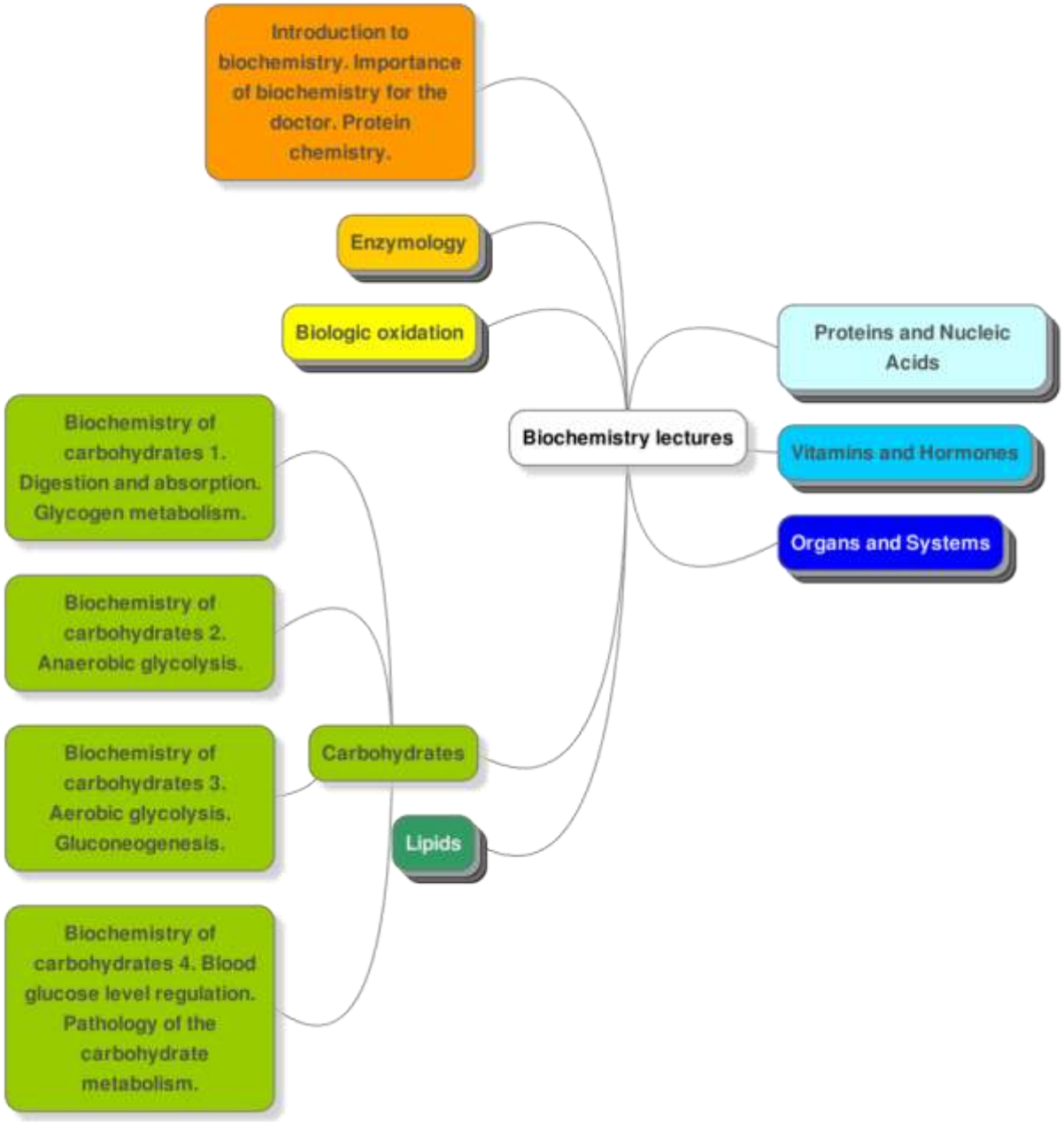
Lecturer KOVAL Alexander N.
PhD, assistant


Introduction to biochemistry. Importance of biochemistry for the doctor. Protein chemistry.
Enzymology
Biologic oxidation
Biochemistry of carbohydrates 1. Digestion and absorption. Glycogen metabolism.
Biochemistry of carbohydrates 2. Anaerobic glycolysis.
Biochemistry of carbohydrates 3. Aerobic glycolysis. Gluconeogenesis.
Biochemistry of carbohydrates 4. Blood glucose level regulation. Pathology of the carbohydrate metabolism.
Carbohydrates
Lipids
Biochemistry lectures
Proteins and Nucleic Acids
Vitamins and Hormones
Organs and Systems

Plan

- Introduction to Carbohydrates
- Carbohydrate Nomenclature
  - Monosaccharides
  - Disaccharides
  - Polysaccharides
    - Glycogen
    - Starch

Introduction

- **Carbohydrates** are carbon compounds that contain large quantities of hydroxyl groups.
- The simplest carbohydrates also contain either
  - an aldehyde moiety (*polyhydroxyaldehydes*)
  - or a ketone moiety (*polyhydroxyketones*).

Function of Carbohydrates

1. Major source of energy
2. Precursors for many organic compounds (fats, amino acids)
3. Components of cell membrane
4. Structural components (cellulose, chytin)
5. Storage form of energy (glycogen).

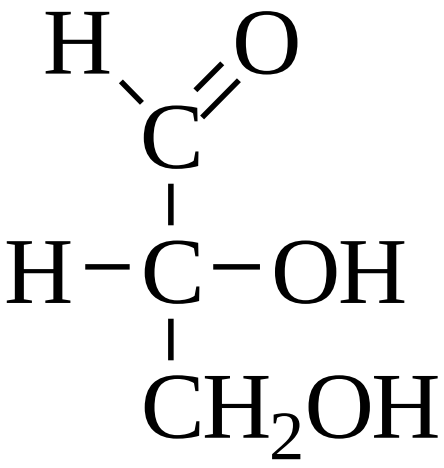
Classification

- All carbohydrates can be classified as either **monosaccharides**, **oligosaccharides** or **polysaccharides**.
  - Anywhere from two to ten **monosaccharide** units, linked by glycosidic bonds, make up an **oligosaccharide**.
  - **Polysaccharides** are much larger, containing hundreds of monosaccharide units.

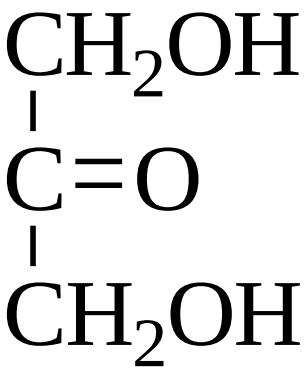
Chemical properties

- **hydroxyl groups**
  - interact with the aqueous environment
  - participate in hydrogen bonding (within and between chains).
- Derivatives of the carbohydrates can contain nitrogens, phosphates and sulfur compounds.
  - Carbohydrates also can combine with lipid to form *glycolipids* or with protein to form *glycoproteins*.

Carbohydrate Nomenclature



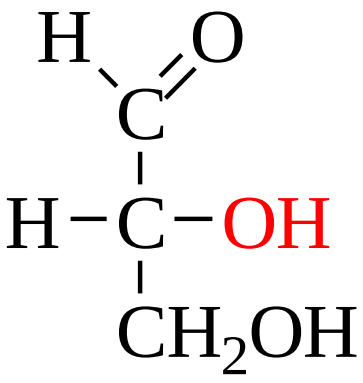
glyceraldehyde



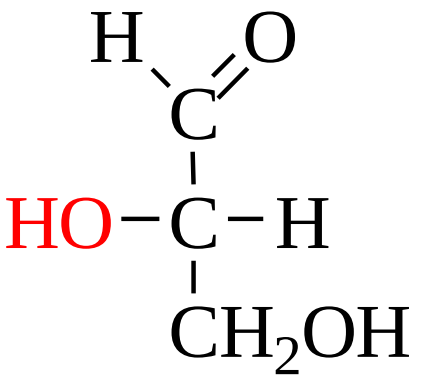
dihydroxyacetone

- The predominant carbohydrates encountered in the body are structurally related
  - to the *aldotriose* **glyceraldehyde** and
  - to the *ketotriose* **dihydroxyacetone**.

Stereoisomery



D-glyceraldehyde



L-glyceraldehyde

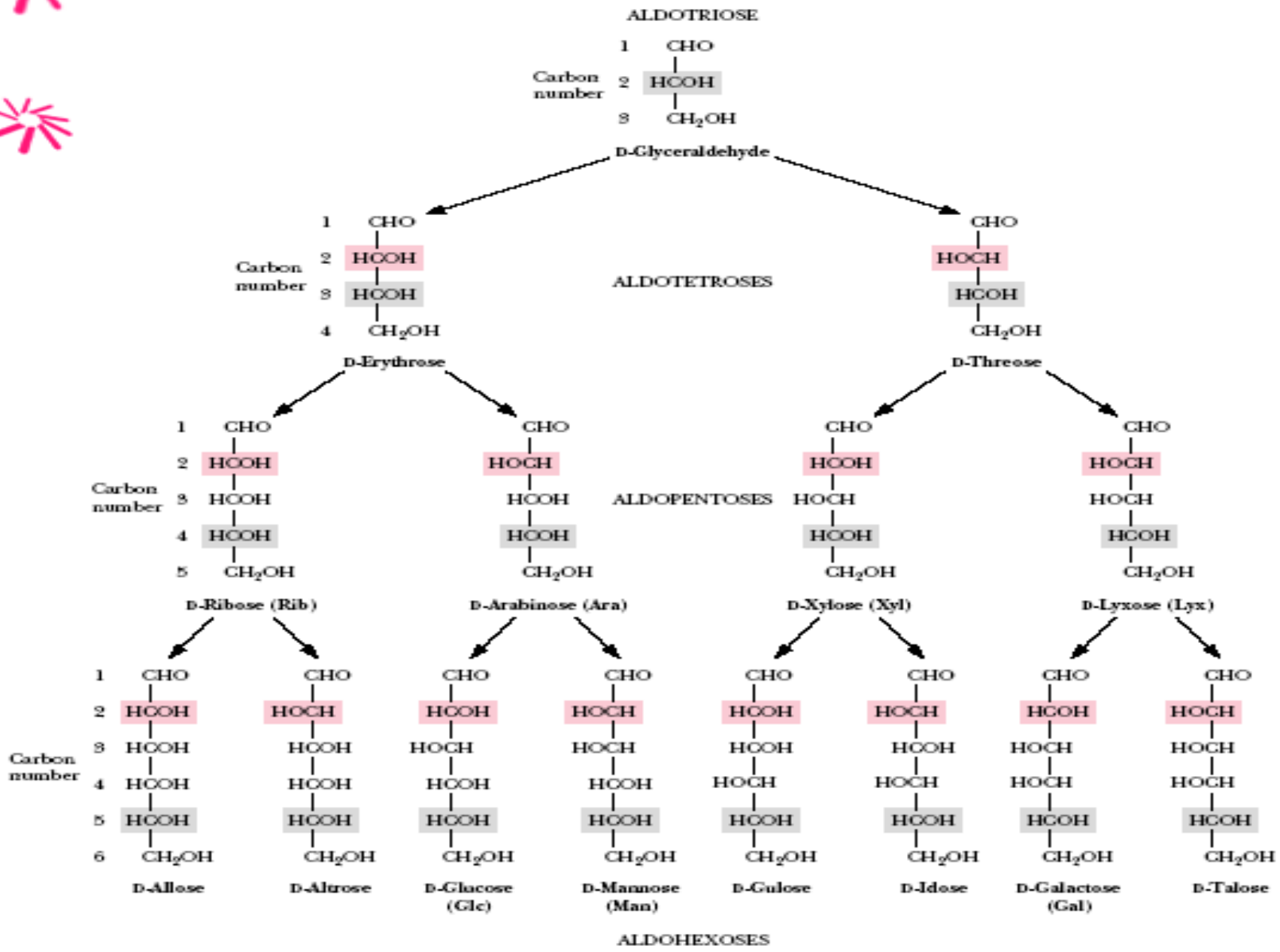
- All carbohydrates contain at least one asymmetrical (chiral) carbon and are optically active.
- Carbohydrates can exist in either of two conformations, as determined by the orientation of the hydroxyl group about the asymmetric carbon farthest from the carbonyl.
- Exist in the D-conformation.
- The mirror-image conformations, called enantiomers, are in the L-conformation.

Monosaccharides

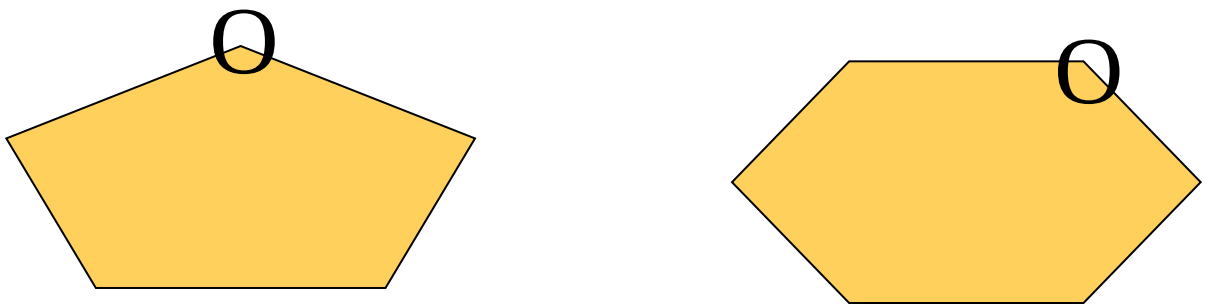
- The common monosaccharides are classified according to the number of carbons they contain in their backbone structures.
  - The major monosaccharides contain 4 to 6 C.

Carbohydrate Classifications

# Carbons	Category Name	Relevant examples
3	Triose	Glyceraldehyde, Dihydroxyacetone
4	Tetrose	Erythrose
5	Pentose	Ribose, Ribulose, Xylulose
6	Hexose	Glucose, Galactose, Mannose, Fructose
7	Heptose	Sedoheptulose
9	Nonose	Neuraminic acid also called sialic acid

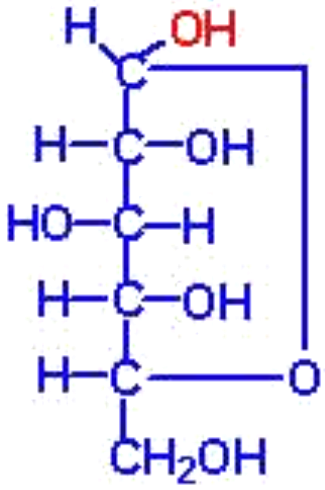

ALDOTRIOSE
Carbon number
D-Glyceraldehyde
ALDOTETROSES
D-Erythrose
D-Threose
ALDOPENTOSES
D-Ribose (Rib)
D-Arabinose (Ara)
D-Xylose (Xyl)
D-Lyxose (Lyx)
D-Allose
D-Altrose
D-Glucose (Glc)
D-Mannose (Man)
D-Gulose
D-Idose
D-Galactose (Gal)
D-Talose
ALDOHEXOSES

Furanoses & Pyranoses

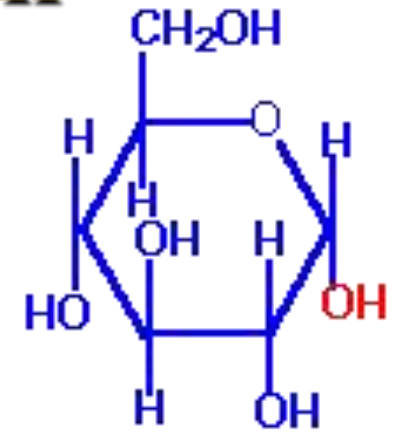


- Intramolecular **hemiacetals** or **hemiketals -** the formation of five- or six-membered rings.
- *Furan-like* derivatives are termed **furanoses**.
- *Pyran-like* **- pyranoses**.

Fischer or Haworth



Cyclic Fischer Projection of α-D-Glucose



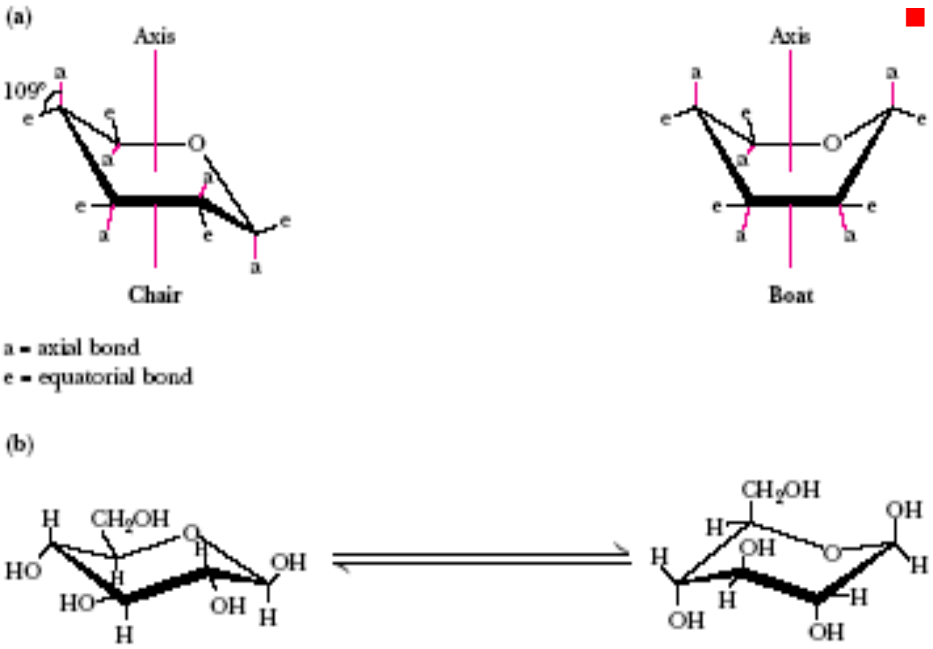
Haworth Projection of α-D-Glucose

- Such structures can be depicted by either Fischer or Haworth style diagrams.
  - The numbering of the carbons in carbohydrates proceeds from the carbonyl carbon, for aldoses, or the carbon nearest the carbonyl, for ketoses.

