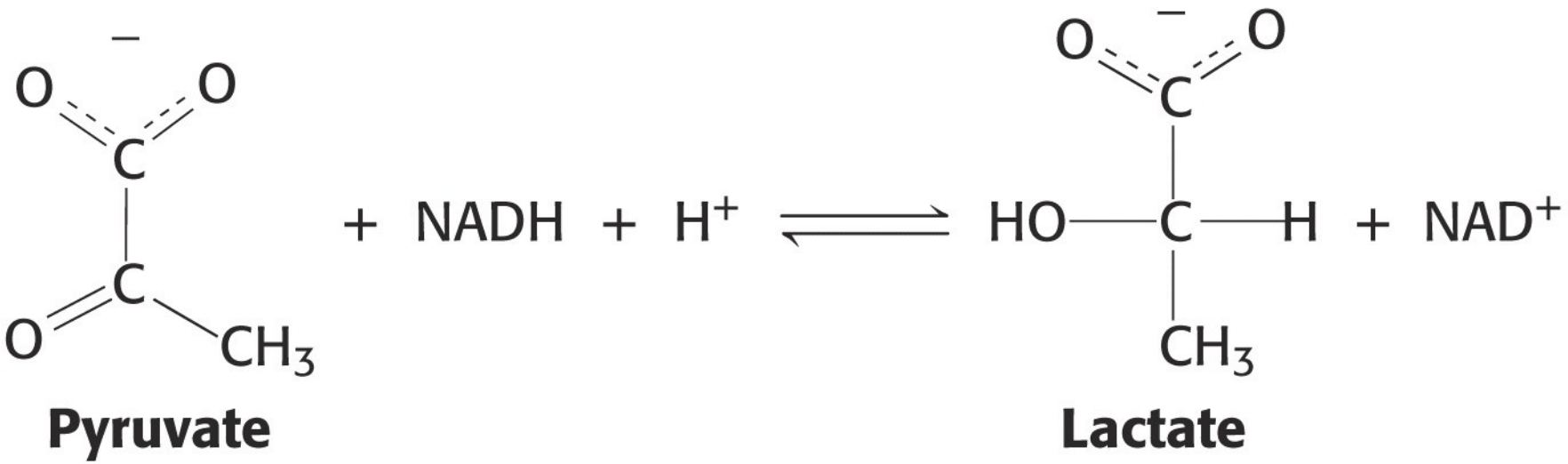
- From the **20th week of gestation** on she began to have episodes in which she had **difficulty breathing** accompanied occasionally by typical **chest pain**.

- Which substrates are oxidized in the respiratory chain?

- What will be the ratio of NADH and NAD^+ concentrations in hypoxia?

- How increased concentrations of NADH will affect upon concentration of lactate?

- Lactate can be elevated up to 30 fold



Hyperoxia

What are free radicals?

- Free radicals are highly reactive molecular species
- with an unpaired electron.

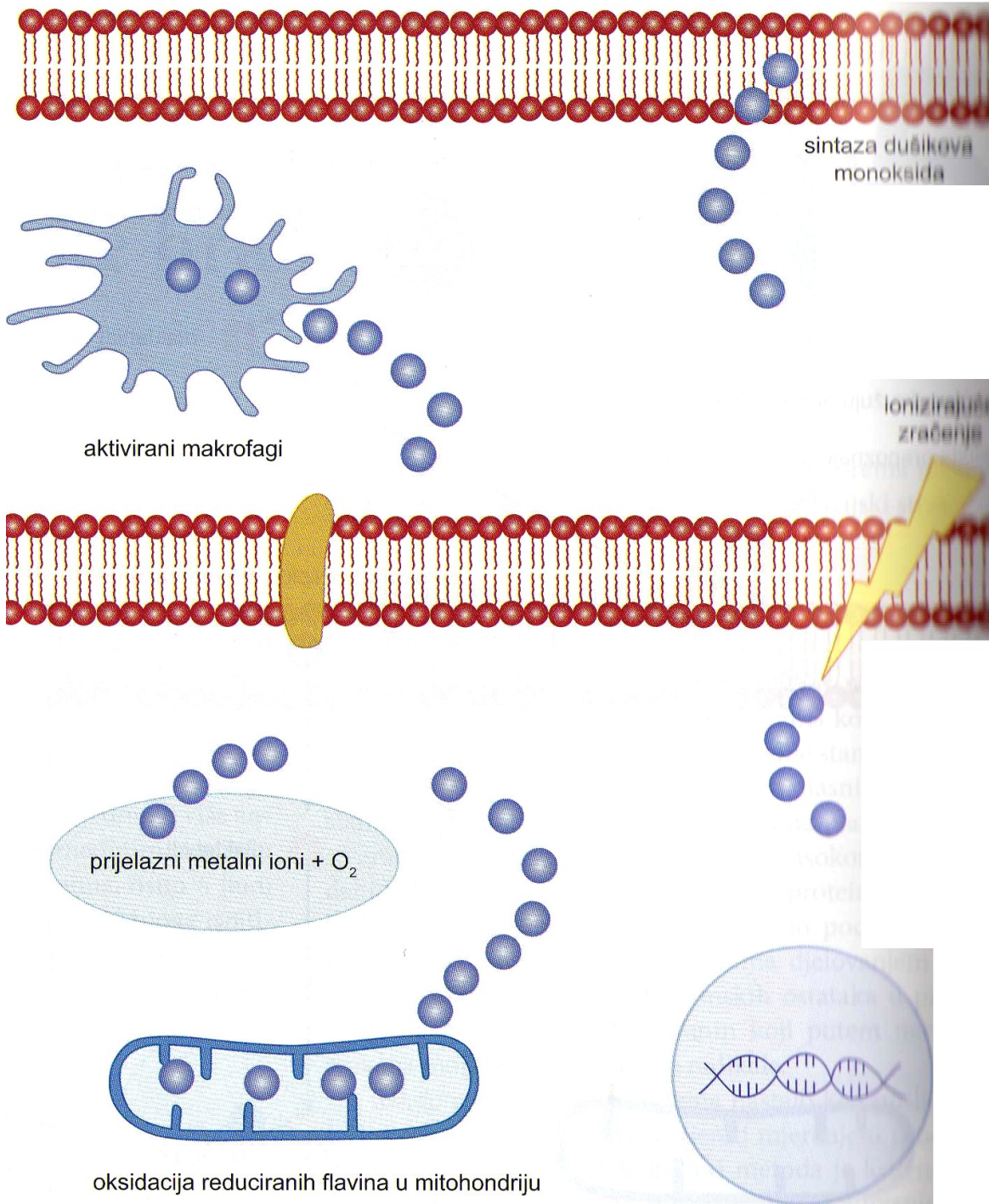
- They can react with, and modify, proteins, nucleic acids and fatty acids in cell membranes and plasma lipoproteins.

