

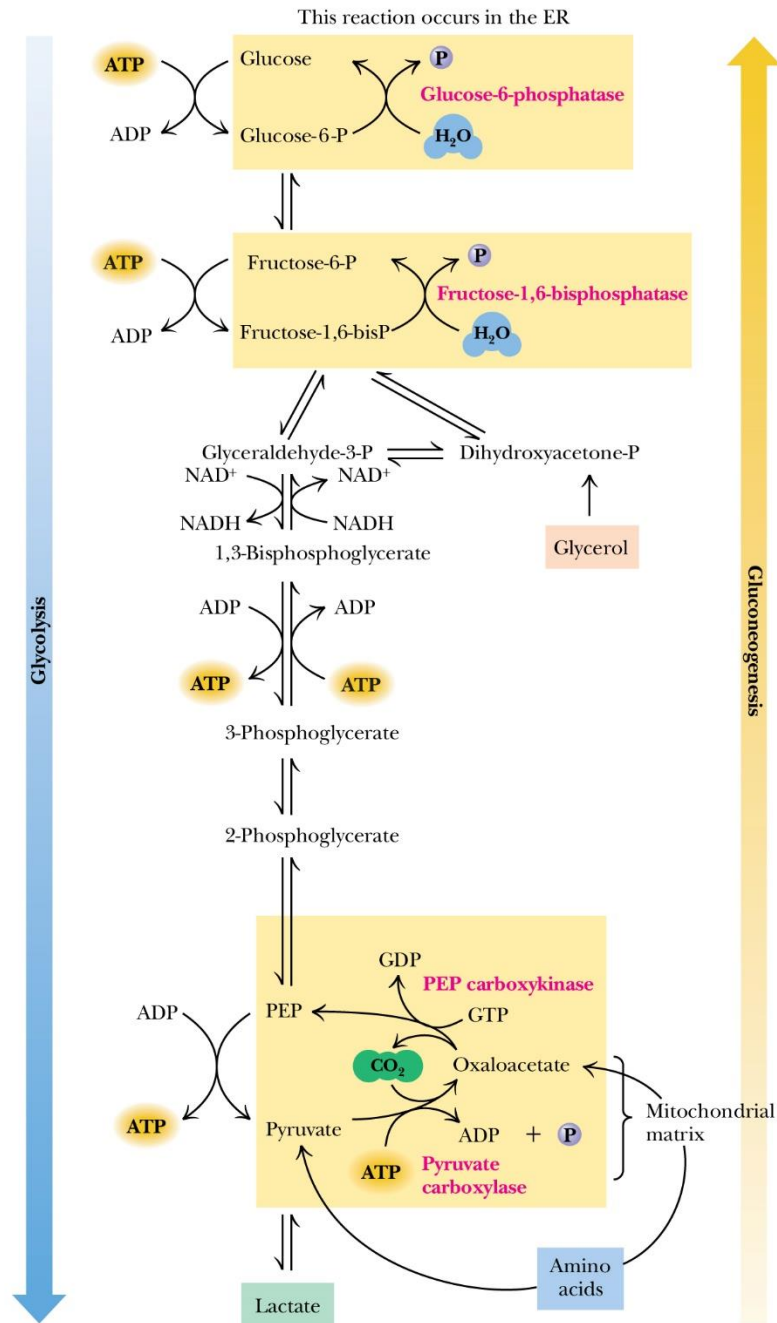
Gluconeogenesis and glycogen metabolism

Gluconeogenesis

- Synthesis of glucose from non-carbohydrate sources
- Major precursors- lactate, pyruvate, glycogenic amino acid, propionate and glycerol
- Mainly in cytosol of hepatocytes and some extent in renal tissue

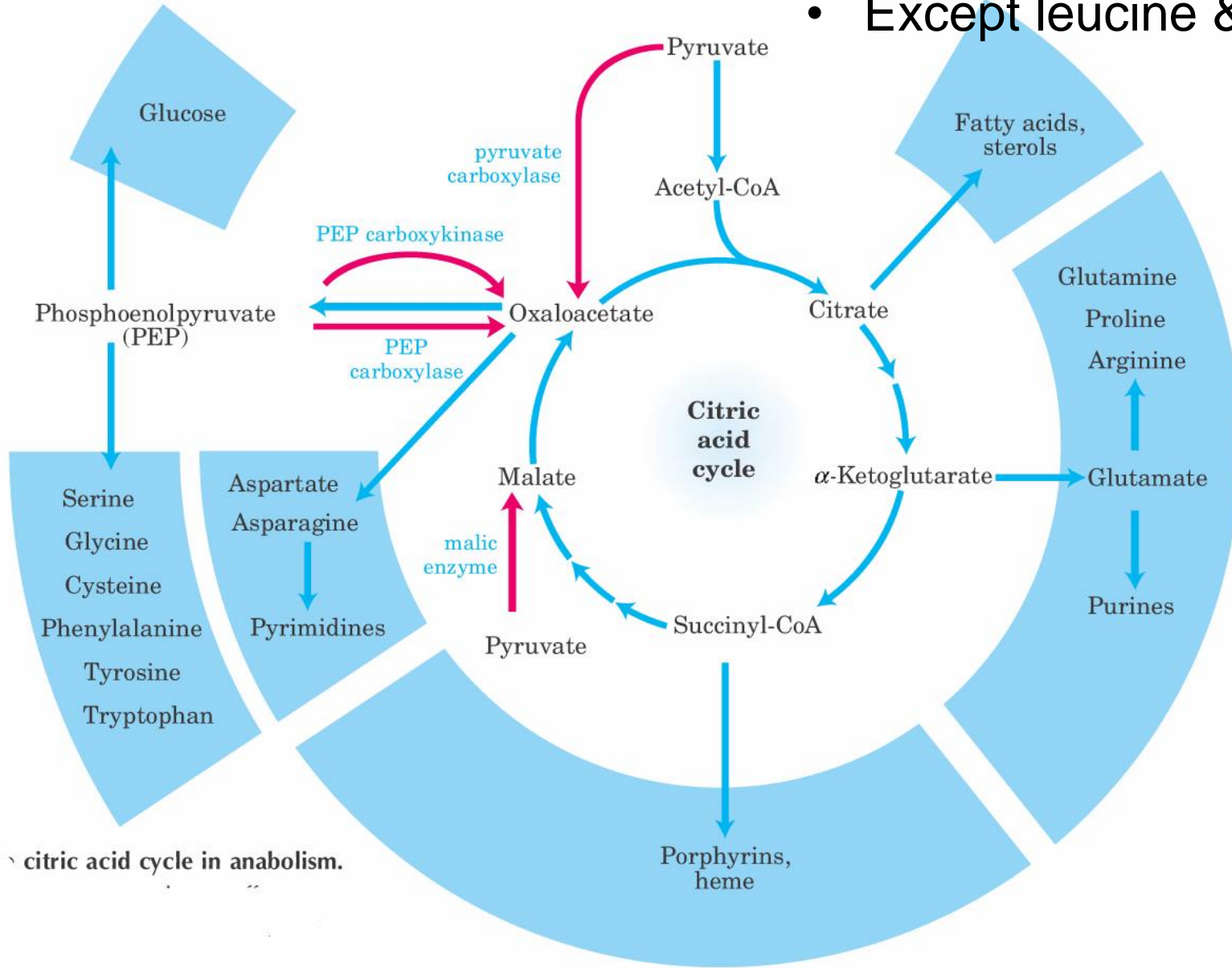
Importance

- Nervous tissue, RBC, Testes and kidney medulla dependent on glucose for energy
- Glucose is only source of energy under anaerobic condition for muscle
- In starvation body glucose is meet by gluconeogenesis
- Certain metabolites (lactate, glycereol etc) are effectively cleared
- converts excess of dietary glucogenic amino acids into glucose
- Lactic acidosis occurs in fructose-1, 6-bis phosphatase deficiency
- Gluconeogenesis is impaired in alcoholics



Amino Acid

- Except leucine & lysine



• citric acid cycle in anabolism.

