Redox homeostasis & oxidative stress

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Redox homeostasis

- natural levels of oxidants (O_2) and antioxidants in each cell

Disruption of redox homeostasis

-> depletion of oxygen: metabolism disruption, acidosis in tissues, cell necrosis

rare: INSIDE TUMORS

-> overproduction of oxidants:

= oxidative stress

GENERAL MECHANISM OF TOXICITY

Overproduction of oxidants

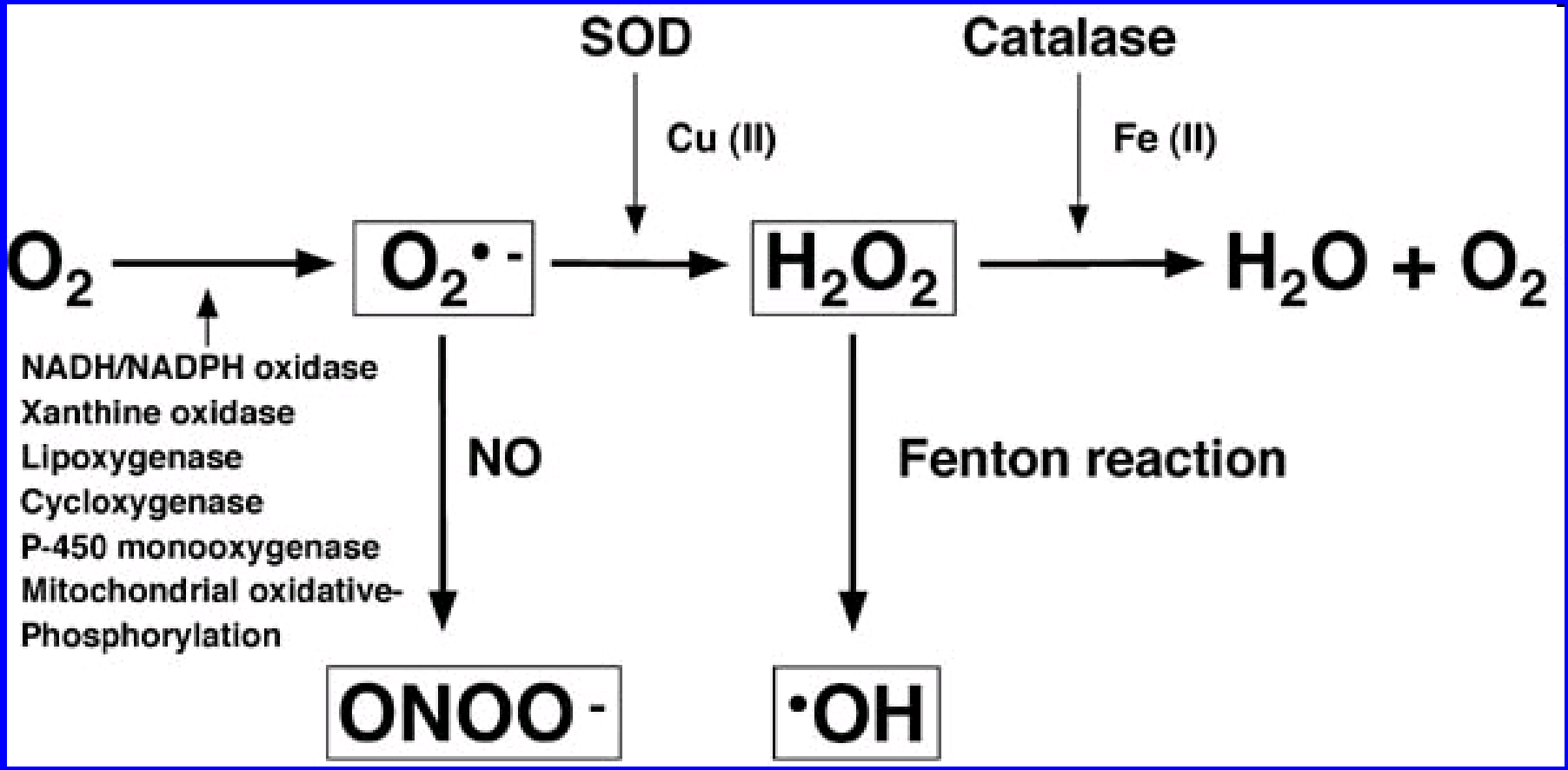
<u>Oxygen</u> – principal molecule in living organisms

