CARBOHYDRATES

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The following subtopics will be discussed:

- Structure & classification of carbohydrates: (linear & cyclic forms, asymmetry, D/L form).
- Digestion of the food carbohydrates;
- Metabolic processes: Glycogenesis, Glycogenolysis, Glycolysis, Krebs cycle, Neoglycogenesis; ETS, PPPW, Cellular aerobic respiration.
- Galactosemia, Hypo/hyperglycemia
- Conversions: carbohydrates →proteins→lipids

General characteristics

The term *carbohydrate* is derived from the French “hydrate de carbone”

Carbohydrates are the compounds composed of carbon (C), hydrogen (H) and oxygen (O).

General characteristics

- $(CH_2O)_n$ (when n = 5, then $C_5H_{10}O_5$)
- not all carbohydrates have this empirical formula: deoxysugars, aminosugars
- carbohydrates are the most abundant compounds found in nature (cellulose: 100 billion tons annually)

Classification of carbohydrates

There are two main groups:

- simple carbohydrates (monomers/ Monosaccharides)
- complex carbohydrates (polymers/ oligosaccharides/polysaccharides)

Classification of carbohydrates

- **Monosaccharides** (monomers):
  Trioses, tetroses, pentoses, hexoses
- **Oligosaccharides:**
  Di, tri, tetra, penta, up to 10
  Most important are the disaccharides (lactose, maltose, sucrose, trehalose)

Classification of carbohydrates

- **Polysaccharides** (polymers)
- Homopolysaccharides (glycogen, starch)
- Heteropolysaccharides (glycoprotein, glycolipids)

Monosaccharides

They are also known as monoses or simple sugars. They are classified according to the number of carbons and by the type of functional group (aldoses or ketoses).

Monosaccharides

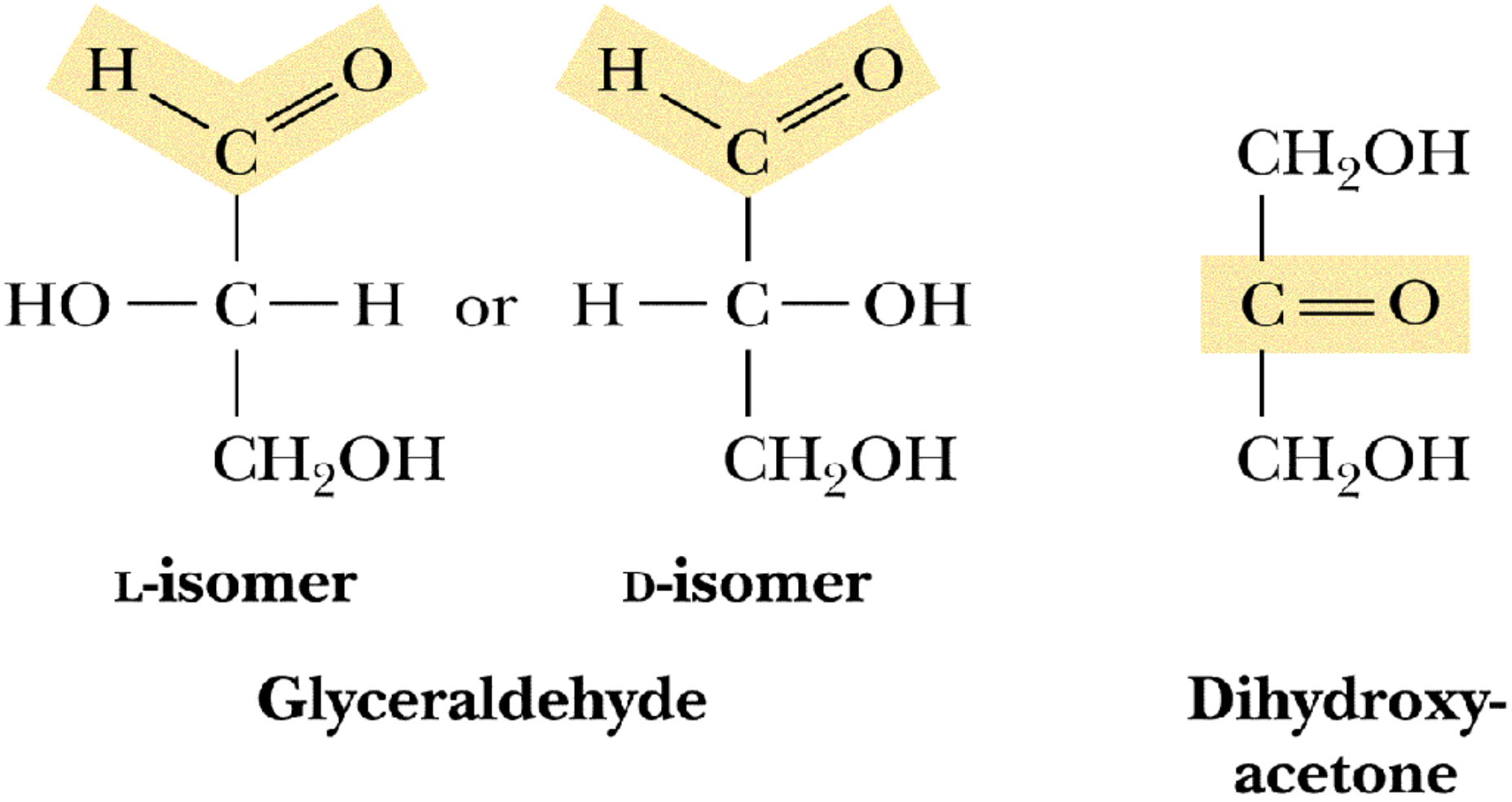
- D-glyceraldehyde is the simplest of the aldoses (aldotriose) and dihydroxyacetone is the simplest ketose (ketotriose).
- All other sugars have the ending ose (glucose, galactose, ribose, lactose, etc…)

Monosaccharides: Nomenclature

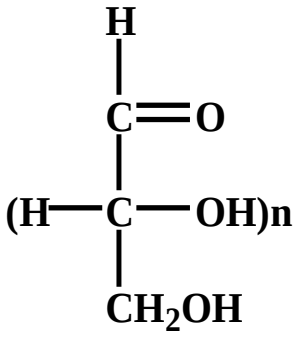
Functional group

Number of carbons	Aldose	Ketose
3	Triose	Trulose
4	Tetrose	Tetrulose
5	Pentose	Pentulose
6	Hexose	Hexulose
7	Heptose	Heptulose

