Carbohydrate Metabolism - 4

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Content

- Pentose phosphate pathway
- Gluconeogenesis
- Regulation of Carbohydrate metabolism

Pentosephosphate Pathway

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Definition

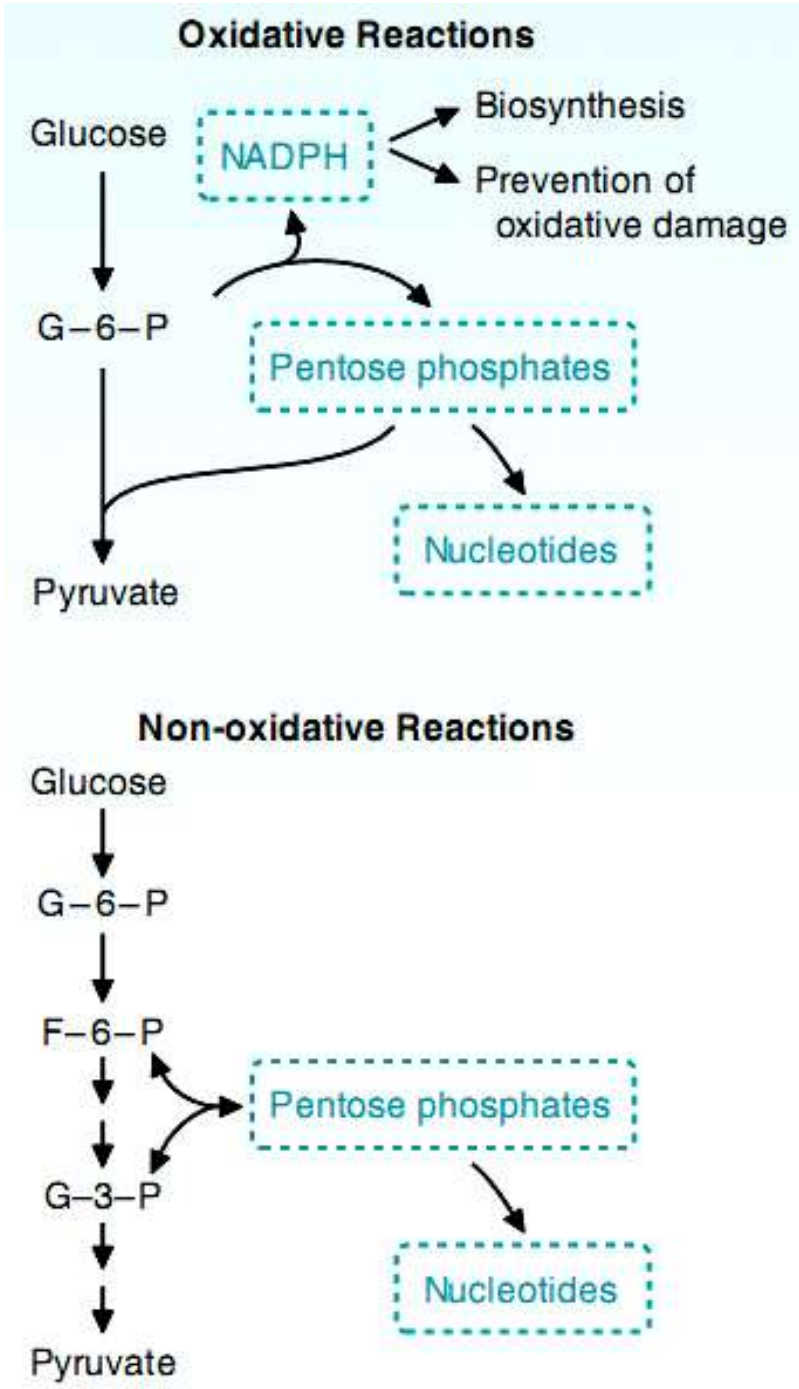
- Pentose phosphate shunt is an alternative route for the oxidation of glucose. Variant of glycolysis for making NAD**P**H.
- Reaction:

$$3\ \text{Glucose 6-phosphate} + 6NADP^{+} \rightarrow 3CO_2 + 2\ \text{Glucose 6-phosphate} + \text{Glyceraldehyde 3-phosphate} + 6\ NADPH + 6H^{+}$$

- Glucose may be completely oxidized by this pathway

Importance

- Ribose for nucleotide and nucleic acid biosyntheses
- Generation of NADPH for reductive syntheses:
  - fatty acid metabolism
  - steroid metabolism
  - xenobiotics metabolism
  - antioxidant system (G-SH, glutathion)



Overview of PPP

- The oxidative reactions generate both NADPH and pentose phosphates.
- The non-oxidative reactions only generate pentose phosphates.

PPP Overview (cont'd)

Oxidative stage

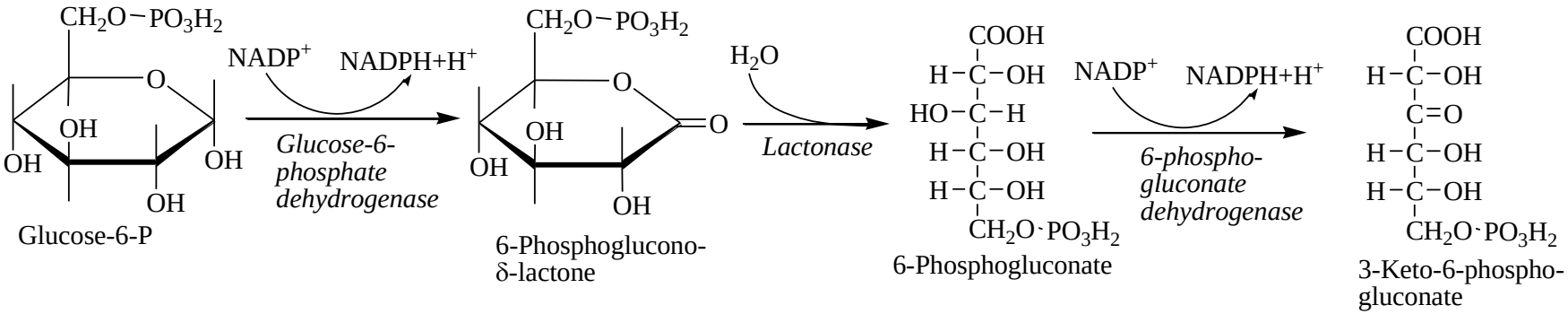
- Oxidative reactions convert 3 G6P to 3 ribulose-5-phosphate (Ru5P); yields 6 NADPH

Non-oxidative stage

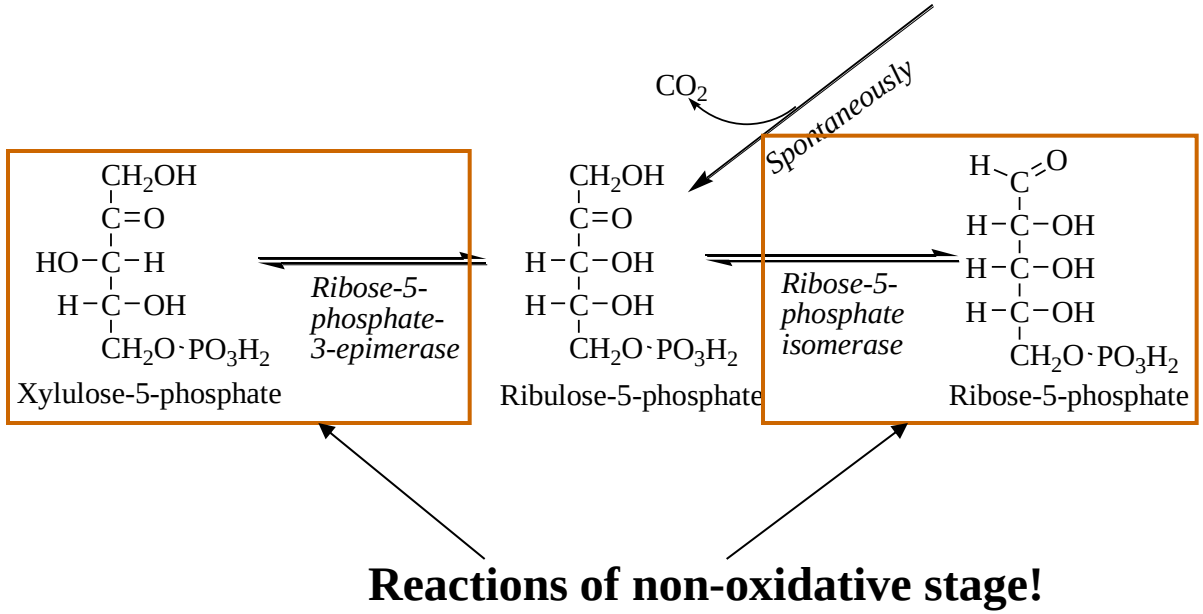
- Isomerization and epimerization reactions convert 3 Ru5P to ribose-5-phosphate (R5P) and 2 Xylulose-5-phosphate (Xu5P)
- Carbon skeleton rearrangements convert 2 Xu5P and 1 R5P to 2 F6P and 1 GAP
- F6P and GAP renter glycolysis pathway

- Production of NADPH at expense of some ATP and NADH production.

Oxidative Stage of PPP



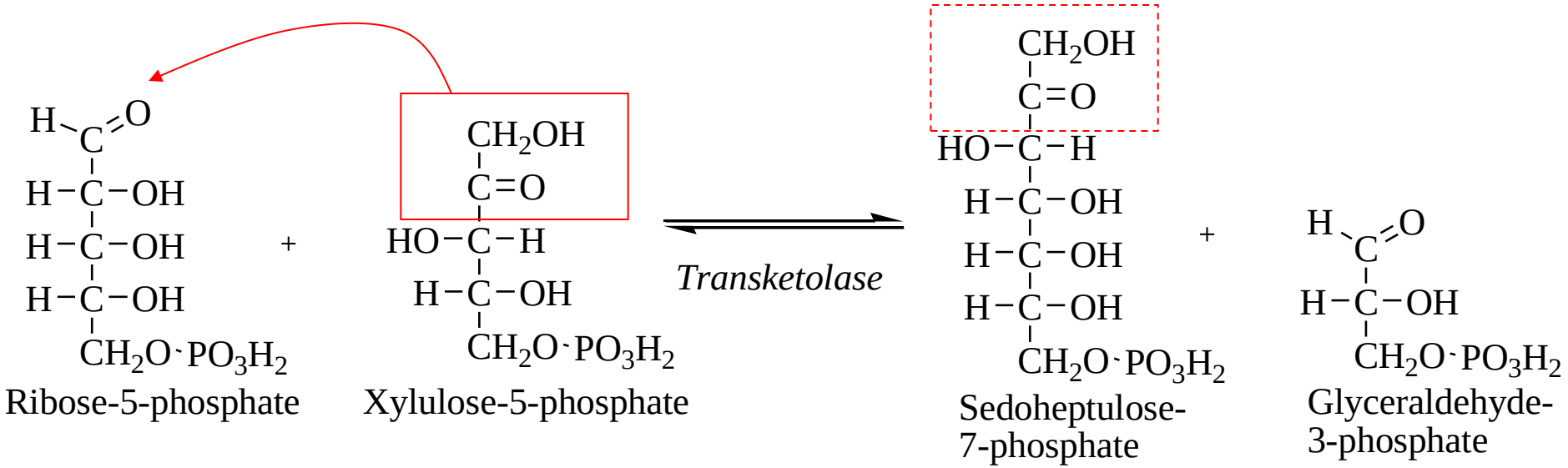
- From Gl-6-P up to Ribulose-5-P (Ru5P)
- 2 dehydrogenases (NAD**P**)
- Ru5P then enters the non-oxidative stage of PPP