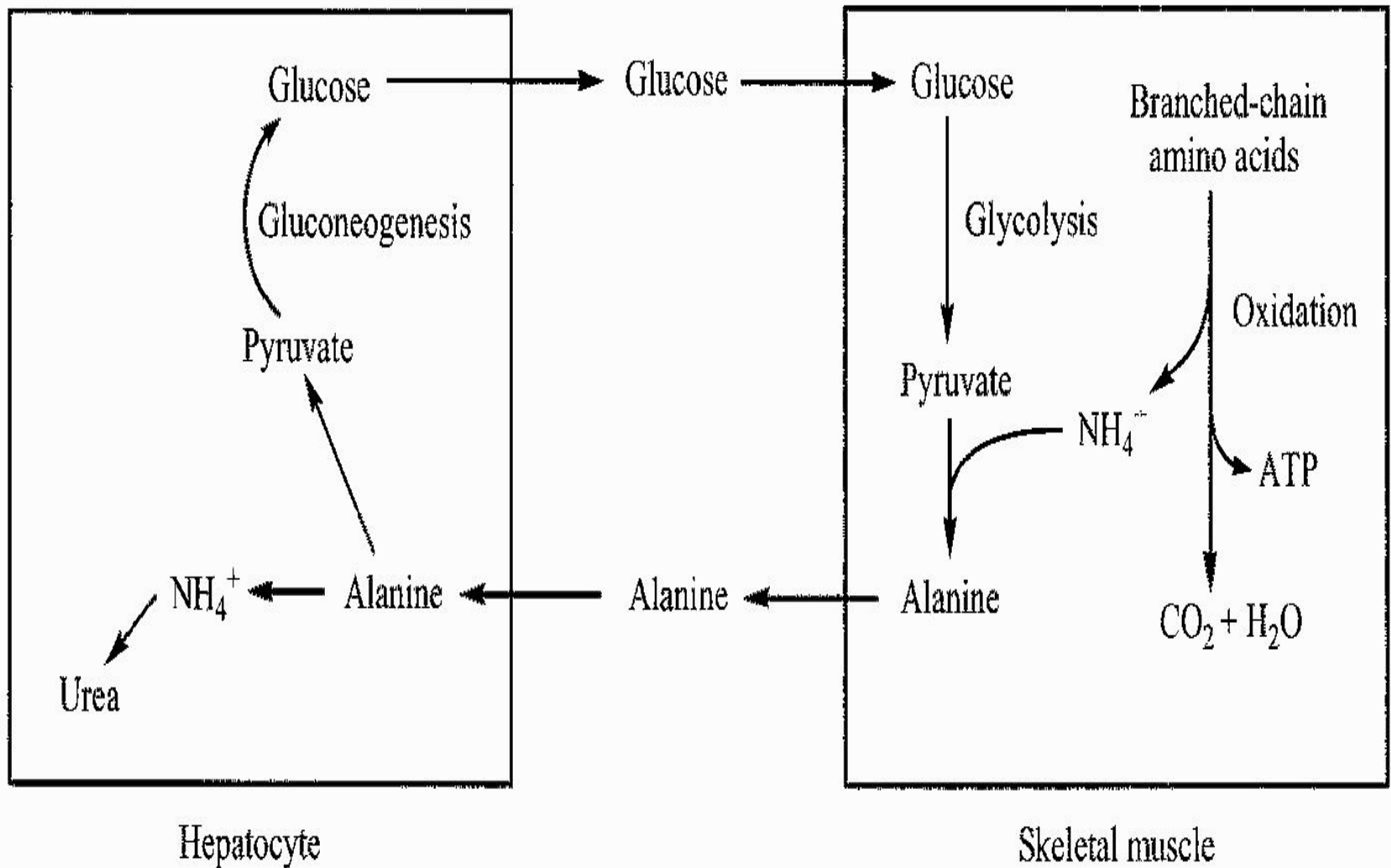
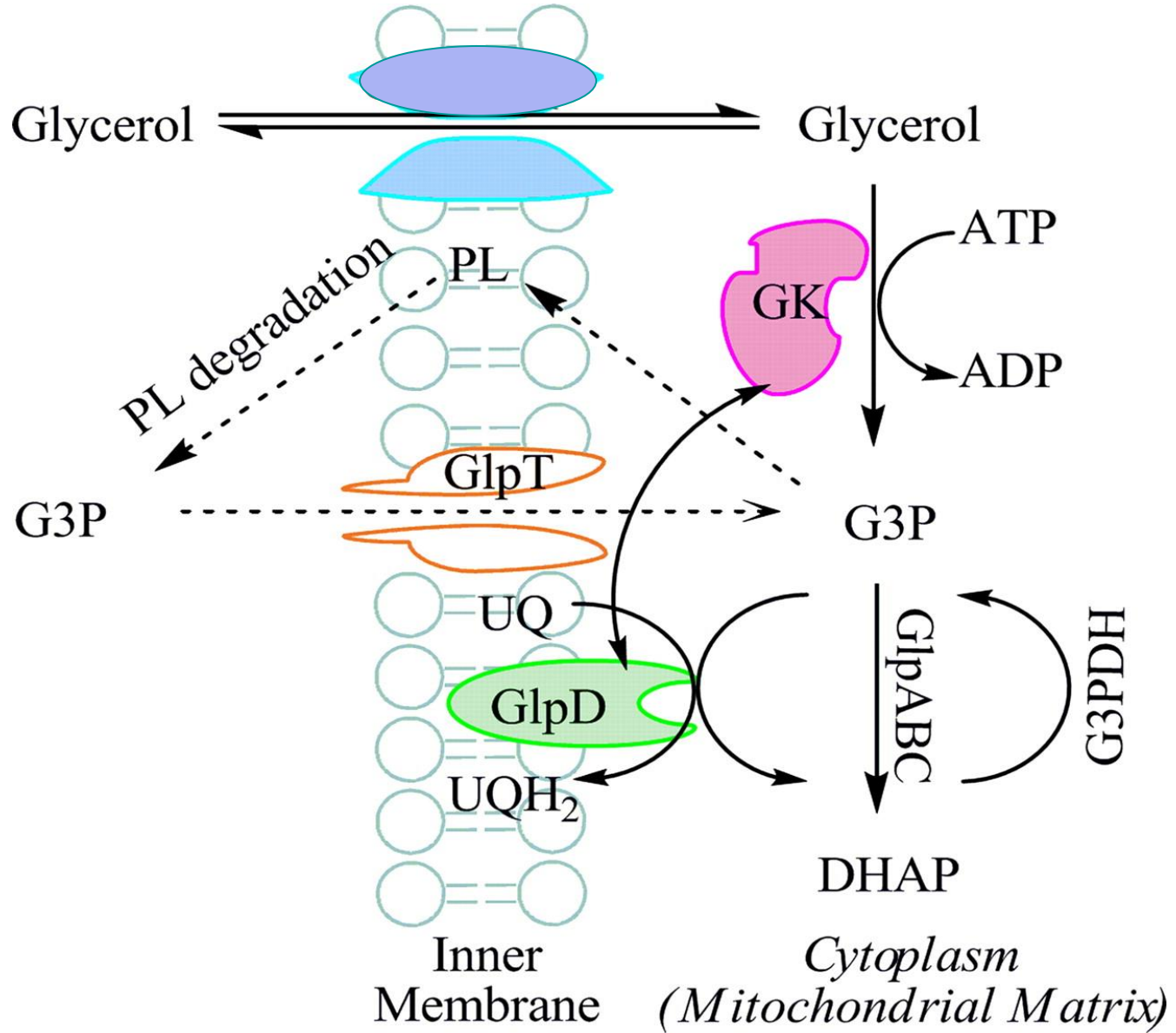


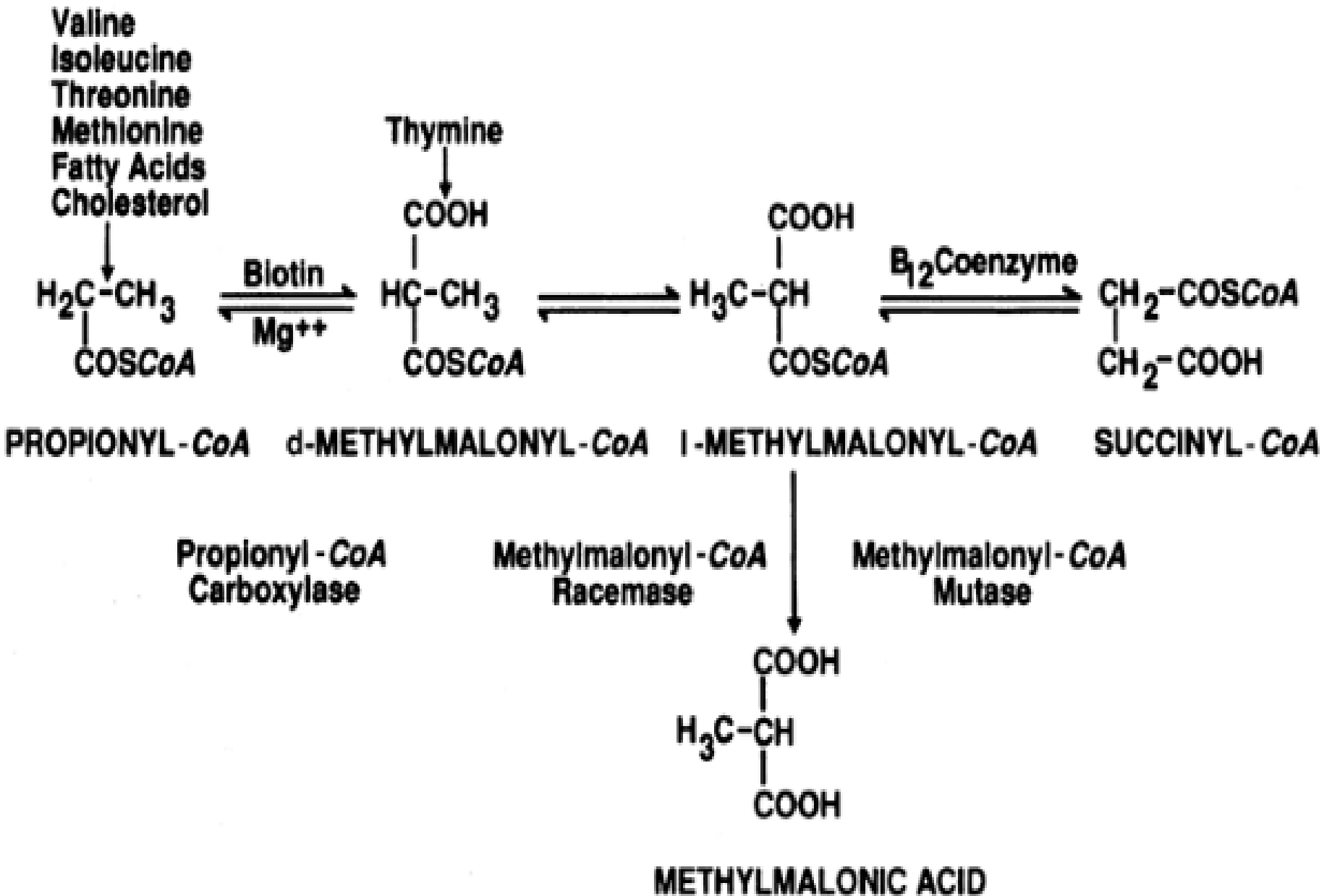
FIGURE 9-4 Alanine cycle.

Glycerol

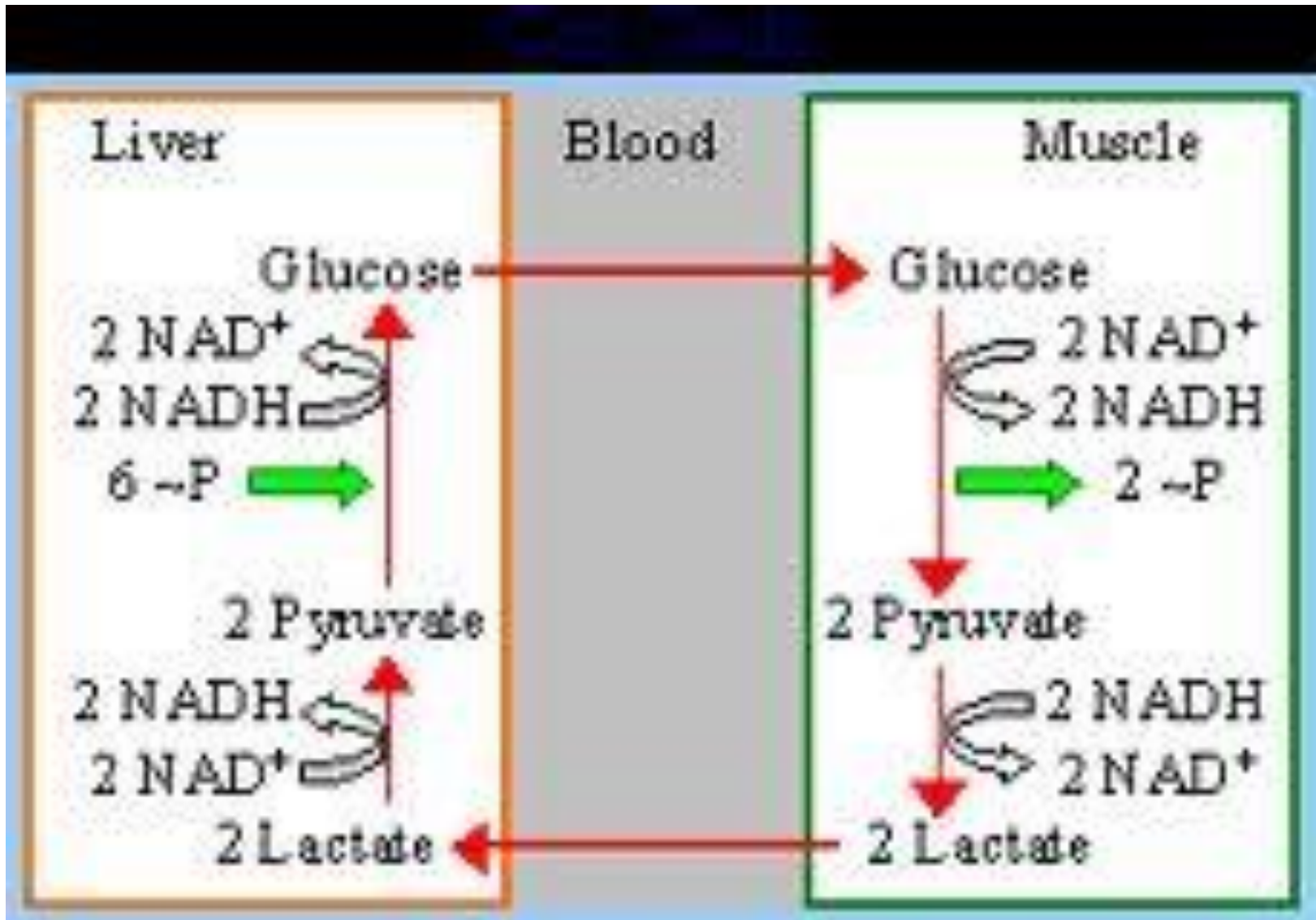
Only in liver and kidney not in adipose tissue