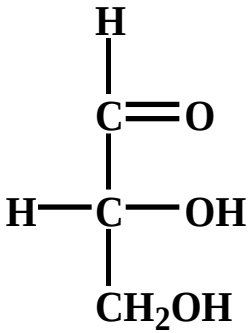
Structure of simple aldose & ketose



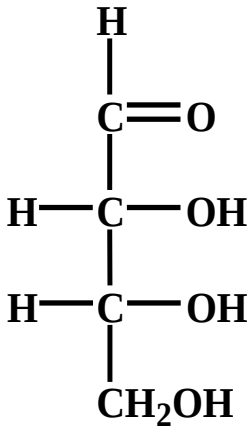
Aldose sugars



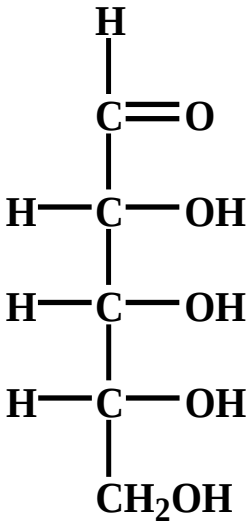
Aldose



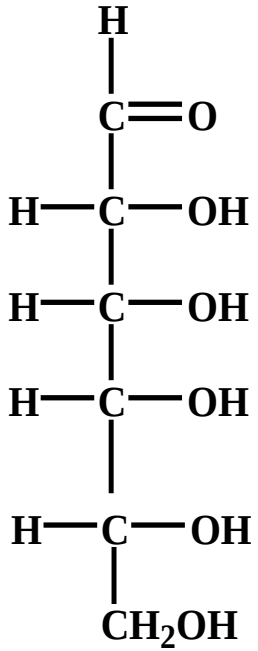
Aldotriose
n = 1



Aldotetrose
n = 2

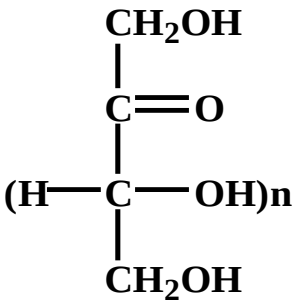


Aldopentose
n = 3

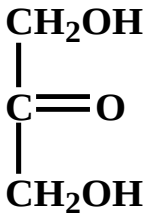


Aldohexose
n = 4

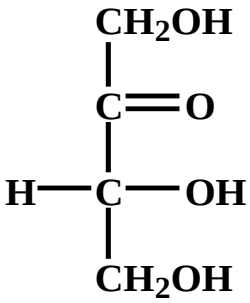