List some of the oxygen radicals (reactive oxygen species)

- superoxide ($O_2 \cdot^-$)
- hydroxyl ($OH\cdot$)
- perhydroxyl ($O_2H\cdot$)

List the sources of oxygen radicals from figure 45-2.

- **Oxygen radicals arise as a result of**
- exposure to ionizing radiation,
- nonenzymic reactions of transition metal ions,
- respiratory burst of activated macrophages,
- and the normal oxidation of reduced flavin coenzymes.



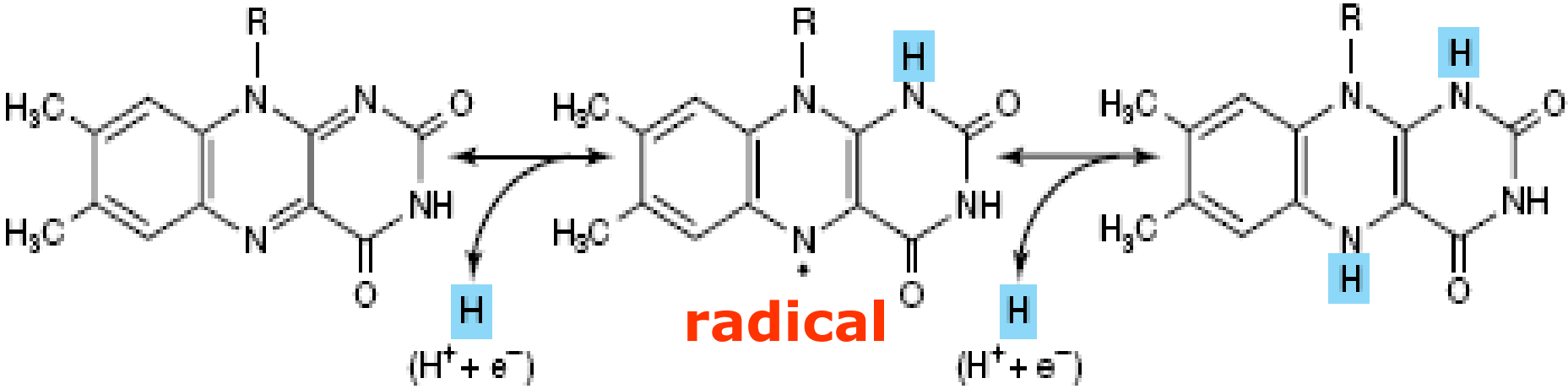
- What is the role of oxygen radicals in activated macrophages?

  Why it is important to have specific protein carriers in the body for transition metal ions?