Anomery

- The rings can open and re-close, allowing rotation to occur about the carbon bearing the reactive carbonyl yielding two distinct configurations (α and β) of the hemiacetals and hemiketals.
  - The carbon about which this rotation occurs is the *anomeric carbon* and the two forms are termed **anomers**.
- Carbohydrates can change spontaneously between the α and β configurations – a process known as **mutarotation**.
- When drawn in the Fischer projection, the α configuration places the hydroxyl attached to the anomeric carbon to the right, towards the ring. When drawn in the Haworth projection, the α configuration places the hydroxyl downward.

Chairs & Boats

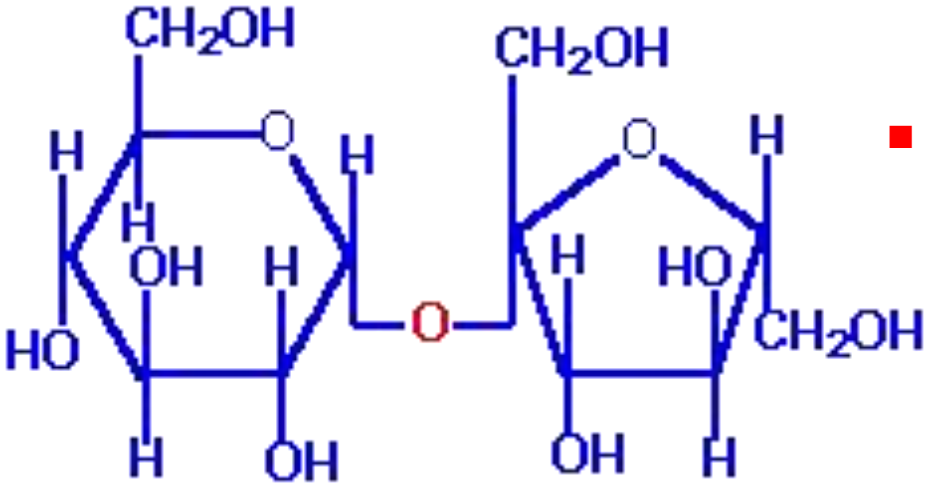


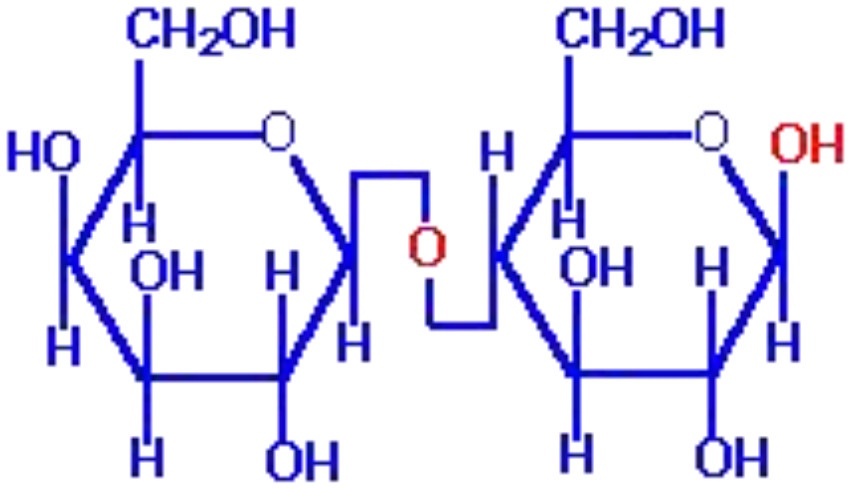
- The spatial relationships of the atoms of the furanose and pyranose ring structures are more correctly described by the two conformations identified as the *chair* form and the *boat* form.
  - The chair form is the more stable of the two. Constituents of the ring that project above or below the plane of the ring are axial and those that project parallel to the plane are equatorial.
  - In the chair conformation, the orientation of the hydroxyl group about the anomeric carbon of α-D-glucose is axial and equatorial in β-D-glucose.

Disaccharides

- Covalent bonds between the anomeric hydroxyl of a cyclic sugar and the hydroxyl of a second sugar (or another alcohol containing compound) are termed **glycosidic bonds**, and the resultant molecules are **glycosides**.
- The linkage of two monosaccharides to form **disaccharides** involves a glycosidic bond.
  - Several physiogically important disaccharides are *sucrose, lactose and maltose*.

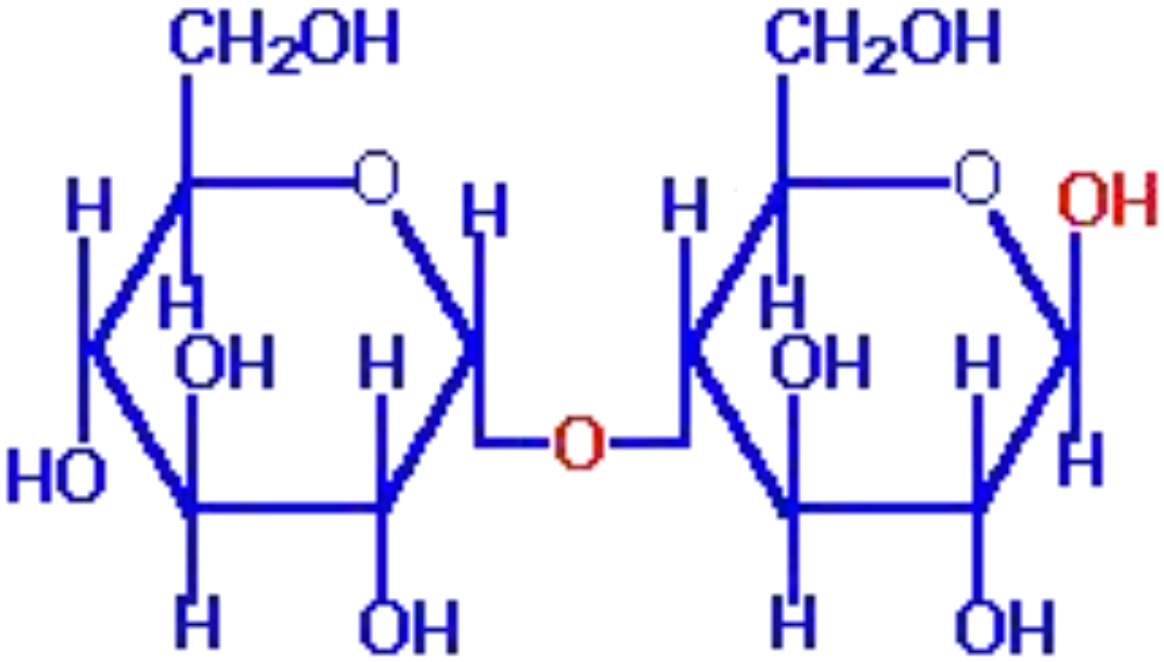
Disaccharides: Sucrose & Lactose





- **Sucrose**: prevalent in sugar cane and sugar beets, is composed of glucose and fructose through an α-(1,2)β-glycosidic bond.
- **Lactose**: is found exclusively in the milk of mammals and consists of galactose and glucose in a β-(1,4) glycosidic bond.

Disaccharides: Maltose



- **Maltose**: the major degradation product of starch, is composed of 2 glucose monomers in an α-(1,4) glycosidic bond.

Polysaccharides

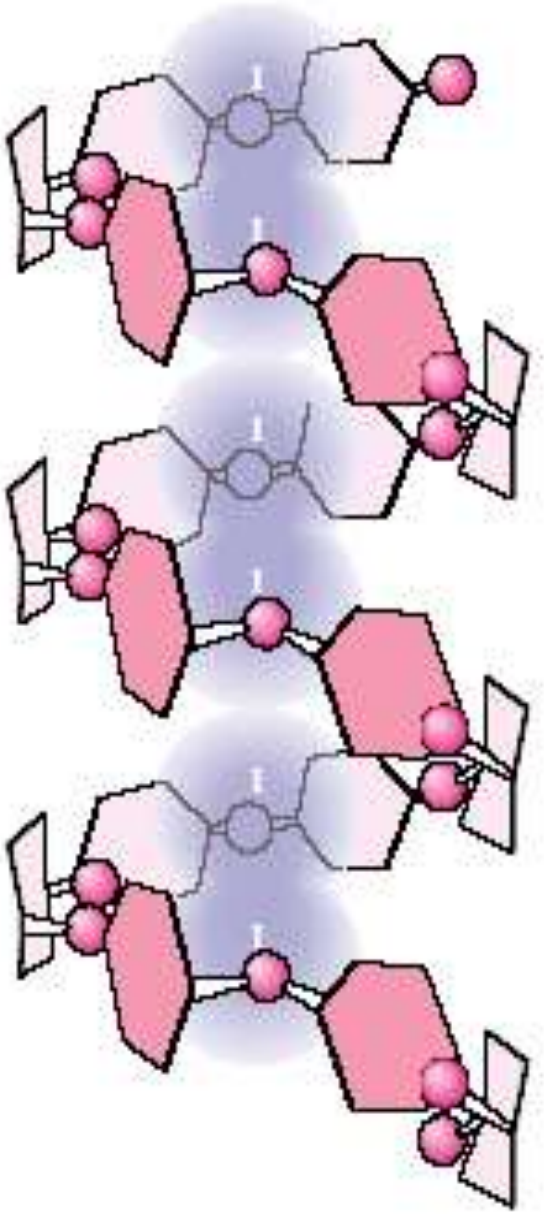
- Most of the carbohydrates found in nature occur in the form of high molecular weight polymers called **polysaccharides**.
- The monomeric building blocks used to generate polysaccharides can be varied; in all cases, however, the predominant monosaccharide found in polysaccharides is D-glucose.
  - When polysaccharides are composed of a single monosaccharide building block, they are termed **homopolysaccharides**.
  - Polysaccharides composed of more than one type of monosaccharide are termed **heteropolysaccharides**.

Glycogen

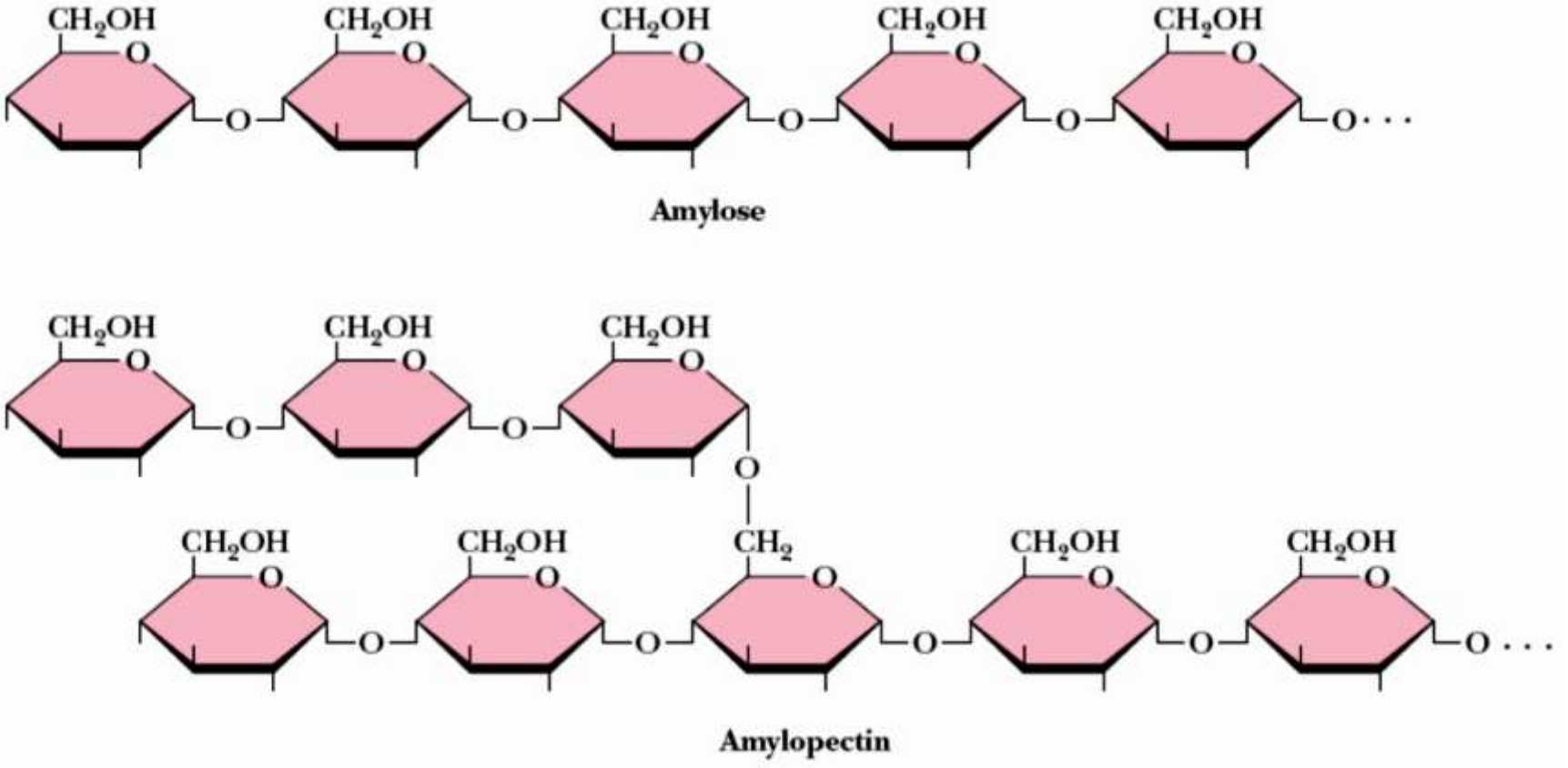
- **Glycogen** is the major form of stored carbohydrate in animals.
  - This crucial molecule is a homopolymer of glucose in α-(1,4) linkage; it is also highly branched, with α-(1,6) branch linkages occurring every 8-10 residues.
  - Glycogen is a very compact structure that results from the coiling of the polymer chains.
  - This compactness allows large amounts of carbon energy to be stored in a small volume, with little effect on cellular osmolarity.

Starch

- **Starch** is the major form of stored carbohydrate in plant cells.
  - Its structure is identical to glycogen, except for a much lower degree of branching (about every 20-30 residues).