Non-oxidative Stage

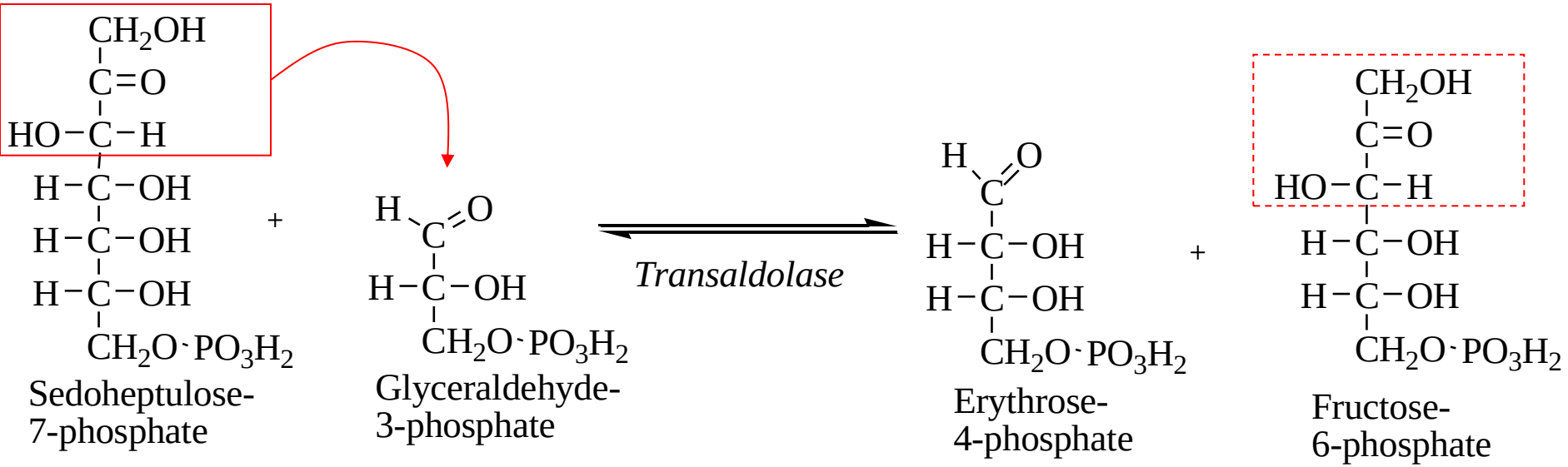
- Reactants:
  - In the next reactions there are always 2 reactants: **ketose** and **aldose**.
  - The 2- or 3-carbon moiety with keto- group should be transferred onto aldose.
- Enzymes:
  - 2-carbon moiety transfers **transketolase**
  - 3-carbon moiety transfers **transaldolase**.

Non-oxidative Stage: 1st Transketolase Reaction



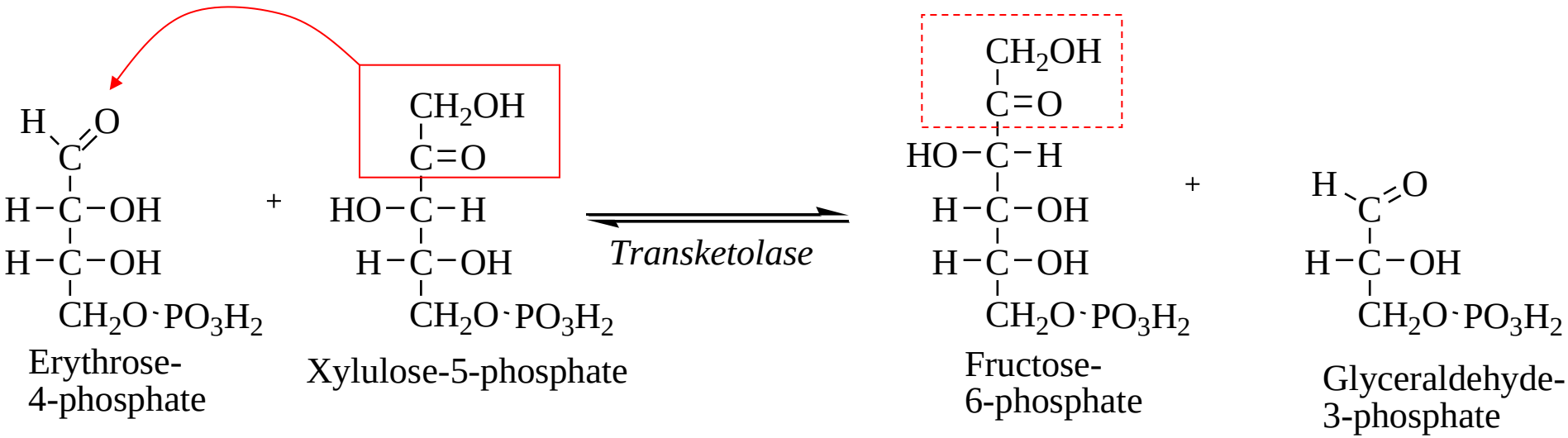
- Transfers 2-carbon moiety.
- Contains TPP.

Non-oxidative Stage: Transaldolase Reaction



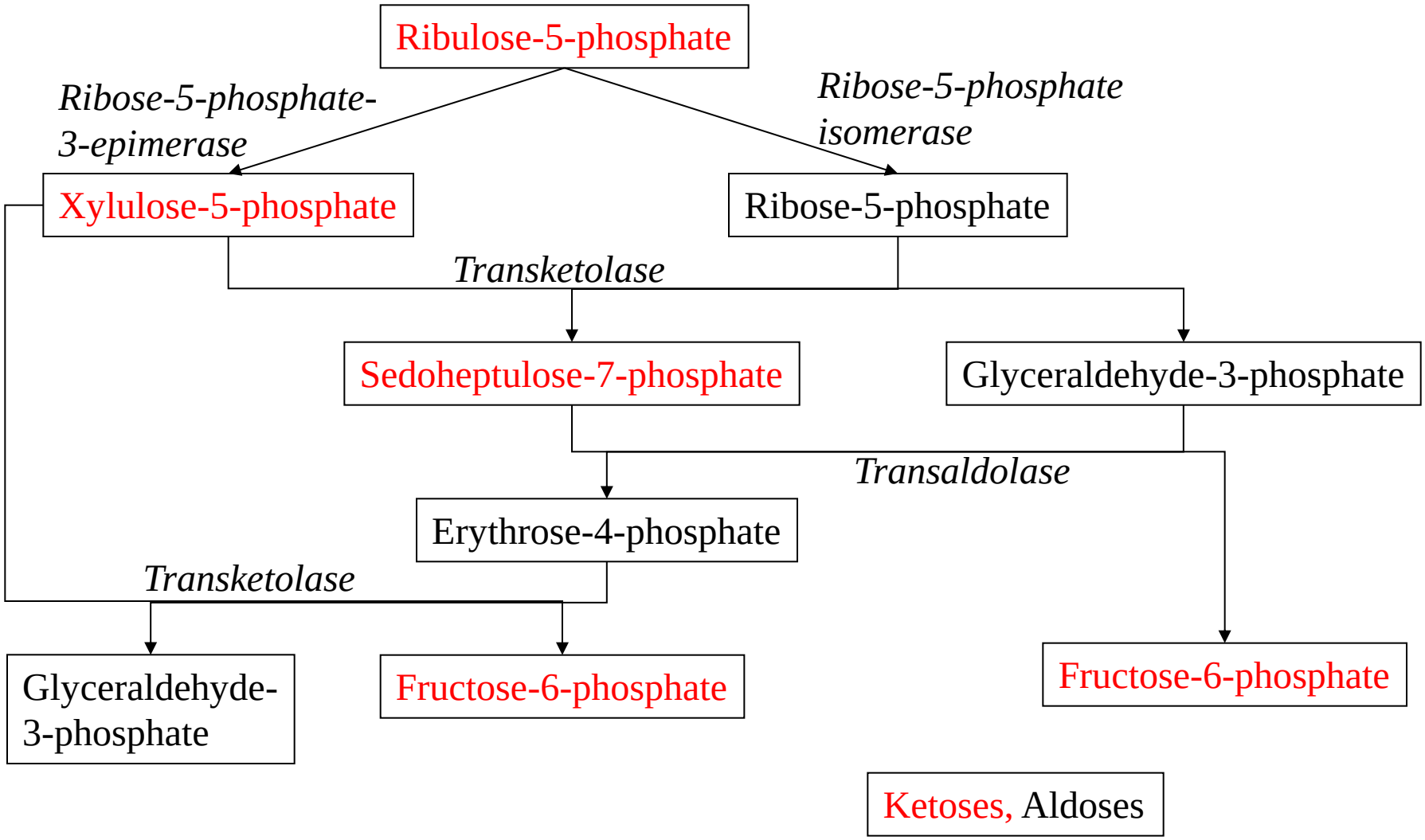
- This time 3-carbon moiety is returned back.