- In the respiratory chain

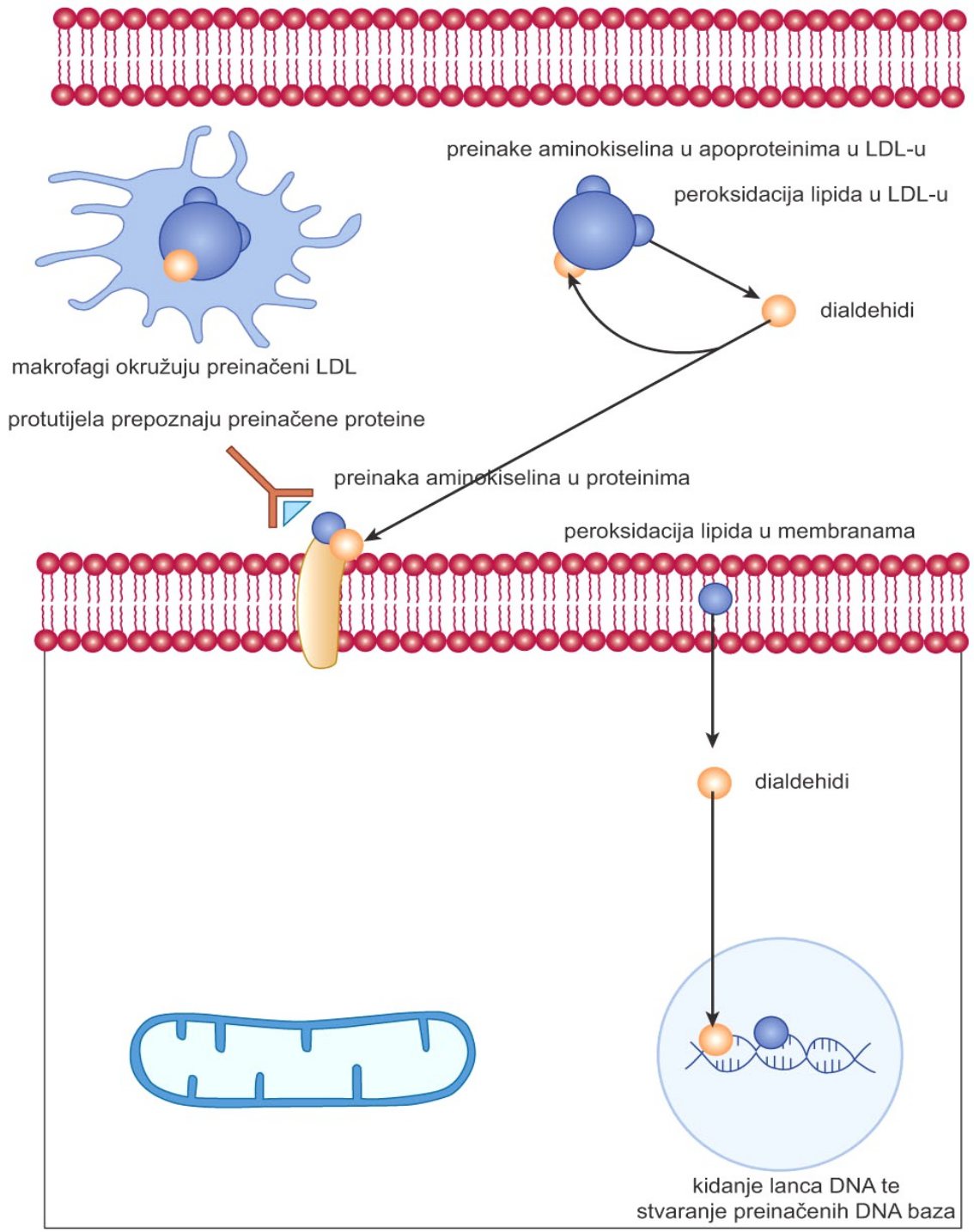
  oxidation of reduced flavin groups

  transfer of electrones results with intermediates - radicals



What diseases are caused by DNA damage?

According to Figure 45-1 explain how radicals can cause autoimmune disease and atherosclerotic plaques.