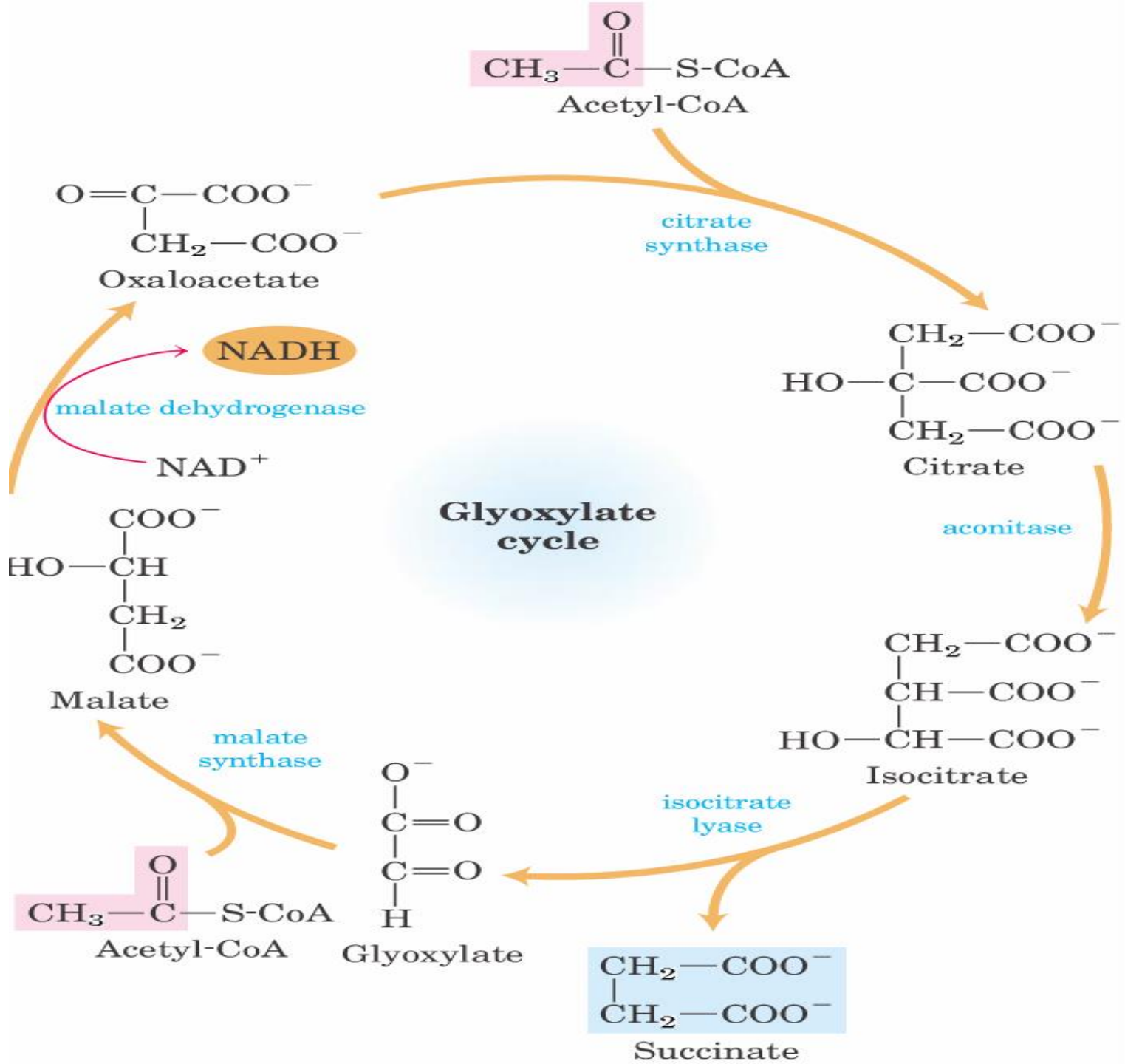


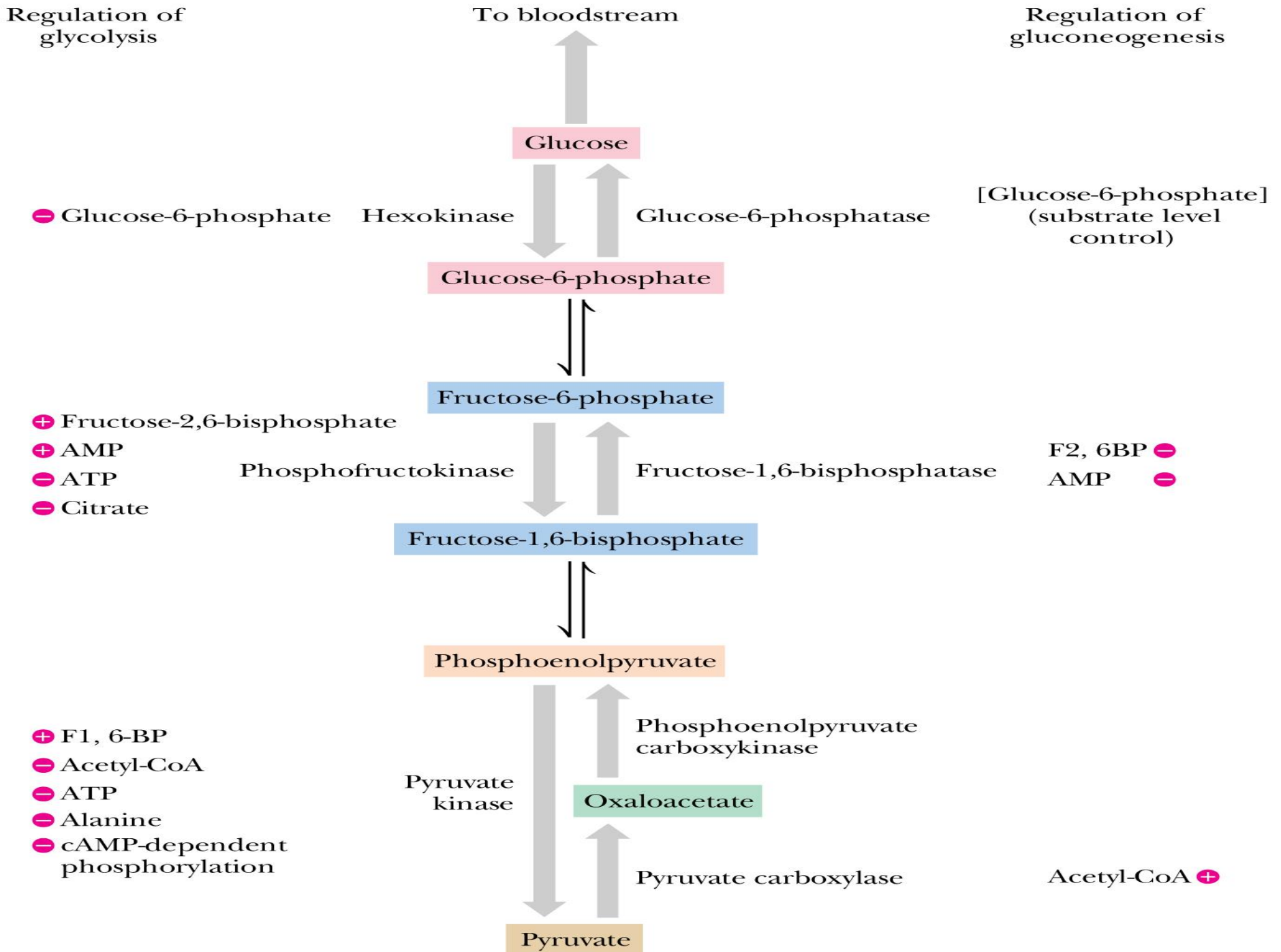
Propionate

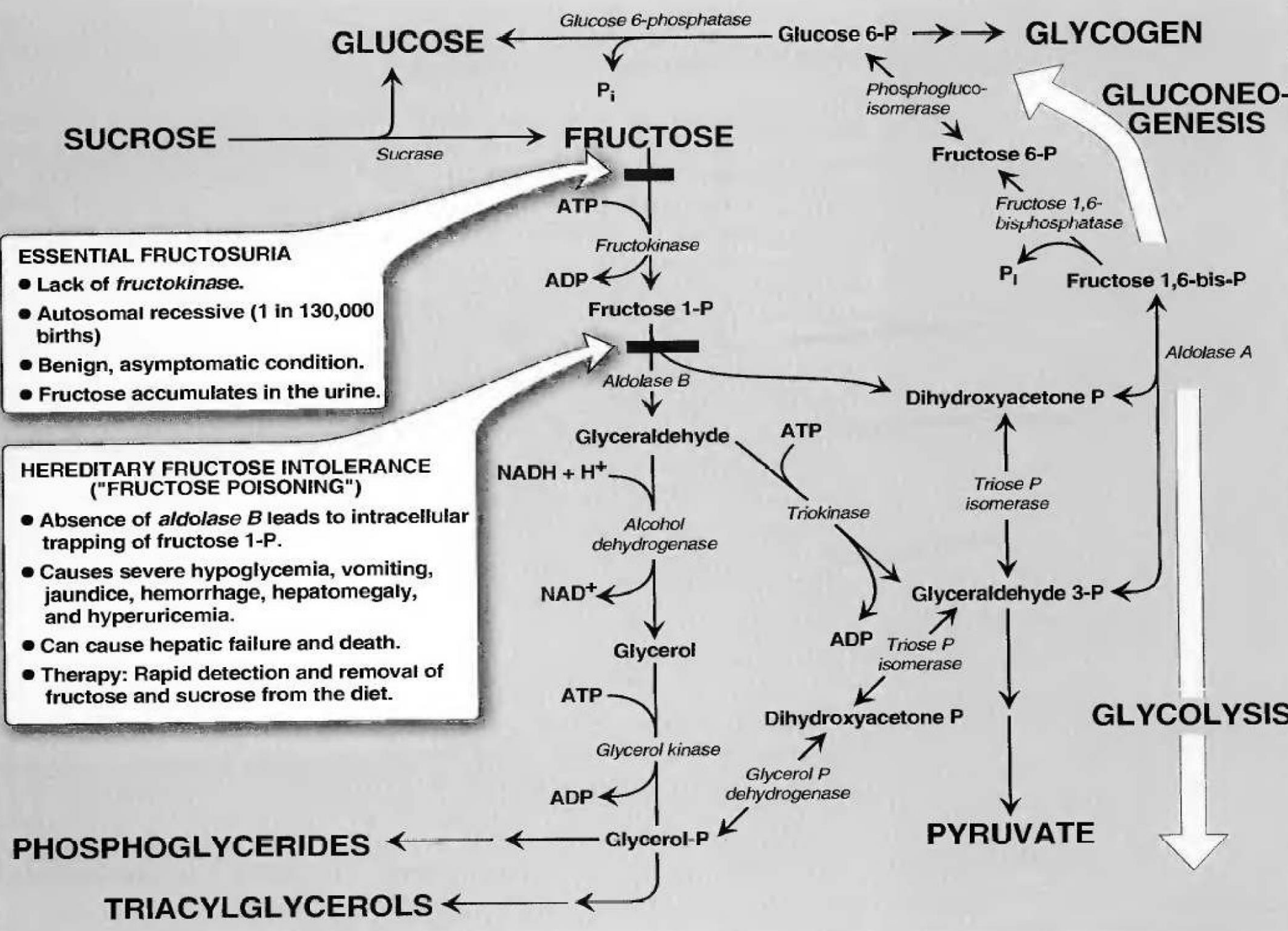


Cori cycle









ESSENTIAL FRUCTOSURIA

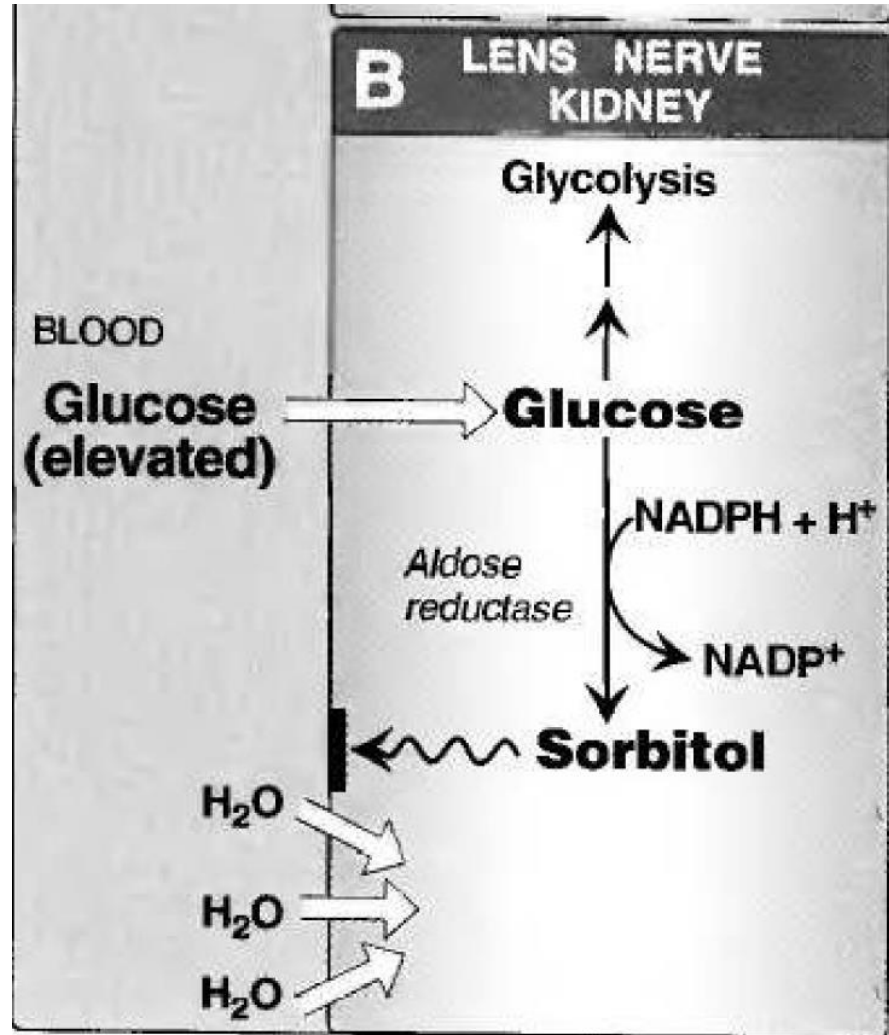
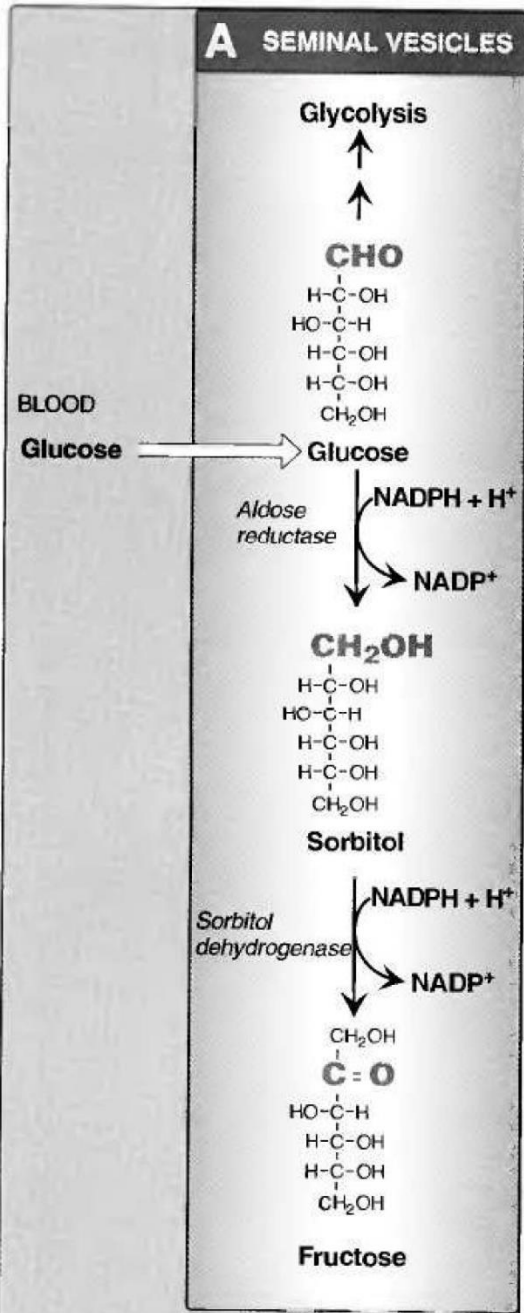
- Lack of *fructokinase*.
- Autosomal recessive (1 in 130,000 births)
- Benign, asymptomatic condition.
- Fructose accumulates in the urine.

HEREDITARY FRUCTOSE INTOLERANCE ("FRUCTOSE POISONING")

- Absence of *aldolase B* leads to intracellular trapping of fructose 1-P.
- Causes severe hypoglycemia, vomiting, jaundice, hemorrhage, hepatomegaly, and hyperuricemia.
- Can cause hepatic failure and death.
- Therapy: Rapid detection and removal of fructose and sucrose from the diet.

Идея-концепция: М.А.А. ст. 1998г., Р. 1

Sorbitol Pathway

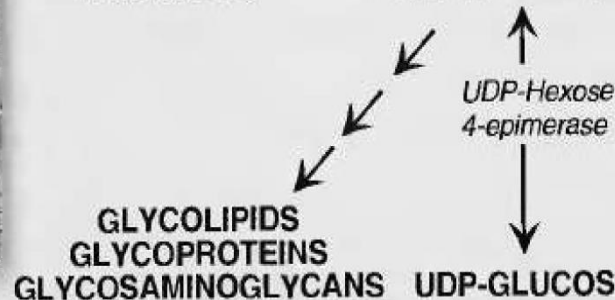
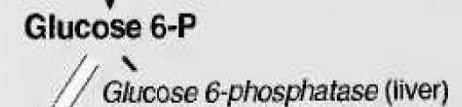