Non-oxidative Stage: 2nd Transketolase Reaction

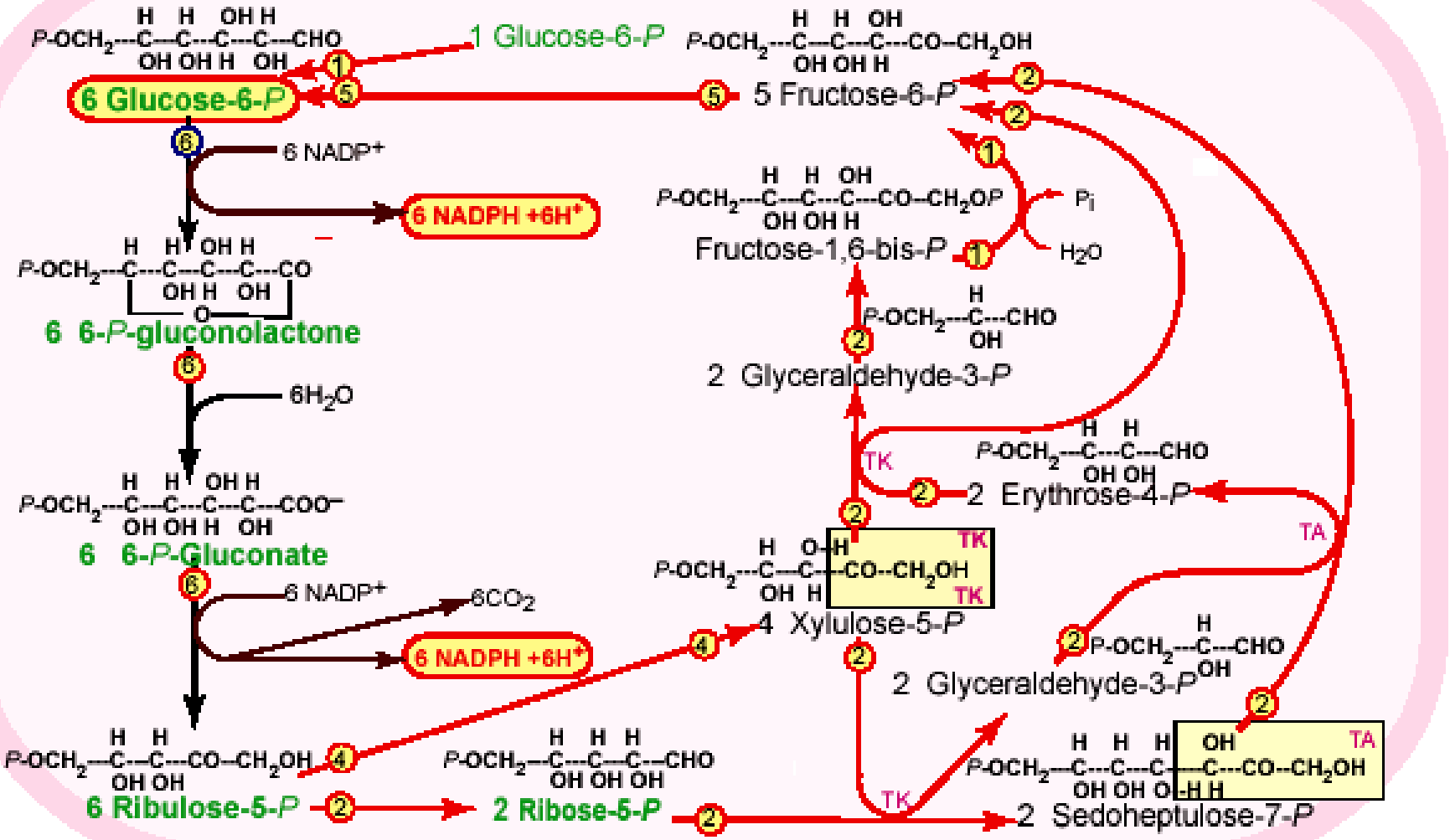


- To complete the pathway (now it becomes almost cyclic!)
- To avoid the accumulation of erythrose-4-phosphate and xylulose-5-phosphate
- Remember: 2-carbon moiety is transferred.

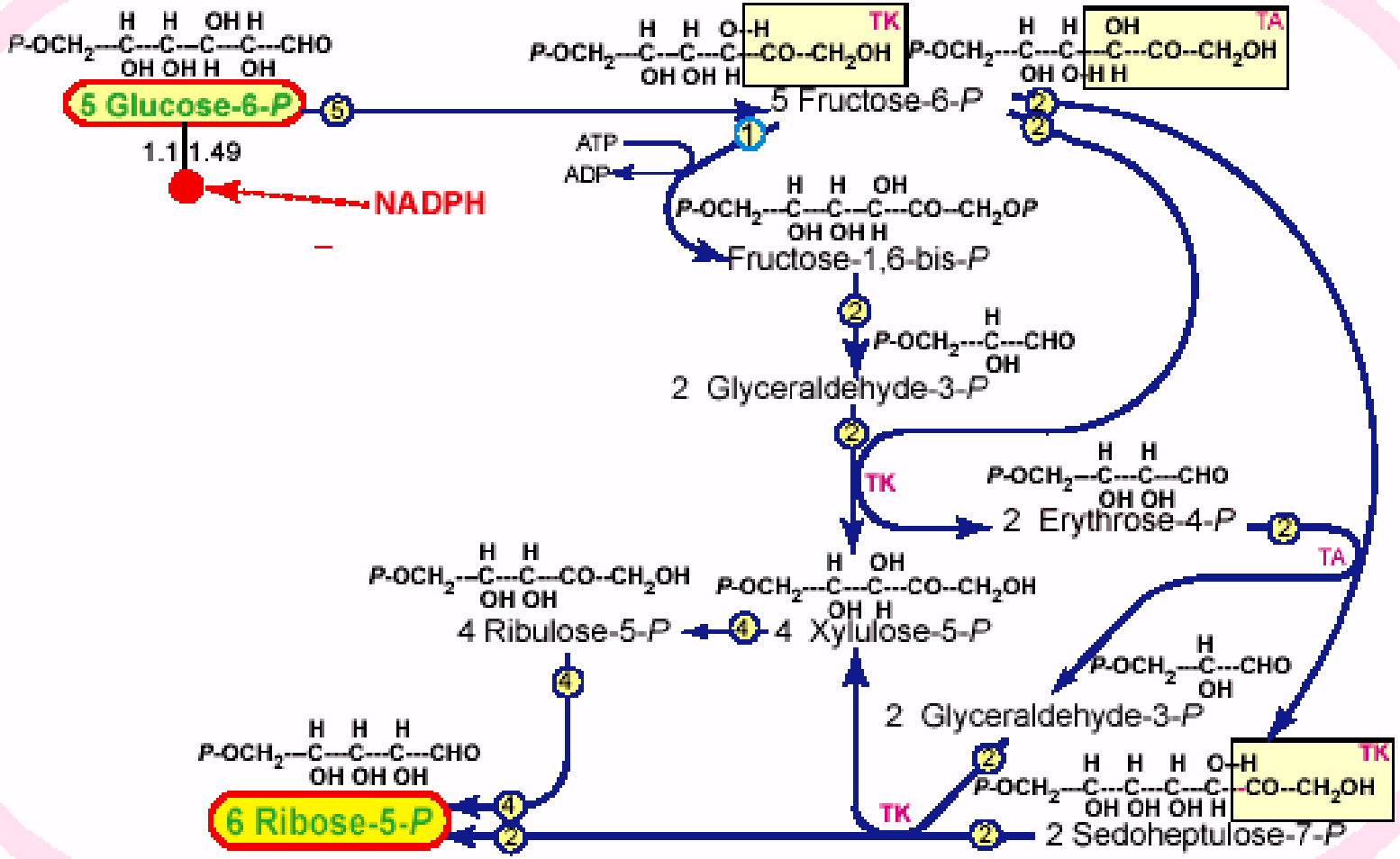
Non-oxidative Stage: Overview

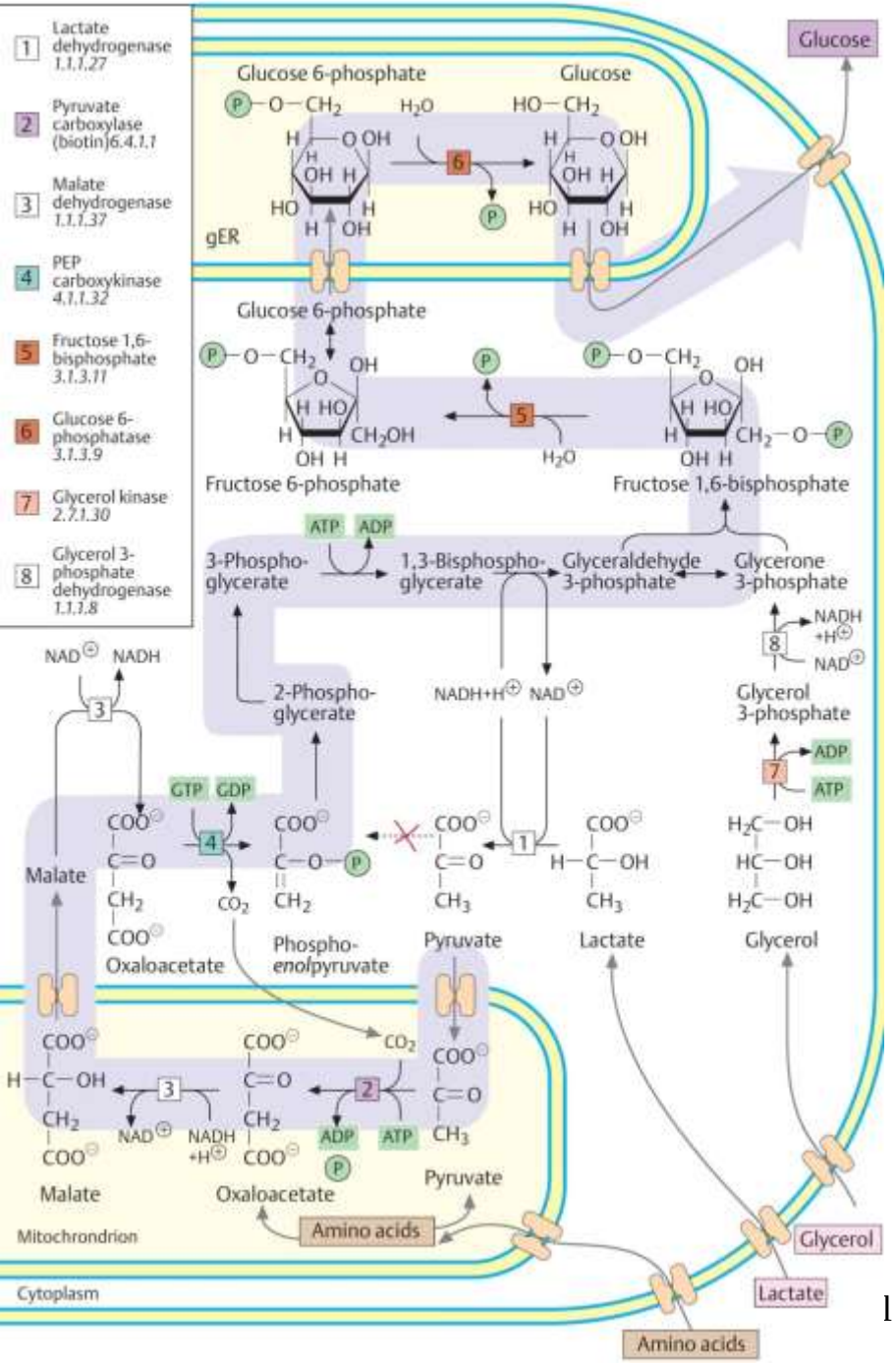


Cell requires NADPH but not RIBOSE



Cell requires RIBOSE but not NADPH





Gluconeogenesis

Brain and erythrocytes, depend on a constant supply of glucose.

De-novo synthesis of glucose – gluconeogenesis (GNG).