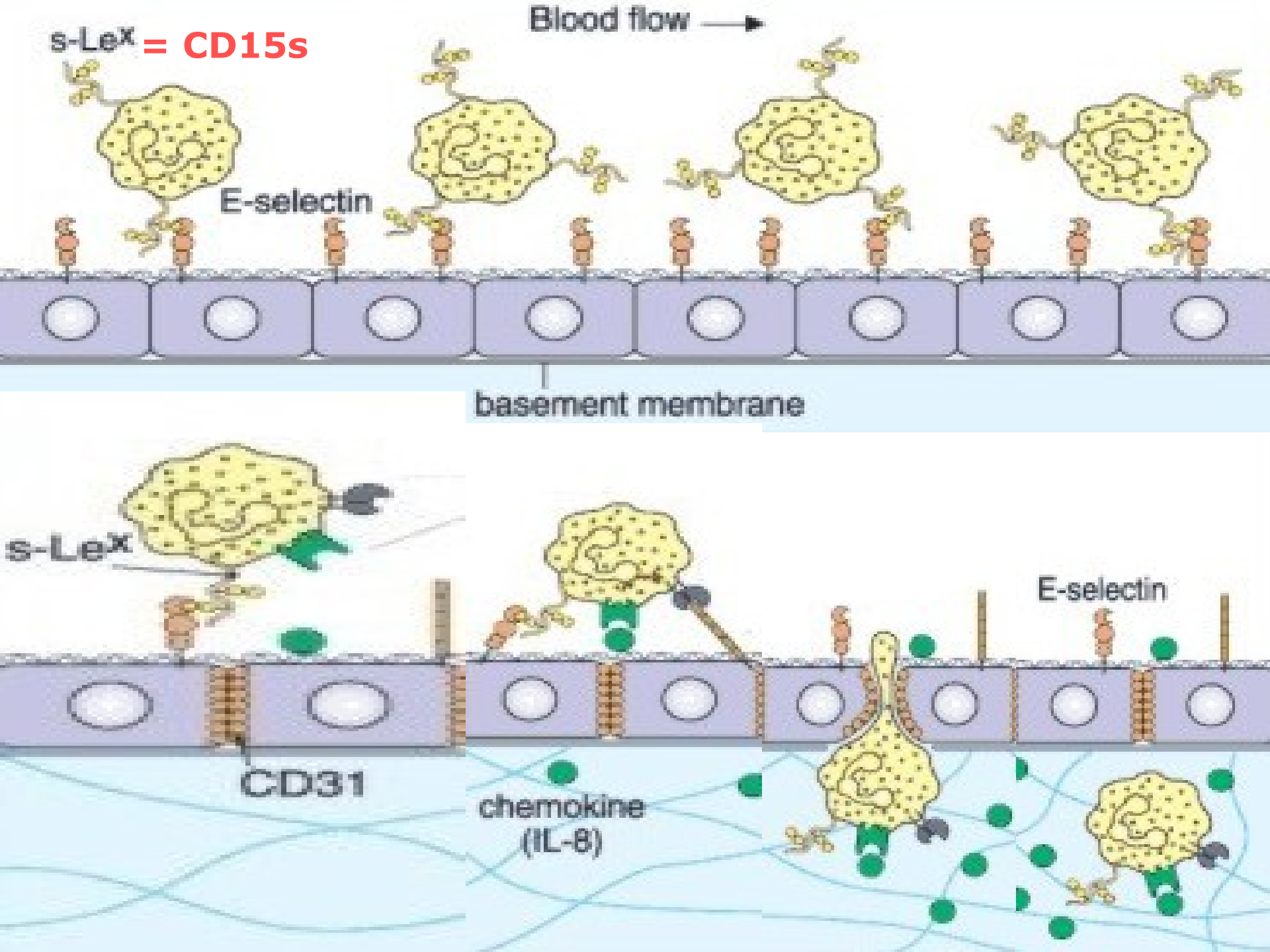


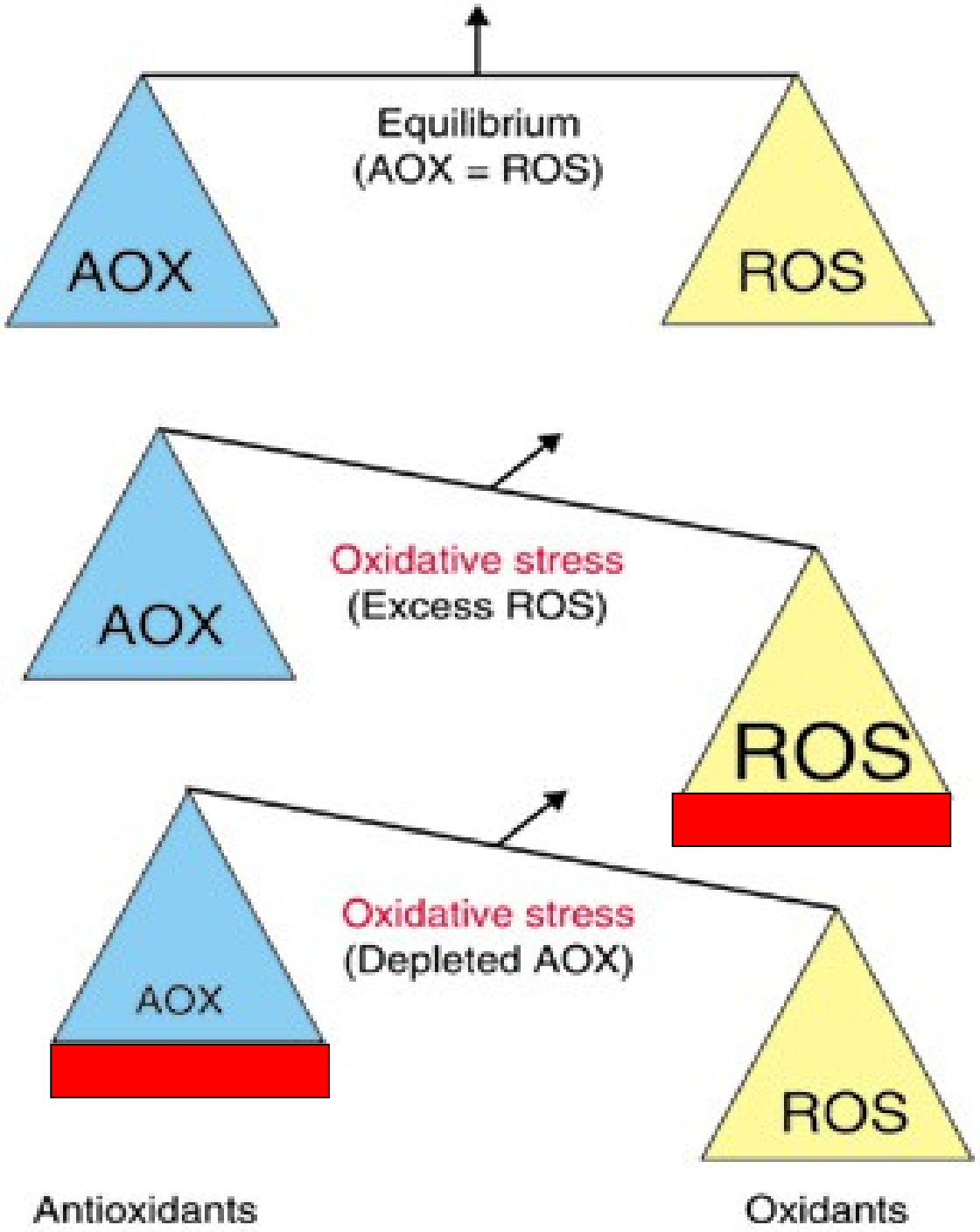
Radical damage to lipids and proteins in **plasma lipoproteins** is a factor in the development of **atherosclerosis** and coronary artery disease;

radical damage to **nucleic acids** may induce heritable mutations and cancer;

radical damage to **proteins** may lead to the development of **autoimmune** diseases.

Slika 45-1. Radikali uzrokuju oštećenje tkiva.


s-Le^x = CD15s
Blood flow
E-selectin
basement membrane
s-Le^x
CD31
chemokine
(IL-8)
E-selectin


Equilibrium
(AOX = ROS)
AOX
ROS
Oxidative stress
(Excess ROS)
AOX
ROS
Oxidative stress
(Depleted AOX)
AOX
ROS
Antioxidants
Oxidants

- List the enzymatic antioxidants
- (Harper, Chapter 12).

- catalase
  superoxide dismutase
  glutathione peroxidase, glutathione reductase

Protection against radical damage is afforded by enzymes and nonenzymic reactions

- **Enzymes**
  - that **remove** **superoxide ions** and **hydrogen peroxide,**
  - enzymic reduction of **lipid peroxides** linked to oxidation of glutathione.