Ketose sugars



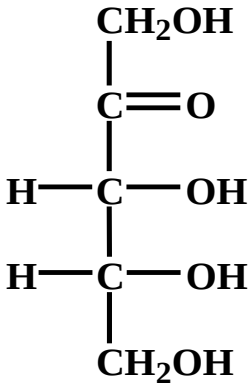
Ketose



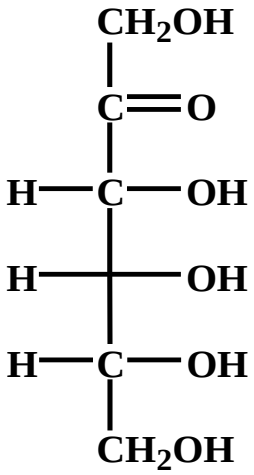
Ketotriose
n = 0



Ketotetrose
n = 1



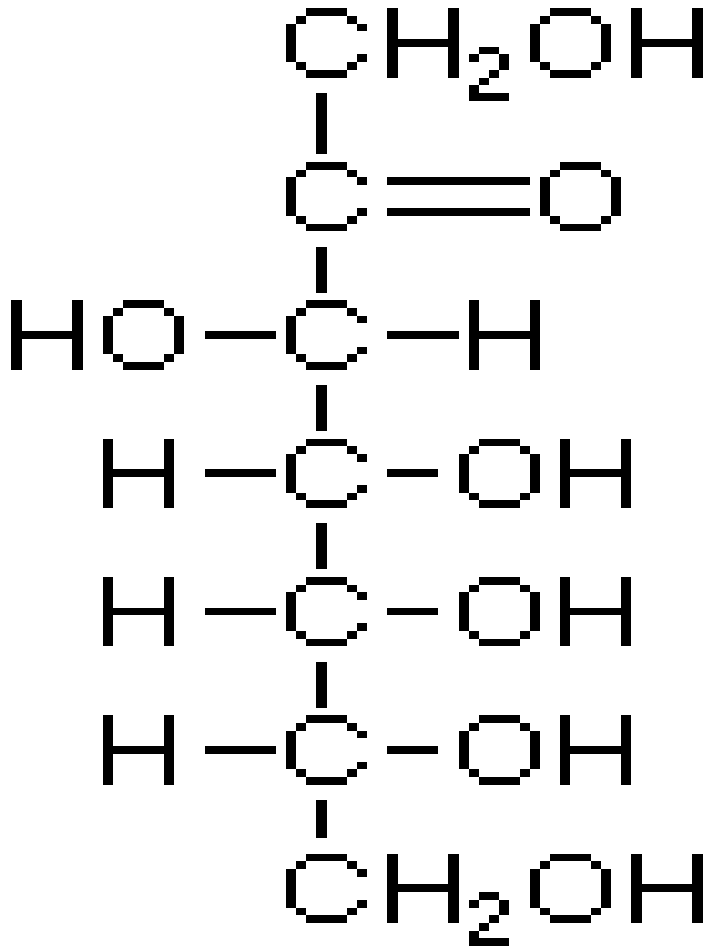
Ketopentose
n = 2



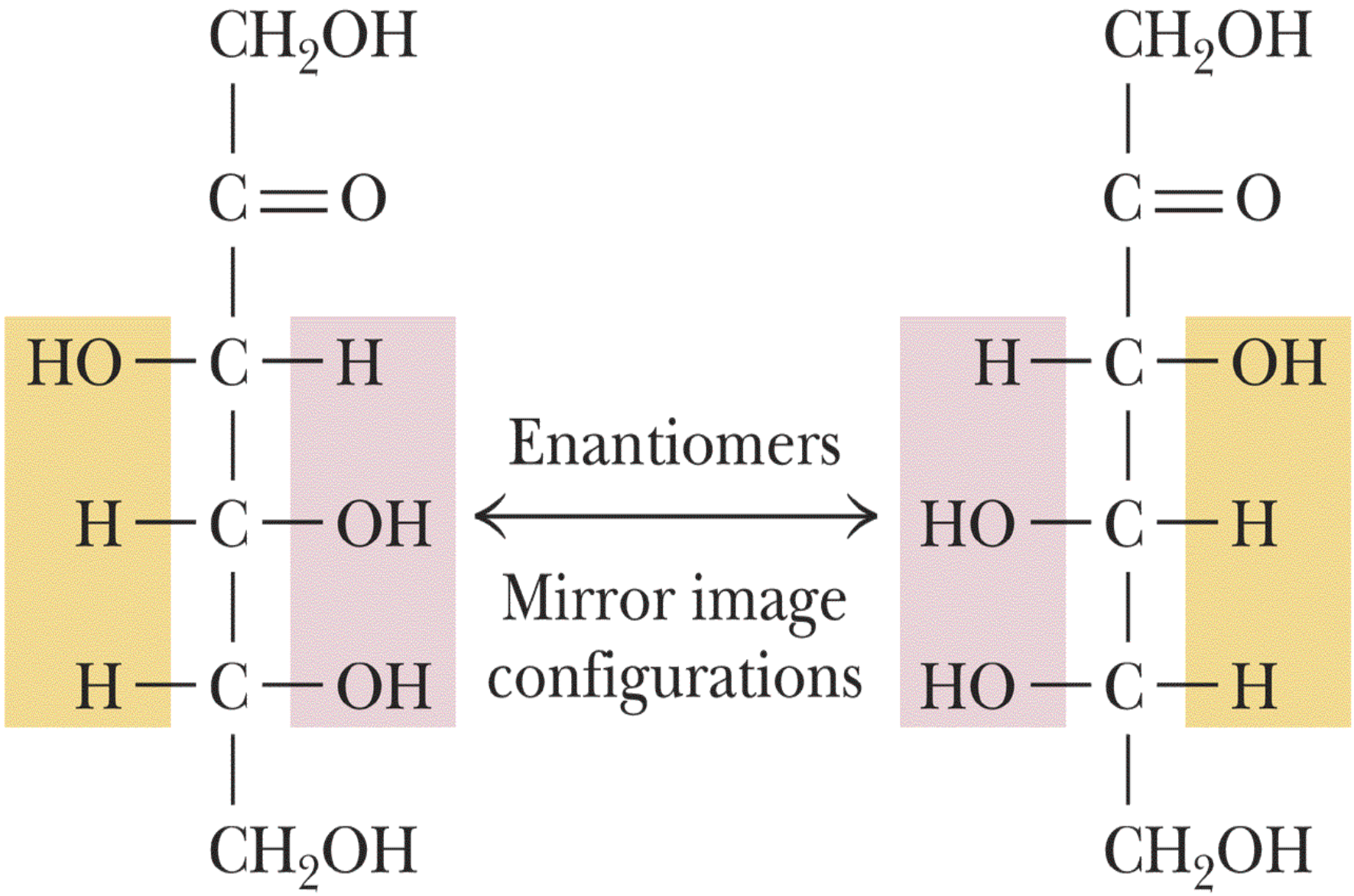
Ketohexose
n = 3

Heptoses

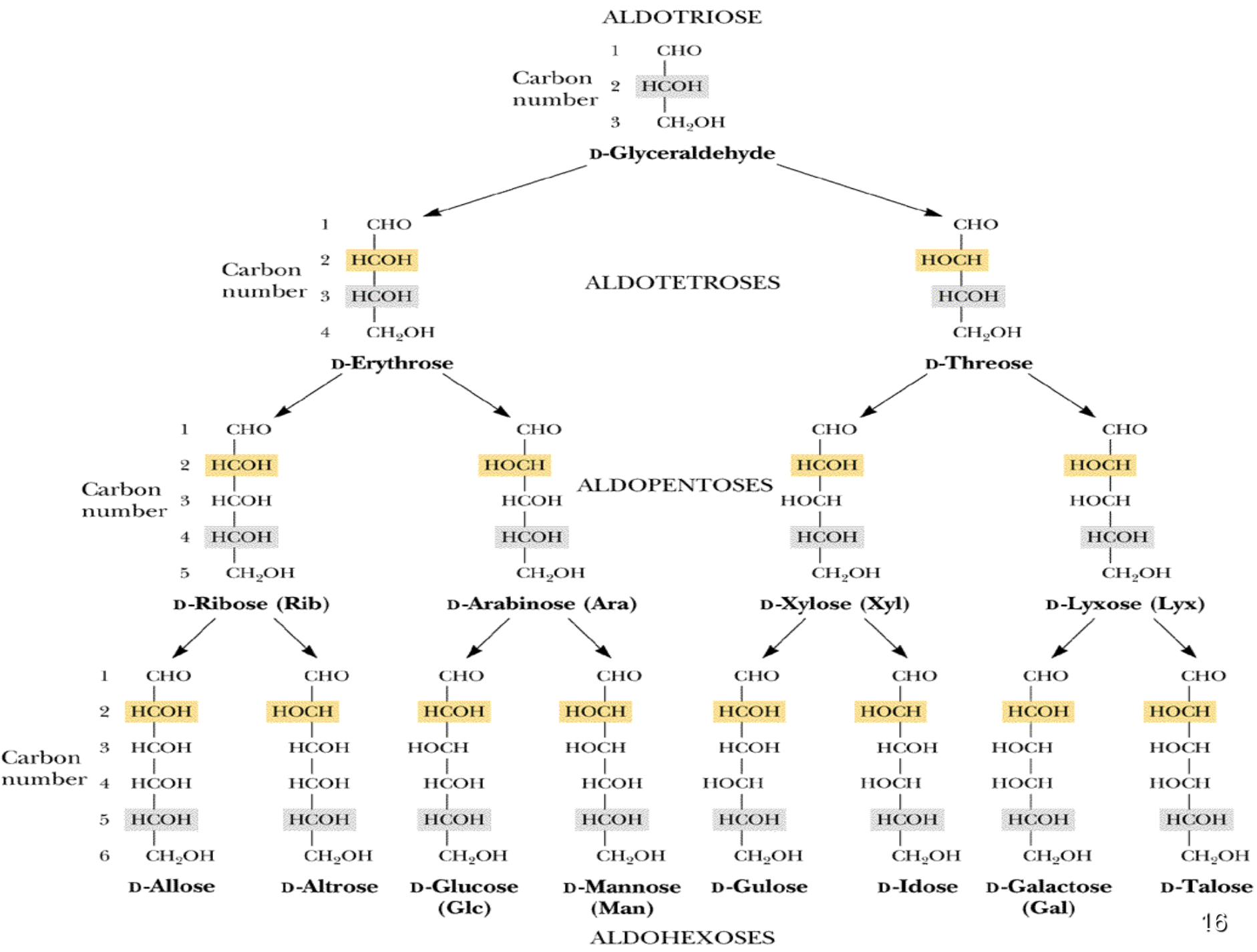
- Sedoheptulose has the same structure as fructose, but it has one extra carbon.