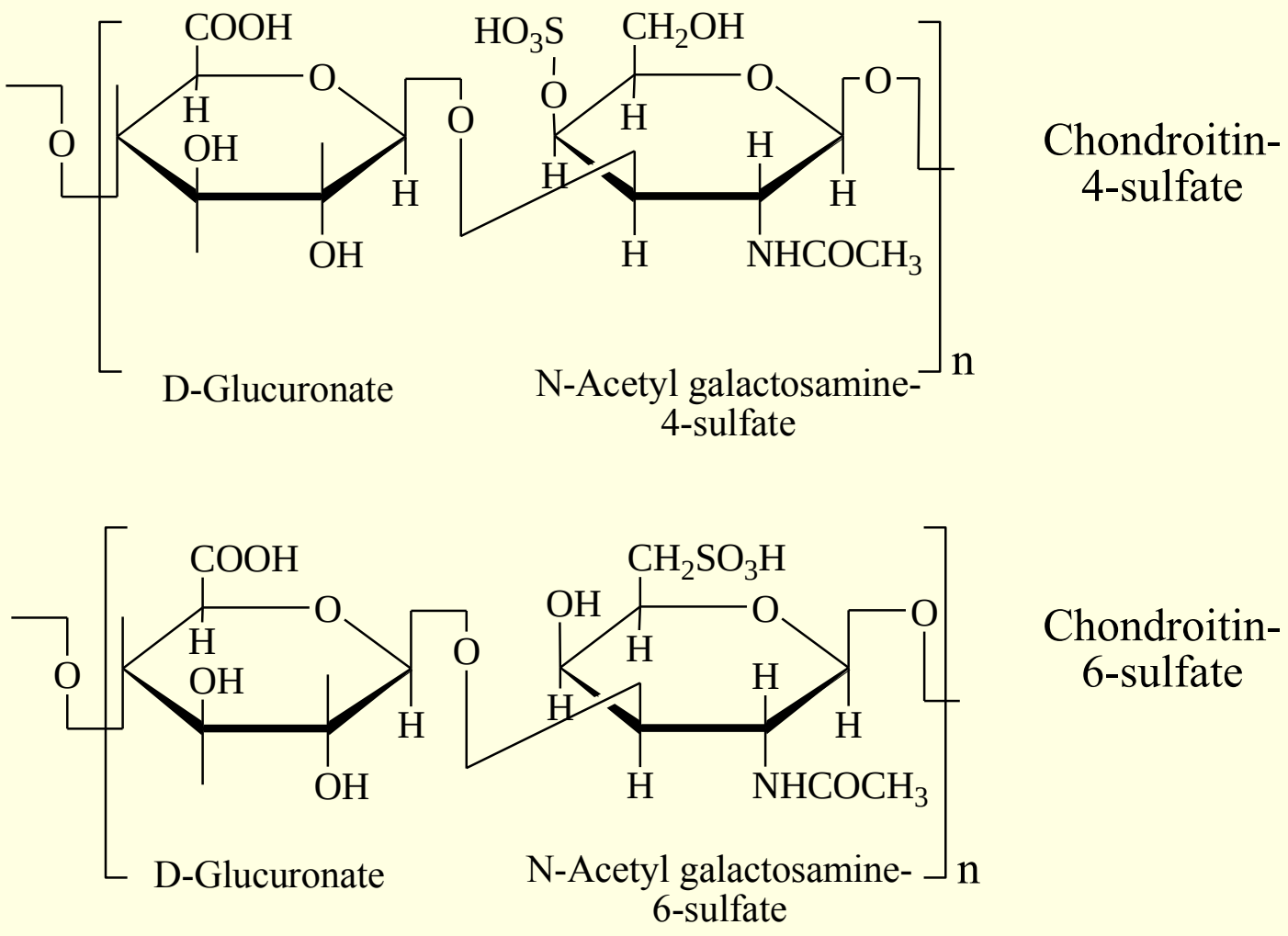


Amylose & Amylopectin



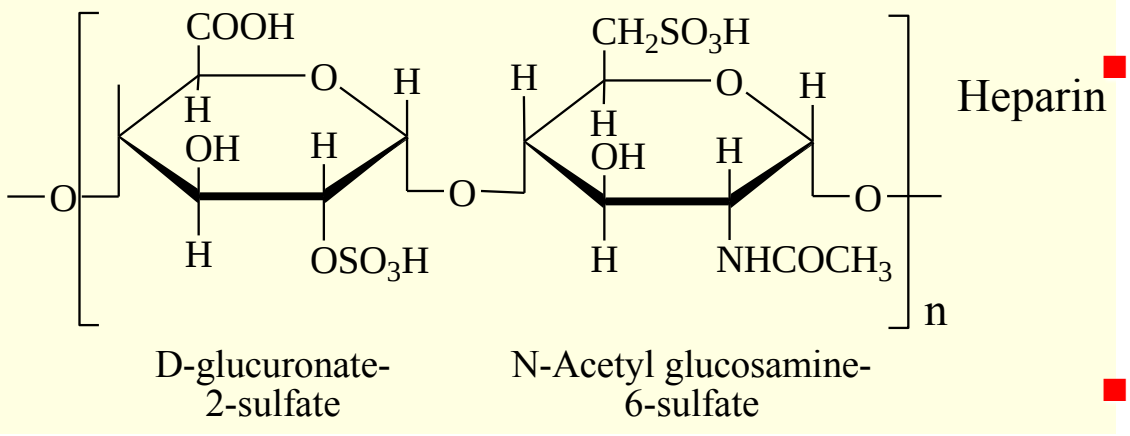
- Unbranched starch is called **amylose**;
- branched starch is called **amylopectin**.

Mucopolysaccharides: Chondroitin-sulfates

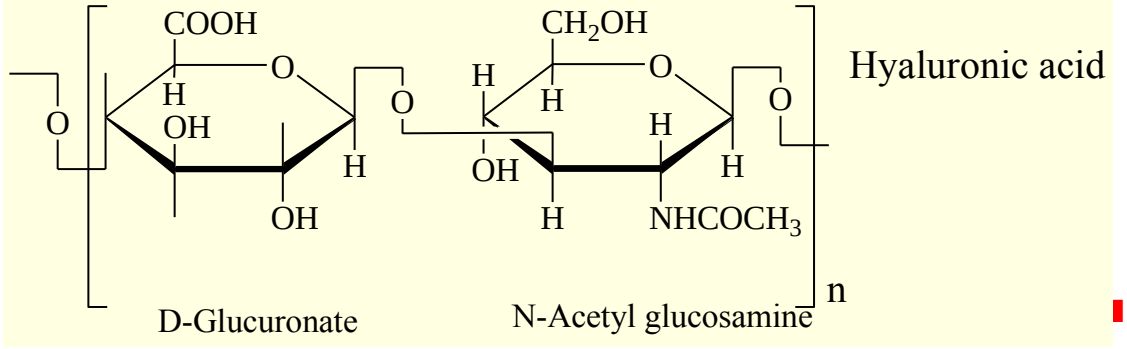


- cartilage, bone, heart valves – most abundant GAG

Mucopolysaccharides: Heparin and Hyaluronate



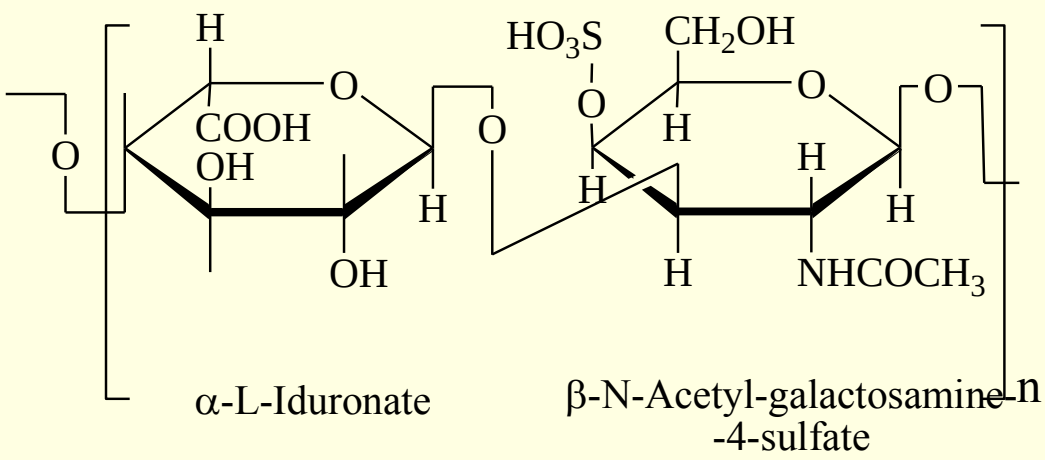
Heparin



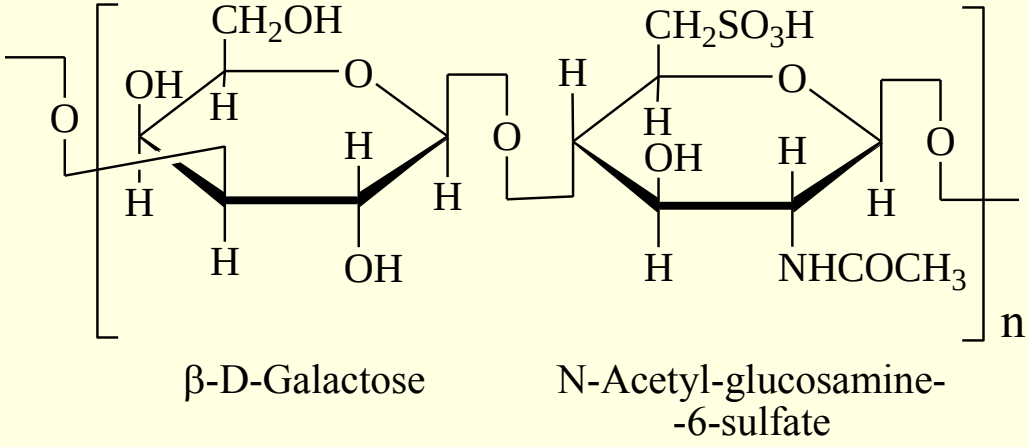
Hyaluronic acid

- component of intracellular granules of mast cells lining the arteries of the lungs, liver and skin.
- more sulfated than heparan sulfates
- Localization: synovial fluid, vitreous humor, ECM of loose connective tissue
- large polymers, shock absorbing

Dermatan Sulfate & Keratan Sulfate



Dermatan sulfate



Keratan sulfate

- DS: Localized in skin, blood vessels, heart valves
- KS: Cornea, bone, cartilage aggregated with chondroitin sulfates

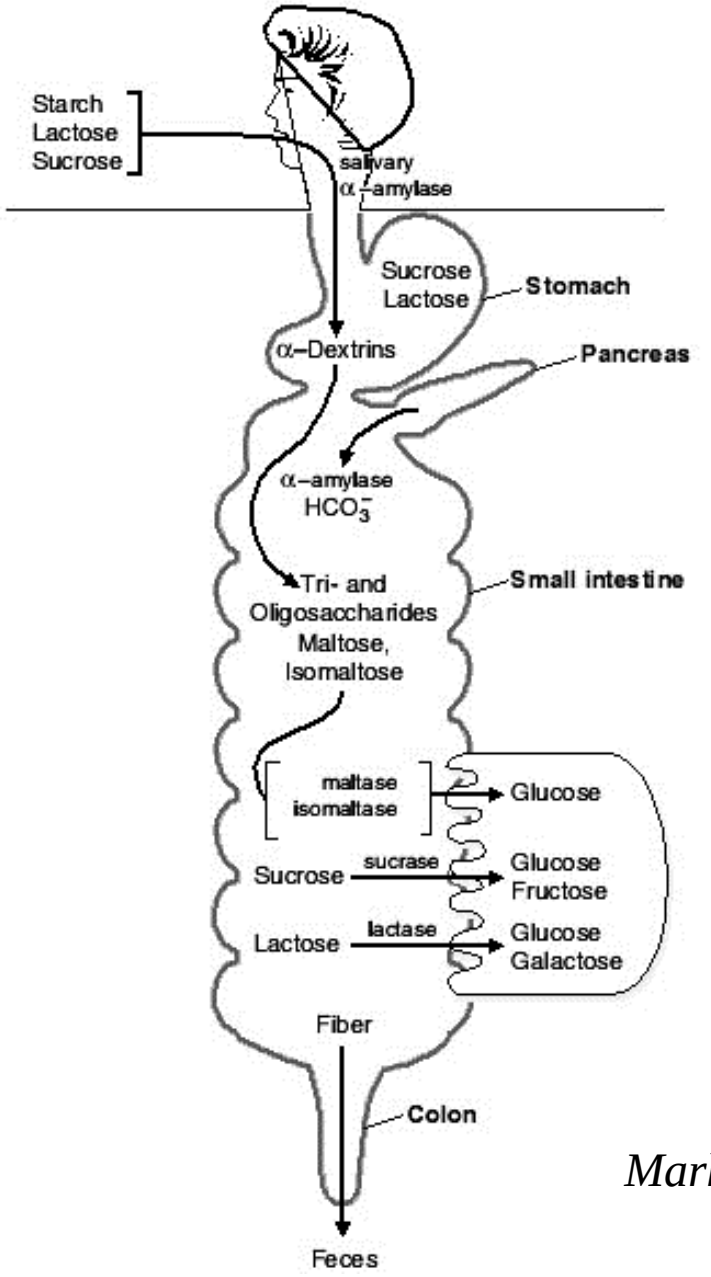
Sources of Blood Glucose

- Blood glucose level: 3.3 – 5.5 mmol/l.
- Dietary sources: (glucose, fructose, galactose).
- Clycogenolysis: degradation of glycogen in liver.
- Gluconeogenesis: synthesis from lactate, glycerol, propionate and some amino acids. Occurs in liver and kidney.

Major Pathways of Glucose Metabolism

1. **Glycolysis** (Embden-Meyerhof pathway)
2. **Glycogenesis** – formation of glucogen from glucose
3. **Pentose phosphate pathway** (hexose monophosphate shunt)
4. **Uronic acid pathway**: formation of glucuronic acid, pentoses and ascorbic acid* (*not in man)
5. **Amino sugar and mucopolysaccharide metabolism**
6. **Synthesis of non-essential amino acids**.
7. **Synthesis of fat.**

Digestion of Carbohydrates



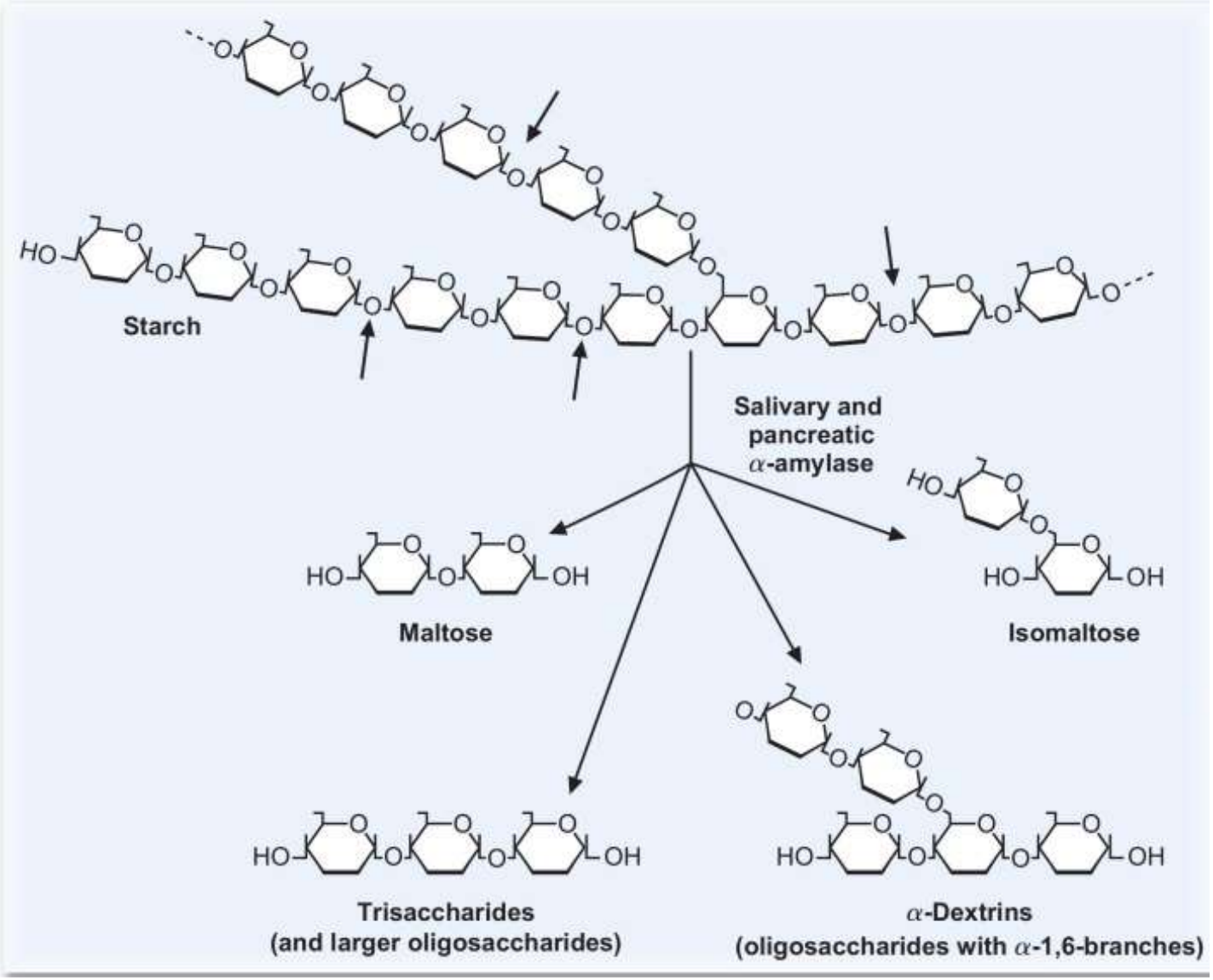
- Mouth – salivary α-amylase
- Duodenum – pancreatic α-amylase
- Small intestine – maltase, isomaltase, sucrase, lactase

Marks, 2005

Digestion: 3 Mechanisms (by *Ugolev*)