Oxygen increases reactive derivatives -> toxicity

ROS = Reactive Oxygen Species: *Sources*

- production in mitochondria (byproducts)
- redox-cycling (quinones of xenobiotics)
- Fenton-reaction (metals)
- oxidations mediated via MFO (CYP)
- depletion of antioxidants (reactive molecules)

Reactive Oxygen Species (ROS)



SOD = Superoxide dismutase

Reduction of molecular oxygen to superoxide radical

$$O2 + e^- \rightarrow {}^{\bullet}O2^-$$

Dismutation of superoxide radical

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

Transition metal catalyzed reaction (Fenton reaction)

$${}^{\bullet}O_2^- + Me^{n+} \rightarrow Me^{(n-1)+} + O_2$$

$$Me^{(n-1)+} + H_2O_2 \rightarrow Me^{n+} + OH^- + {}^{\bullet}OH$$

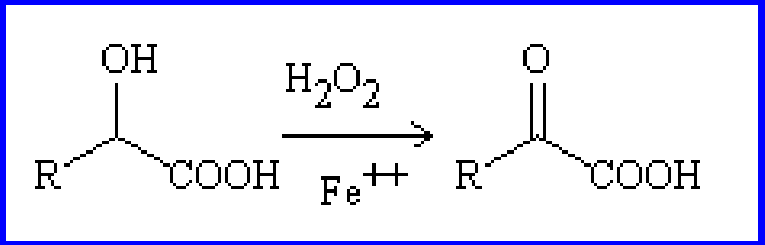
Haber-Weiss reaction

$${}^{\bullet}O2^- + H_2O_2 \rightarrow O_2 + OH^- + {}^{\bullet}OH$$

Me = metal (e.g. Fe^{3+}/Fe^{2+})