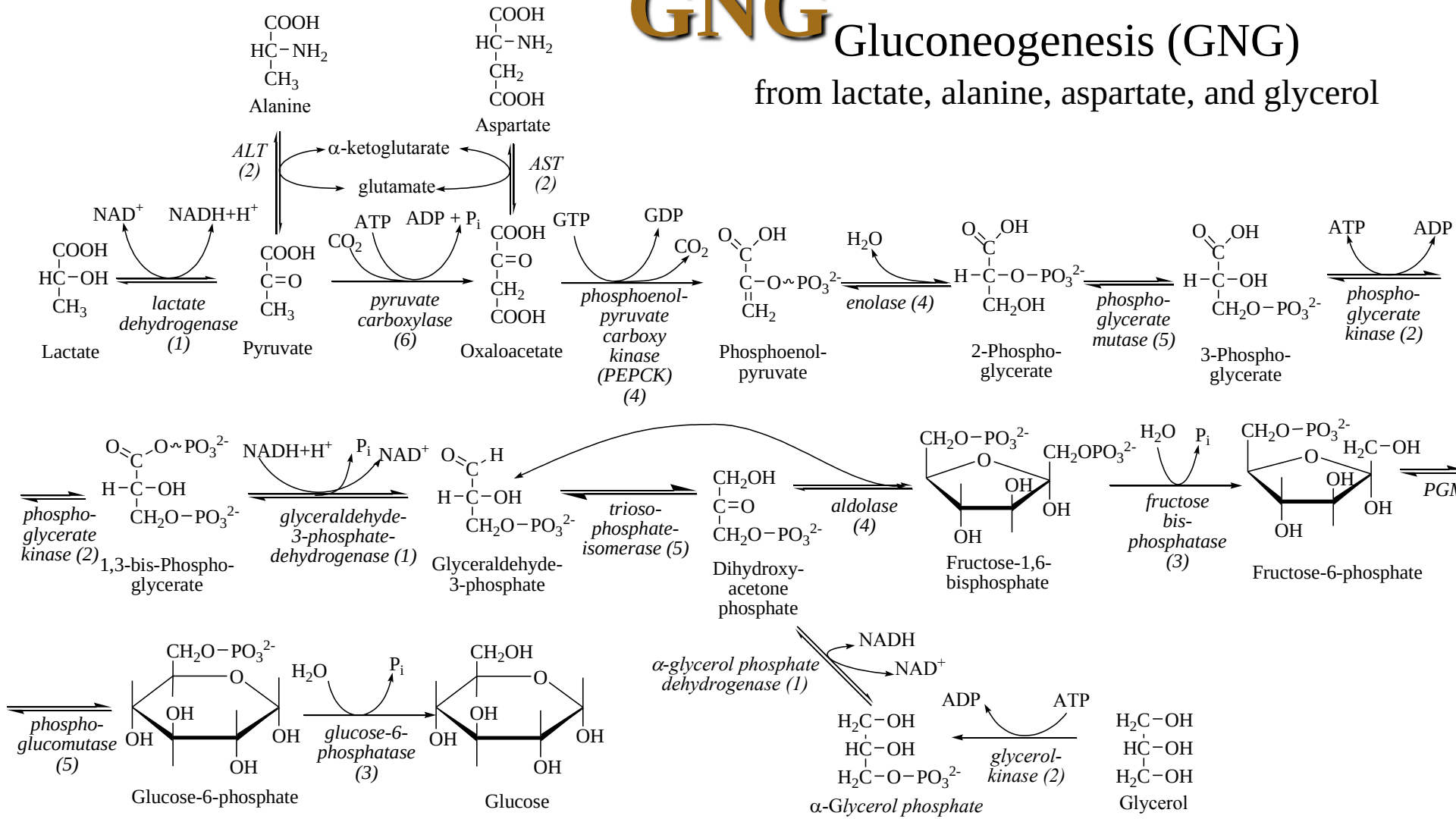
The main precursors for GNG are amino acids derived from muscle proteins.

Another important precursor is lactate, which is formed in erythrocytes and muscle proteins.

Glycerol produced from the degradation of fats can also be used for gluconeogenesis.

GNG Gluconeogenesis (GNG)

from lactate, alanine, aspartate, and glycerol



Pathology of Carbohydrate Metabolism

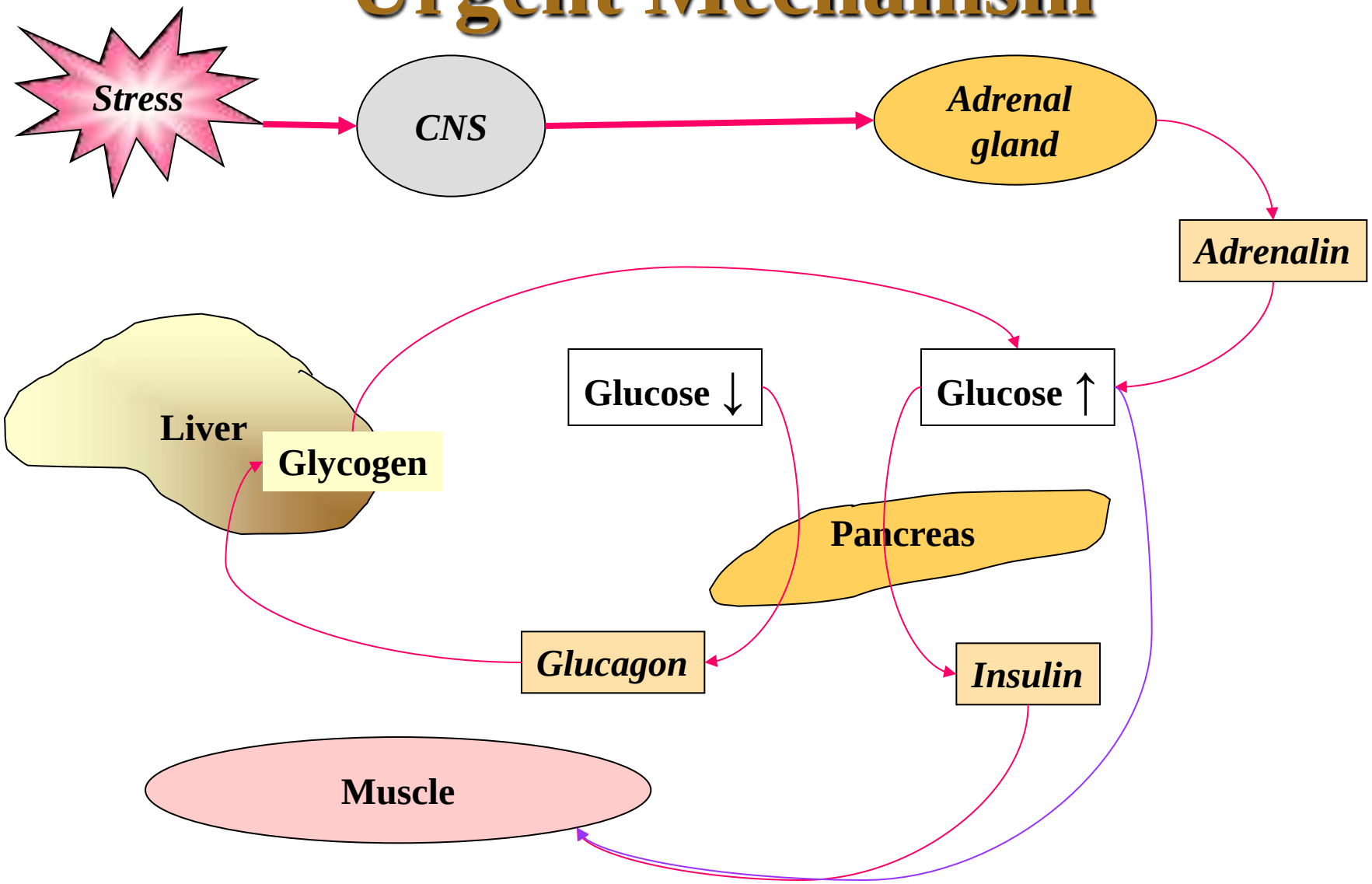
Content

- Mechanisms of blood glucose level regulation
- Diabetes mellitus (type I and II)
- Disorders of digestion and absorption of carbohydrates
- Galactose and fructose metabolism impairments
- Metabolic Disorders Associated with the Pentose Phosphate Pathway
- Glycogen storage diseases
- Mucopolysaccharidoses

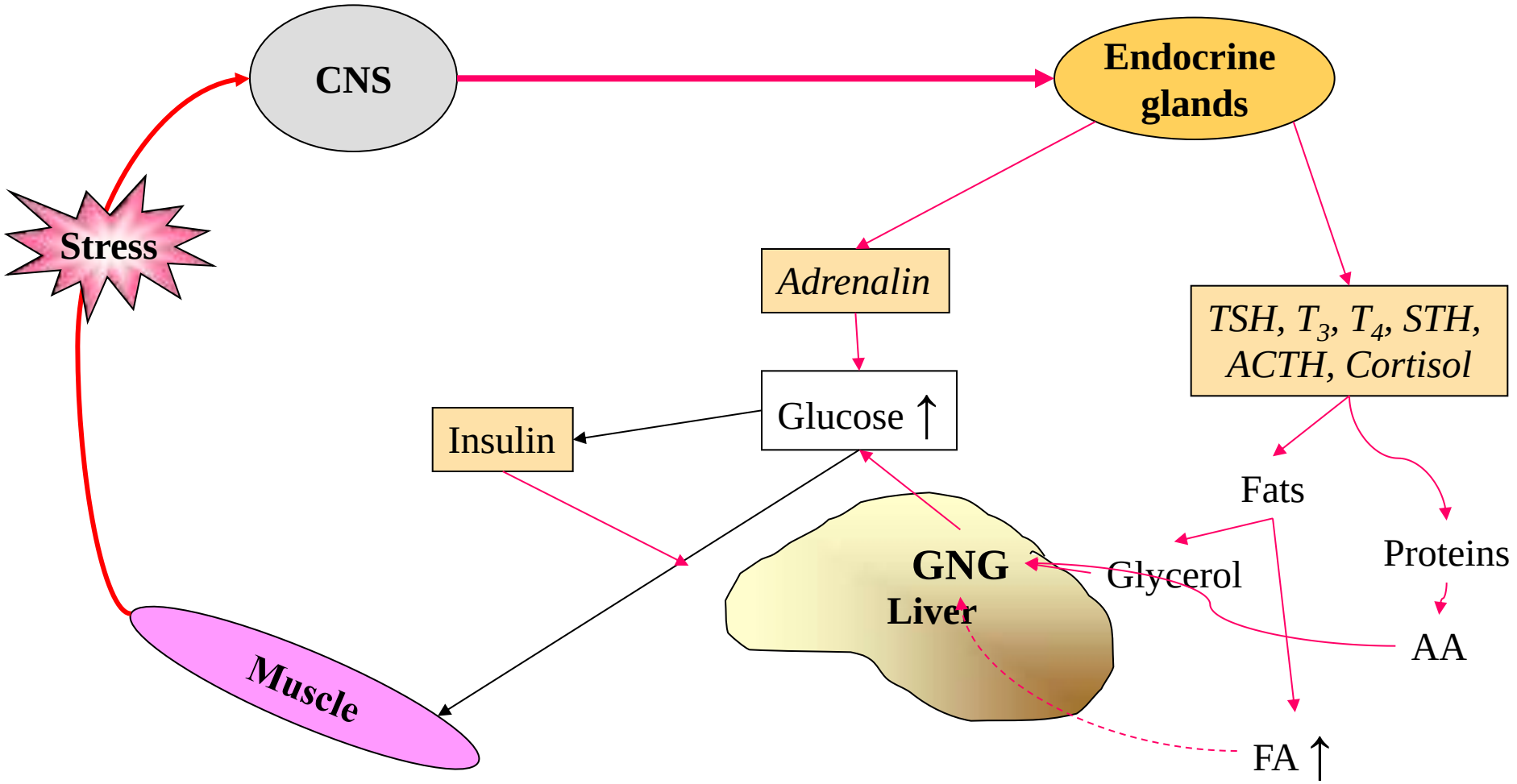
Mechanisms of blood glucose level regulation