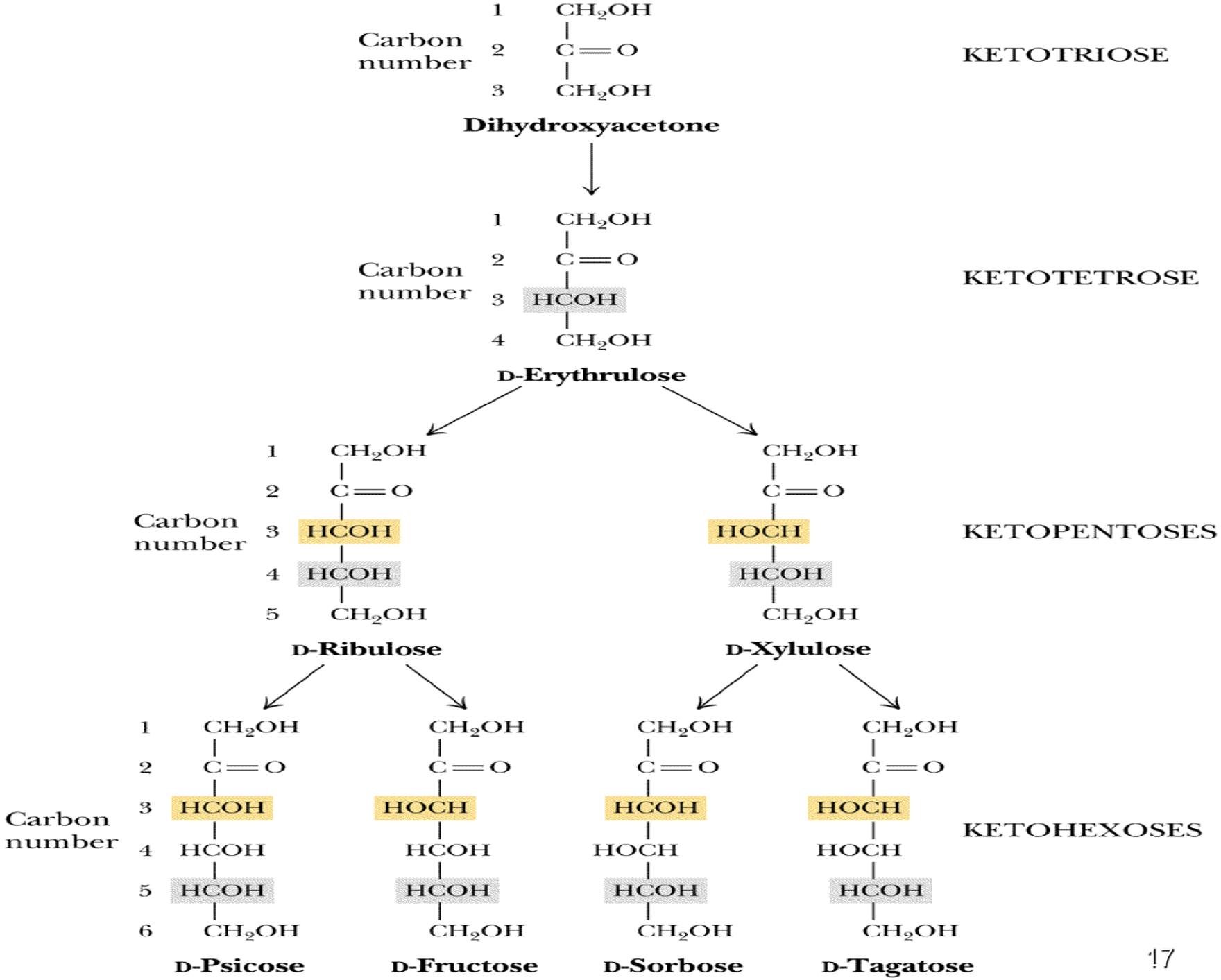


D-Sedoheptulose



D-Fructose **L-Fructose**


ALDOTRIOSE
Carbon number
1 CHO
2 HCOH
3 CH2OH
D-Glyceraldehyde
ALDOTETROSES
Carbon number
1 CHO
2 HCOH
3 HCOH
4 CH2OH
D-Erythrose
CHO
HOCH
HCOH
CH2OH
D-Threose
ALDOPENTOSES
Carbon number
1 CHO
2 HCOH
3 HCOH
4 HCOH
5 CH2OH
D-Ribose (Rib)
CHO
HOCH
HCOH
HCOH
CH2OH
D-Arabinose (Ara)
CHO
HCOH
HOCH
HCOH
CH2OH
D-Xylose (Xyl)
CHO
HOCH
HOCH
HCOH
CH2OH
D-Lyxose (Lyx)
ALDOHEXOSES
Carbon number
1 CHO
2 HCOH
3 HCOH
4 HCOH
5 HCOH
6 CH2OH
D-Allose
CHO
HOCH
HCOH
HCOH
HCOH
CH2OH
D-Altrose
CHO
HCOH
HOCH
HCOH
HCOH
CH2OH
D-Glucose (Glc)
CHO
HOCH
HOCH
HCOH
HCOH
CH2OH
D-Mannose (Man)
CHO
HCOH
HCOH
HOCH
HCOH
CH2OH
D-Gulose
CHO
HOCH
HCOH
HOCH
HCOH
CH2OH
D-Idose
CHO
HCOH
HOCH
HOCH
HCOH
CH2OH
D-Galactose (Gal)
CHO
HOCH
HOCH
HOCH
HCOH
CH2OH
D-Talose


Carbon number
KETOTRIOSE
Dihydroxyacetone
KETOTETROSE
D-Erythrulose
KETOPENTOSES
D-Ribulose
D-Xylulose
KETOHEXOSES
D-Psicose
D-Fructose
D-Sorbose
D-Tagatose

Monosaccharides

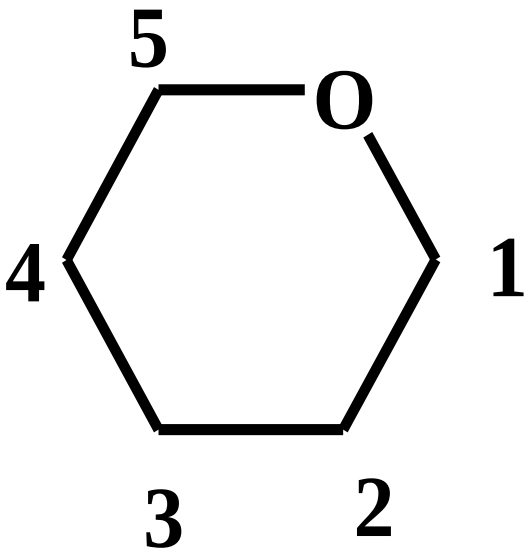
The most important monosaccharide is **Glucose**.

- Fructose and Galactose are also monosaccharides, they all have the same chemical formula but different structures.