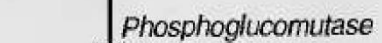
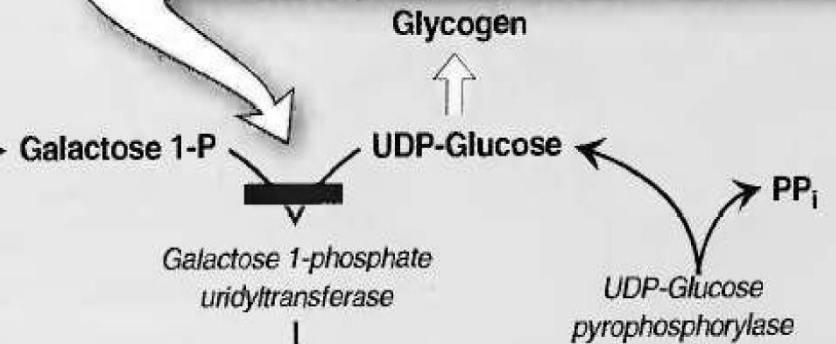
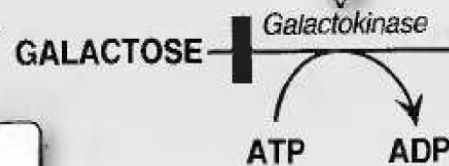
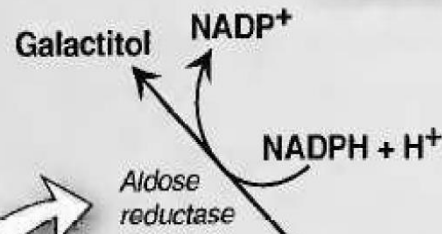


CLASSIC GALACTOSEMIA

- *Uridyltransferase* deficiency.
- Autosomal recessive disorder (1 in 23,000 births).
- It causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
- Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
- Antenatal diagnosis is possible by chorionic villus sampling.
- Therapy: Rapid diagnosis and removal of galactose (therefore, lactose) from the diet.

GALACTOKINASE DEFICIENCY

- This causes galactosemia and galactosuria.
- It causes galactitol accumulation if galactose is present in the diet.



ALDOSE REDUCTASE

- The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
- It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
- Elevated galactitol can cause cataracts.