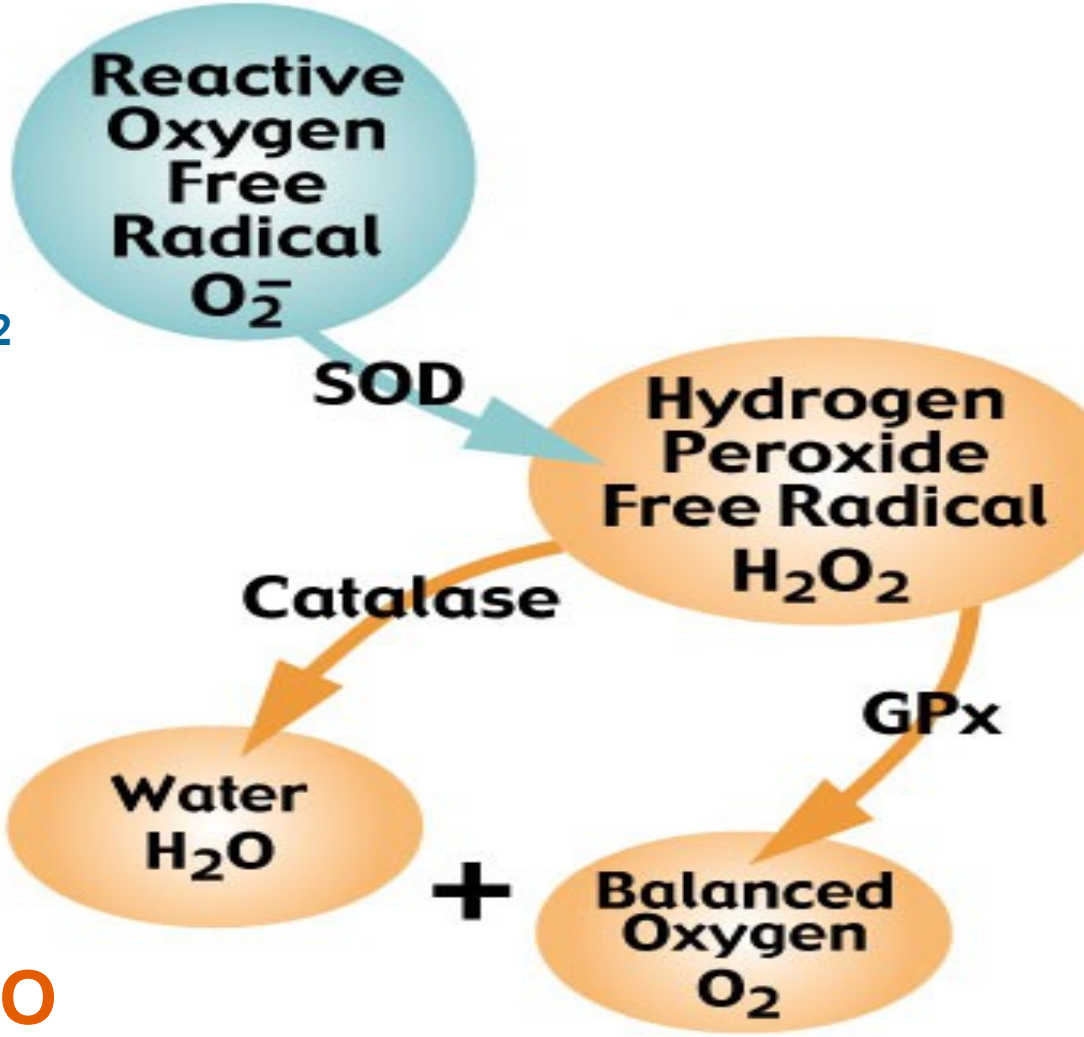
What is the substrate and the product of the enzyme **catalase** (Table 52-5)?

What is the substrate and the product of the enzyme **superoxide dismutase?**

Which reaction catalyzes **glutathione peroxidase**?