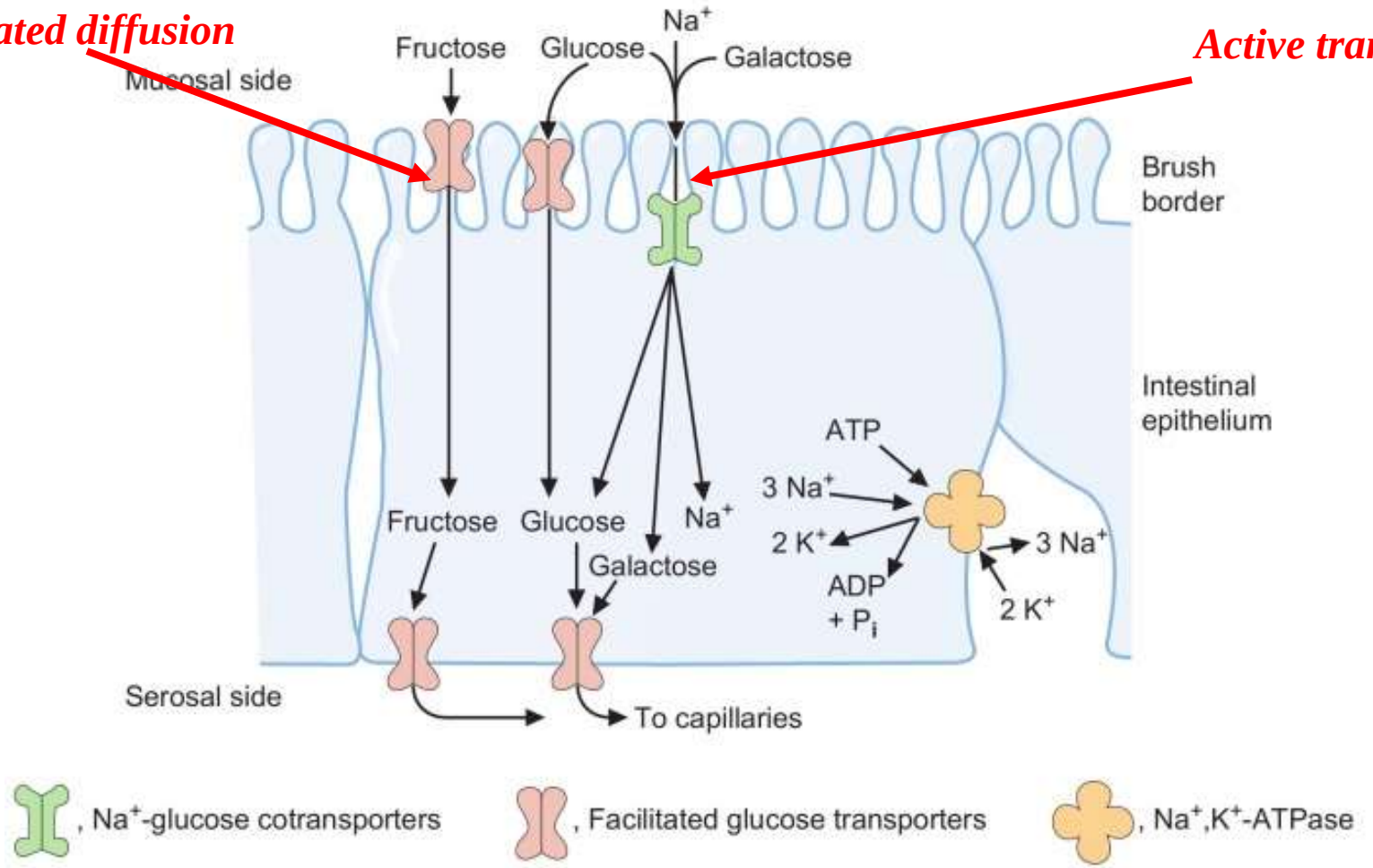
1. Cavitary
   - In the cavity (mouth, intestine).
   - When there is a lot of substrate (starch)
     - α-amylase
2. Luminal
   - On the brush board of the enterocytes (immobilized enzymes).
     - The enzymes are shed by glycocalyx: they are not digested by proteases.
   - When there is a little of substrate in the lumen of small intestine.
     - sucrase, lactase maltase, isomaltase
   - Followed by absorption.
3. Endocellular
   - In the cell, by cytosolic or lysosomal enzymes.

Starch Digestion in the Small Intestine



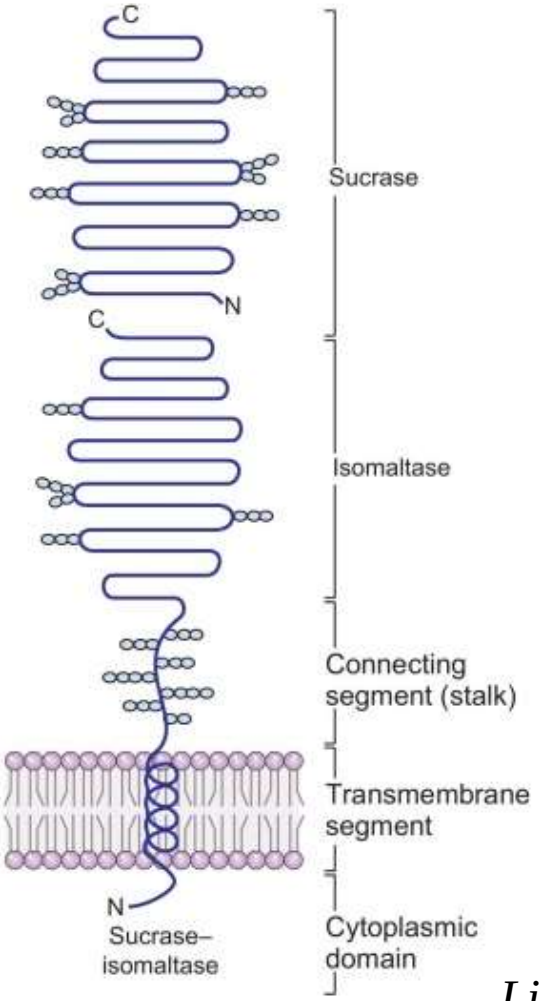
Liberman, Marks, 2012

Absoprtion of Digested Carbohydrates



Liberman, Marks, 2012

Sucrase-Isomaltase Complex

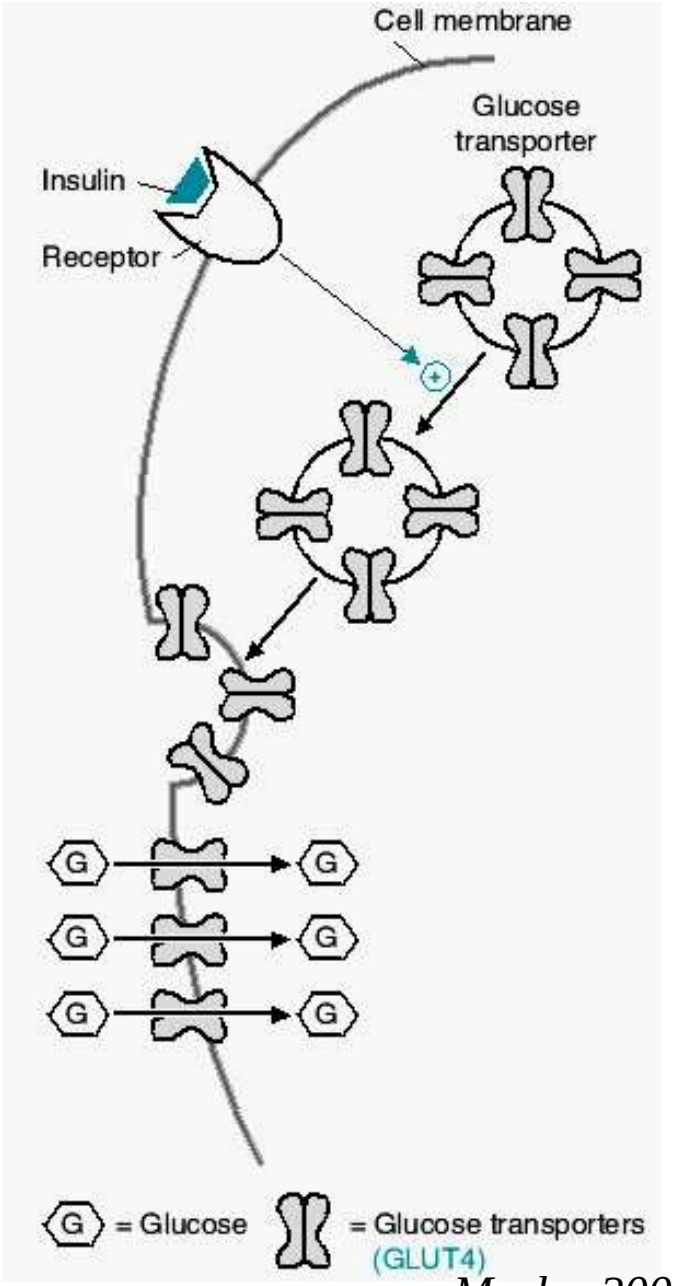


- The major portion of the sucrase-isomaltase complex, containing the catalytic sites, protrudes from the absorptive cells into the lumen of the intestine. Other domains of the protein form a connecting segment (stalk) and an anchoring segment that extends through the membrane into the cell. The complex is synthesized as a single polypeptide chain that is split into its two enzyme subunits extracellularly. Each subunit is a domain with a catalytic site (distinct sucrase–maltase and isomaltase–maltase sites). In spite of their maltase activity, these catalytic sites are often called just sucrase and isomaltase.

Liberman, Marks, 2012

Classification of Glucose Transporters

Transporter	K_t for D-glucose transport (mM)	Substrate	Major sites of expression
Facilitated diffusion (uniporter) (passive transport)			
GLUT-1	1-2	glucose, galactose, mannose	ubiquitous (erythrocyte, blood-tissue barriers)
GLUT-2	15-20	glucose, fructose	liver, intestine, kidney, pancreatic β-cells, brain
GLUT-3	1.8	glucose	ubiquitous
GLUT-4	5	glucose	skeletal and cardiac muscles, adipose tissues
GLUT-5	6-11	fructose	intestine
Na^+-coupled symporter (active transport)			
SGLT-1	0.35	glucose ($2Na^+$/1glucose), galactose	intestine, kidney
SGLT-2	1.6	glucose ($1Na^+$/1glucose)	kidney

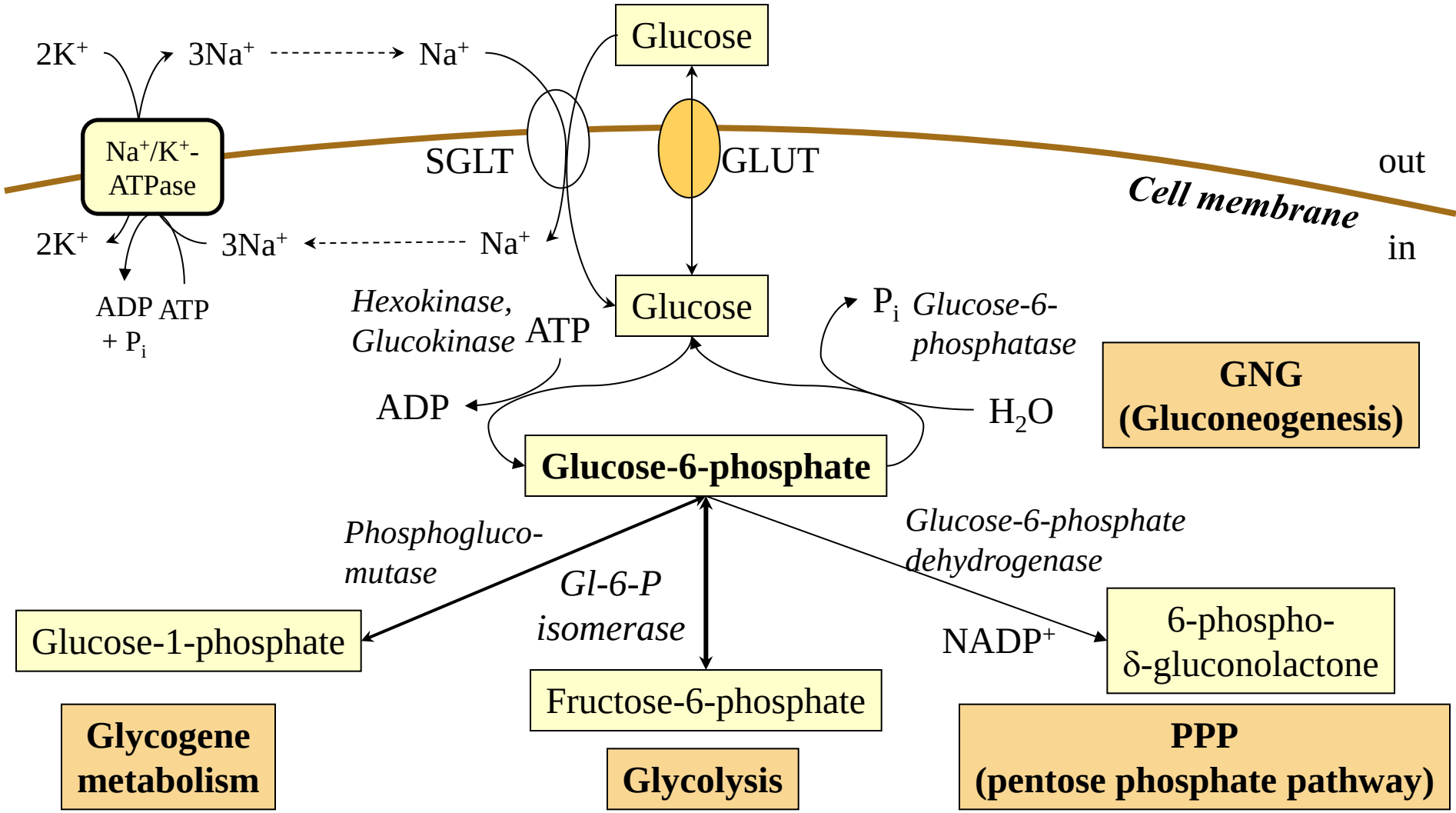


Insulin Stimulates Glucose Transport

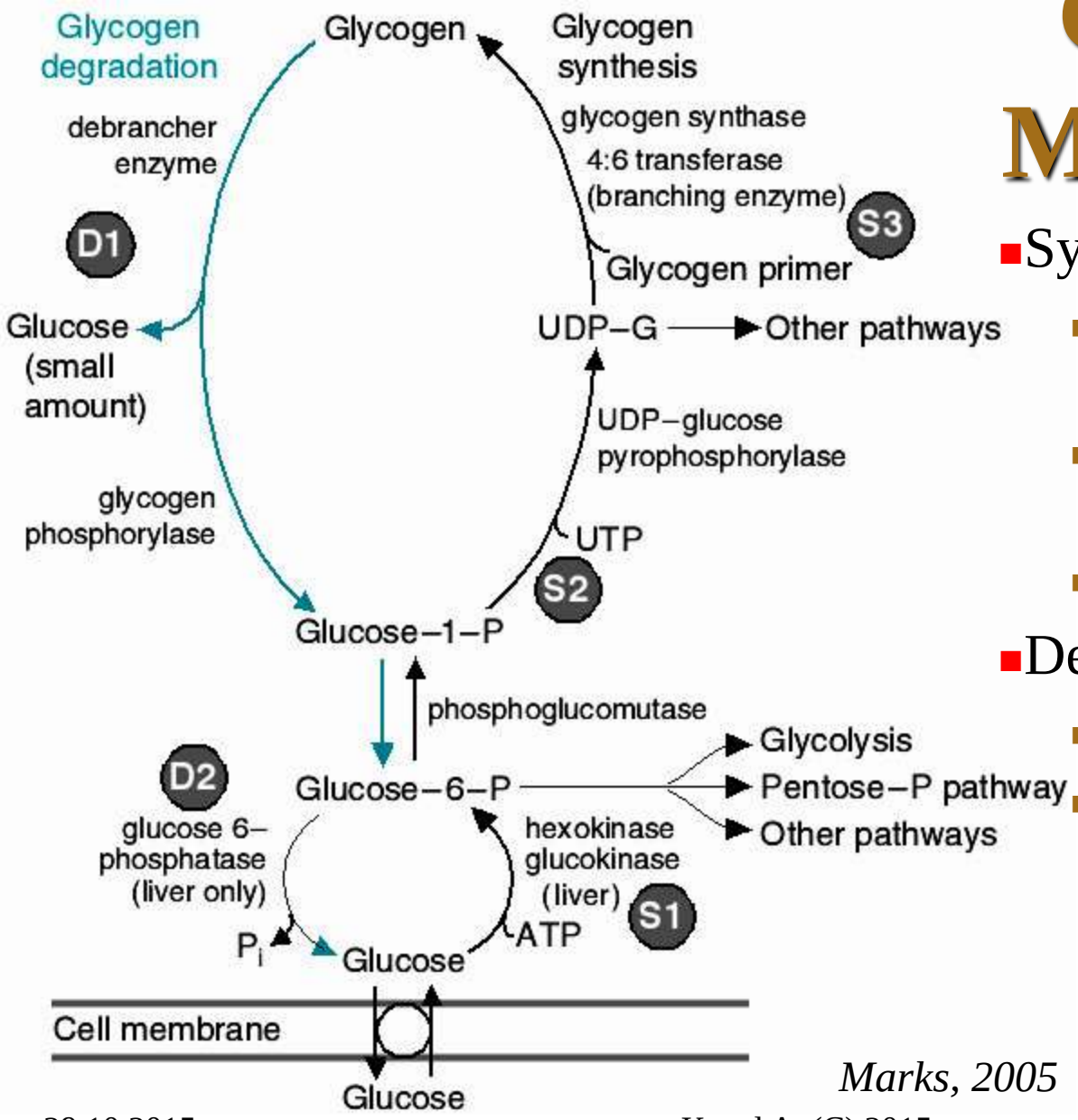
- Binding of insulin to its cell membrane receptors causes vesicles containing GLUT-4 to move from inside the cell to the cell membrane.
- After the fusion to membrane, the number of GLUT-4 ”gates” is much increased, also the glucose transport into the cell.

