

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

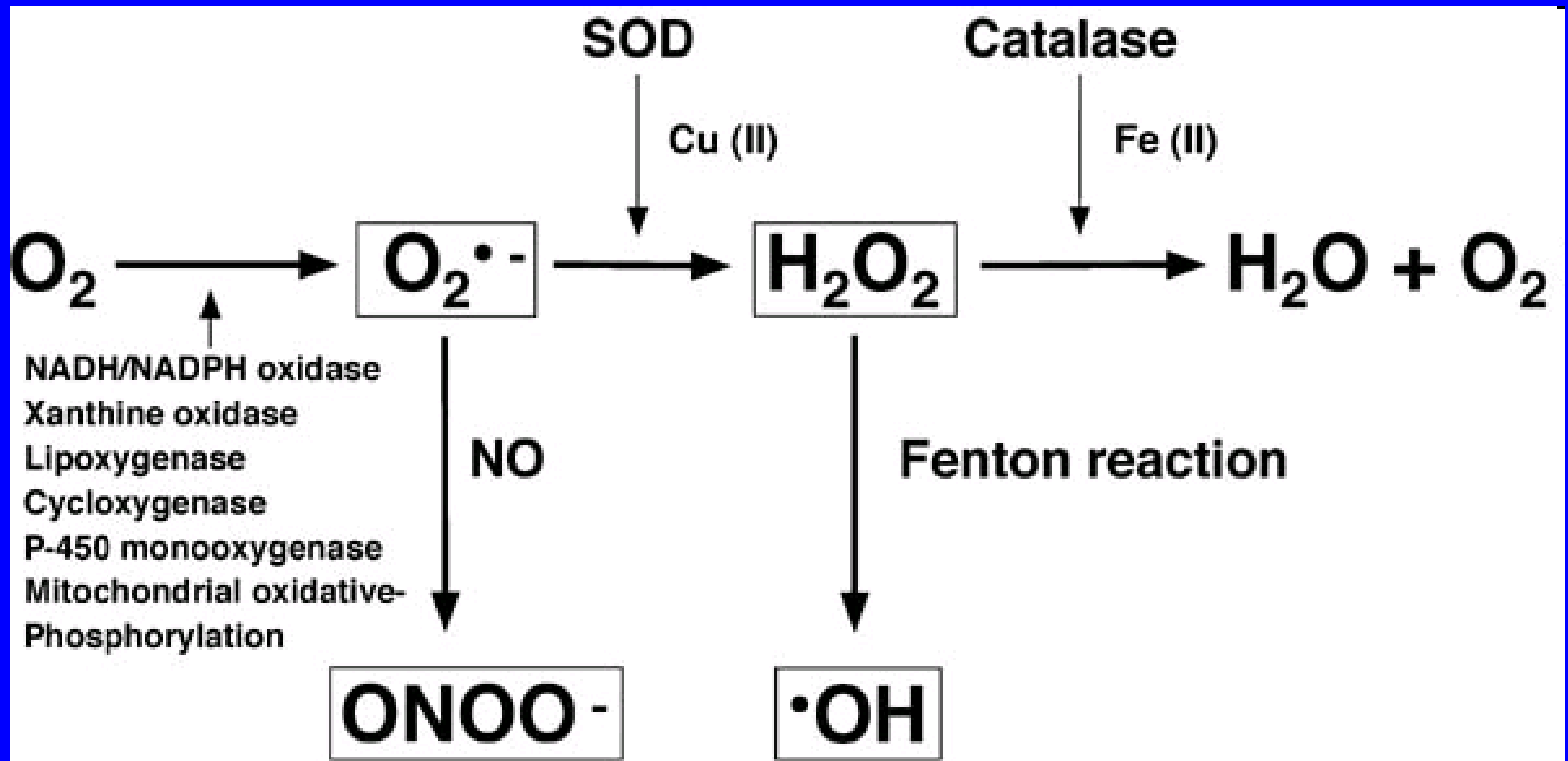
Oxygen – principal molecule in living organisms