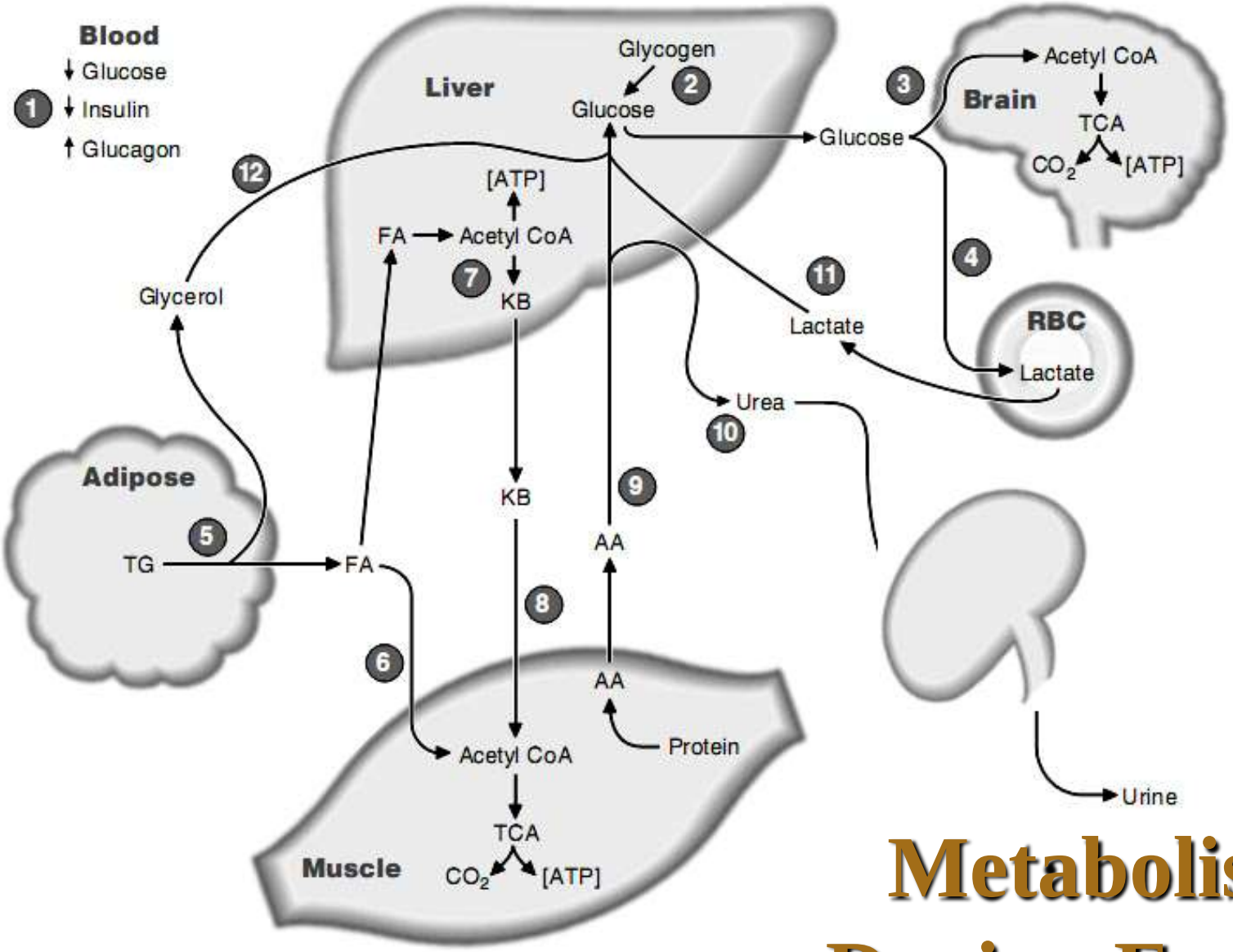
- Urgent mechanism – when there is a glycogen in liver and muscles: post-absorptive (fed) state.
- Constant mechanism – when there no glycogen storage in liver and muscles: starving state.

Urgent Mechanism



Constant Mechanism



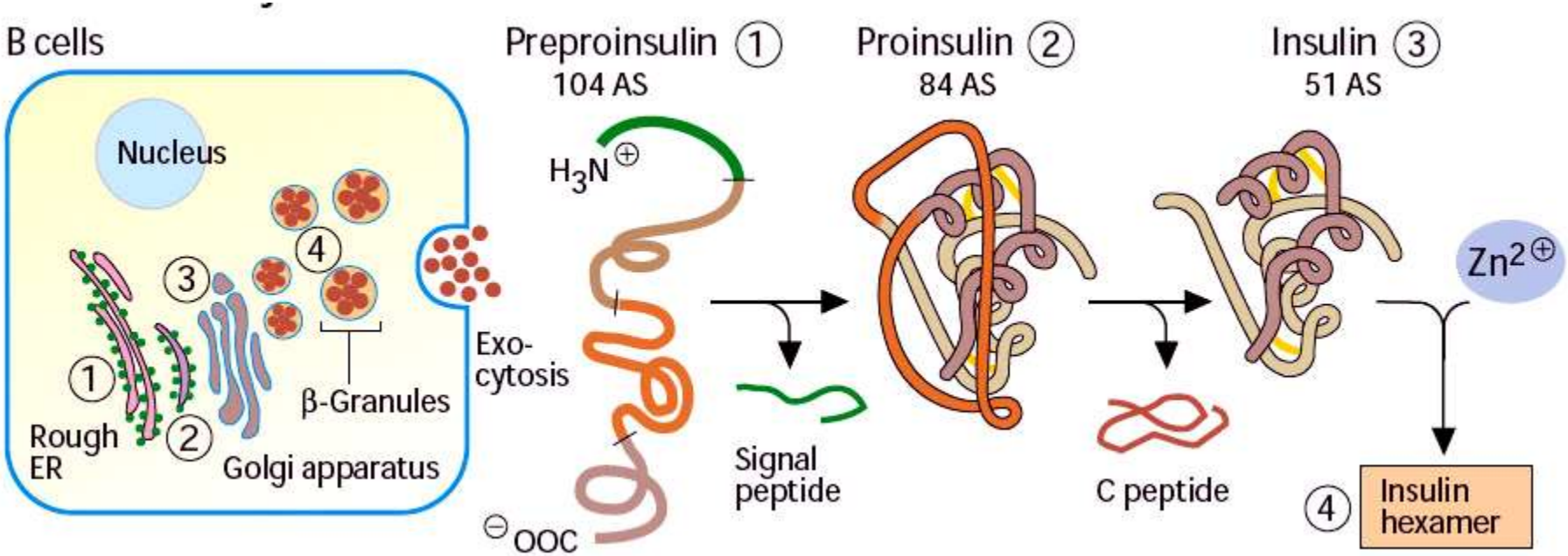


Metabolism During Fasting

Diabetes mellitus (type I and II)

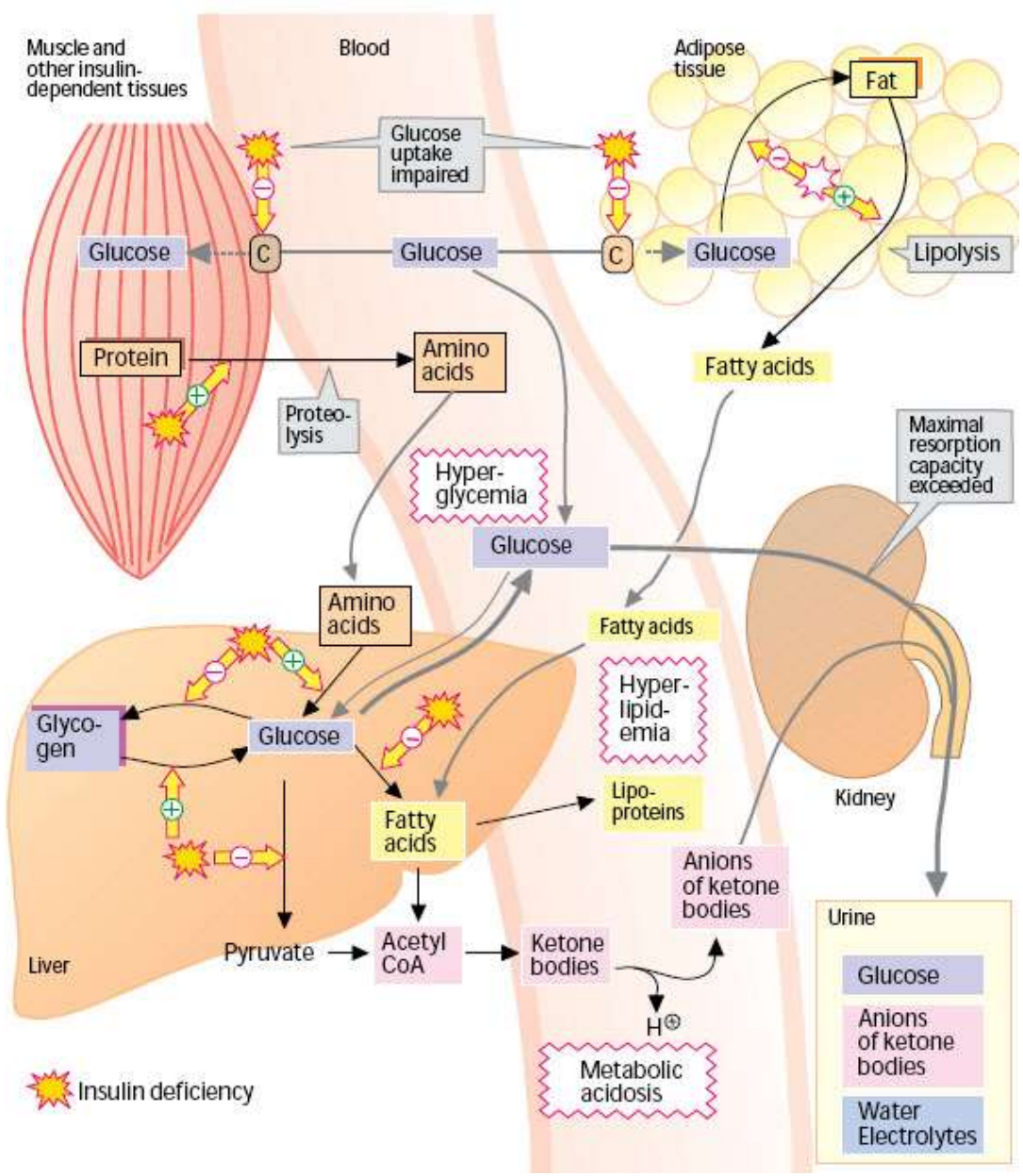
- Diabetes type I: insulin-dependent diabetes mellitus, IDDM, juvenile-onset diabetes:
  - because of deficiency of insulin.
- Diabetes type II: noninsulin-dependent diabetes mellitus, NIDDM:
  - Because of inability of tissues (adipose and muscles) to take up glucose in the presence of normal amounts of insulin.