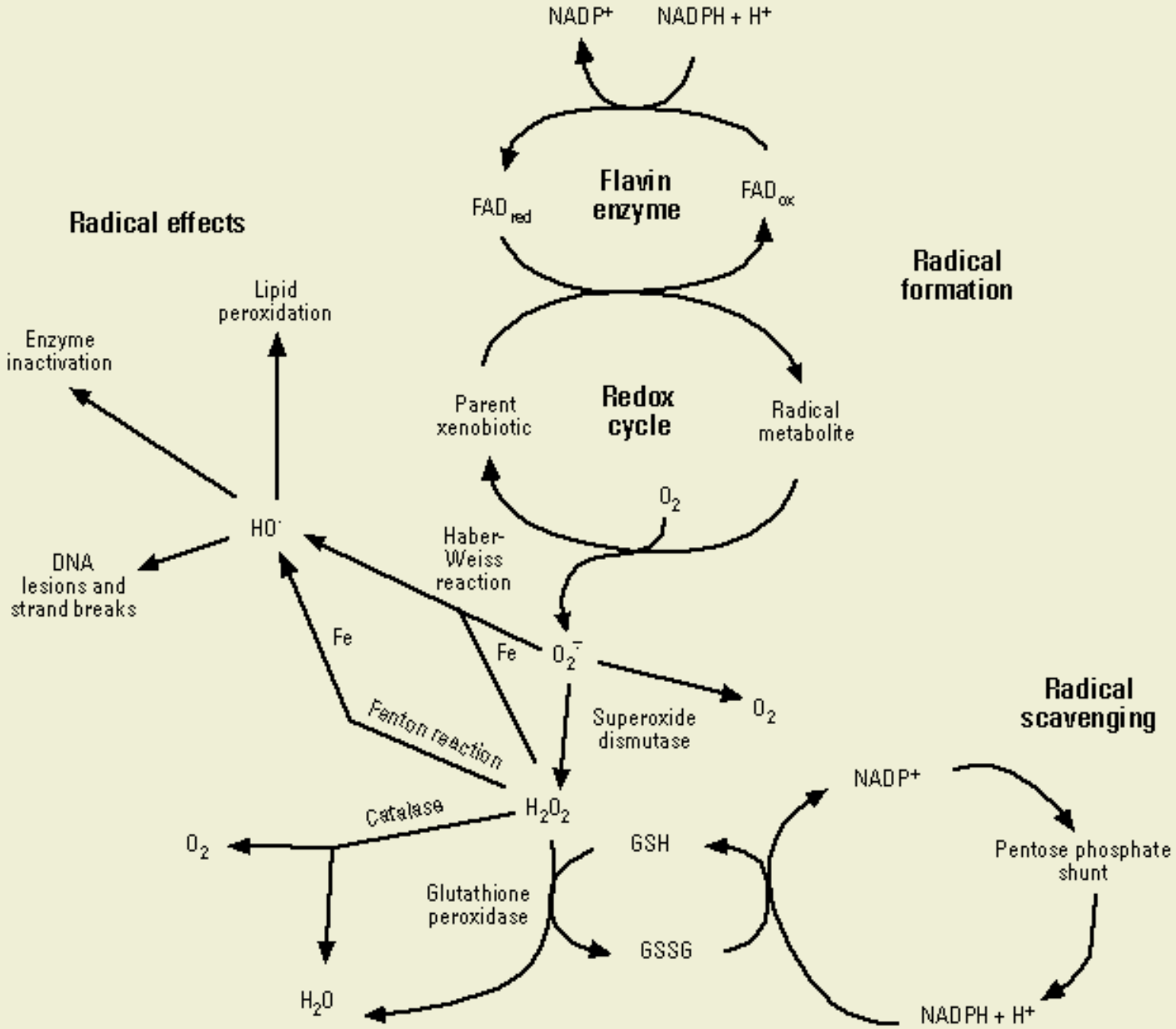
${}^{\bullet}O_2^-$ = superoxide radical (superoxide anion)
${}^{\bullet}OH$ = hydroxyl radical
OH^- = hydroxyl anion
H_2O_2 = hydrogen peroxide