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

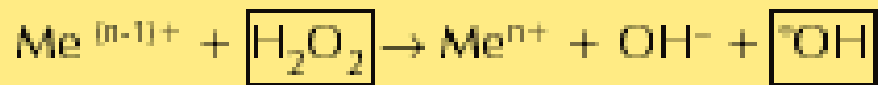
Reduction of molecular oxygen to superoxide radical



Dismutation of superoxide radical



Transition metal catalyzed reaction (Fenton reaction)



Haber-Weiss reaction



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

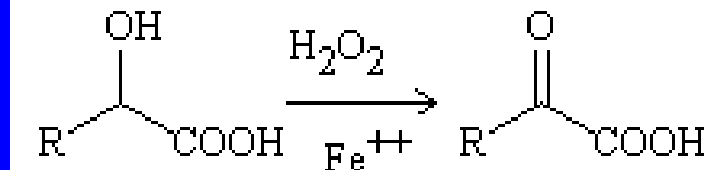
O_2^- = superoxide radical (superoxide anion)

OH = hydroxyl radical

OH^- = hydroxyl anion

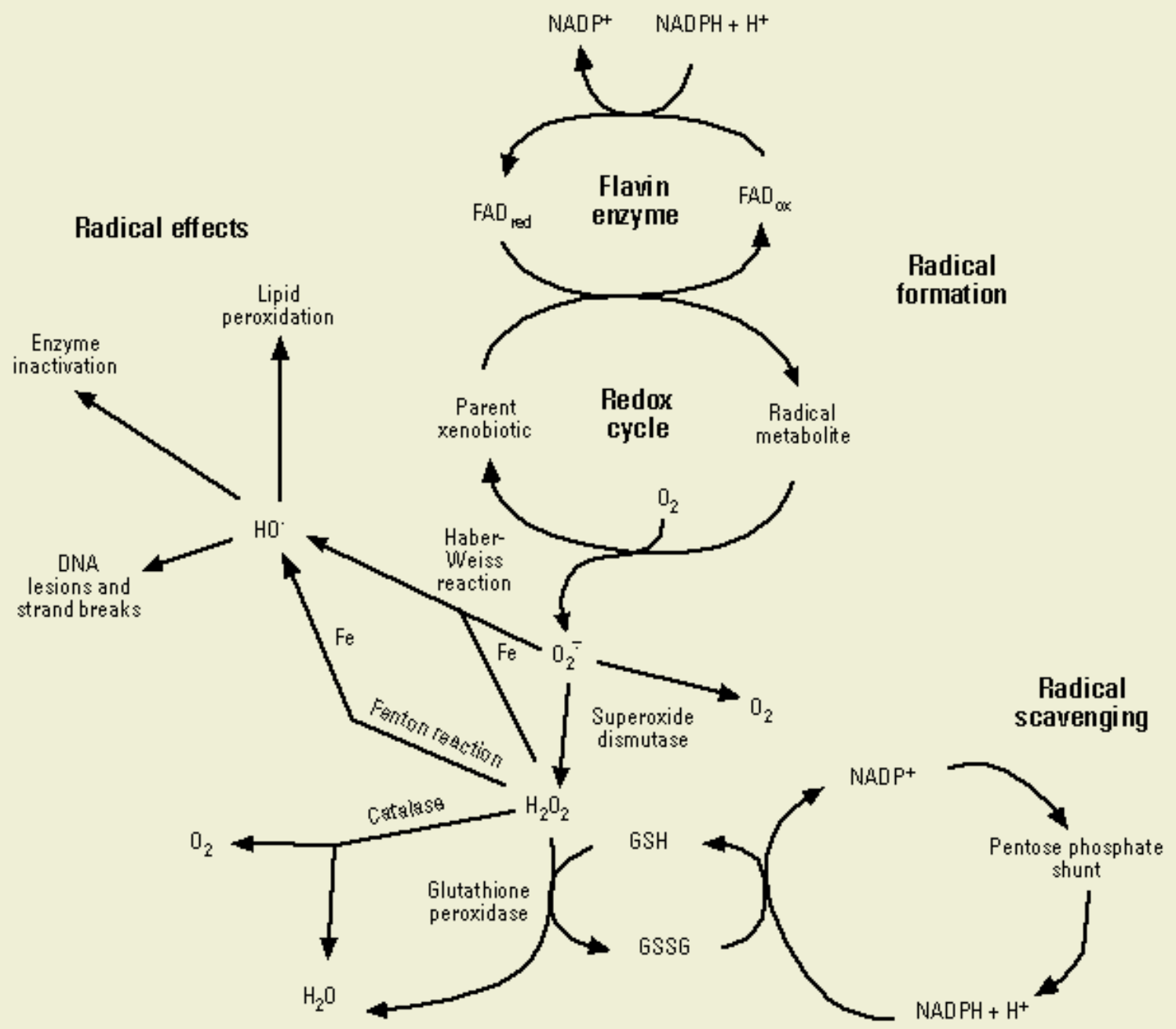
H_2O_2 = hydrogen peroxide

Fenton reaction



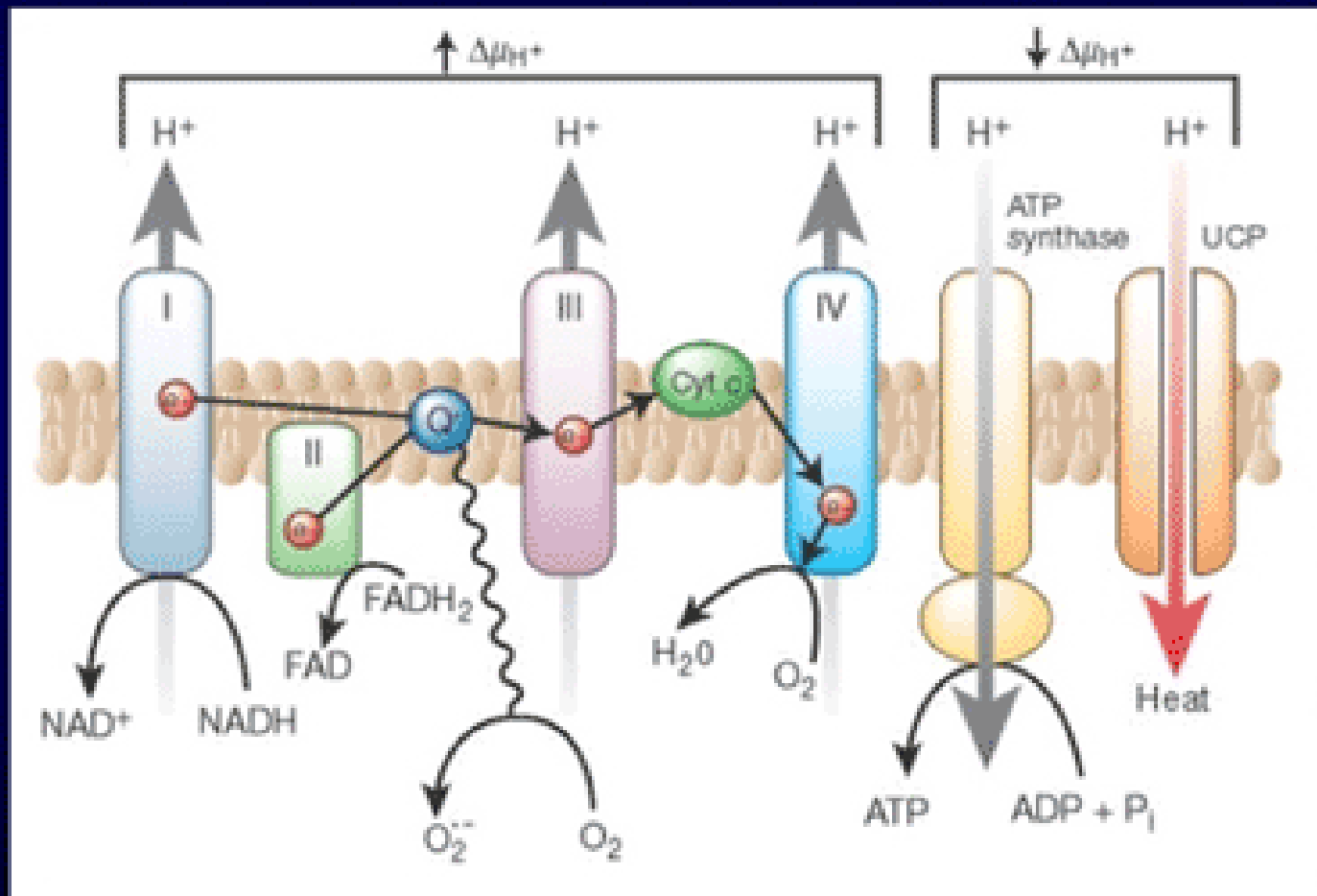
Reactive Oxygen Species (ROS)