GLYCOLYSIS

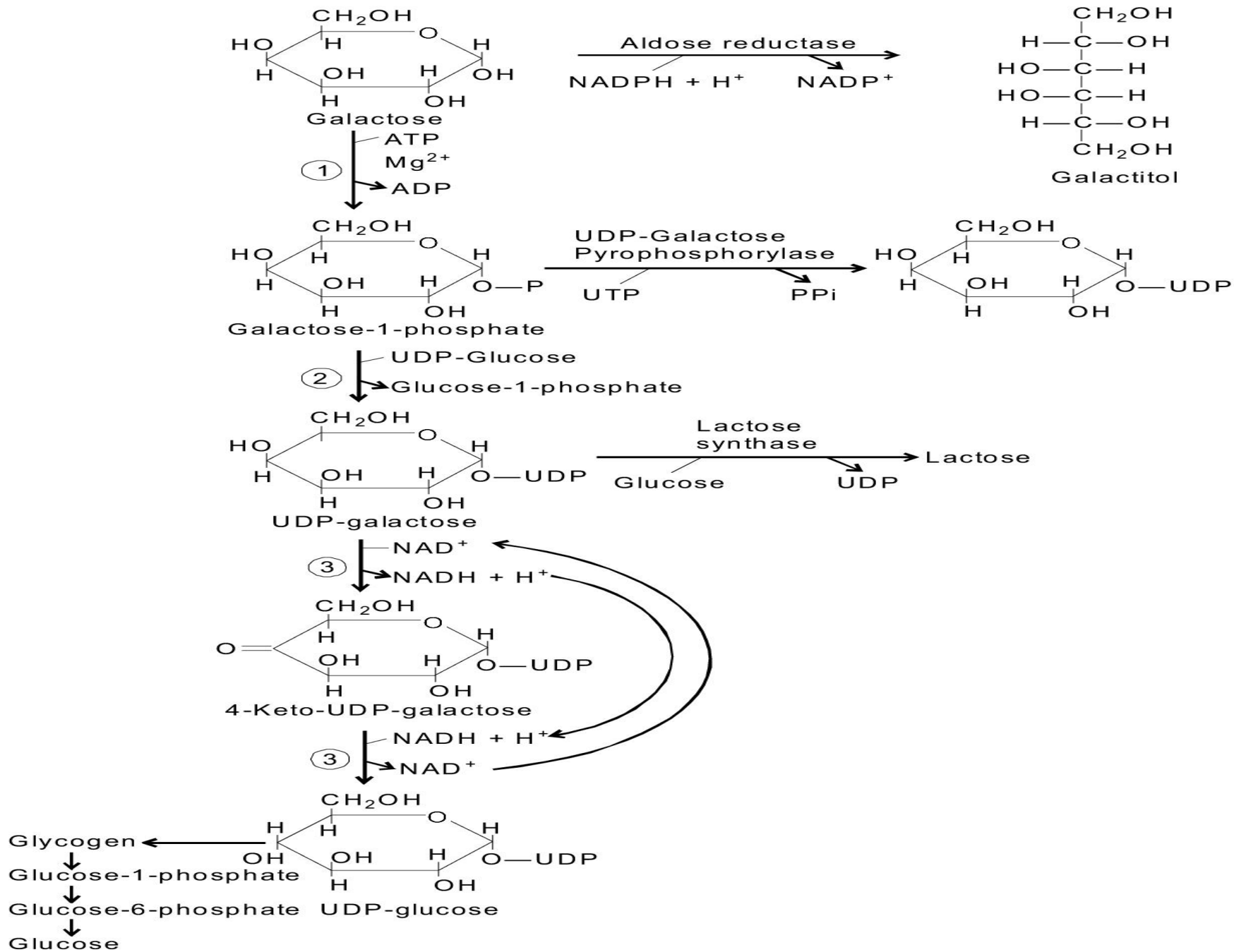
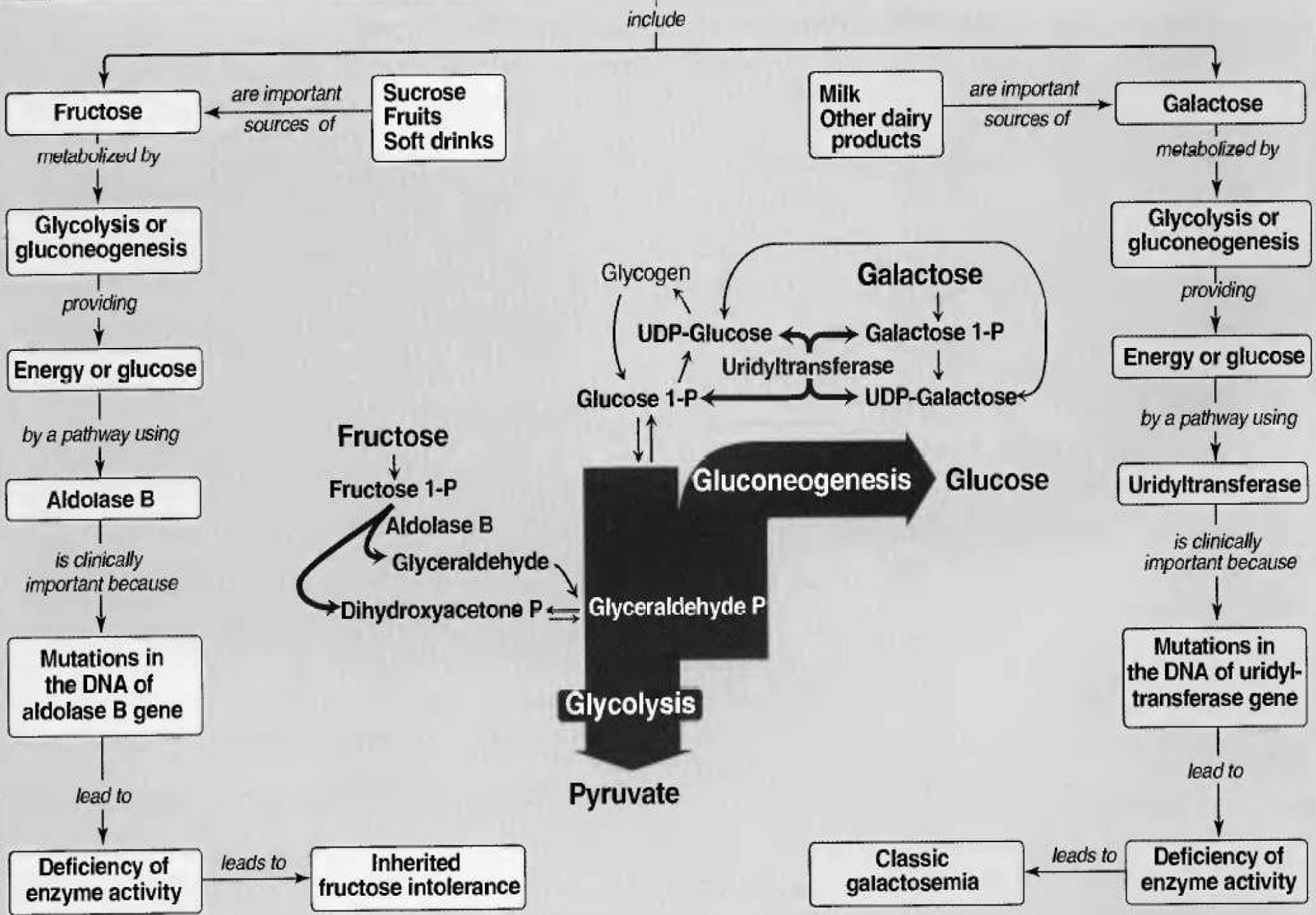
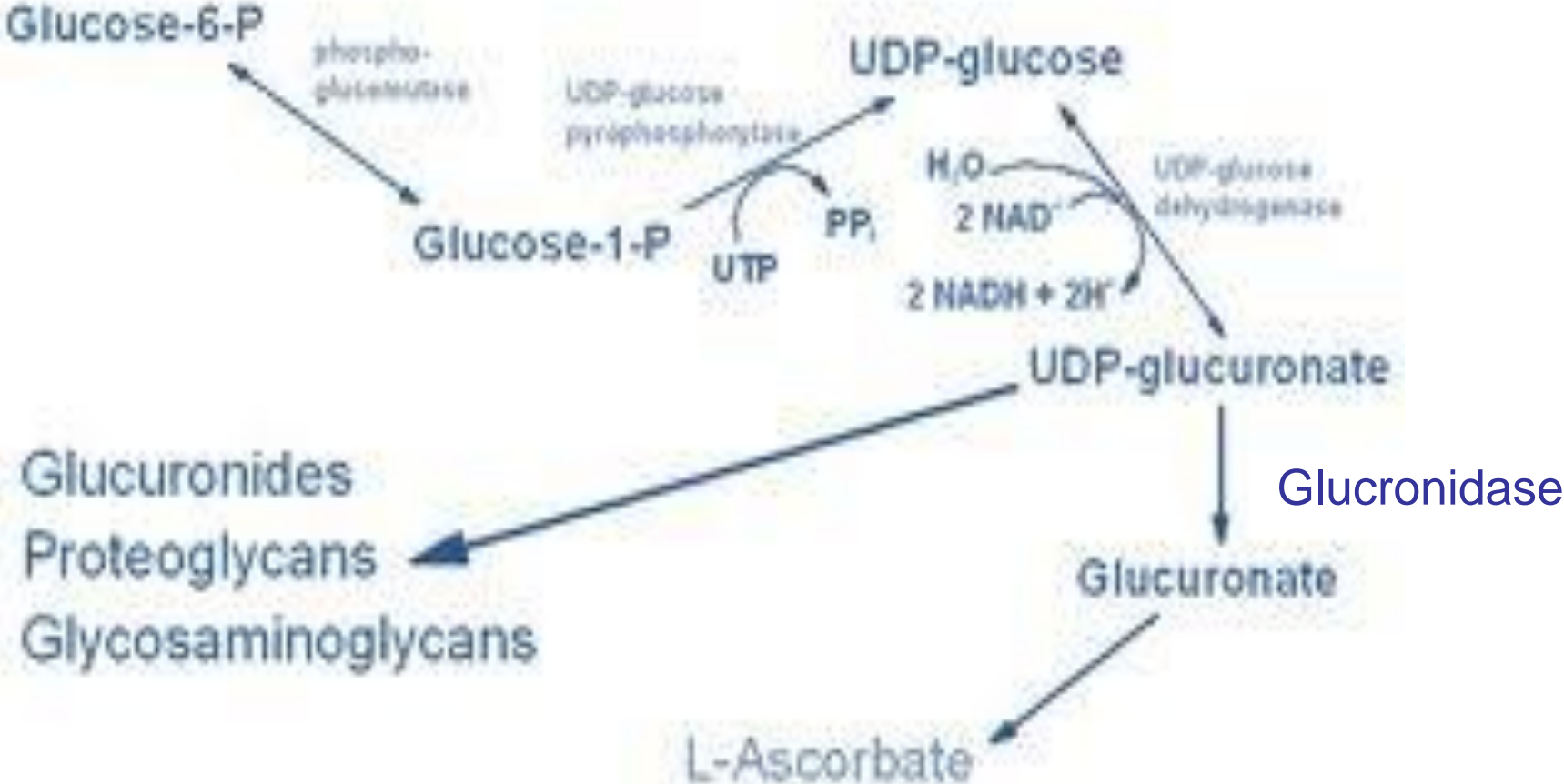


Fig. 9.20 Synthesis of glucose from galactose

Important dietary monosaccharides



Glucuronic Acid Synthesis



D- Glucuronic acid

Glucuronate
reductase



L- Gulonate

Aldonolactonase



L- Gulono lactone



Gulonolactone oxidase

2- keto-gulonolactone



L- Ascorbic acid



**Pentose phosphate
Pathway**

The metabolism of glycogen in animals

- Glycogenesis: formation of glycogen (de novo or enlarge)
- Glycogenolysis: mobilizing glycogen
- Dietary glycogen breakdown

Structure of glycogen particles

- Glycogen can represent up to 10% of the weight of the liver and 1%~2% of the weight of the muscle.
- The elementary particle of glycogen (β -particle) is about 21nm in diameter, consists of up to 55,000 glucose residues with about 2,000 nonreducing ends. Twenty to 40 of these particles cluster together to form α -rosettes (fig. 15-2, p. 562).