Marks, 2005

Glucose-6-phosphate Metabolism



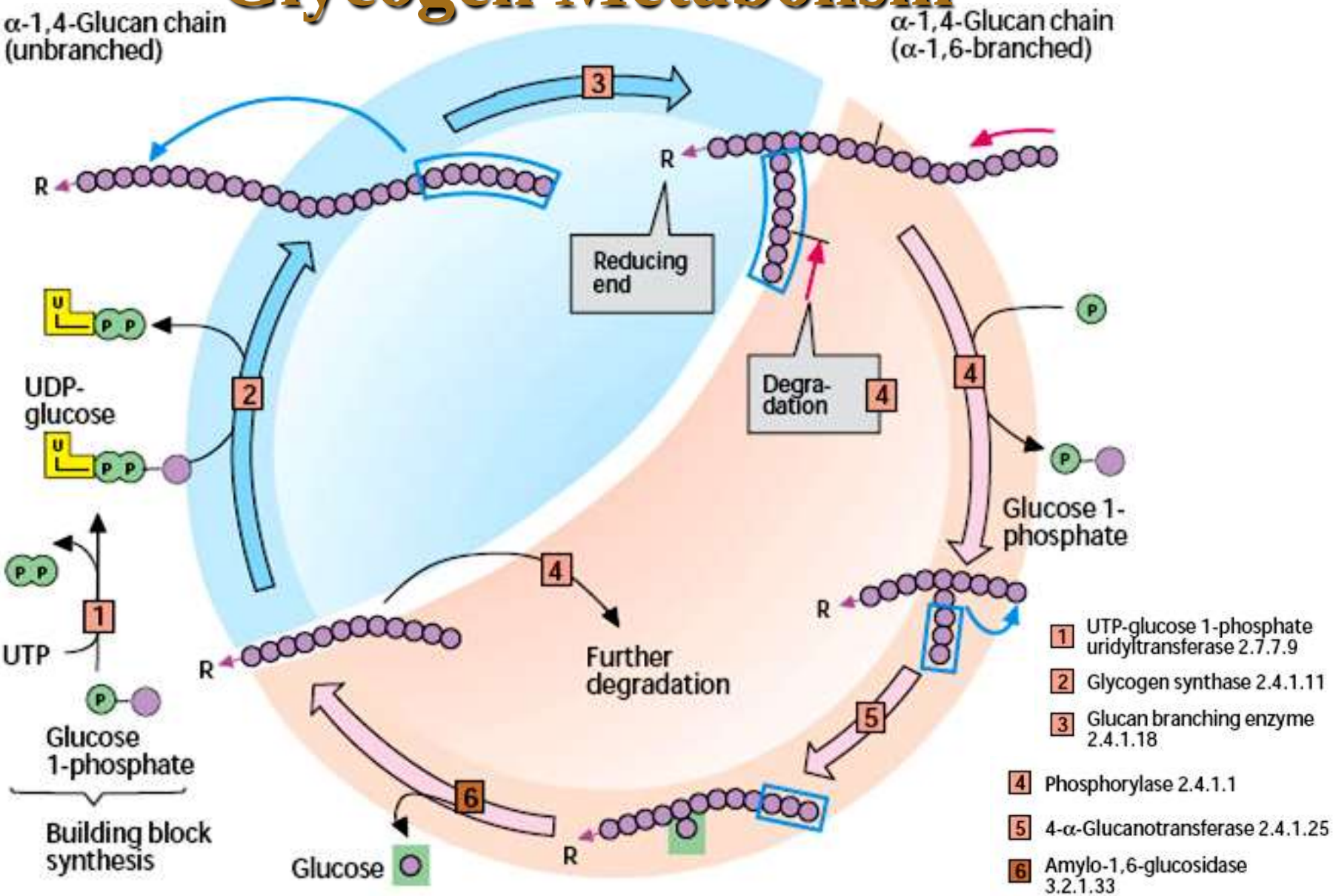
Glycogen Metabolism



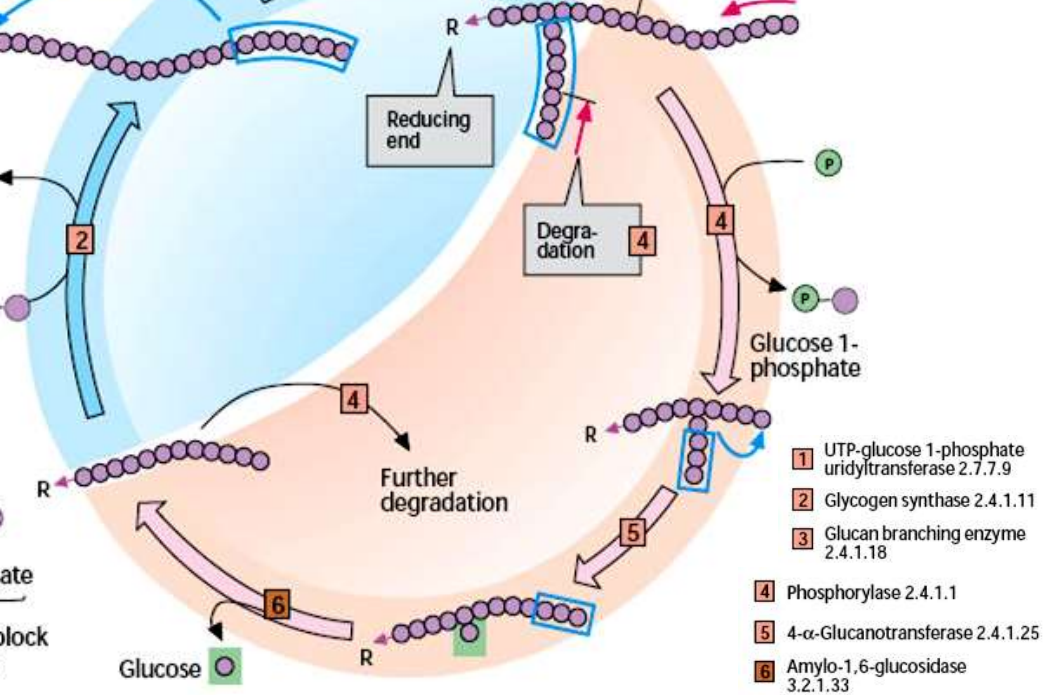
- Synthesis (S)
  - S1 – Glucose-6-phosphate formation
  - S2 – UDP-Glucose formation
  - S3 – Glycogen synthesis
- Degradation (D)
  - D1 – Glycogen → Gl-6-P
  - D2 – Gl-6-P → Glucose

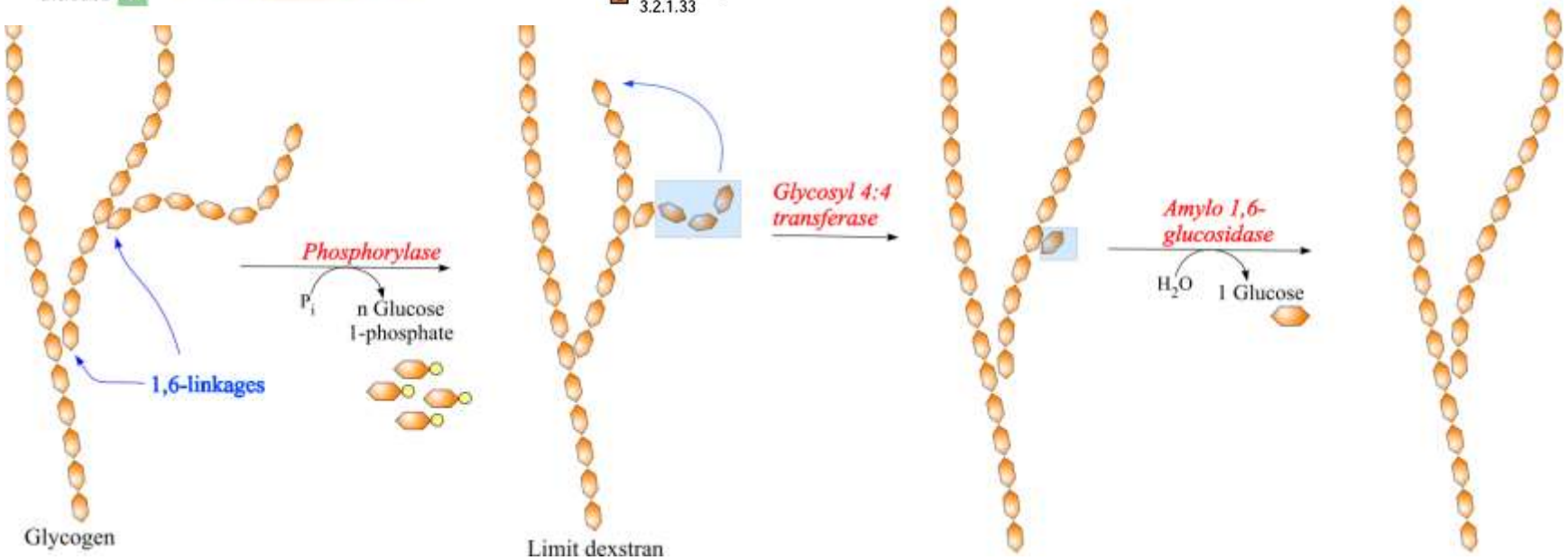
Marks, 2005

Glycogen Metabolism

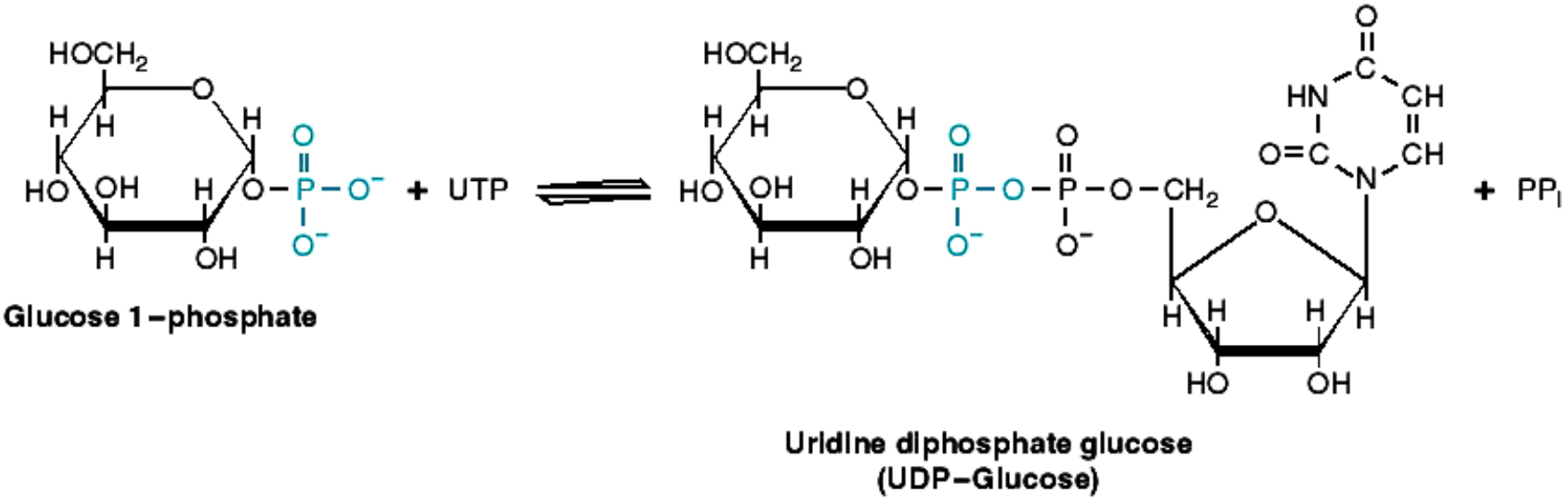


Glycogen debranching mechanism

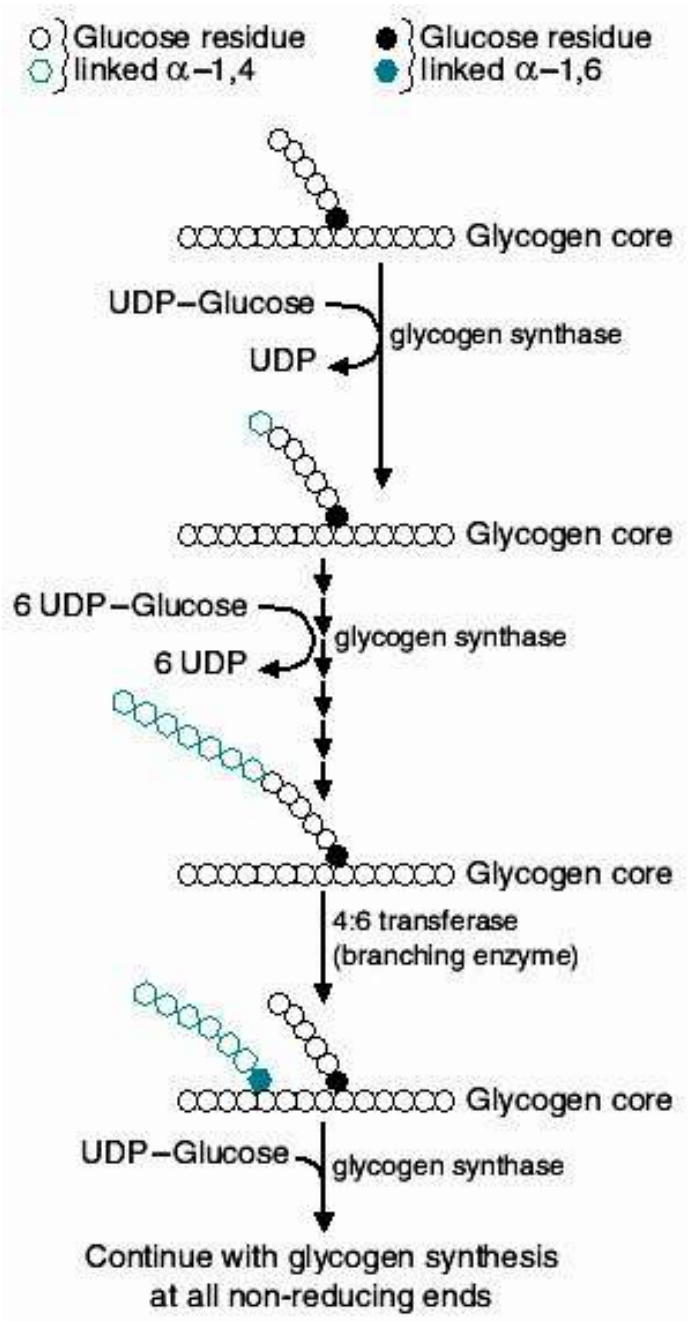




UDP-glucose Formation

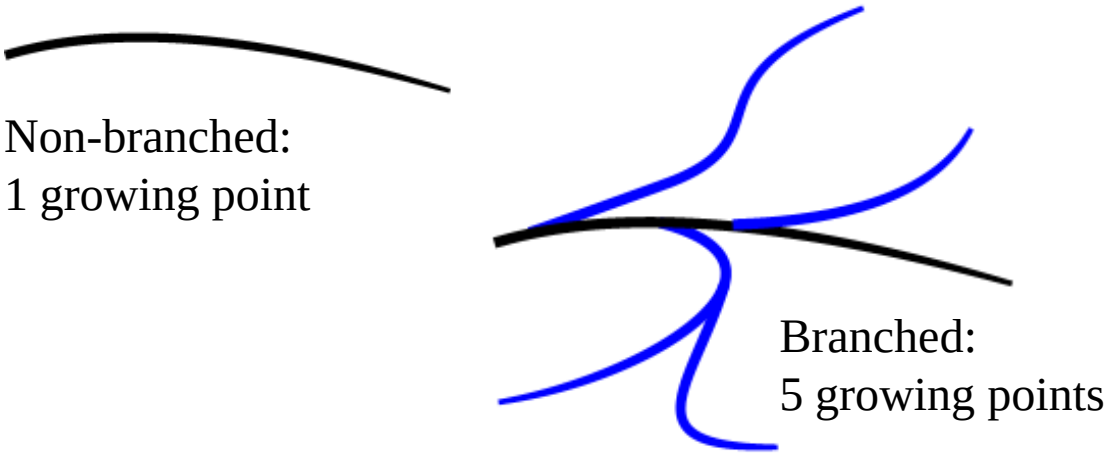


- The high-energy phosphate bond of UTP provides the energy for the formation of a high-energy bond in UDP-glucose.
- Pyrophosphate (PP_i) released by the reaction, is cleaved to 2 P_i by pyrophosphatase.