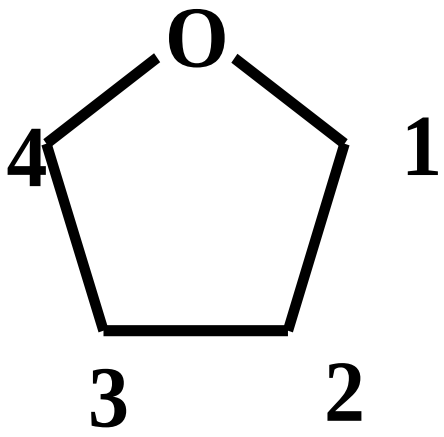
Cyclization of monosaccharides

There are 2 main cyclic forms:

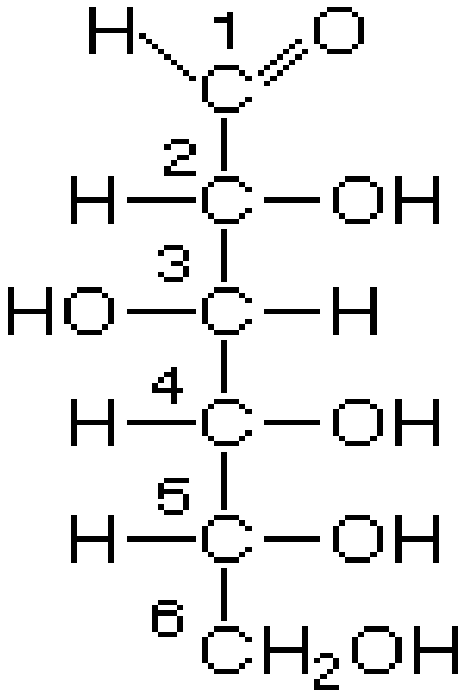
pyranose



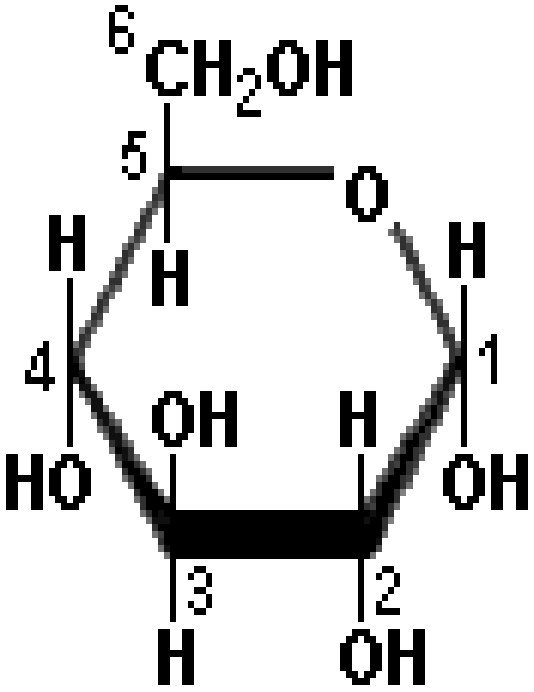
furanose



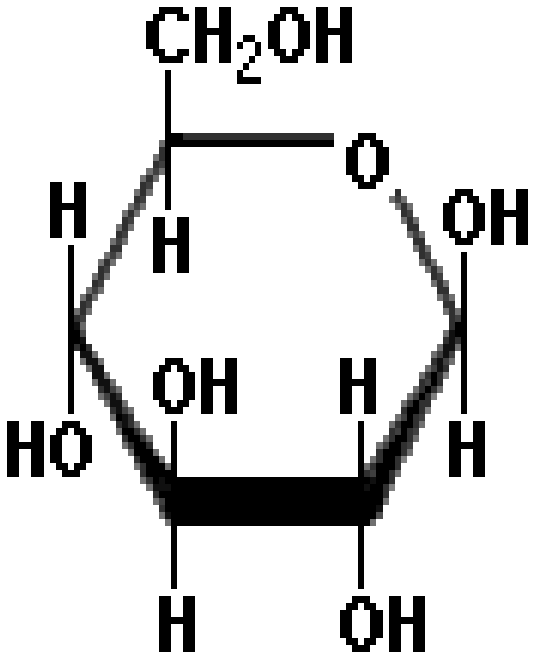
Cyclization of glucose



D-Glucose



α-D-Glucose



β-D-Glucose

Oxidation reactions

Aldoses can be oxidized to 3 types of acids:

- *Aldonic acids*: aldehyde group is converted to a carboxyl group: glucose becomes *gluconic acid*.
- *Uronic acids*: aldehyde group is left intact and primary alcohol at the other end is oxidized to COOH: glucose becomes *glucuronic acid* & galactose becomes *galacturonic acid.*

Oxidation reactions

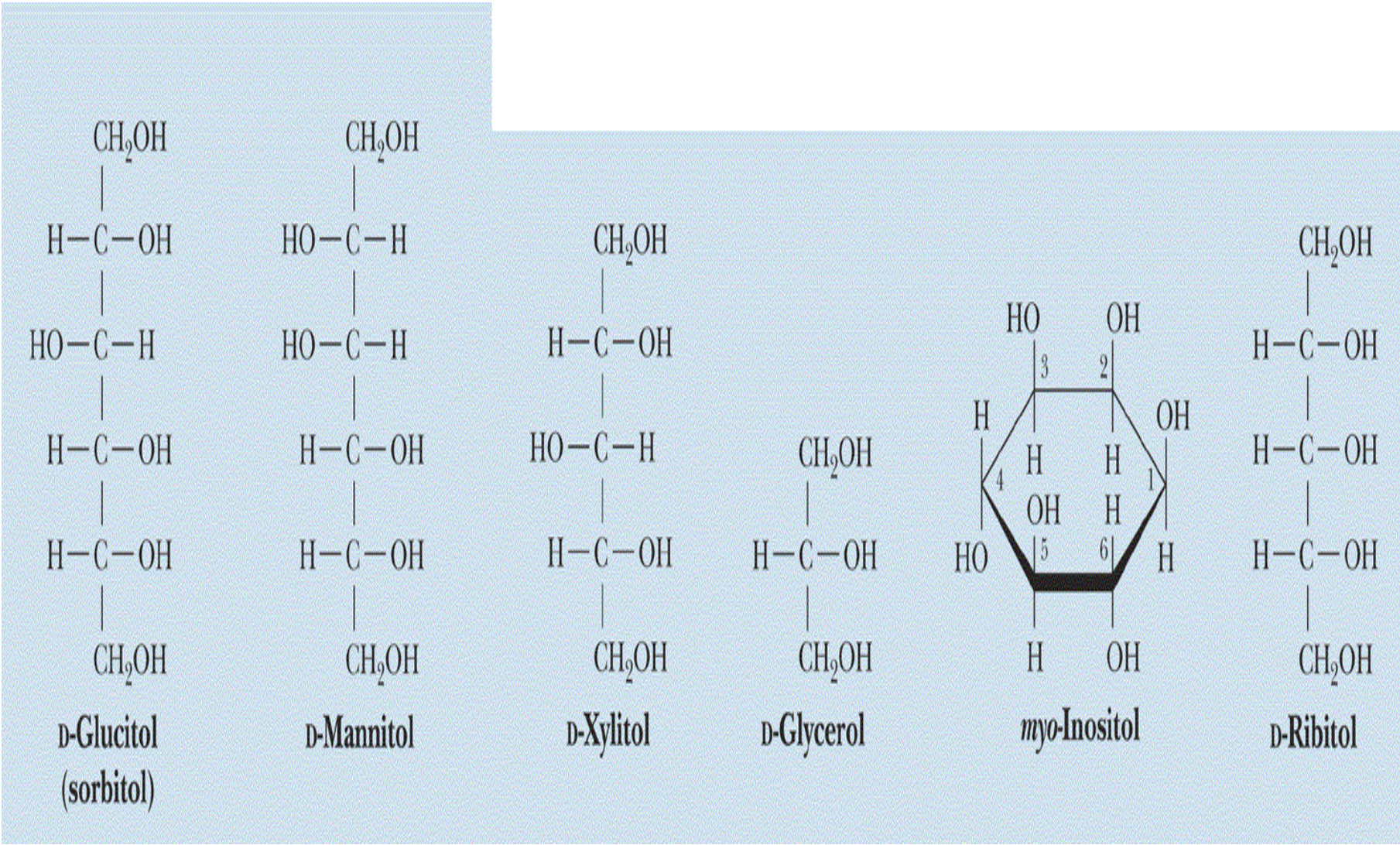
- *Saccharic acids* (glycaric acids)- oxidation at both ends of monosaccharide)
  - Glucose= saccharic acid
  - Galactose= mucic acid
  - Mannose= mannaric acid