SOD

$2\ O_2^{-} + 2\ H^{+} \rightarrow H_2O_2 + O_2$

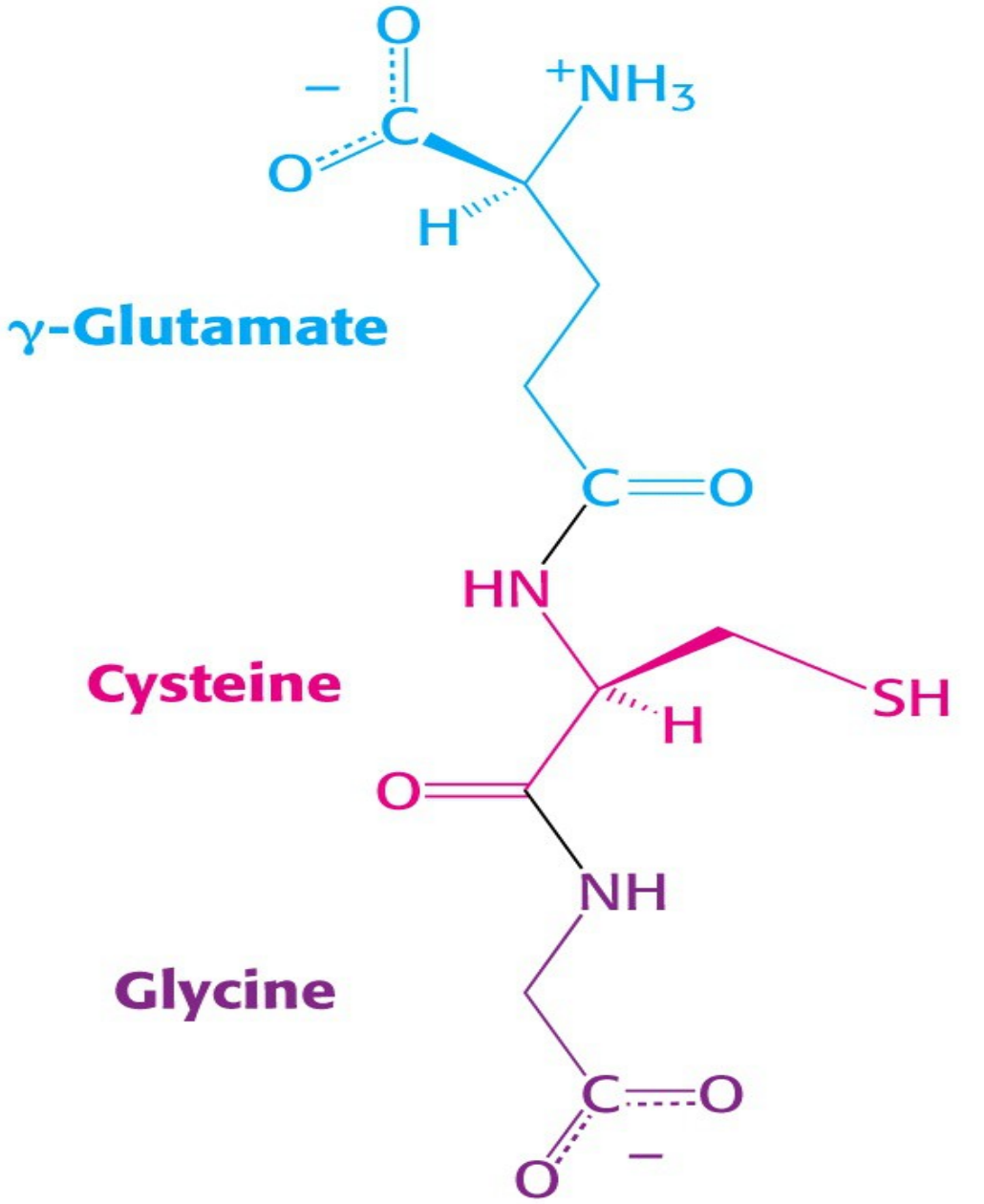


2. catalase

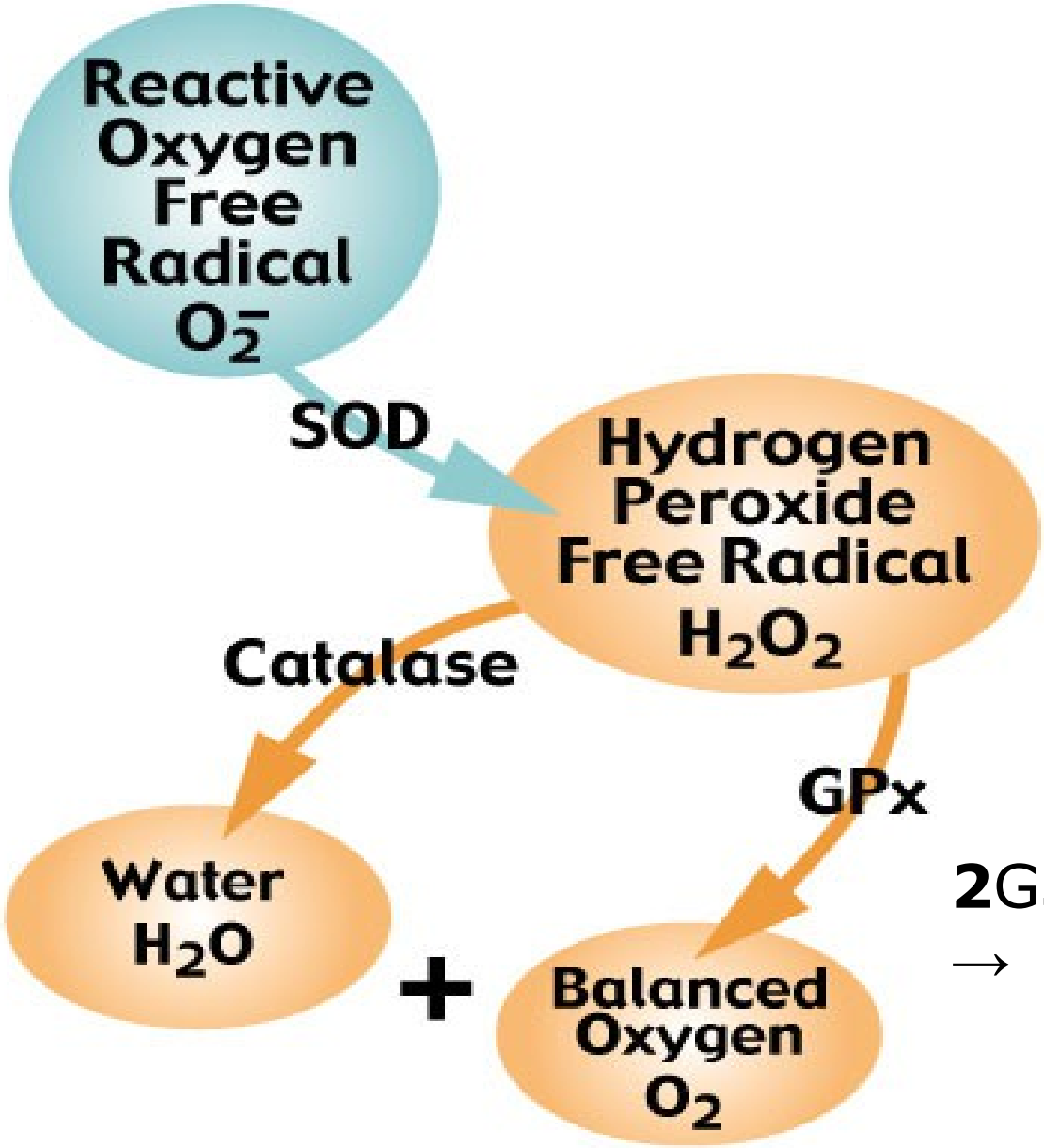
$RH_2 + H_2O_2 \rightarrow R + 2\ H_2O$

3. glutathione peroxidase (GPx; contains Se)

GSH



Glutathione (reduced)
(γ-Glutamylcysteinylglycine)