Insulin Biosynthesis



- C-peptide produces can serve as diagnostic marker of insulin biosynthesis.

Effects of Insulin Deficiency



- Hyperglycemia
  - glucosuria
- Hyperlipidemia
  - atherosclerosis
- Metabolic acidosis
  - Ketosis
  - Diabetic coma
- Hyperosmolarity of blood

Fig. 12.11 ► **Regulation of glycogen metabolism by insulin**

In muscle and liver cells, the regulation of glycogenesis by insulin is mediated by phosphorylation and dephosphorylation events, respectively, catalyzed by protein kinase B (PKB) and protein phosphatase1 (PP1), which culminates in (**A**) the activation of glycogen synthase and (**B**) inhibition of glycogen phosphorylase. Glucose, glucose 6-phosphate, and ATP exert allosteric control over the activity of glycogen synthase and glycogen phosphorylase that favors glycogenesis. ATP, adenosine triphosphate; Glc, glucose; GSK3, glycogen synthase kinase 3; PK, phosphorylase kinase.

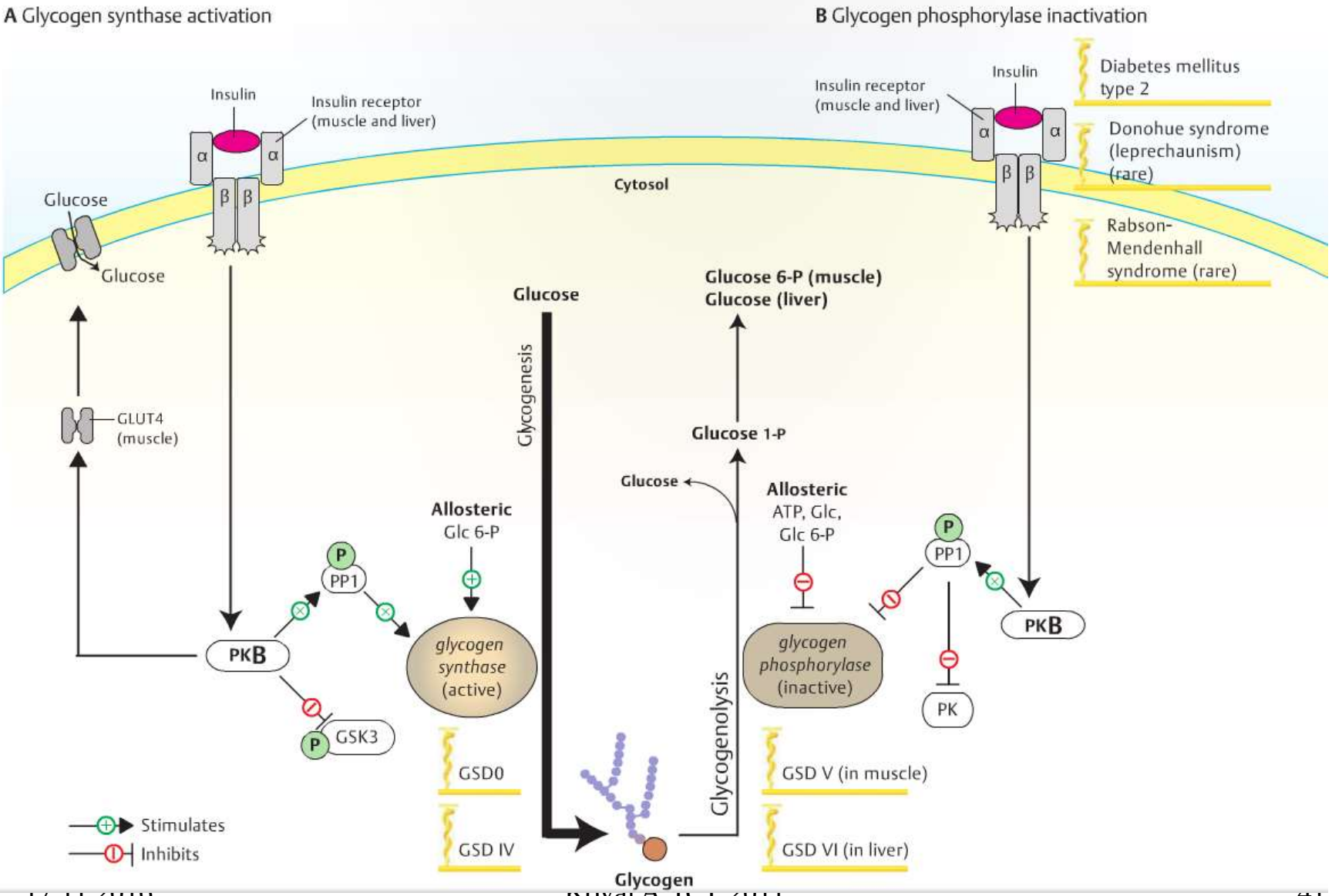
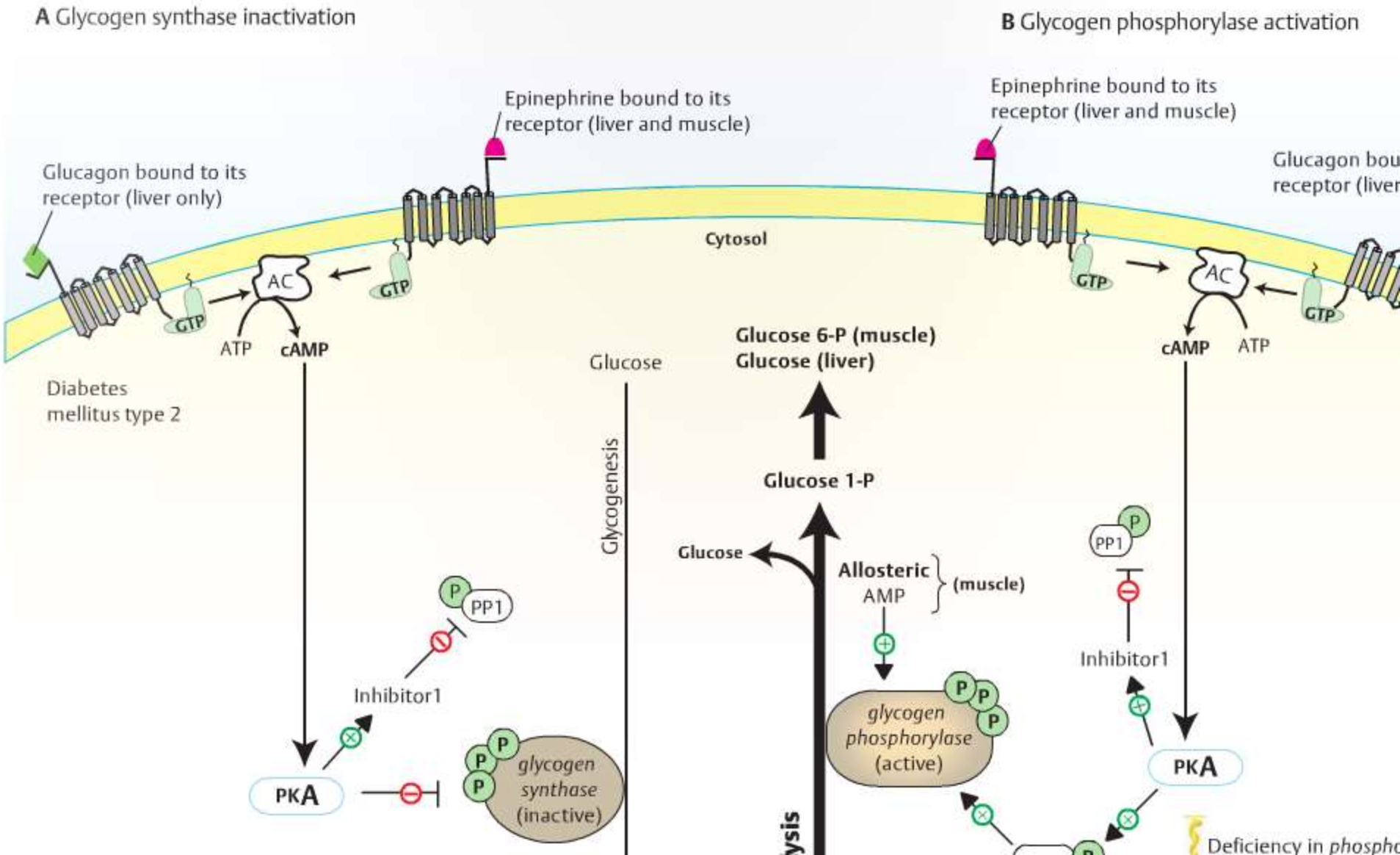
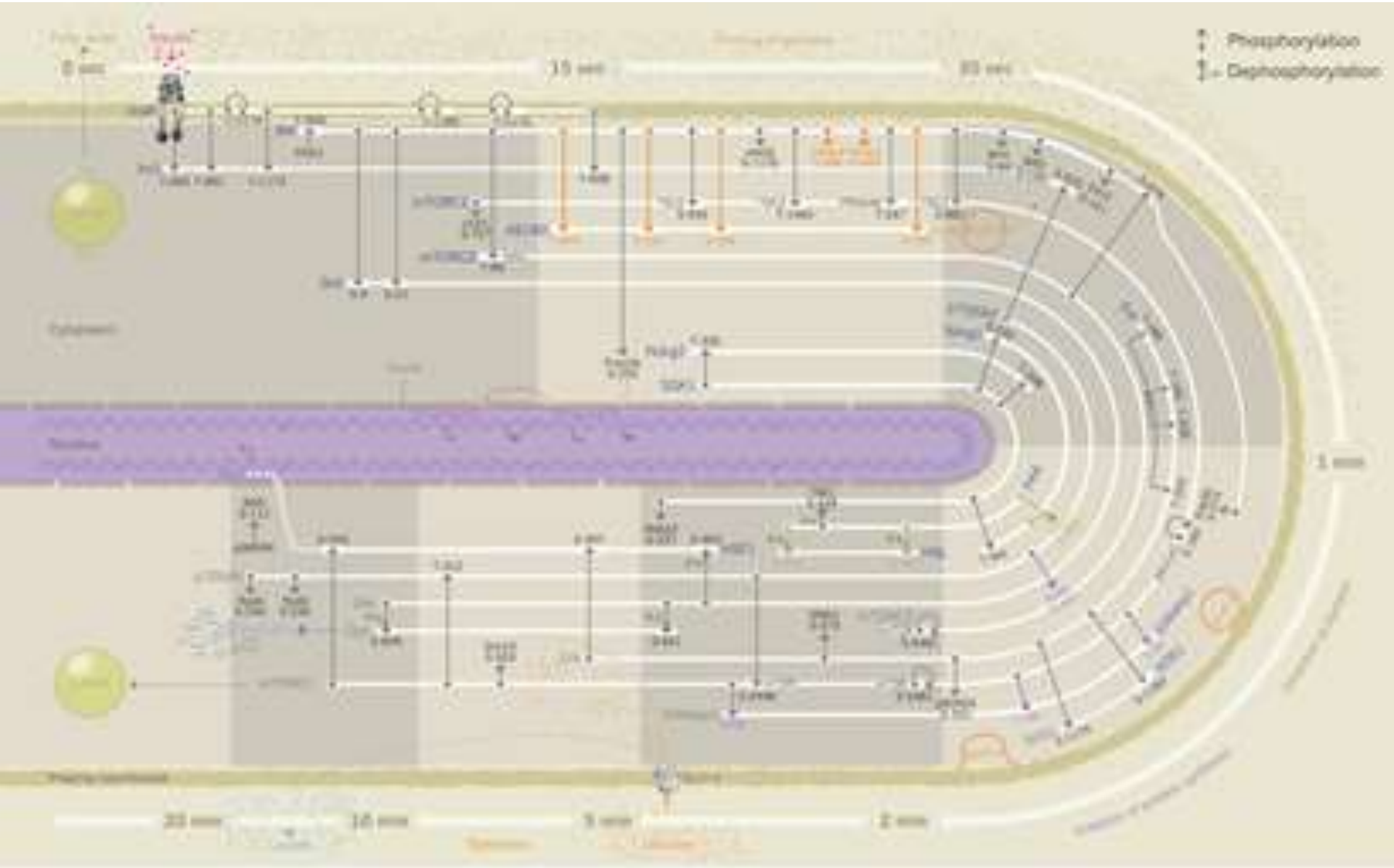