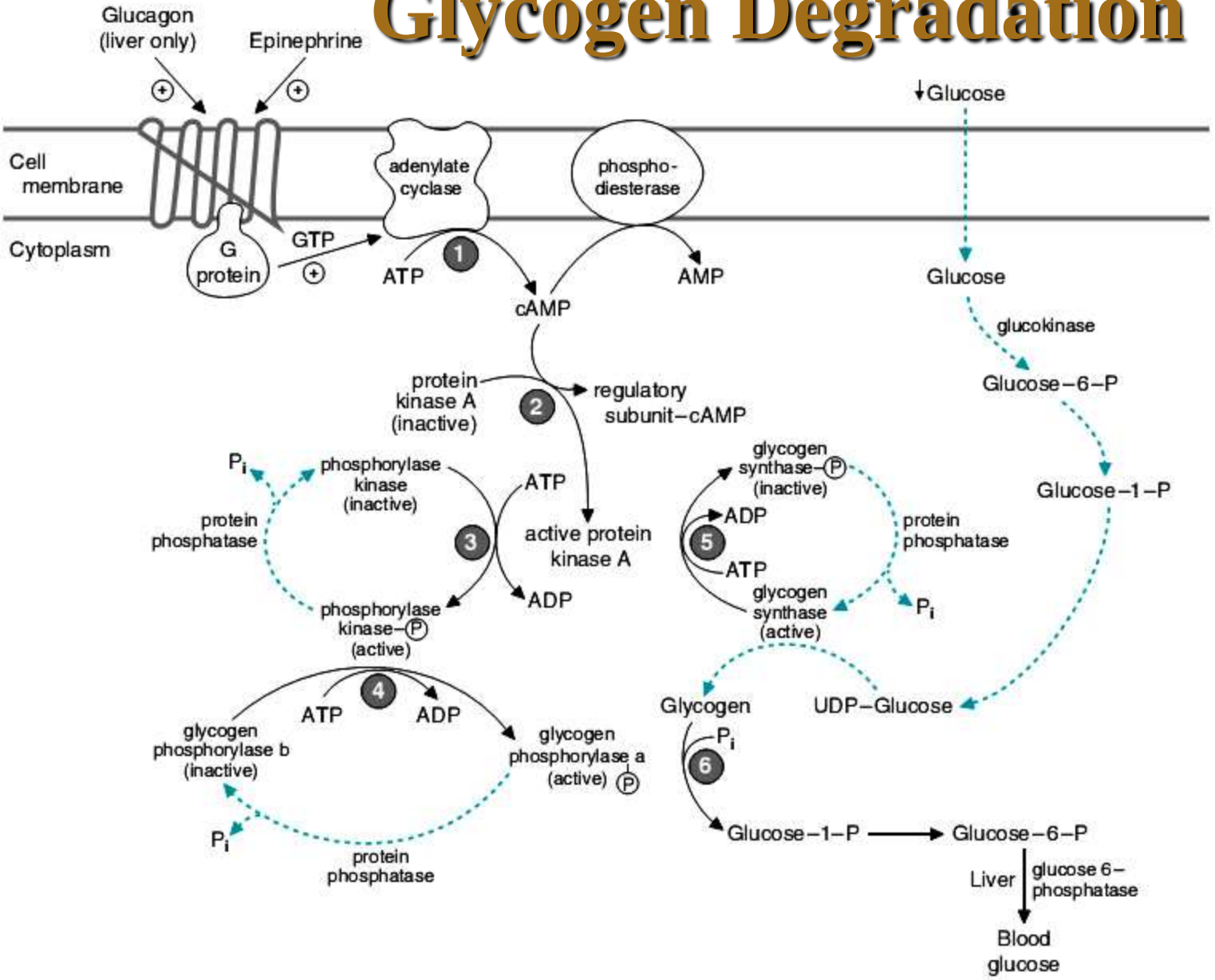


Glycogen Branching

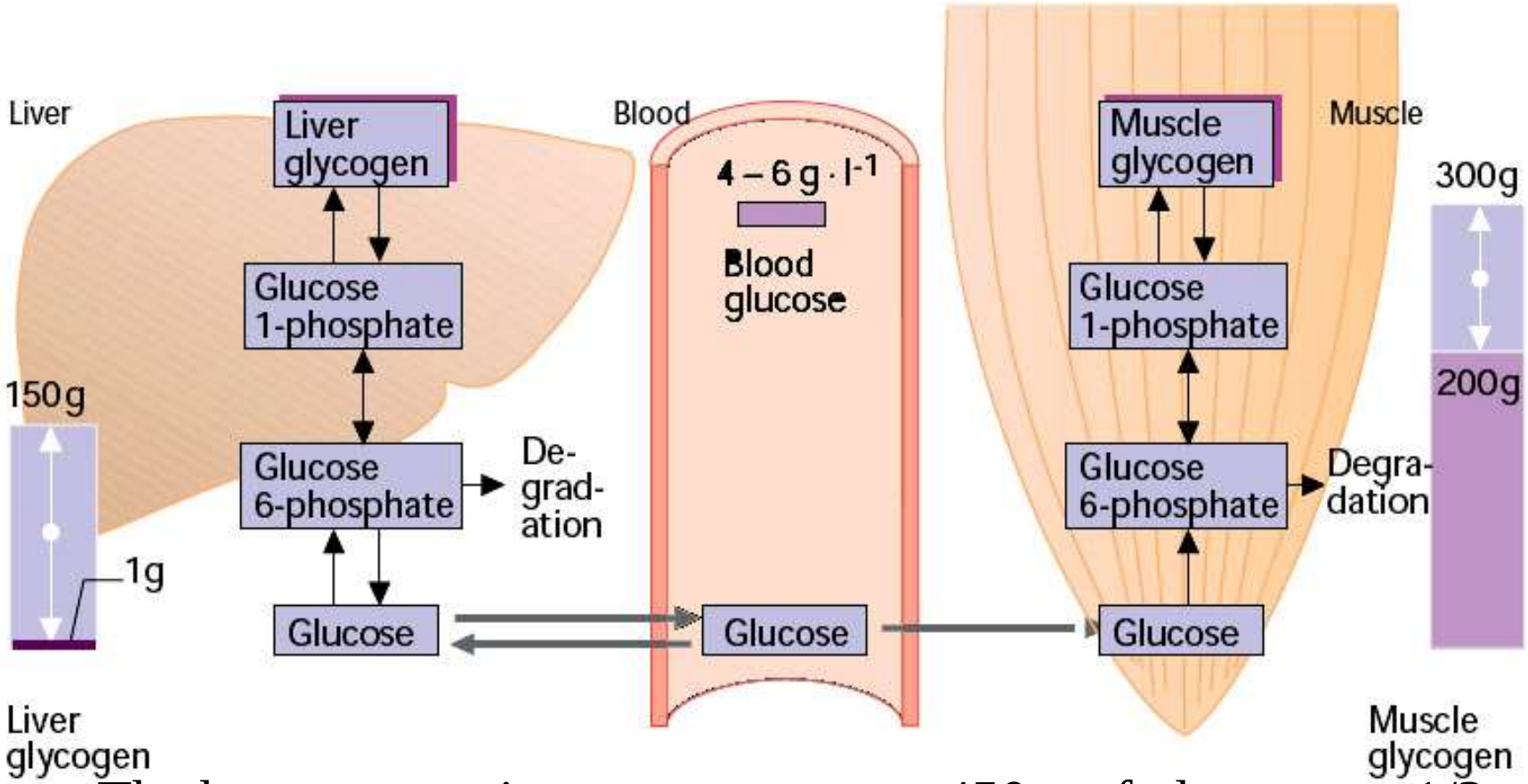
- 2 roles:
  - Increases sites for synthesis and degradation;
  - Enhances the solubility of the molecule.



Glycogen Degradation



Glycogen Balance



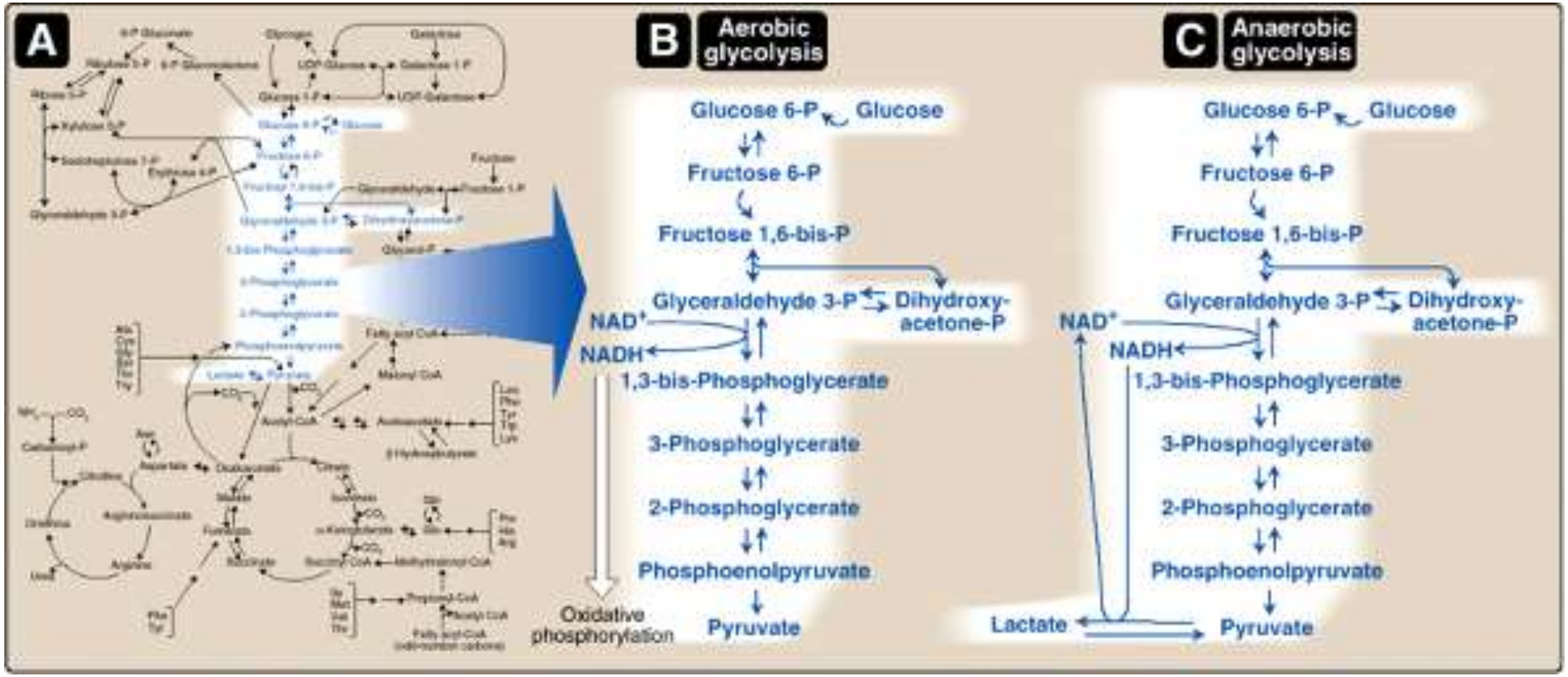
- The human organism can store up to 450 g of glycogen – 1/3 third in the **liver** and almost all of the remainder in **muscle.**
- The glycogen content of the other organs is low.

Glycolysis

- Flash animations:
  - figure19_1[1].swf – glycolysis
  - figure19_4[1].swf – glucose transport
  - glycolysis[1].swf – drill

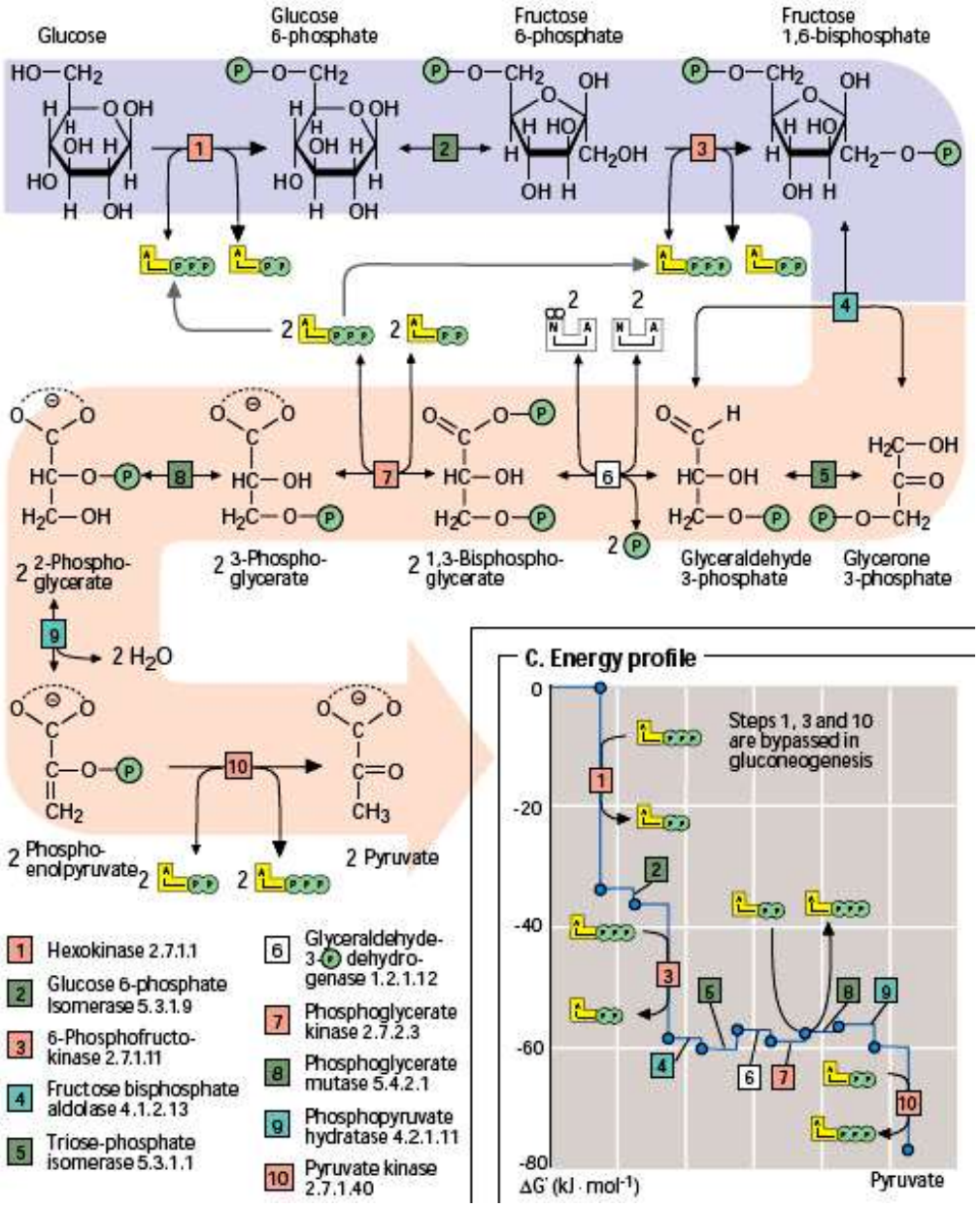
  - *gluconeogenesis[1].swf –for future*