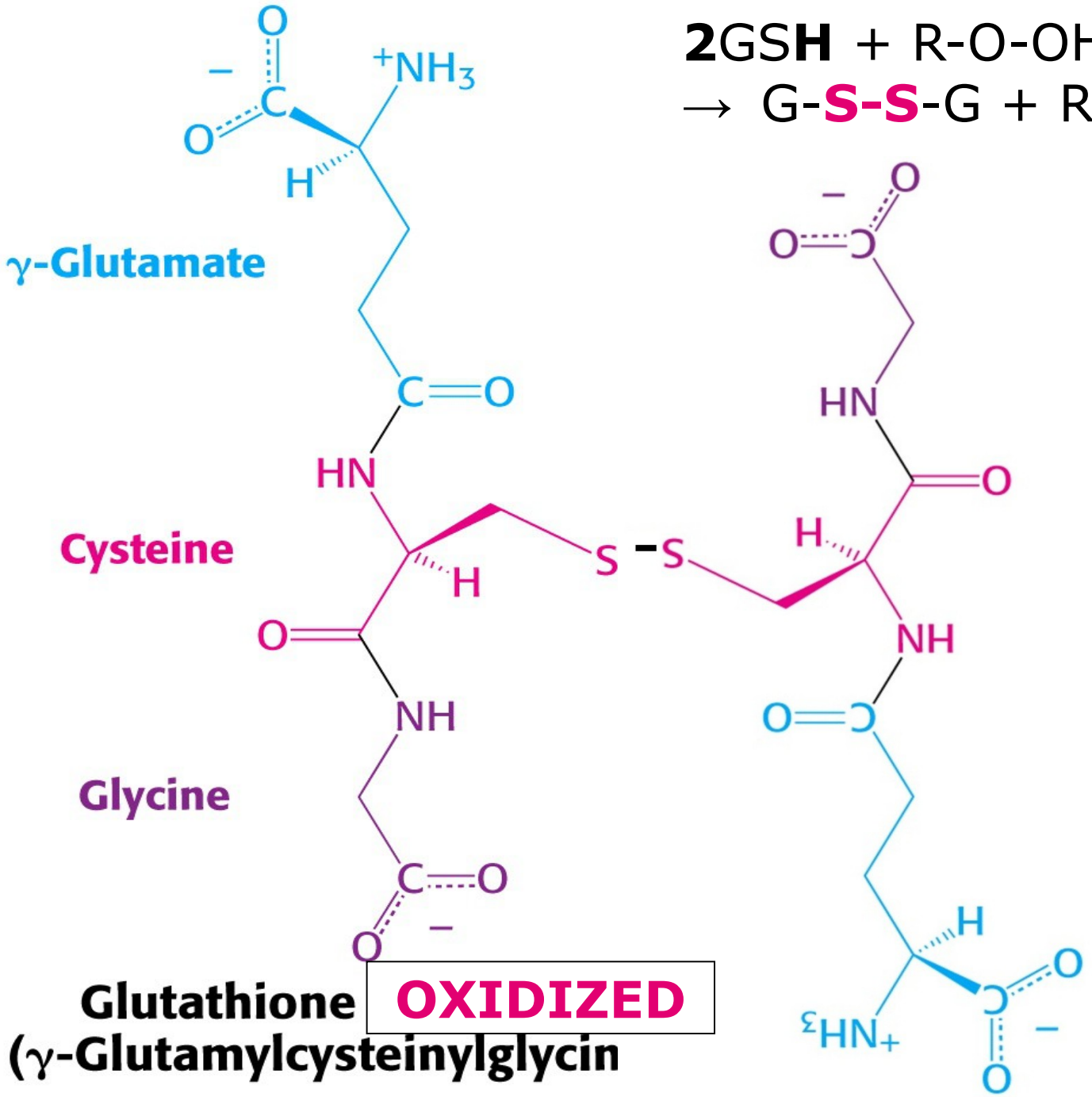


Which reaction catalyzes glutathione peroxidase?

2GS**H** + R-O-OH →
→ G-**S-S**-G + R-OH + H_2O

2GSH + R-O-OH →

→ G-**S-S**-G + R-OH + H_2O



- Which reaction catalyzes **glutathione**-reductase?

2GSH + R-O-OH → G-S-S-G + R-OH + H_2O

G-**S-S**-G + NADPH + H^+ → **2**GS**H** + $NADP^+$

TABLE 8.8 Enzymes for which k_{cat}/K_M is close to the diffusion-controlled rate of encounter

Enzyme	k_{cat}/K_M ($s^{-1}M^{-1}$)
Acetylcholinesterase	1.6×10^8
Carbonic anhydrase	8.3×10^7
Catalase	4×10^7
Crotonase	2.8×10^8
Fumarase	1.6×10^8
Triose phosphate isomerase	2.4×10^8
β-Lactamase	1×10^8
Superoxide dismutase	7×10^9

The fastest!

Source: After A. Fersht, *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding* (W. H. Freeman and Company, 1999), Table 4.5.

- Describe the mechanisms
- and dietary factors
- that protect against radical damage.

List the non-enzymatic antioxidants (Harper, Chapter 45).

Protection against radical damage is afforded by enzymes and nonenzymic reactions

- **Nonenzymic reactions**
  - of **lipid peroxides** with vitamin E,
  - reaction of **radicals** with compounds such as vitamins C and E, carotene, ubiquinone, uric acid, and dietary polyphenols that form relatively stable radicals that persist long enough to undergo reaction to nonradical products.

VITAMINs – exogenous non-enzymatic antioxidant

- **vitamin E**
- **vitamin A**
  - antioxidant in **membranes**
- **vitamin C**
  - operates in **aqueous compartments** of the cells and in the extracellular fluid

What effects show carotene and vitamin E in high doses?