Reduction reactions

The reduction reaction can be either done catalytically (hydrogen and a catalyst) or enzymatically:

- the resultant product is a polyol or sugar alcohol (alditol)
- glucose form *sorbitol (glucitol)*
- mannose forms *mannitol*
- fructose forms a mixture of *mannitol* & *sorbitol*
- glyceraldehyde gives *glycerol*

Structures of some sugar alcohols



Sugar alcohols

Sugar alcohols are very useful intermediates:

- Glycerol is used as a humectant and can be nitrated to nitroglycerin.
- Sorbitans are converted to detergents known as spans and tweens (used in emulsification procedures)

Sugar alcohols

Sugar alcohols are very useful intermediates:

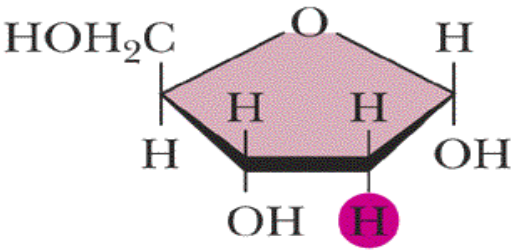
- Sorbitol can also be dehydrated to 1,4,3,6-dianhydro-D-sorbitol (isosorbide) which is nitrated to isosorbide-dinitrate *(ISDN)* and isosorbide-mononitrate*(ISMN).*

  Both ISDN & ISMN are used in treatment of angina.

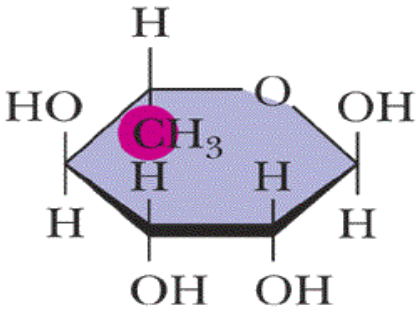
Deoxy sugars

These are monosaccharides which lack one or more hydroxyl groups on the molecule

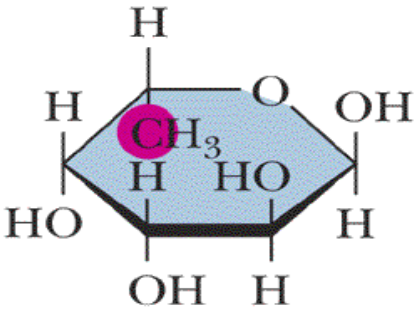
- one commonly occurring deoxy sugar is *2'-deoxy ribose* which is the sugar found in DNA
- 6-deoxy-L-mannose (*L-rhamnose*) is used as a *fermentative reagent in bacteriology*