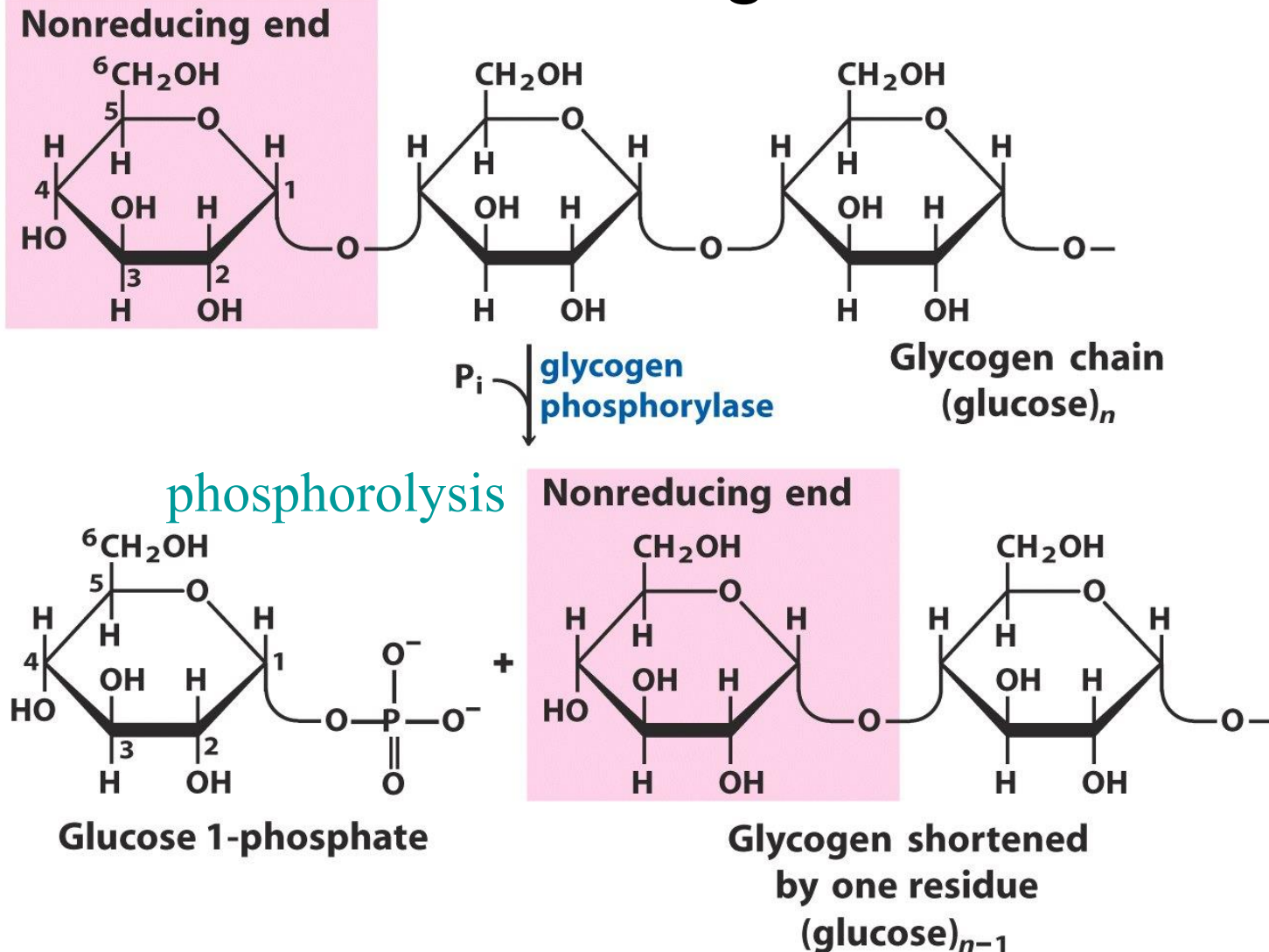
Glycogenolysis: mobilizing glycogen

While liver glycogen can be depleted in 12 to 24 hours, muscle glycogen will not last for an hour.

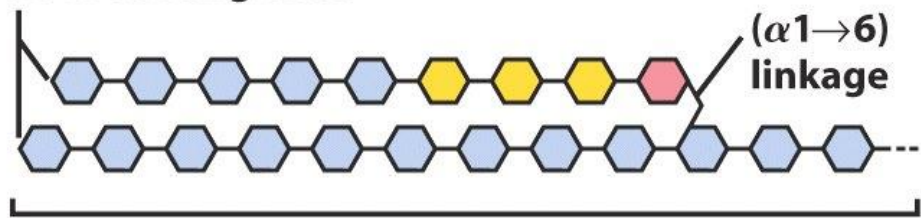
Glycogenolysis

- To mobilizing glycogen, three enzymes are required: **glycogen phosphorylase**, **debranching enzyme**, and **phosphoglucomutase**.
- The end product of glycogenolysis is glucose 6-phosphate.

Glycogen phosphorylase use inorganic phosphate to attack nonreducing ends

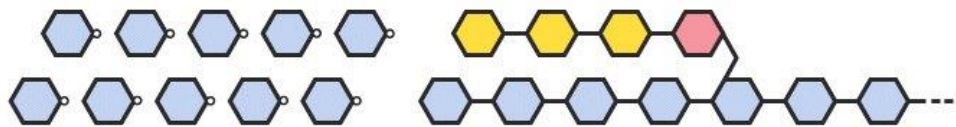


Nonreducing ends



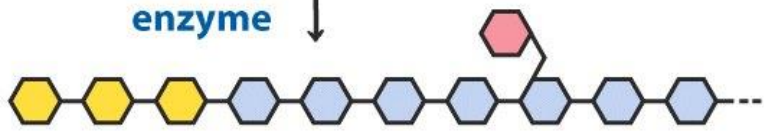
Glycogen

glycogen phosphorylase

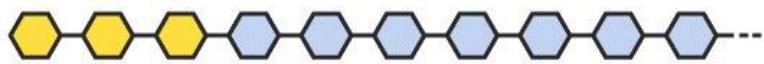


Glucose 1-phosphate molecules

transferase activity of debranching enzyme







(α1→6) glucosidase activity of debranching enzyme

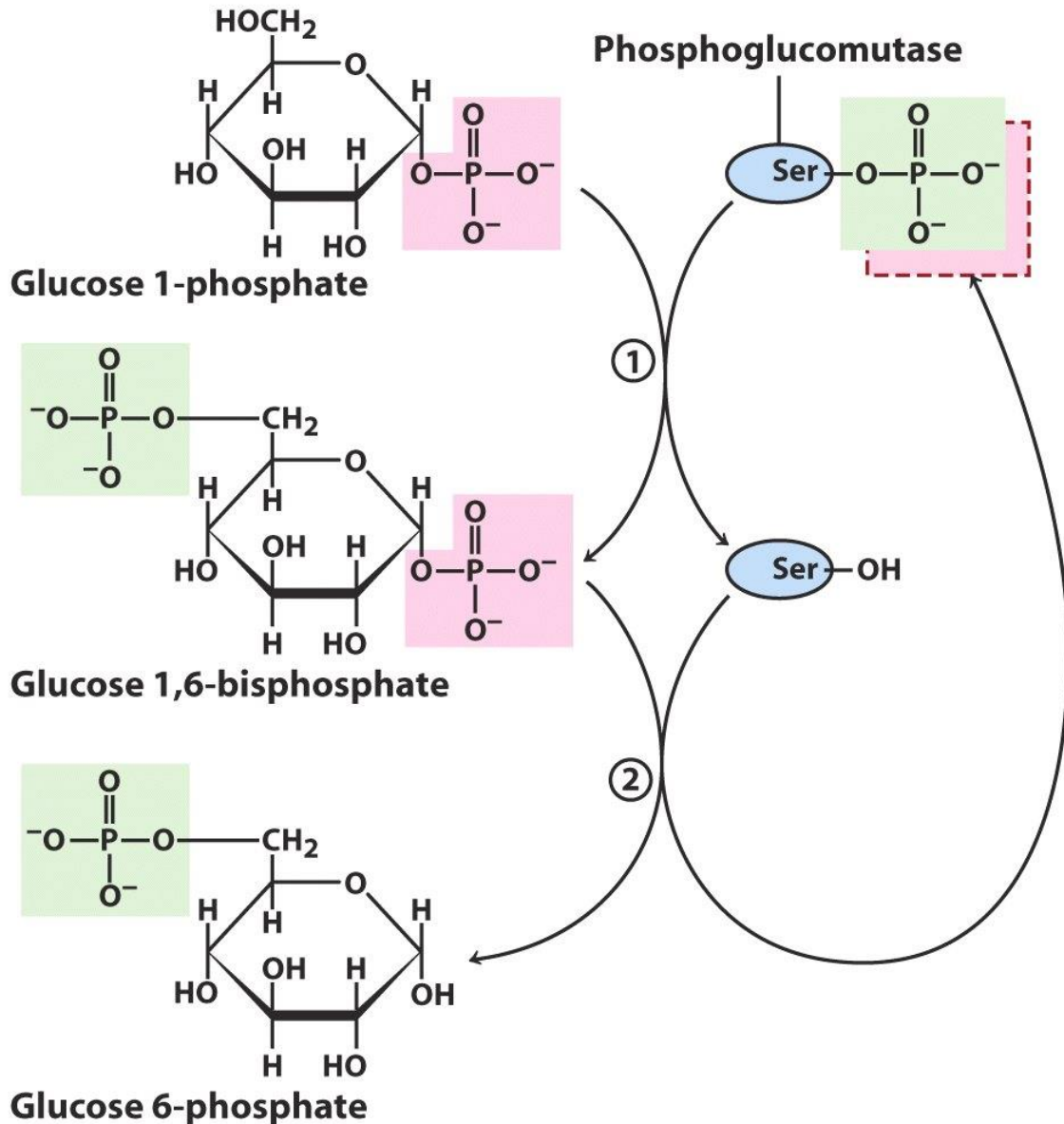


Unbranched (α1→4) polymer; substrate for further phosphorylase action

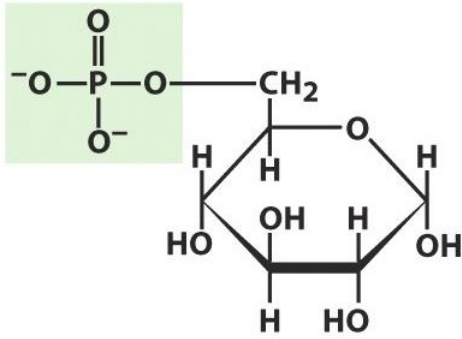
Debranching enzyme

- Debranching enzyme transfer the    as whole from the branch to the main chain, then it will use its (α1→6) glucosidase activity to hydrolyze the  from glycogen for glycogen

Phosphoglucomutase



- Phosphoglucomutase uses its phosphorylated Ser residue to convert G-1-P to G-6-P.