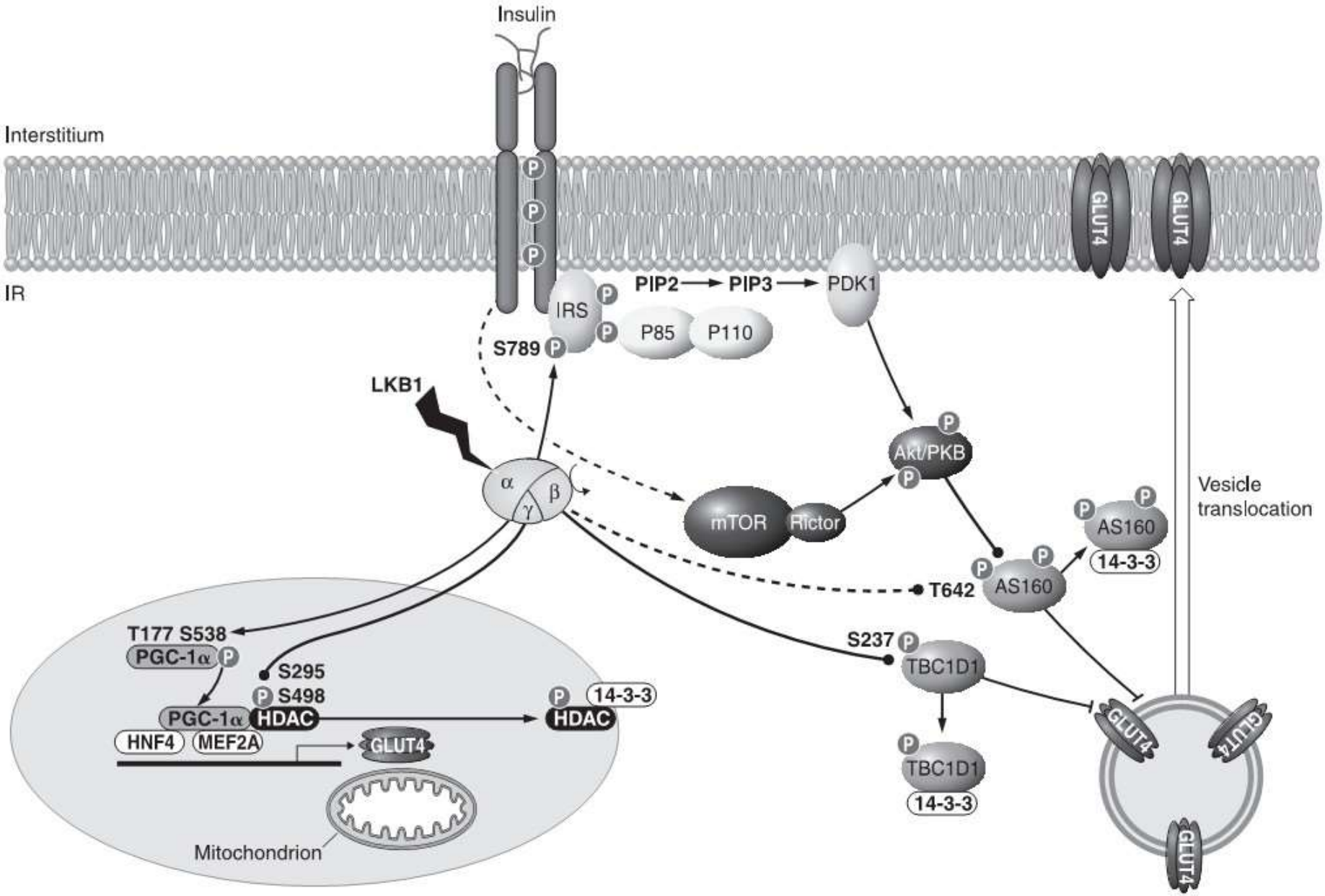
Fig. 12.12 ▶ **Regulation of glycogenolysis**

Glycogenolysis is regulated by glucagon (in liver cells only) and epinephrine (in liver and muscle cells) via signaling pathways that involve ac
of their respective G protein–coupled receptor (GPCR), increase in cyclic adenosine monophosphate (cAMP) levels, activation of protein kin
(PKA), and various phosphorylation/dephosphorylation events that result in (**A**) the inhibition of glycogen synthase and (**B**) activation of gly
phosphorylase. Additional regulators of glycogenolysis include Ca^{2+} and AMP, which both activate glycogen phosphorylase. AC, adenylate
ATP, adenosine triphosphate; GSD, glycogen storage disease; GTP, guanosine triphosphate; PK, phosphorylase kinase; PP1, protein phospha





A 'Minardo' chart that visualizes a cascade of protein phosphorylation after a cell is treated with insulin.


Insulin
Interstitium
IR
GLUT4
GLUT4
PIP2 → PIP3 → PDK1
IRS
P85
P110
S789
LKB1
α
β
γ
Akt/PKB
mTOR
Rictor
AS160
14-3-3
T642
AS160
Vesicle translocation
T177 S538
PGC-1α
S295
S498
PGC-1α
HDAC
HDAC
14-3-3
HNF4
MEF2A
GLUT4
Mitochondrion
S237
TBC1D1
TBC1D1
14-3-3
GLUT4
GLUT4
GLUT4

Secondary Effects of Diabetes

- A constantly raised blood sugar level can lead in the long term to
  - changes in the blood vessels (diabetic angiopathy),
  - kidney damage (nephropathy) and
  - damage to the nervous system (neuropathy), as well as to cataracts in the eyes.
- All these effects are **irreversible.**
- Monitoring of blood glucose level in diabetics can postpone these effects.

Clinical Manifestation of Diabetes Mellitus

- “3 P” syndrome: polydypsia, polyuria, polyphagia
- Ipmaired tissue regeneration
- Multiple tooth decay
- Atherosclerosis
- Angiopathies
- Neuropathies
- Blindness, ec.

Laboratory Diagnostics

- Blood glucose level
- Glucose tolerance test
  - There are a lot of diseases which are accompanied with hyperglycemia
- Ketone bodies in blood and urine
- Glycosylated hemoglobin
- Insulin
- C-peptide

Disorders of Digestion and Absorption of Carbohydrates

- Digestion:
  - Disaccharidase deficiency (sucrase, lactase, maltase, isomaltase)
- Absorption
  - Malabsorption of monosugars
  - Dyspepsia

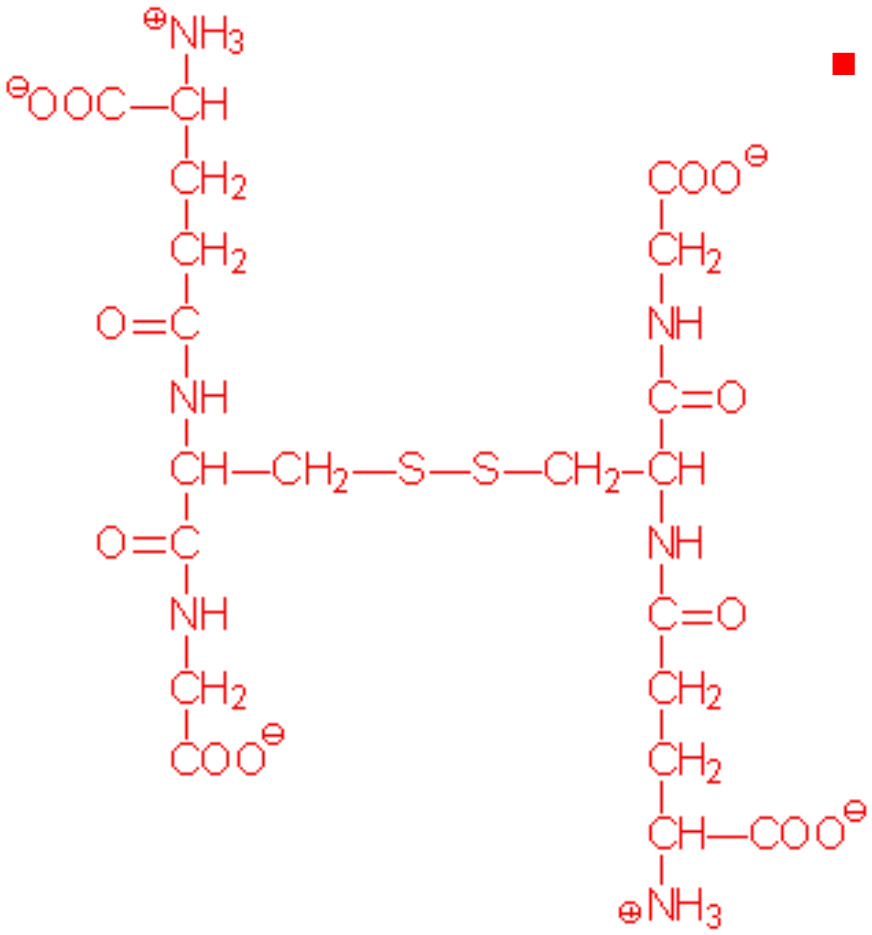
Galactose and fructose metabolism impairments