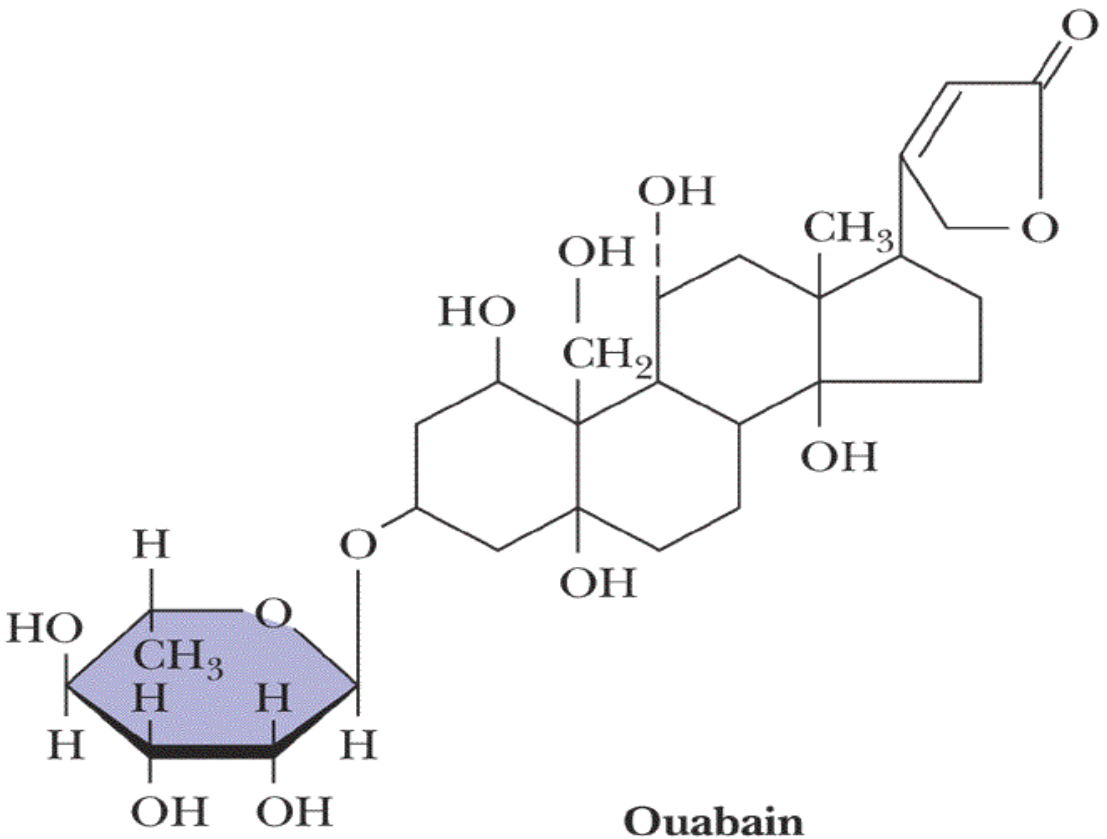
2-Deoxy-α-D-Ribose



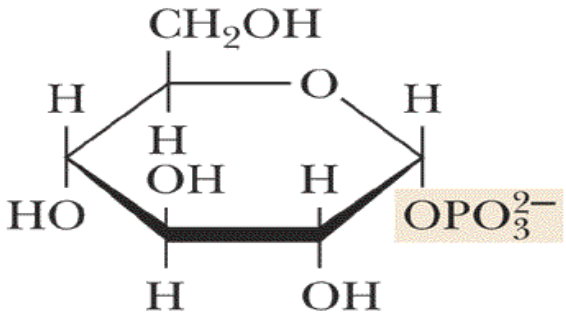
α-L-Rhamnose (Rha)



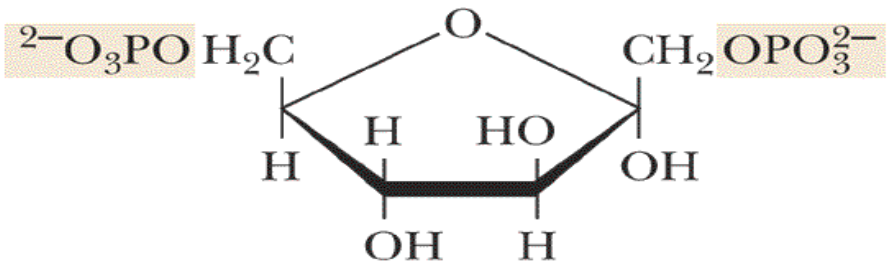
α-L-Fucose (Fuc)



Ouabain

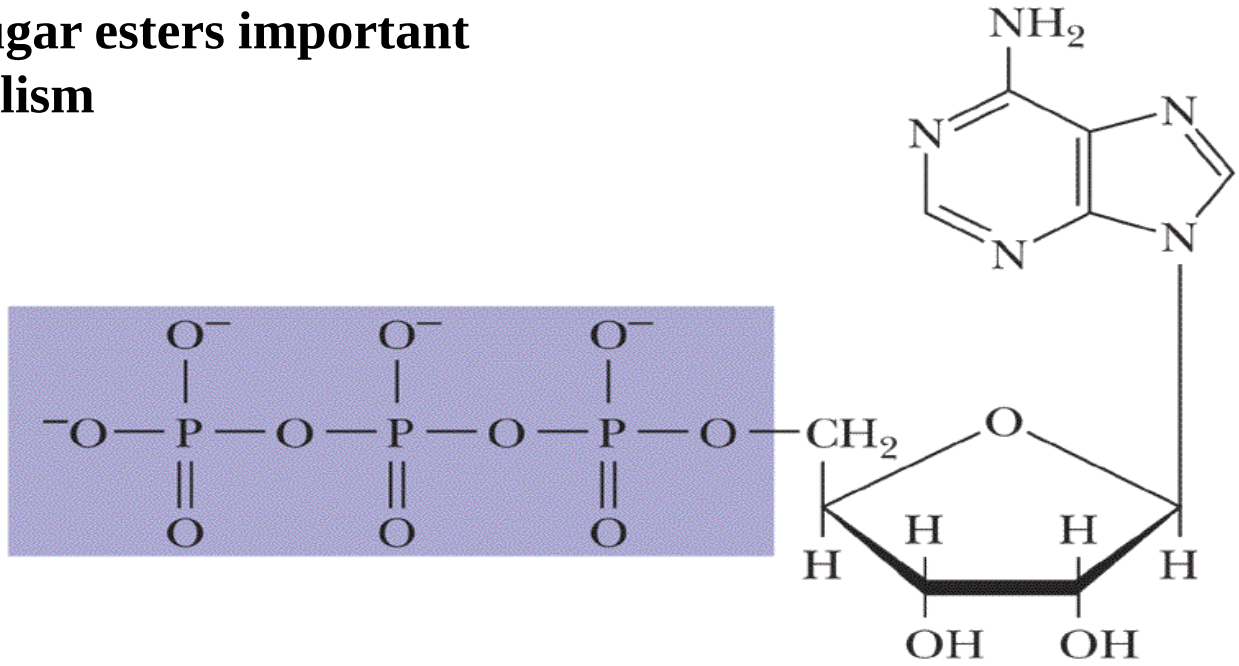


α-D-Glucose-1-phosphate



α-D-Fructose-1,6-bisphosphate

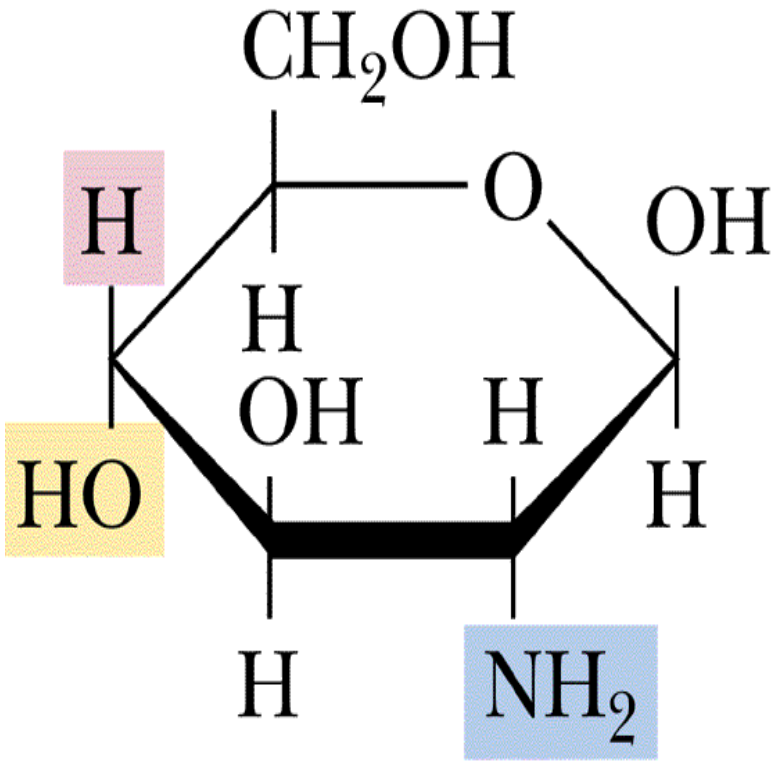
Several sugar esters important in metabolism