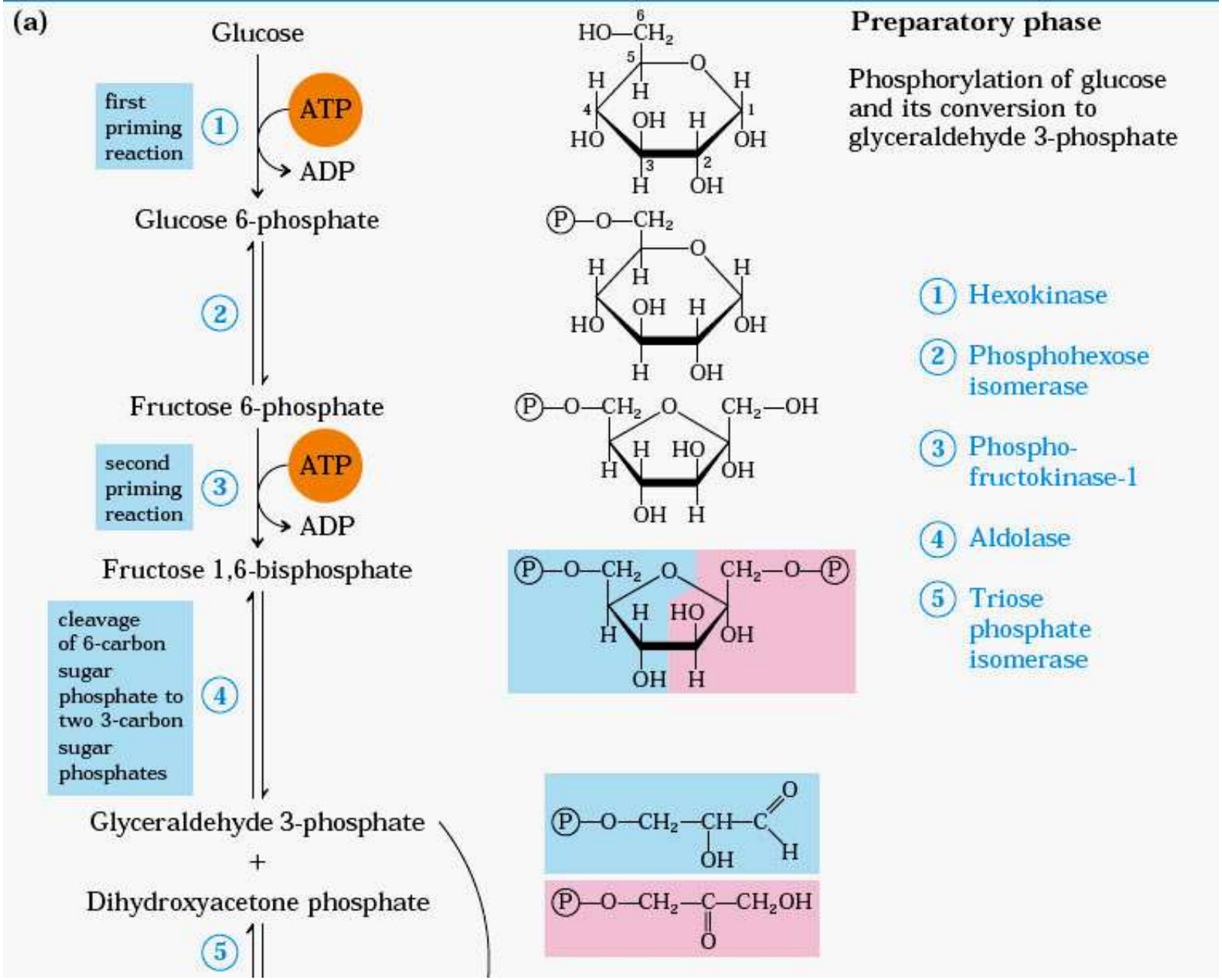
Aerobic & Anaerobic Glycolysis

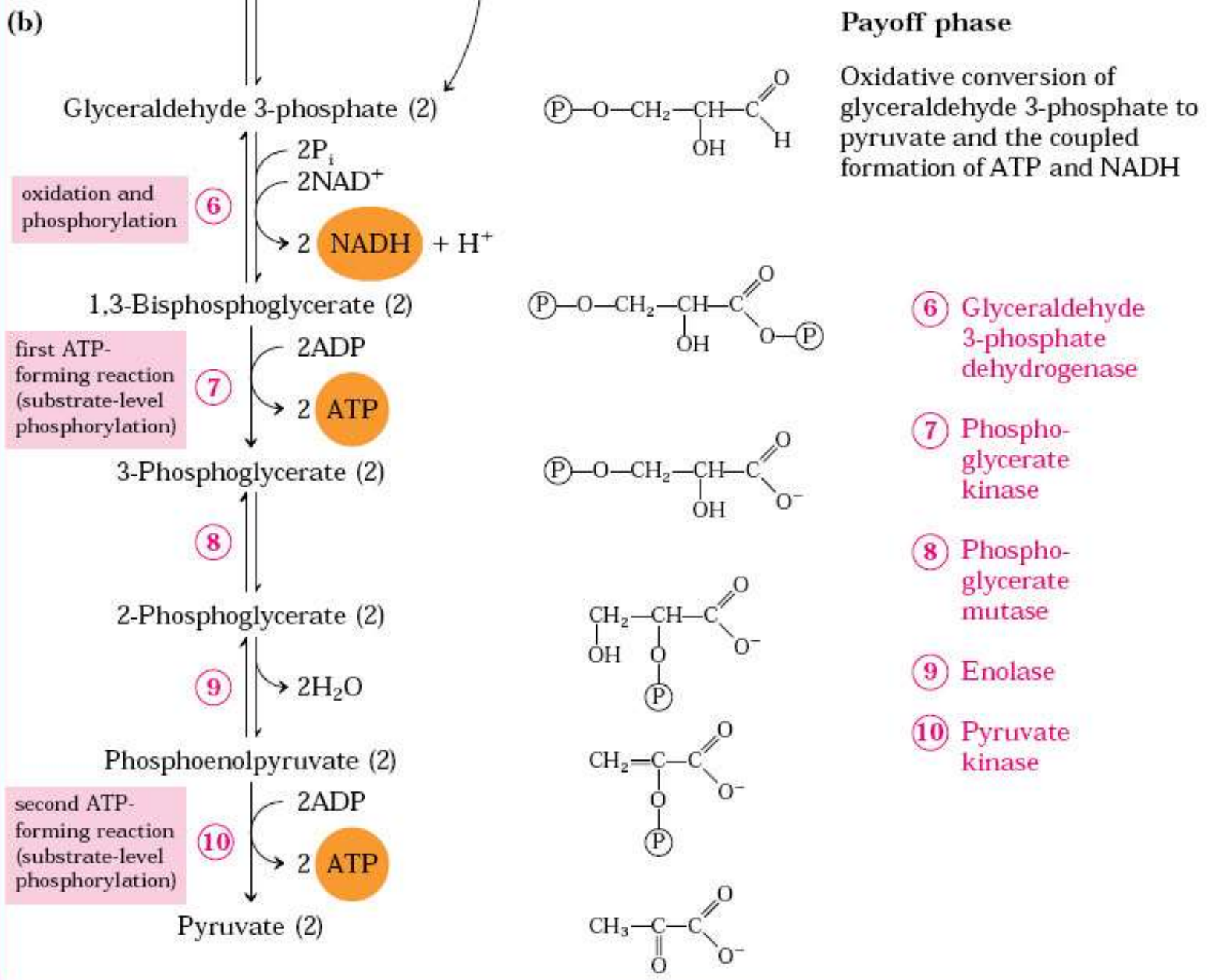


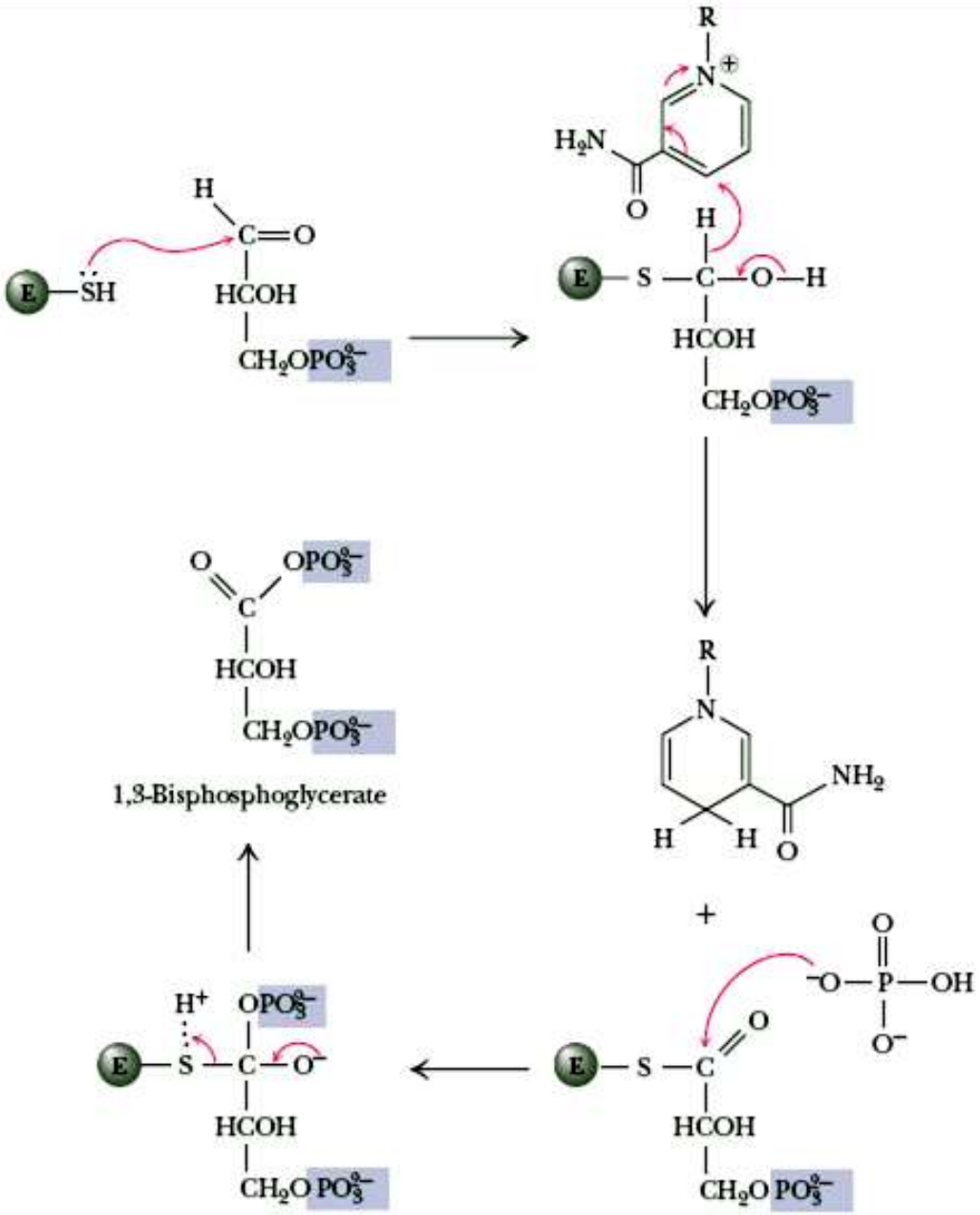
Lippincot, 2012

Glycolysis: Reactions




(a)
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to two 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase

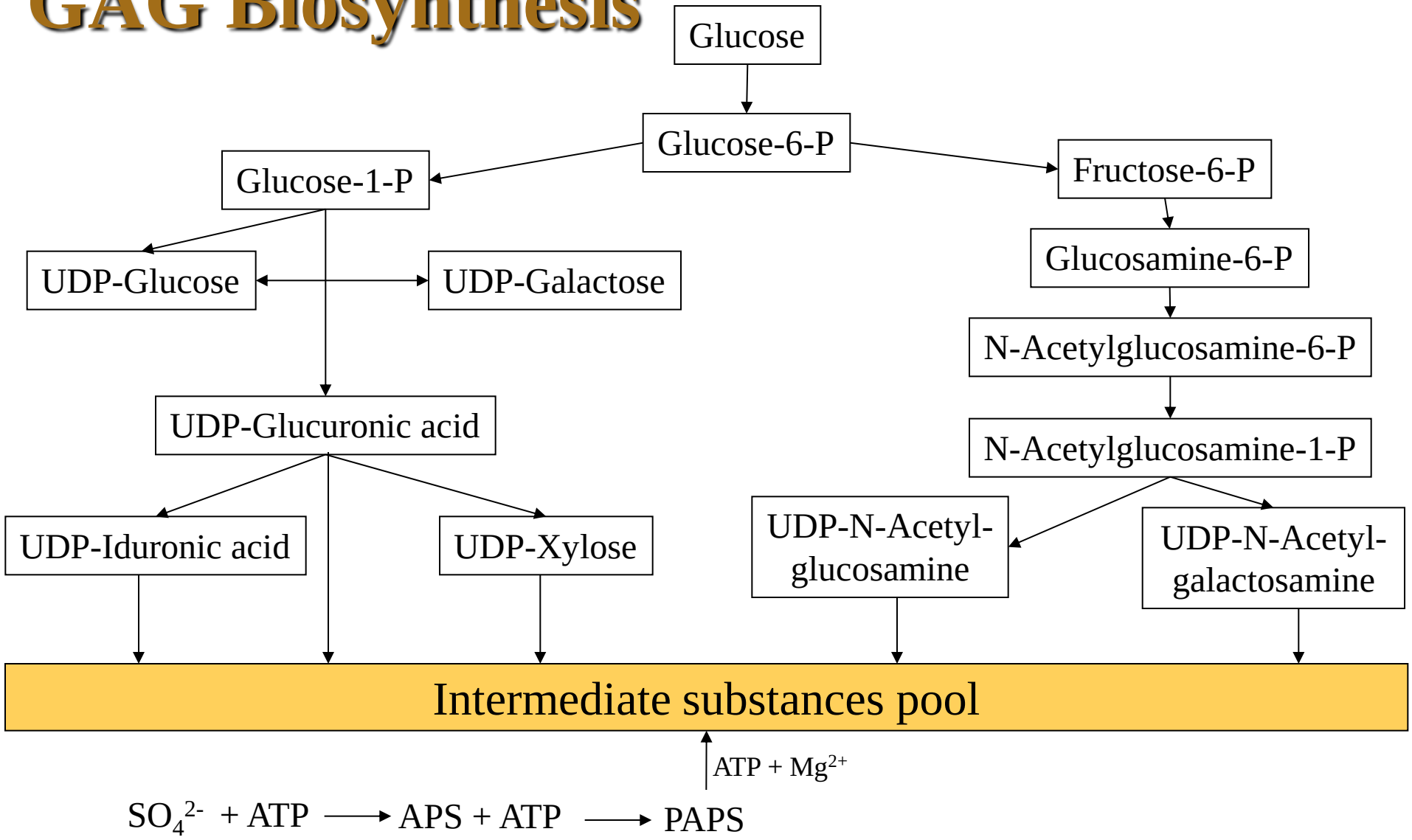

(b)
Payoff phase
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
Glyceraldehyde 3-phosphate (2)
2P$_i$
2NAD$^+$
oxidation and phosphorylation
6
2 NADH + H$^+$
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
7
2ADP
2 ATP
3-Phosphoglycerate (2)
8
2-Phosphoglycerate (2)
9
2H$_2$O
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
10
2ADP
2 ATP
Pyruvate (2)
6 Glyceraldehyde 3-phosphate dehydrogenase
7 Phospho-glycerate kinase
8 Phospho-glycerate mutase
9 Enolase
10 Pyruvate kinase



Mechanism of **3-PG DH reaction**

- A mechanism for the *glyceraldehyde-3-phosphate dehydrogenase* reaction.

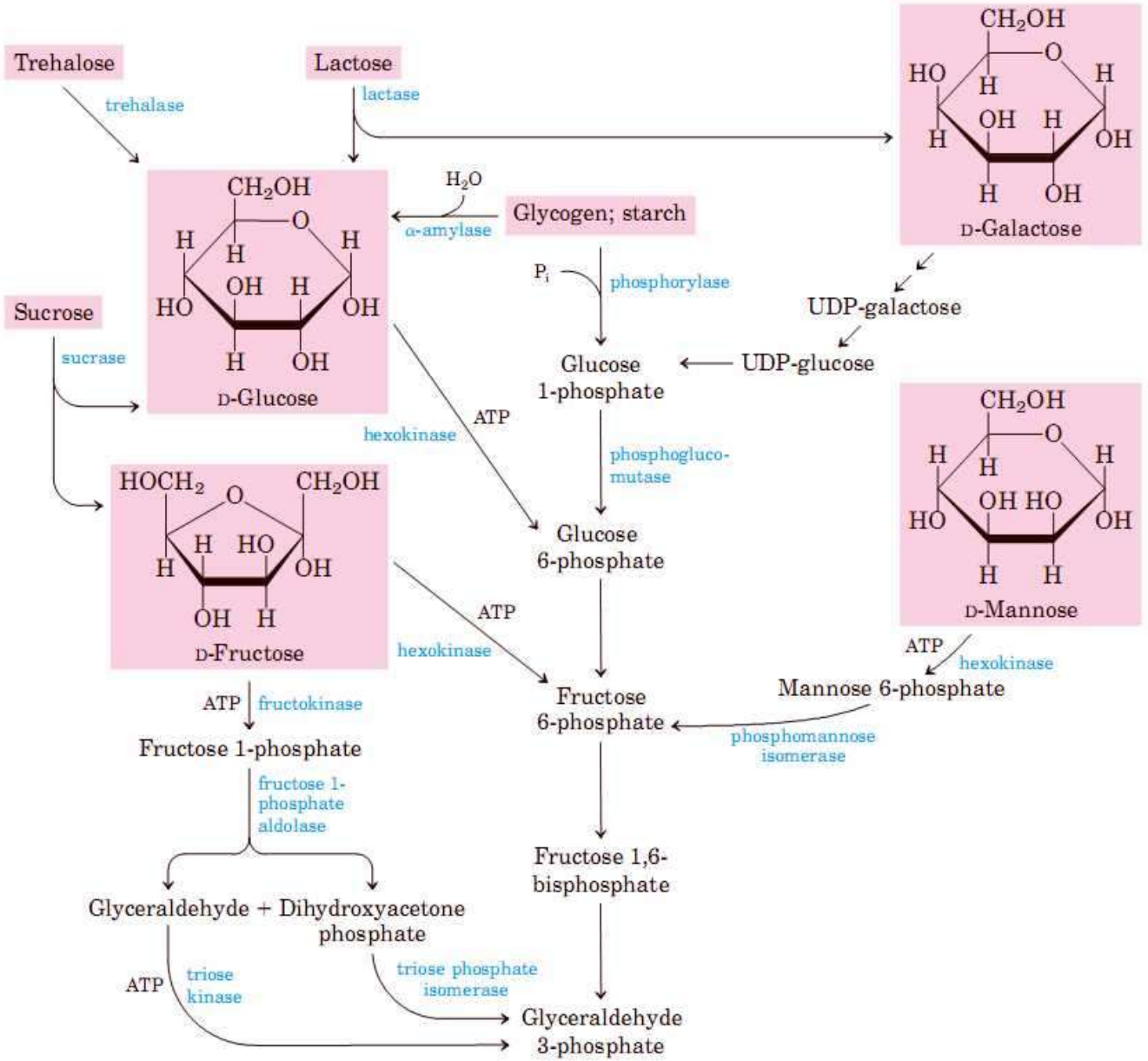
GAG Biosynthesis



Non-Glucose Carbons in Glycolysis

- Fructose Metabolism
  - *Clinical Significances of Fructose Metabolism*
- Galactose Metabolism
  - *Clinical Significances of Galactose Metabolism*
- Mannose Metabolism
- Glycerol Metabolism
- Glucuronate Metabolism
  - *Clinical Significances of Glucuronate*