- Galactosemia
- Essential fructosuria
- Fructose intolerance
  - *see Danchenko book*

Metabolic Disorders Associated with the Pentose Phosphate Pathway

- Oxidative stress within cells is controlled primarily by the action of the peptide, **glutathione, GSH.**

Glutathione structure



Glutathione disulfide (GSSG)

- Glutathione (GSH, tripeptide γ-glu-cys-gly). The sulfhydryl side chains of the cysteine residues of two glutathione molecules form a disulfide bond (GSSG) during the course of being oxidized in reactions with various oxides and peroxides in cells. Reduction of GSSG to two moles of GSH is the function of glutathione reductase, an enzyme that requires coupled oxidation of NADPH

Glutathione can reduce disulfides nonenzymatically

- Oxidative stress also generates peroxides that in turn can be reduced by glutathione to generate water and an alcohol, or 2 waters if the peroxide were hydrogen peroxide.
- Regeneration of reduced glutathione is carried out by the enzyme, glutathione reductase. This enzyme requires the co-factor NADPH when operating in the direction of glutathione reduction which is the thermodynamically favored direction of the reaction.
- It should be clear that any disruption in the level of NADPH may have a profound effect upon a cells ability to deal with oxidative stress. No other cell than the erythrocyte is exposed to greater oxidizing conditions. After all it is the oxygen carrier of the body.

Erythrocytes and the Pentose Phosphate Pathway

- The predominant pathways of carbohydrate metabolism in the red blood cell (RBC) are glycolysis, the PPP and 2,3-bisphosphoglycerate (2,3-BPG) metabolism.
  - Glycolysis provides ATP for membrane ion pumps and NADH for re-oxidation of methemoglobin.
  - The PPP supplies the RBC with NADPH to maintain the reduced state of glutathione.
  - 2,3-BPG is an regulatory compound.
- The inability to maintain reduced glutathione in RBCs leads to increased accumulation of peroxides, predominantly H_2O_2, that in turn results in a weakening of the cell wall and concomitant hemolysis. Accumulation of H_2O_2 also leads to increased rates of oxidation of hemoglobin to methemoglobin that also weakens the cell wall.

Erythrocyte survival

- Glutathione removes peroxides via the action of glutathione peroxidase. The PPP in erythrocytes is essentially the only pathway for these cells to produce NADPH. Any defect in the production of NADPH could, therefore, have profound effects on erythrocyte survival.
  - Several deficiencies in the level of activity (not function) of glucose-6-phosphate dehydrogenase have been observed to be associated with resistance to the malarial parasite, *Plasmodium falciparum*, among individuals of Mediterranean and African descent. The basis for this resistance is the weakening of the red cell membrane (the erythrocyte is the host cell for the parasite) such that it cannot sustain the parasitic life cycle long enough for productive growth.

Glycogen Storage Diseases

Glycogenosis	Name	Defective enzyme
Type I	Von Gierke's disease	Glucose-6-phosphatase
Type II	Pompe's disease	Lysosomal α-1,4- and 1,6-glucosidase
Type III	Forbe's, Cori's disease	Debranching enzyme
Type IV	Andersen's disease	Branching enzyme
Type V	McArdle's disease	Muscle phosphorylase
Type VI	Hers' disease	Liver phosphorylase
Type VII	Tarui disease	Muscle, RBC phosphofructokinase
Type VIII	-	Liver phosphorylase kinase
Type 0	-	Glycogen synthase

See textbook of Danchenko

Mucopolysaccharidoses

MPS	Name	Defective Enzyme
Type I	Hurler Syndrome Scheie Syndrome Hurler-Scheie Syndrome	α-L-Iduronidase
Type II	Hunter Syndrome	Iduronate-2-sulphatase
Type IIIA	Sanfilippo Syndrome A	Heparan-N-sulphatase
Type IIIB	Sanfilippo Syndrome B	α-N-Acetylglucosaminidase
Type IIIC	Sanfilippo Syndrome C	AcetylCoA:N-acetyltransferase
Type IIID	Sanfilippo Syndrome D	N-Acetylglucosamine 6-sulphatase
Type IVA	Morquio Syndrome	Galactose 6-sulphatase
Type IVB	Morquio Syndrome	β-Galactosidase
Type VI	Maroteaux-Lamy Syndrome	N-Acetylglucosamine 4-sulphatase
Type VII	Sly Syndrome	β-Glucuronidase
Type IX	-	hyaluronoglucosaminidase-1

http://www.mpssociety.org.au/table_of_diseases.htm

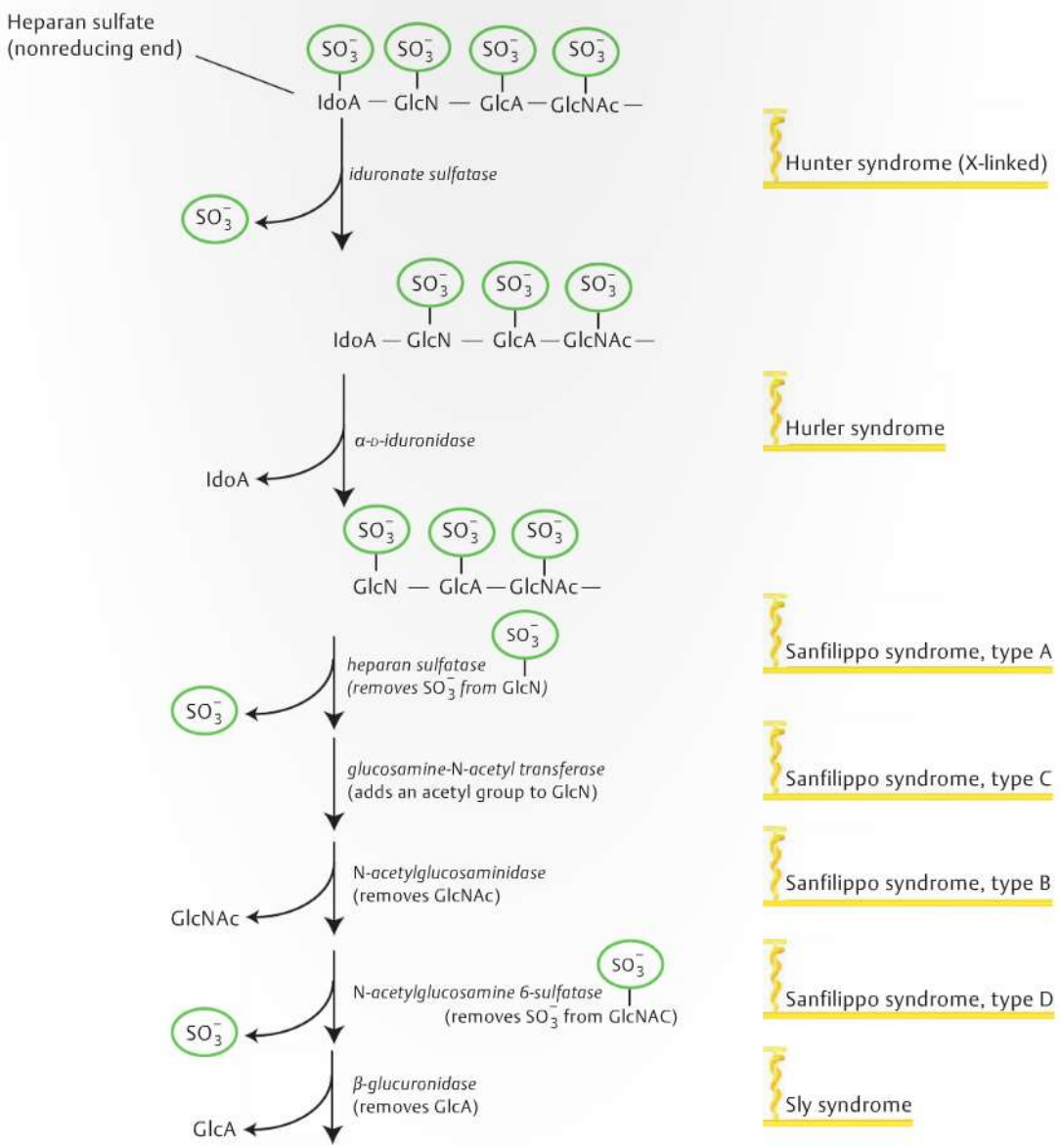


Fig. 12.23 ▶ **Glycosaminoglycan degradation**
Enzymes involved in the removal of sulfate groups and acidic or amino sugars during glycosaminoglycan degradation. The sugars are removed from the nonreducing ends. An endo-β-glucuronidase first cleaves large chains into smaller fragments, and each monosaccharide is then removed from the nonreducing end. *N*- and *O*-sulfate groups must first be removed before exoglycosidases can act. An unusual feature of heparin sulfate degradation is that this process also involves a synthetic step. After removal of the *N*-sulfate residue on $GlcNSO_3^-$, the nonacetylated glucosamine must first be *N*-acetylated using acetyl CoA before α-*N*-acetylglucosaminidase can cleave this residue. Disorders (known as mucopolysaccharidoses) associated with defects in particular degradation enzymes are noted. GlcA, D-glucuronic acid; GlcN; glucosamine; GlcNAc, *N*-acetyl-D-glucosamine; IdoA, L-iduronic acid; SO_3^-, sulfate group.

nose residues. After their synthesis in the rough endoplasmic reticulum (RER), the mannose residues on these proteins need to be phosphorylated for the proteins to be properly sorted through the *cis*- and *trans*-Golgi to the lysosomes. In I-cell disease, the enzyme *N*-acetylglucosamine-1-phosphotransferase (GlcNAc-PT) is deficient. As a result, all lysosomal hydrolases fail to be sorted properly and are instead secreted out into the bloodstream. Detection of lysosomal hydrolases in the plasma distinguishes between defective synthesis and defective sorting.

Osteoarthritis

Osteoarthritis is a noninflammatory degenerative joint disease caused by wear and tear on the joints. The articular cartilage becomes depleted, destroying chondroitin sulfate, and there are bony outgrowths at the margins. It commonly affects the joints of the hand, hip, and knee and the zygapophyseal (facet) joints of the cervical and lumbar spine, causing pain, stiffness, and joint instability.

Conclusion


Thank you
for your attention