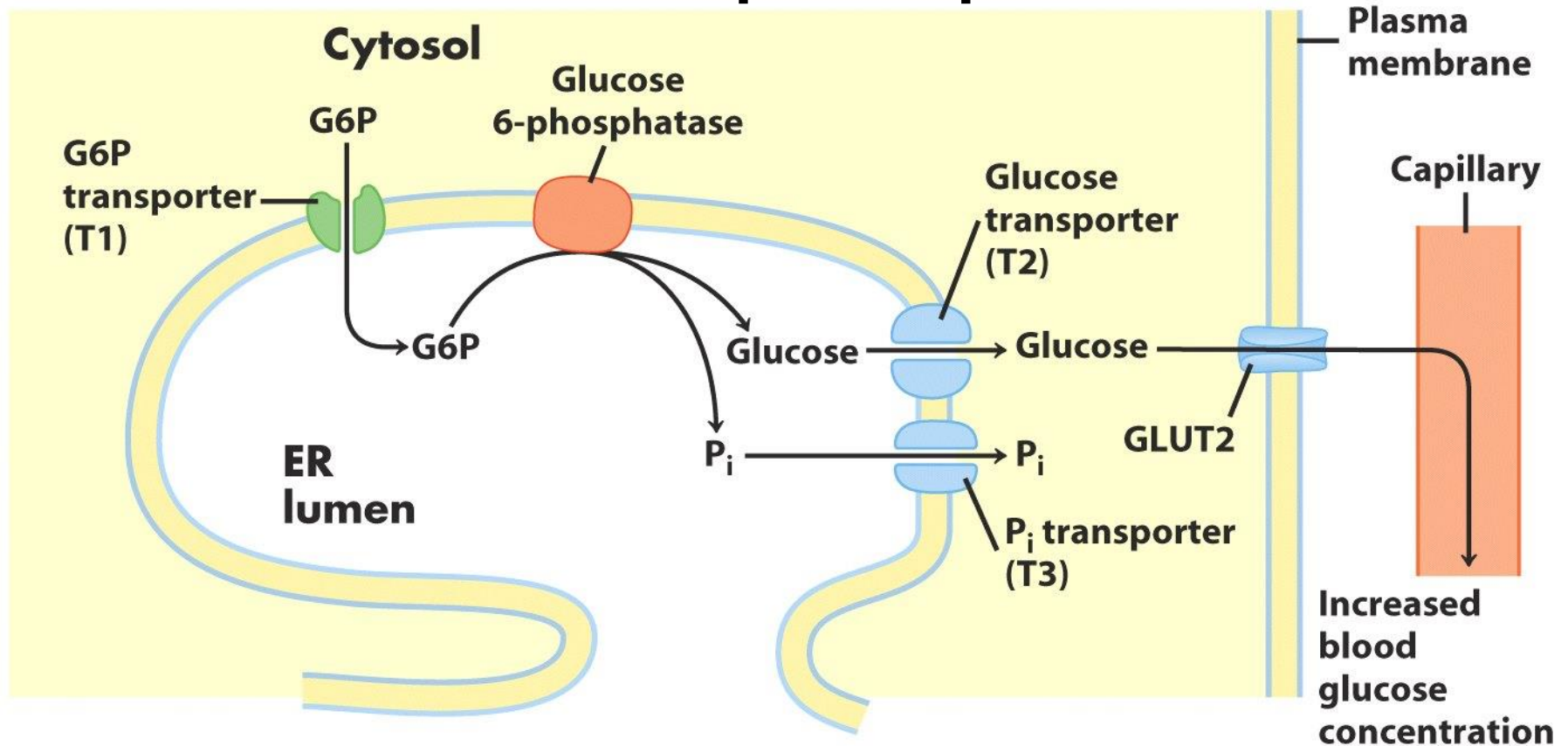
Glucose 6-phosphate

Glucose 6-phosphate

formed in the muscle can enter glycolysis (energy source).

- G-6-P formed in the liver will not enter glycolysis. Instead, it is transported into lumen of the ER, where it will be converted to glucose by glucose 6-phosphatase.

Glucose 6-phosphatase



- Glucose 6-phosphatase converted T1 transported G-6-P to glucose and P_i. Then glucose and P_i are transported to cytosol by T2 and T3, and glucose leave the hepatocyte by GLUT2 transporter

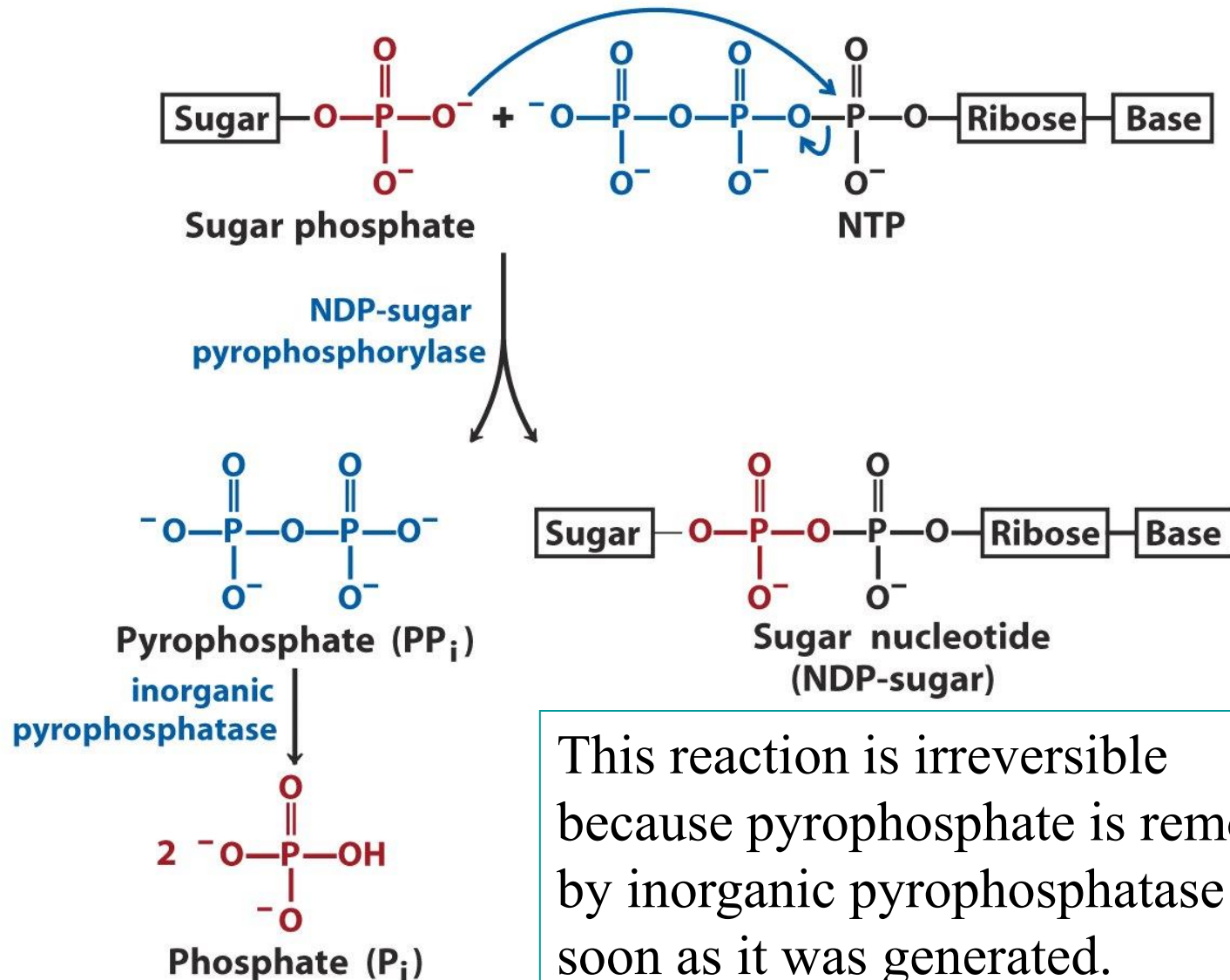
Glycogenesis: formation of glycogen

Glycogenin, glycogen synthase, glycogen-branching enzyme, and UDP-glucose pyrophosphorylase are required for the formation of glycogen.

Glycogenesis

- Glycogenesis can be separated into two issues: formation of new glycogen particle and enlargement of existing glycogen particle.
- Both of them require UDP-glucose as precursor, which is synthesized by UDP-glucose pyrophosphorylase.

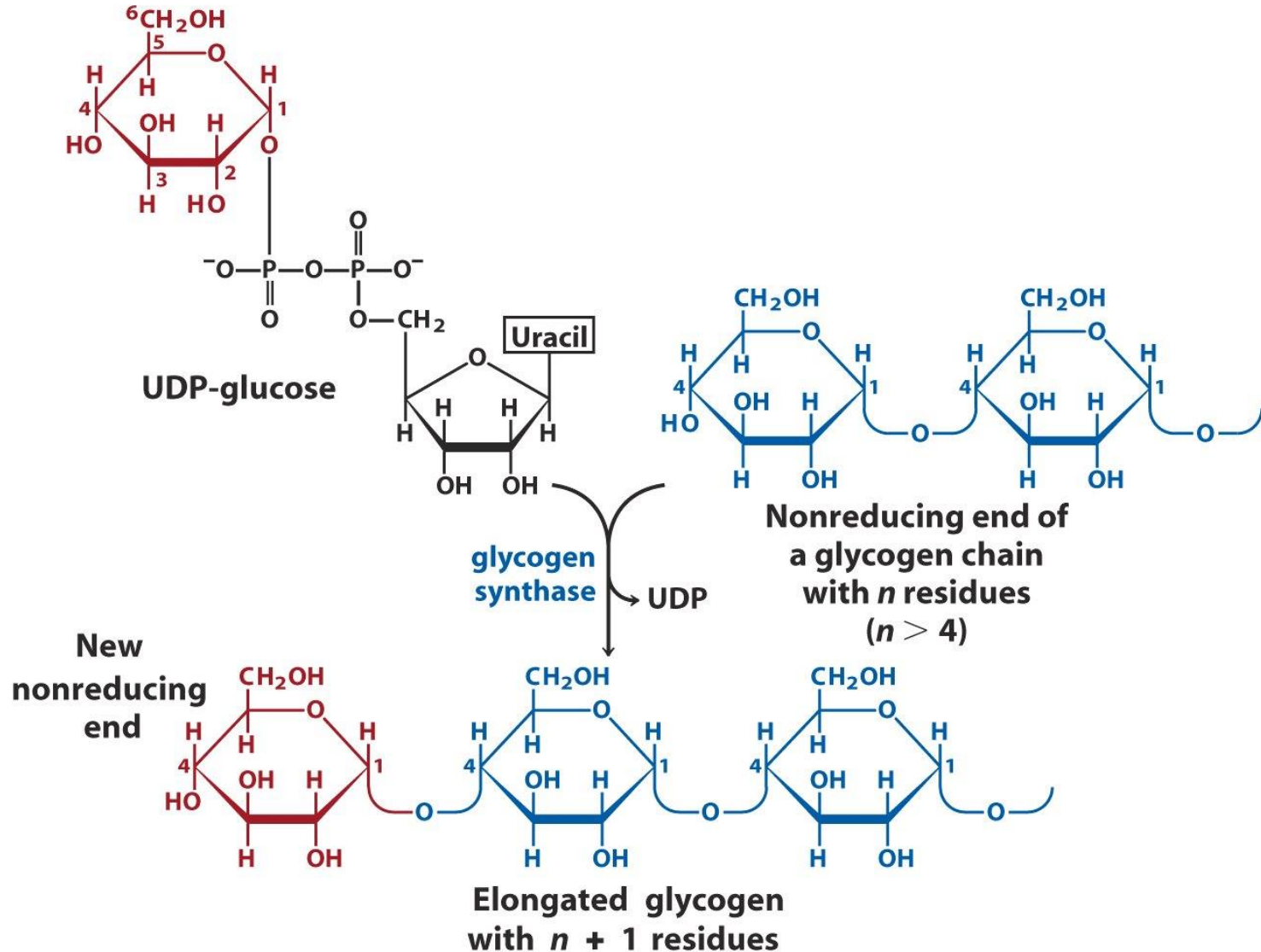
Formation of UDP-glucose



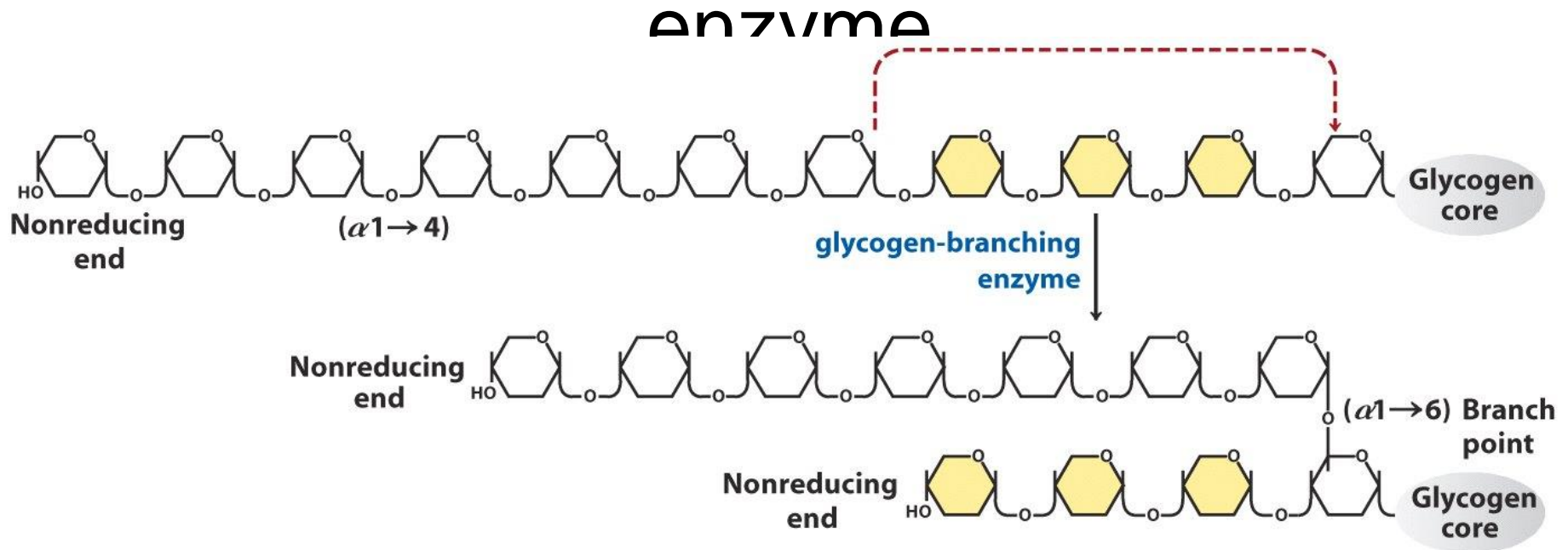
This reaction is irreversible because pyrophosphate is removed by inorganic pyrophosphatase as soon as it was generated.