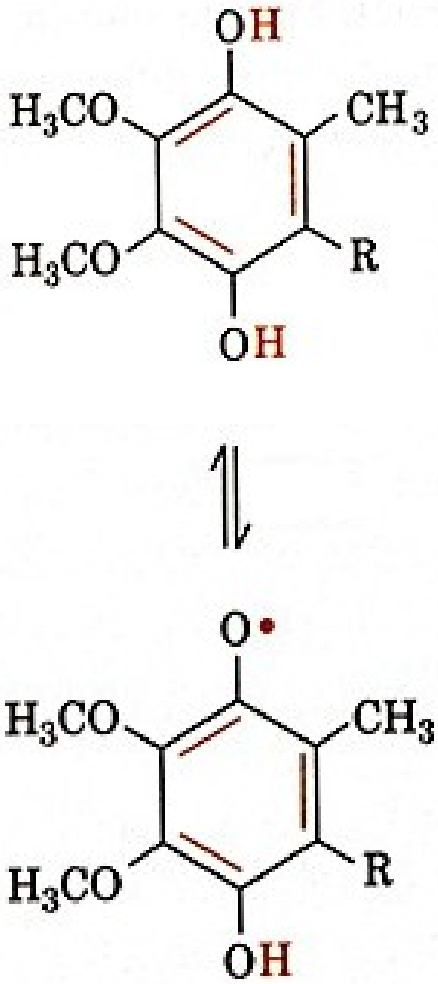
- **Except in** people who were initially **deficient**,
- Intervention trials of vitamin **E and carotene** have generally shown **increased mortality** among those taking the supplements.

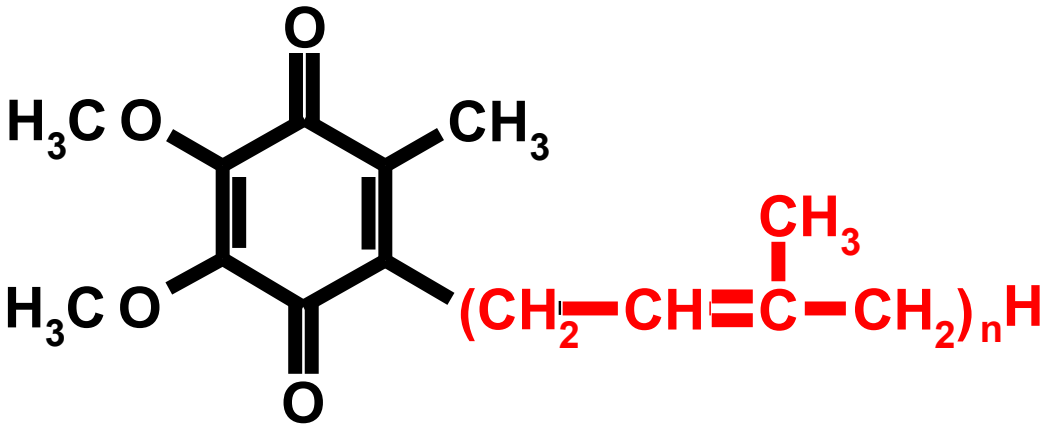
- Carotene is only an antioxidant at low concentrations of oxygen;
- at **higher concentrations** of oxygen it is an autocatalytic **prooxidant.**

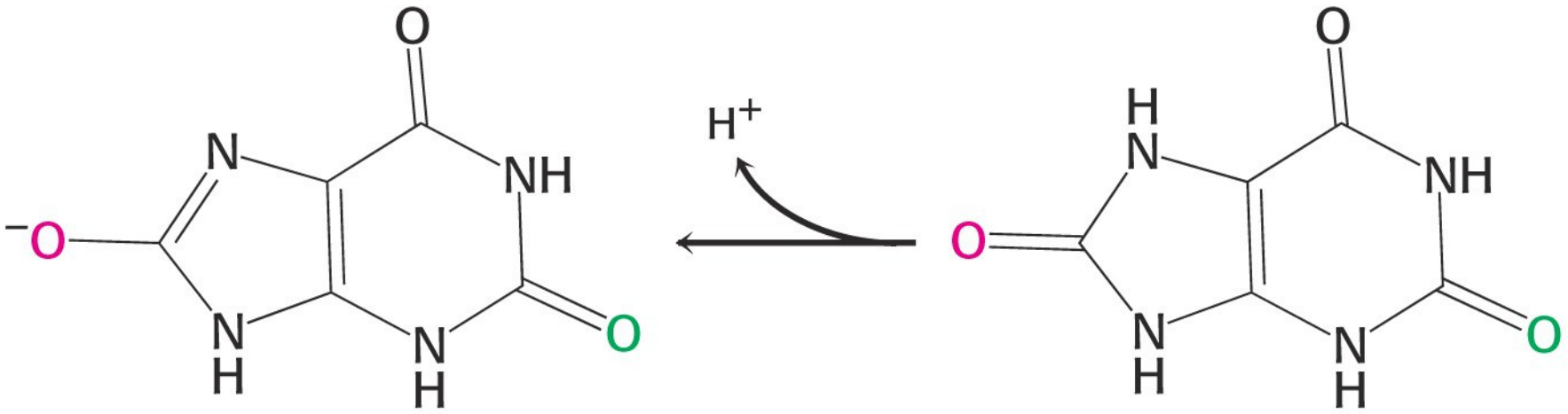
- Vitamin E forms a stable radical that is capable of either undergoing reaction with water-soluble antioxidants or penetrating further into lipoproteins and tissues, so increasing radical damage.

Endogenous non-enzymatic antioxidant

Coenzyme Q
(ubiquinol / ubiquinon)







urate

uric acid