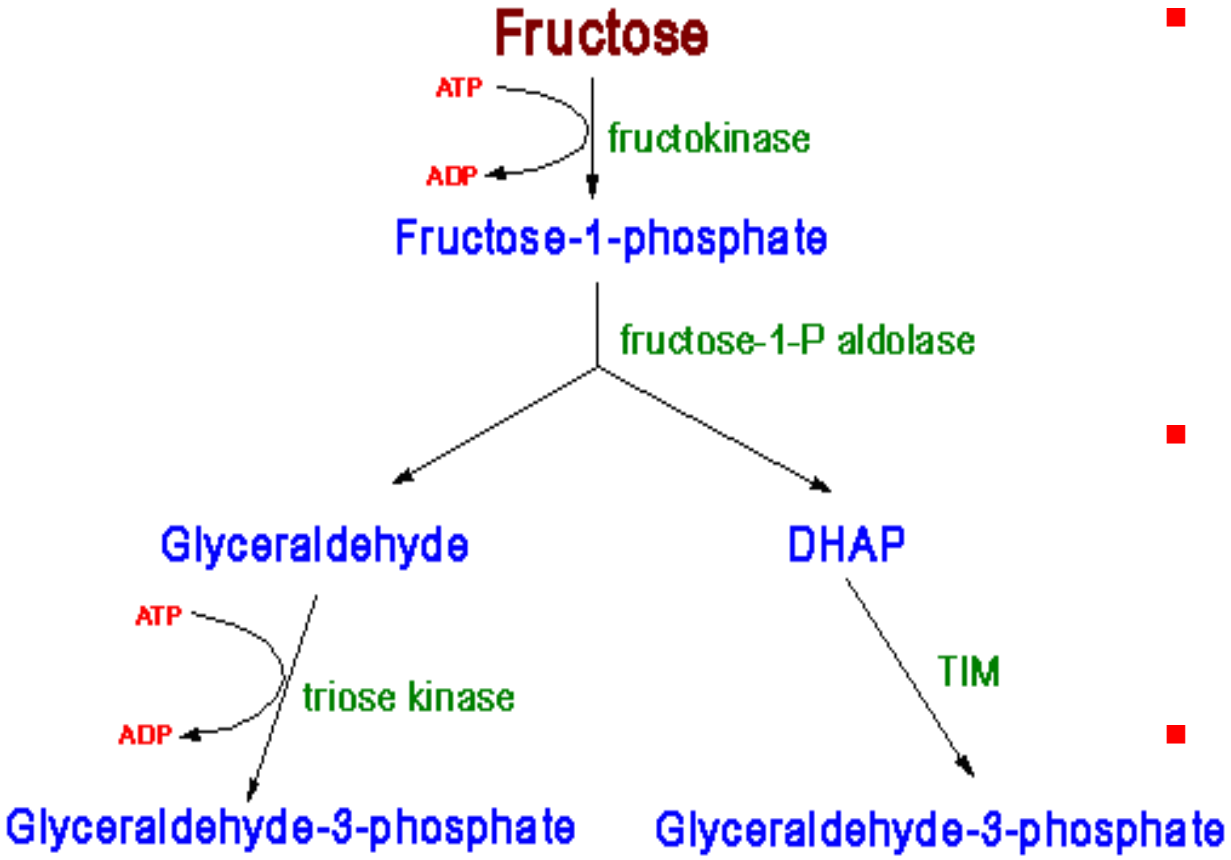
Entry of Glycogen, Starch, Disaccharides etc into Glycolysis



Fructose Metabolism

- Diets containing large amounts of sucrose (a disaccharide of glucose and fructose) can utilize the fructose as a major source of energy.
- The pathway to utilization of fructose differs in muscle and liver.
  - Muscle which contains only hexokinase can phosphorylate fructose to F6P which is a direct glycolytic intermediate.

Entry of Fructose Carbon Atoms into the Glycolytic Pathway in Hepatocytes

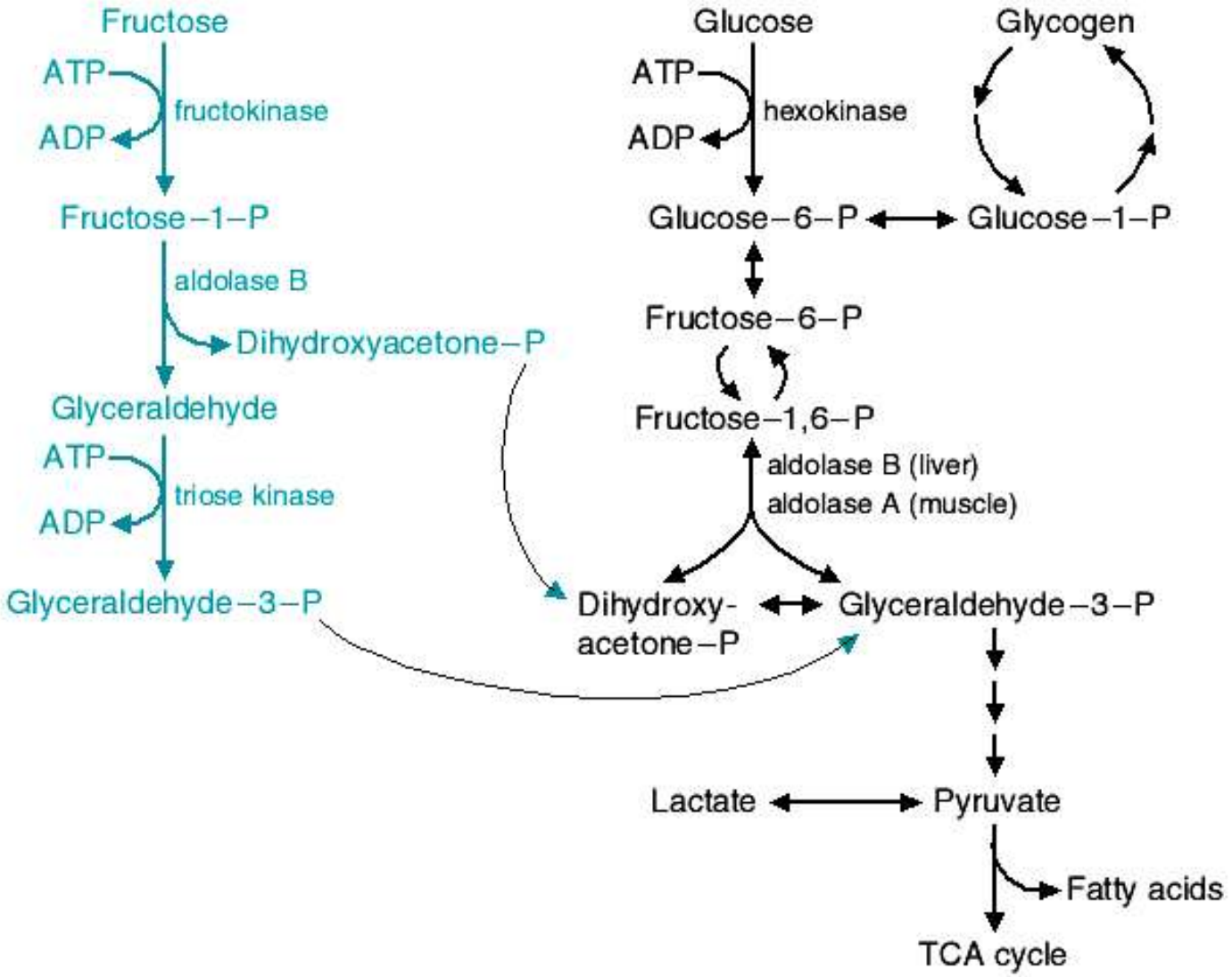


- In the liver which contains mostly glucokinase, which is specific for glucose as its substrate, requires the function of additional enzymes to utilize fructose in glycolysis.
- Hepatic fructose is phosphorylated on C-1 by fructokinase yielding fructose-1-phosphate (F1P).
- In liver the form of aldolase that predominates (aldolase B) can utilize both F-1,6-BP and F1P as substrates.

Fate of DHAP and Glyceraldehyde

- Therefore, when presented with F1P the enzyme generates DHAP and glyceraldehyde.
  - The DHAP is converted, by *triose phosphate isomerase*, to G3P and enters glycolysis.
  - The glyceraldehyde can be phosphorylated to G3P by *glyceraldehyde kinase* or converted to DHAP through the concerted actions of *alcohol dehydrogenase, glycerol kinase and glycerol phosphate dehydrogenase.*

Fructose Metabolism: Integration with Glycolysis



Clinical Significances of Fructose Metabolism: Essential Fructosuria

- Three inherited abnormalities in fructose metabolism have been identified.
- **Essential fructosuria** is a benign metabolic disorder caused by the lack of *fructokinase* which is normally present in the liver, pancreatic islets and kidney cortex.
  - The fructosuria of this disease depends on the time and amount of fructose and sucrose intake. Since the disorder is asymptomatic and harmless it may go undiagnosed.

Fructose Metabolism: Hereditary fructose intolerance

- **Hereditary fructose intolerance** is a potentially lethal disorder resulting from a lack of *aldolase B* which is normally present in the liver, small intestine and kidney cortex.
  - The disorder is characterized by severe hypoglycemia and vomiting following fructose intake.
  - Prolonged intake of fructose by infants with this defect leads to vomiting, poor feeding, jaundice, hepatomegaly, hemorrhage and eventually hepatic failure and death.
  - The hypoglycemia that result following fructose uptake is caused by fructose-1-phosphate inhibition of glycogenolysis, by interfering with the phosphorylase reaction, and inhibition of gluconeogenesis at the deficient aldolase step.
  - Patients remain symptom free on a diet devoid of fructose and sucrose.

Fructose Metabolism: Hereditary Fructose-1,6-bisphosphatase Deficiency

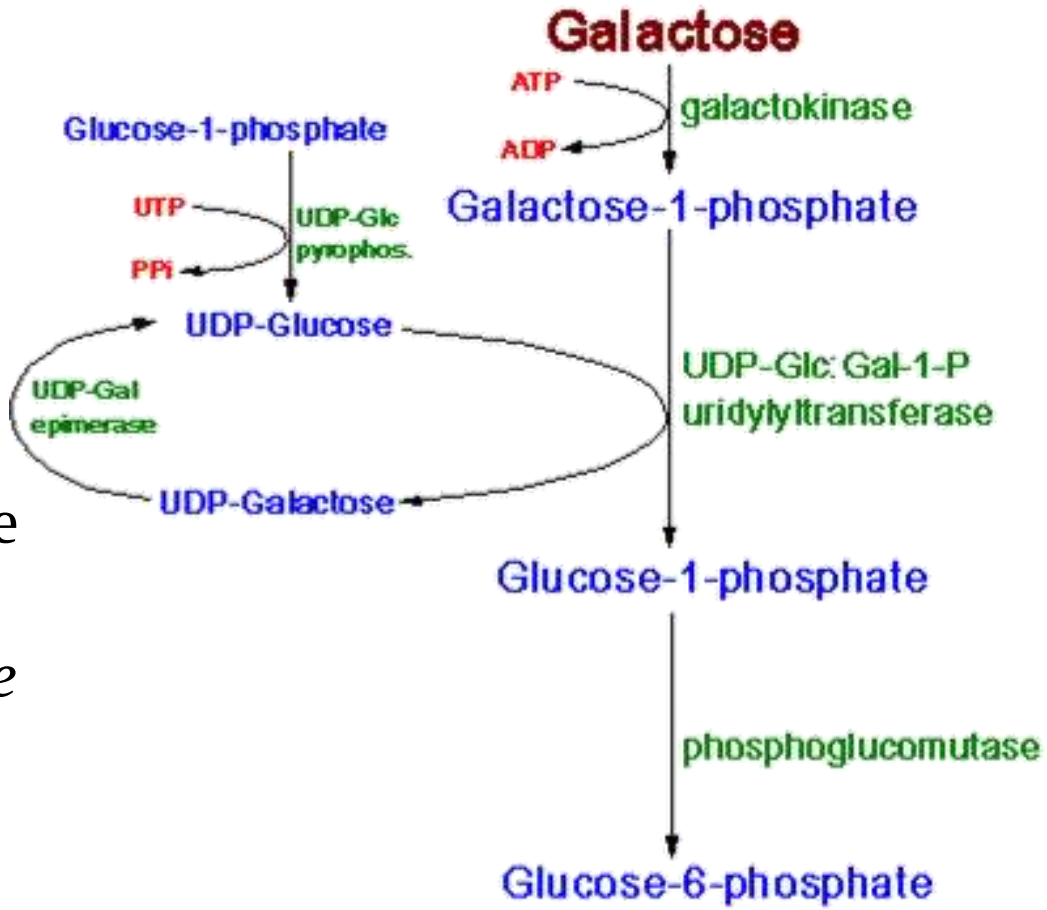
- **Hereditary fructose-1,6-bisphosphatase deficiency** results in severely impaired hepatic gluconeogenesis and leads to episodes of hypoglycemia, apnea, hyperventillation, ketosis and lactic acidosis.
- These symptoms can take on a lethal course in neonates.
- Later in life episodes are triggered by fasting and febrile infections.

Galactose Metabolism

- **Galactose**, which is metabolized from the lactose, enters glycolysis by its conversion to glucose-1-phosphate (G1P).
  - This occurs through a series of steps.
  - 1) galactose is phosphorylated by *galactokinase* to yield galactose-1-phosphate.
  - Epimerization of galactose-1-phosphate to G1P requires the transfer of UDP from uridine diphosphoglucose (UDP-glucose) catalyzed by *galactose-1-phosphate uridyl transferase*. This generates UDP-galactose and G1P.
  - The UDP-galactose is epimerized to UDP-glucose by *UDP-galactose-4 epimerase*.
  - The UDP portion is exchanged for phosphate generating glucose-1-phosphate which then is converted to G6P by *phosphoglucose mutase*.

Entry of Galactose Carbon Atoms into the Glycolytic Pathway

- The full name for the enzyme UDP-Glc pyrophos. is *UDP-glucose pyrophosphorylase*,
- that of UDP-Glc:Gal-1-P uridylyltransferase is *UDP-glucose:a-D-galactose-1-phosphate uridylyltransferase*.



Clinical Significances of Galactose Metabolism

- Three inherited disorders of galactose metabolism have been delineated.
  - Classic **galactosemia** is a major symptom of two enzyme defects.
  - One results from loss of the enzyme *galactose-1-phosphate uridyl transferase*.
  - The second – from a loss of *galactokinase*.
  - These two defects are manifest by a failure of neonates to thrive. Vomiting.

Clinical Findings of Galactosemias

- Clinical findings of these disorders include impaired liver function (which if left untreated leads to severe cirrhosis), elevated blood galactose, hypergalactosemia, hyperchloremic metabolic acidosis, urinary galactitol excretion and hyperaminoaciduria.
  - Unless controlled by exclusion of galactose from the diet, these galactosemias can go on to produce blindness and fatal liver damage.
  - Even on a *galactose-restricted diet*, transferase-deficient individuals exhibit urinary galacitol excretion and persistently elevated erythrocyte galactose-1-phosphate levels.

Galactosemia & Blindness

- **Blindness** is due to the conversion of circulating galactose to the sugar alcohol galacitol, by an *NADPH-dependent galactose reductase* that is present in neural tissue and in the lens of the eye.
  - At normal circulating levels of galactose this enzyme activity causes no pathological effects. However, a high concentration of galacitol in the lens causes osmotic swelling, with the resultant formation of cataracts and other symptoms.
  - The principal treatment of these disorders is to eliminate lactose from the diet.

Deficiency of UDP-Galactose-4-epimerase

- The third disorder of galactose metabolism result from a deficiency of *UDP-galactose-4-epimerase*. Two different forms of this deficiency have been found.
  - One is benign affecting only red and white blood cells.
  - The other affects multiple tissues and manifests symptoms similar to the transferase deficiency. Treatment involves restriction of dietary galactose.

Mannose Metabolism

- The digestion of many polysaccharides and glycoproteins yields **mannose** which is phosphorylated by *hexokinase* to generate mannose-6-phosphate.
  - Mannose-6-phosphate is converted to fructose-6-phosphate, by the enzyme *phosphomannose isomerase*, and then enters the glycolytic pathway or is converted to glucose-6-phosphate by the gluconeogenic pathway of hepatocytes.


Thank you
for your attention!