Enlargement of existing glycogen particle



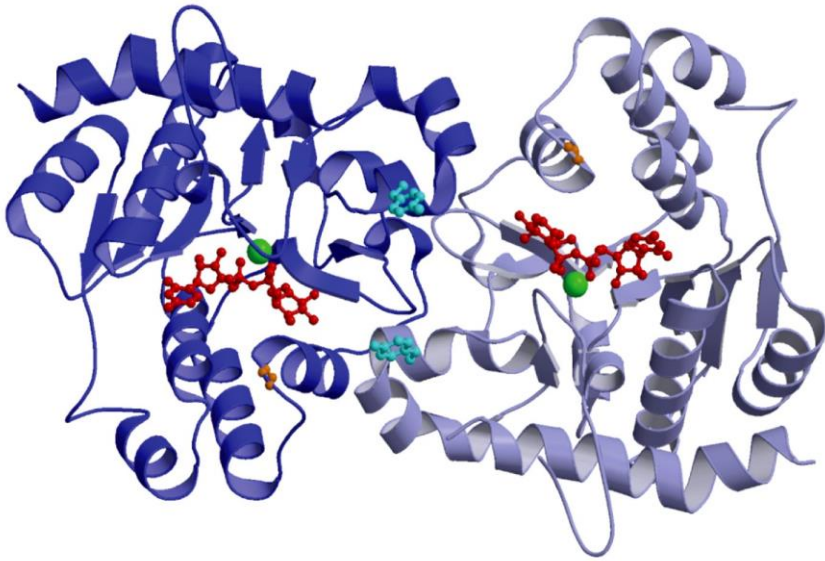
Branching by glycogen-branching



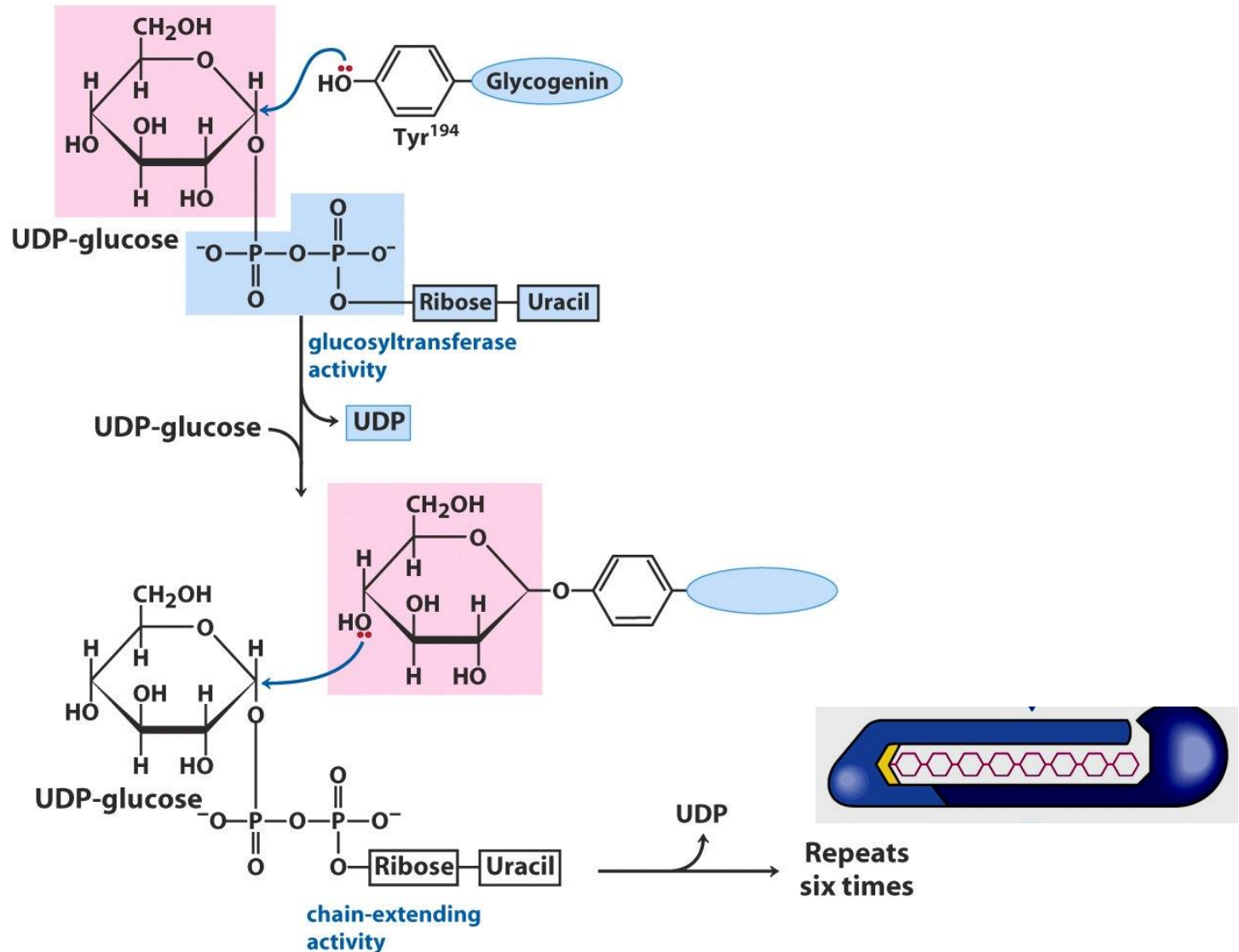
- Glycogen-branching enzyme transfer of a terminal fragment of 6 or 7 glucose residues from the nonreducing end of a glycogen branch having at least 11 residues to the C-6 hydroxyl group of a glucose residue at a more interior position of the same or another glycogen chain.

Formation of new glycogen particle

- Although glycogen synthase can enlarge existing glycogen particles, it cannot synthesize new glycogen particle because it need nonreducing ends from existing glycogen as primer.

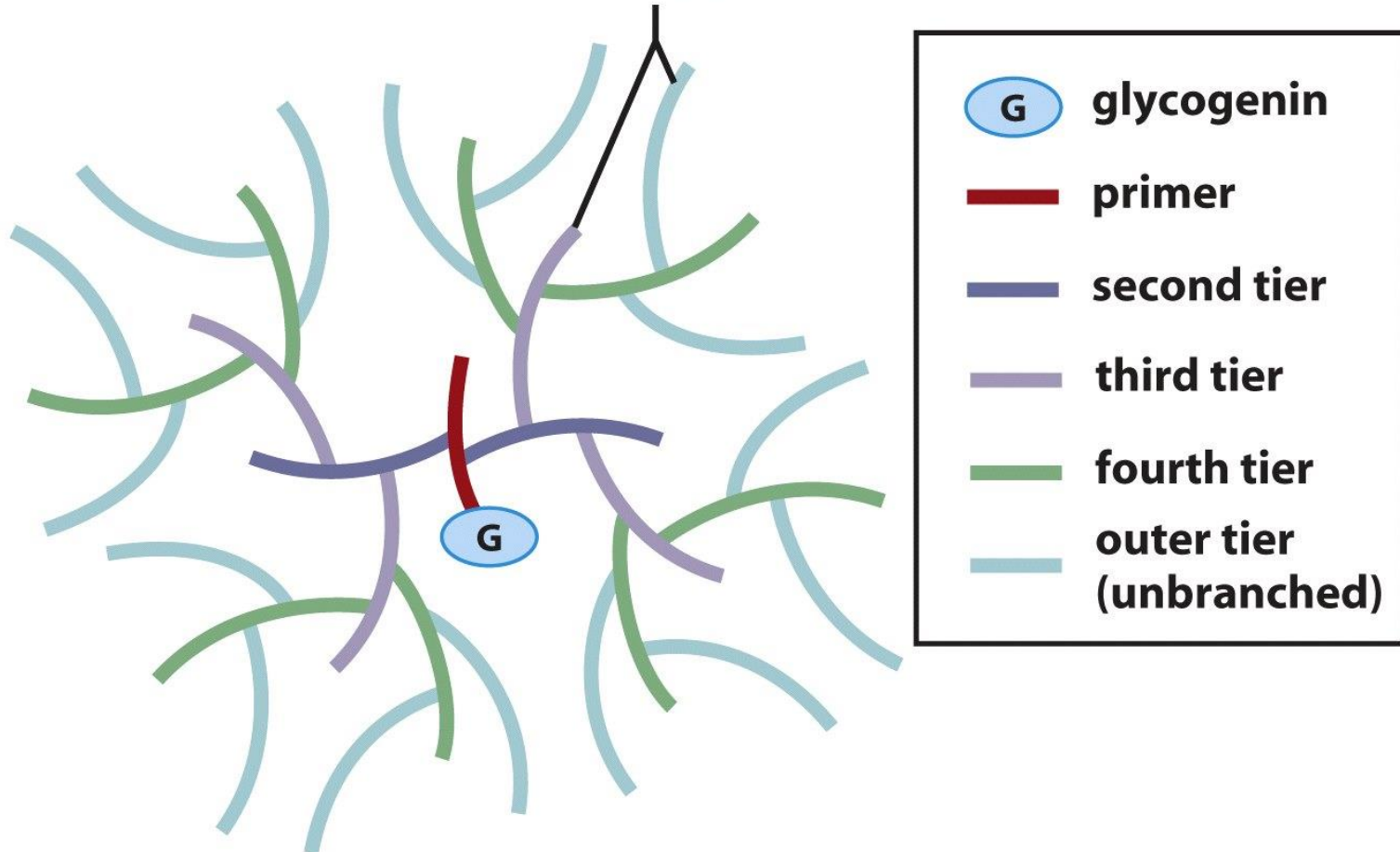


Glycogenin serves as primer for synthesis of new glycogen particles



Every glycogen particle has a glycogenin buried inside

Each chain has
12 to 14 glucose
residues



Glycogenesis