Fenton reaction



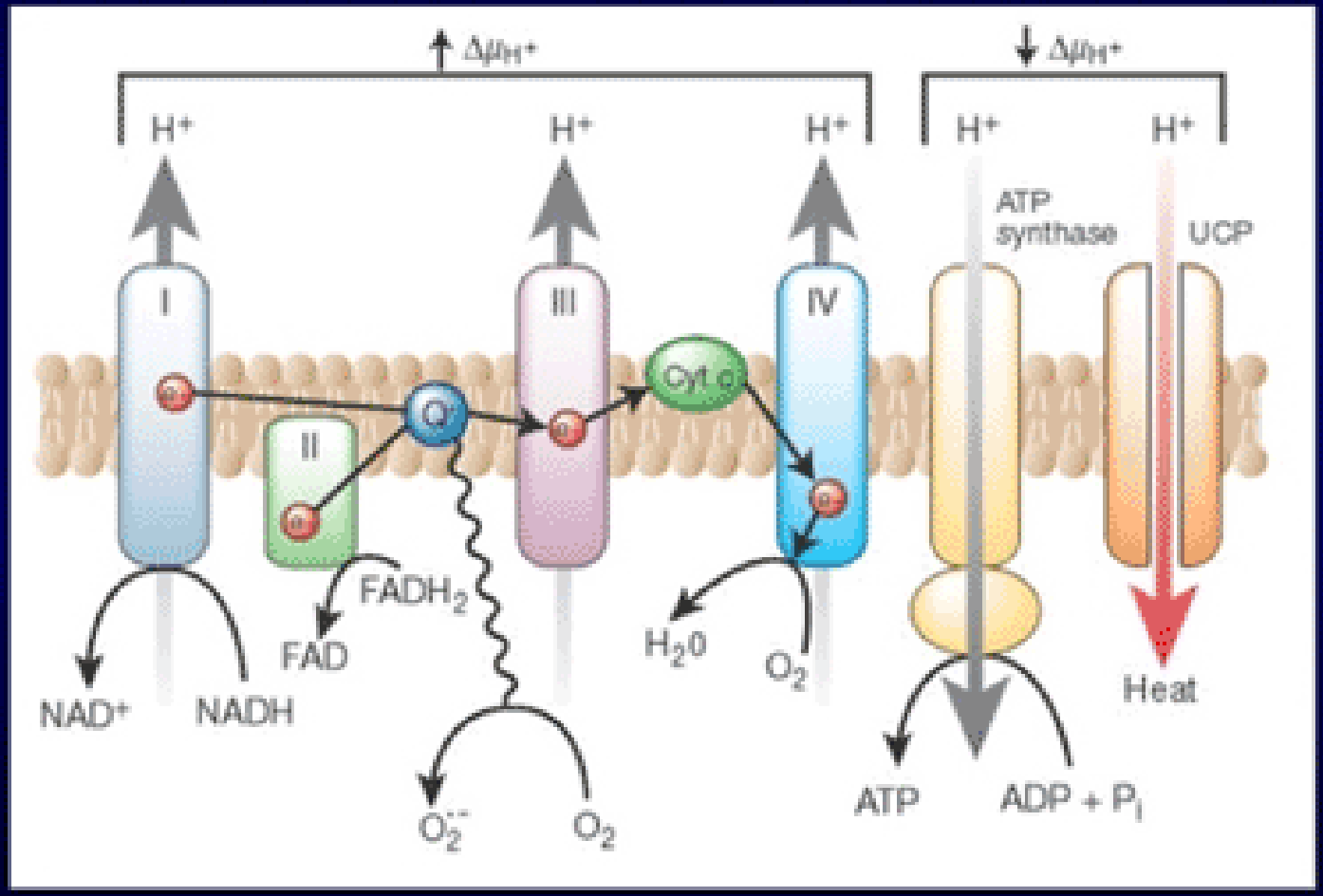
Reactive Oxygen Species (ROS)

ROS	Antioxidant	Rate constant, $M^{-1} \cdot sec^{-1}$
Superoxide anion of oxygen	carnosine	$5.0 \cdot 10^{-5}$
	carnosine	$0.8 \cdot 10^{-5}$
	ascorbate	$2.7 \cdot 10^{-5}$
	α-tocopherol	$2.0 \cdot 10^{-5}$
Singlet oxygen	carnosine	$3 \cdot 10^{-7}$
	imidazole	$2 \cdot 10^{-7}$
	ergothioneine	$2 \cdot 10^{-7}$
	NaN_3	$44 \cdot 10^{-7}$
Hydroxyl radical	carnosine	$(5\text{-}8) \cdot 10^{-9}$
		$9 \cdot 10^{-9}$


NADP+
NADPH + H+
Flavin enzyme
FAD red
FAD ox
Radical effects
Radical formation
Lipid peroxidation
Enzyme inactivation
Parent xenobiotic
Redox cycle
Radical metabolite
O2
HO·
Haber-Weiss reaction
DNA lesions and strand breaks
Fe
Fe
O2−
Superoxide dismutase
O2
Radical scavenging
Fenton reaction
H2O2
Catalase
O2
GSH
NADP+
Pentose phosphate shunt
Glutathione peroxidase
GSSG
H2O
NADPH + H+