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	$(5-8) \cdot 10^{-9}$
		$9 \cdot 10^{-9}$



ROS & mitochondria

Glucose-Derived ROS: Mitochondrial Electron Transport System



Examples of chemical-induced oxidative stress

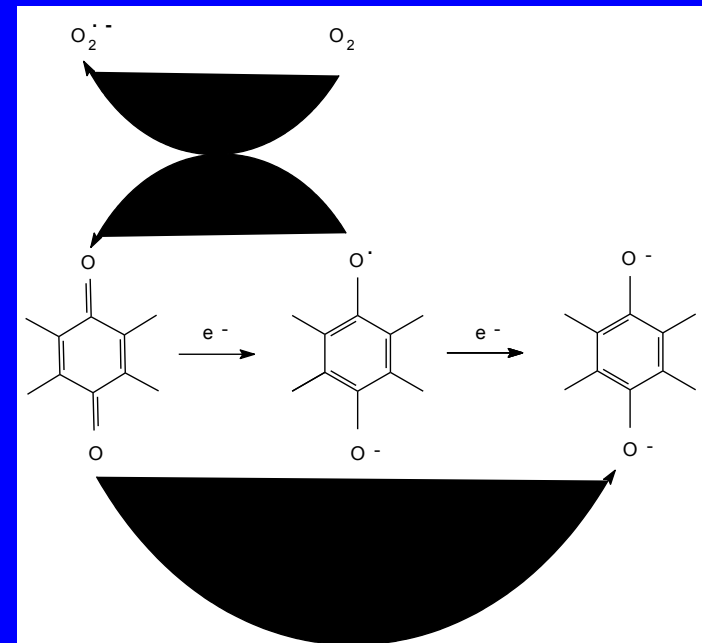
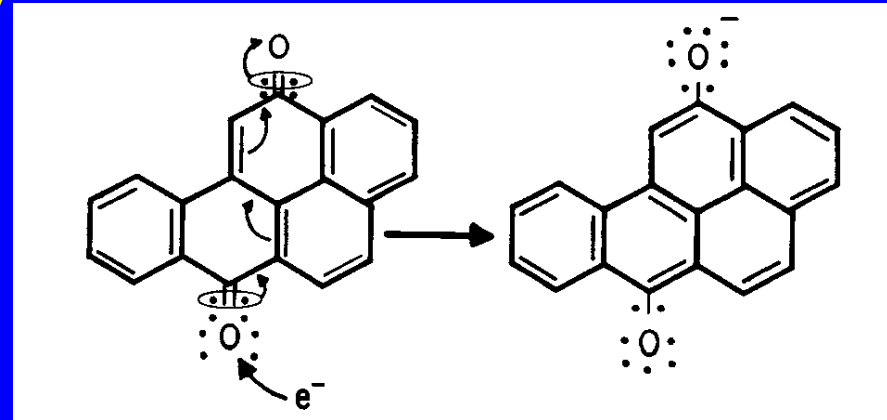
- Metals:

fenton reaction \rightarrow OH^*

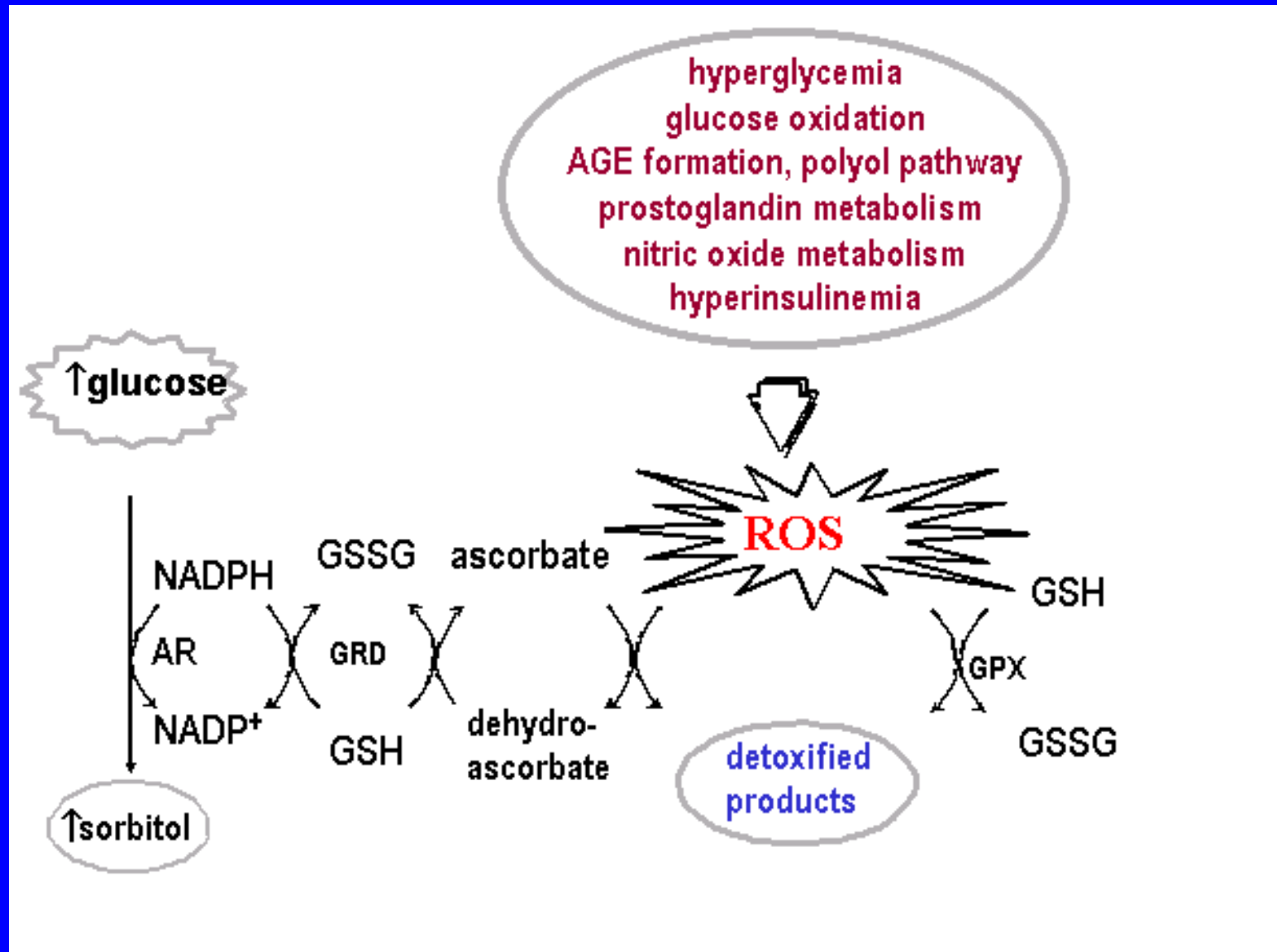
- Redox-cycling chemicals:
oxy-PAHs

- 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*