ROS & mitochondria

Glucose-Derived ROS: Mitochondrial Electron Transport System



Examples of chemical-induced oxidative stress

- **Metals:**

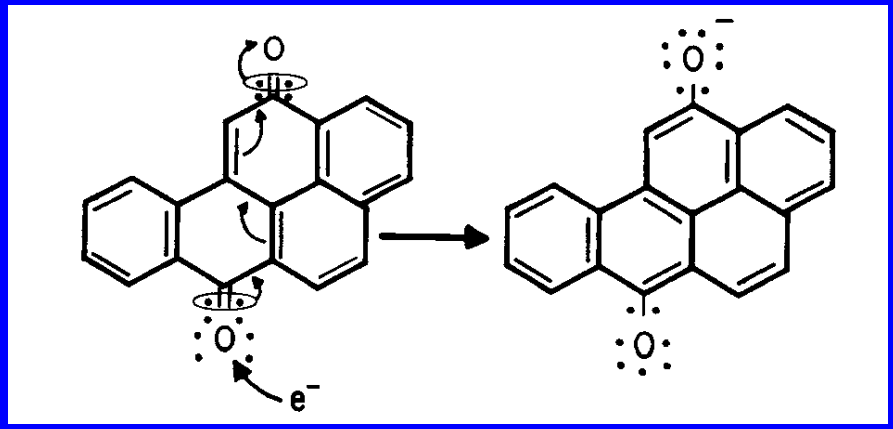
  fenton reaction -> OH*

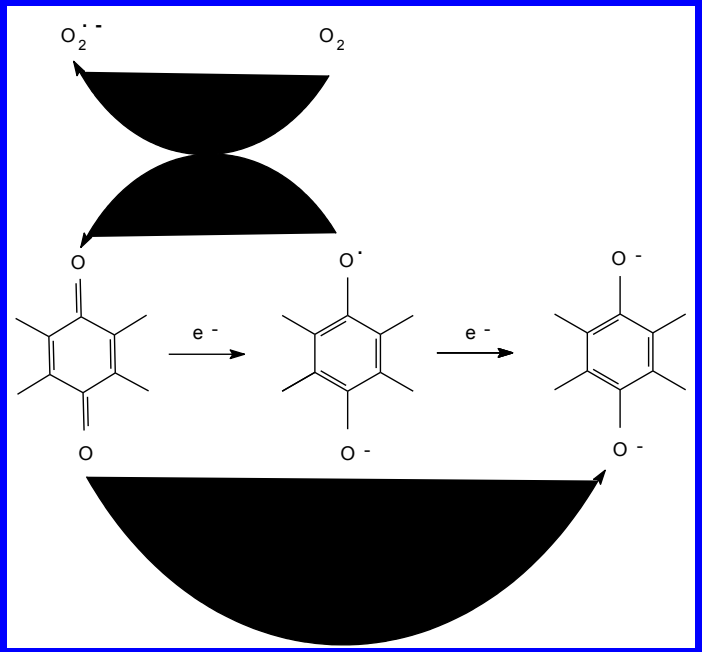
- **Redox-cycling chemicals:**

  oxy-PAHs

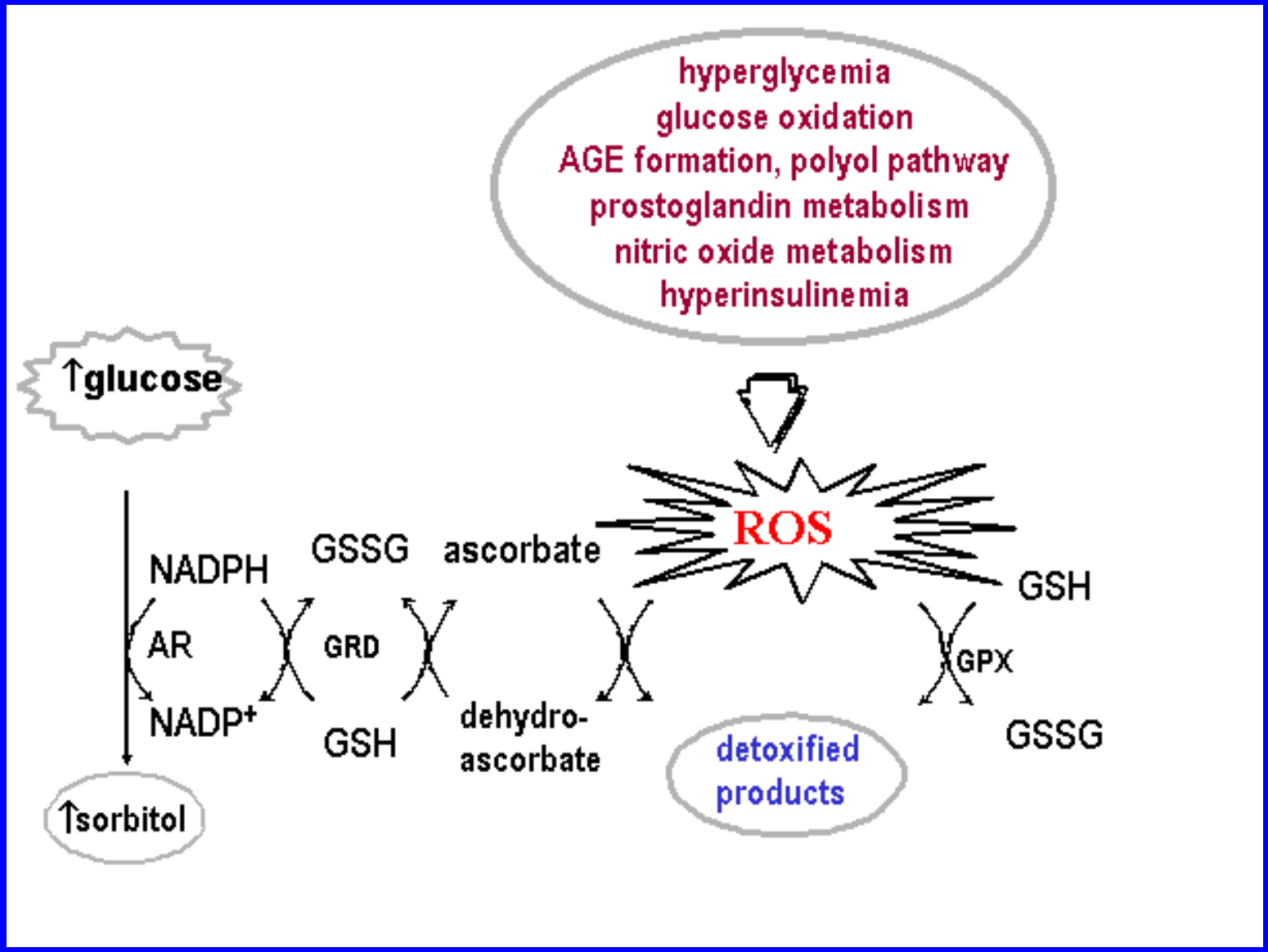
- Depletion of GSH:

  reactive molecules,
  GST-conjugation,
  metals: SH oxidation ...





Antioxidant depletion
GSH (glutathione)



Biomarkers of oxidative damage (will be discussed later)

BIOMARKER	AVAILABILITY	FREQUENTLY USED ASSAYS
Lipid Peroxidation		
F_2-isoprostanes	Plasma, urine	GC/MS, HPLC-MS/MS
Oxidized low-density lipoprotein (oxLDL)	Plasma, serum	ELISA
Malondialdehyde (MDA)	Plasma, serum, saliva, urine, exhaled breath condensate	Colorimetry, spectrophotometry, HPLC +fluorescence, GC/MS
Protein Oxidation		
Protein carbonyls	Plasma, serum	ELISA
DNA Oxidation		
8-hydroxy-2-deoxyguanosine (8-OHdG)	Plasma, serum, urine	HPLC-EC, HPLC-MS/MS*, GC/MS, Comet assay*