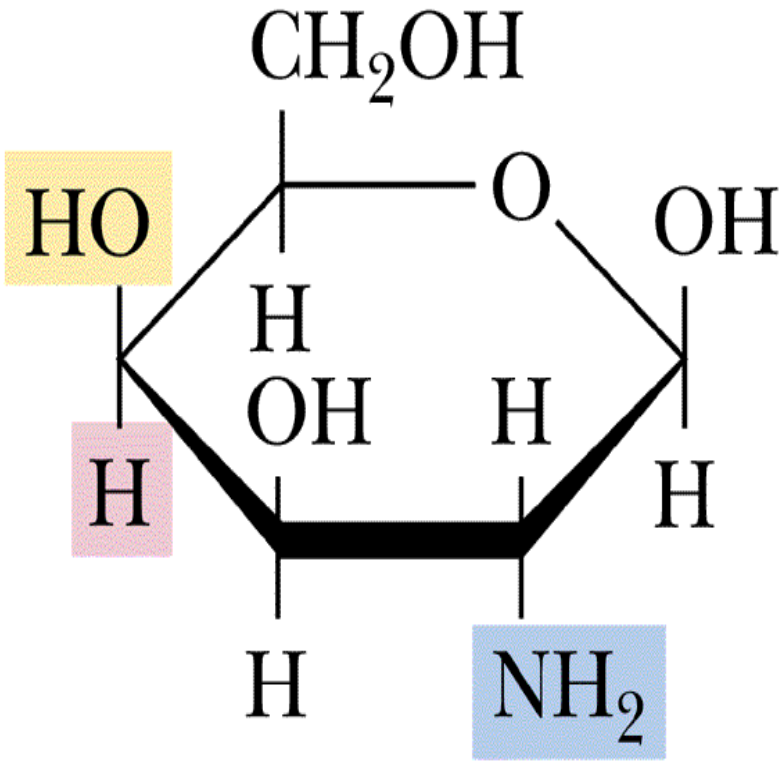
Adenosine-5'-triphosphate

Special monosaccharides: amino sugars

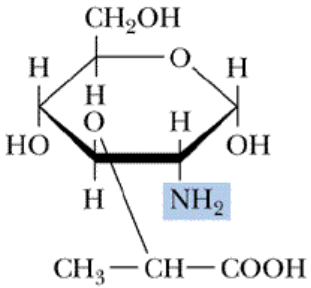
They are constituents of mucopolysaccharides



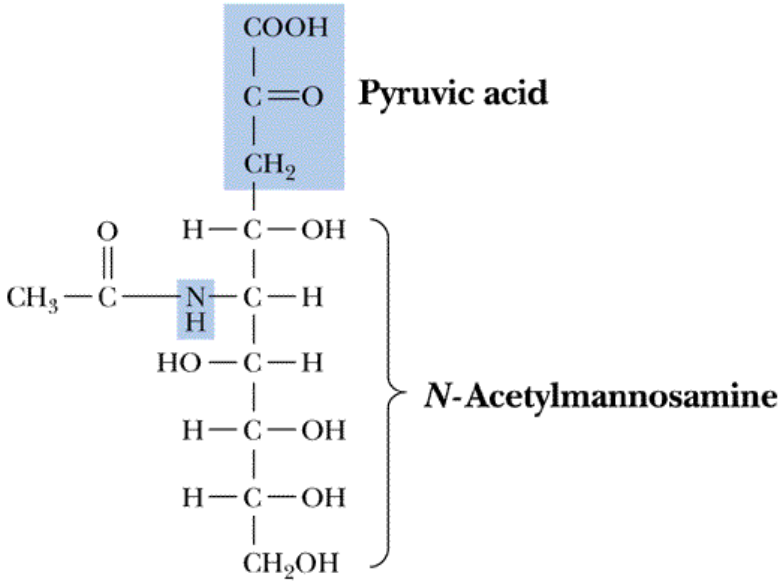
β-D-Glucosamine



β-D-Galactosamine



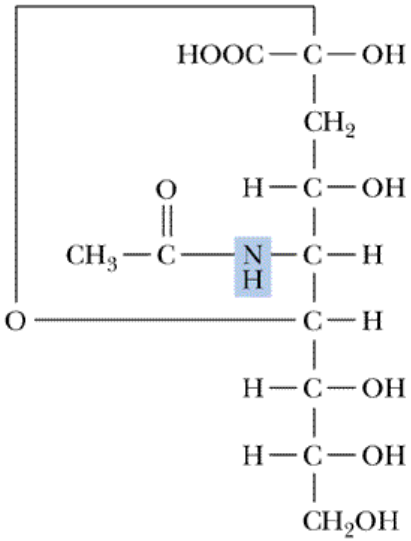
Muramic acid



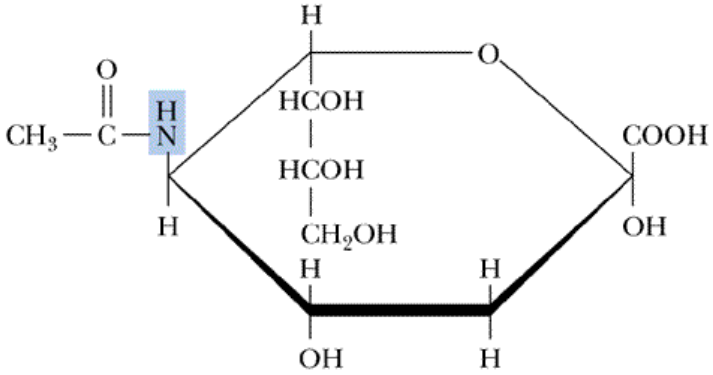
Pyruvic acid

N-Acetylmannosamine

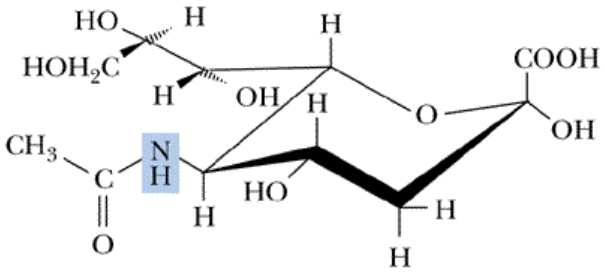
N-Acetyl-D-neuraminic acid (NeuNAc)



Fischer projection



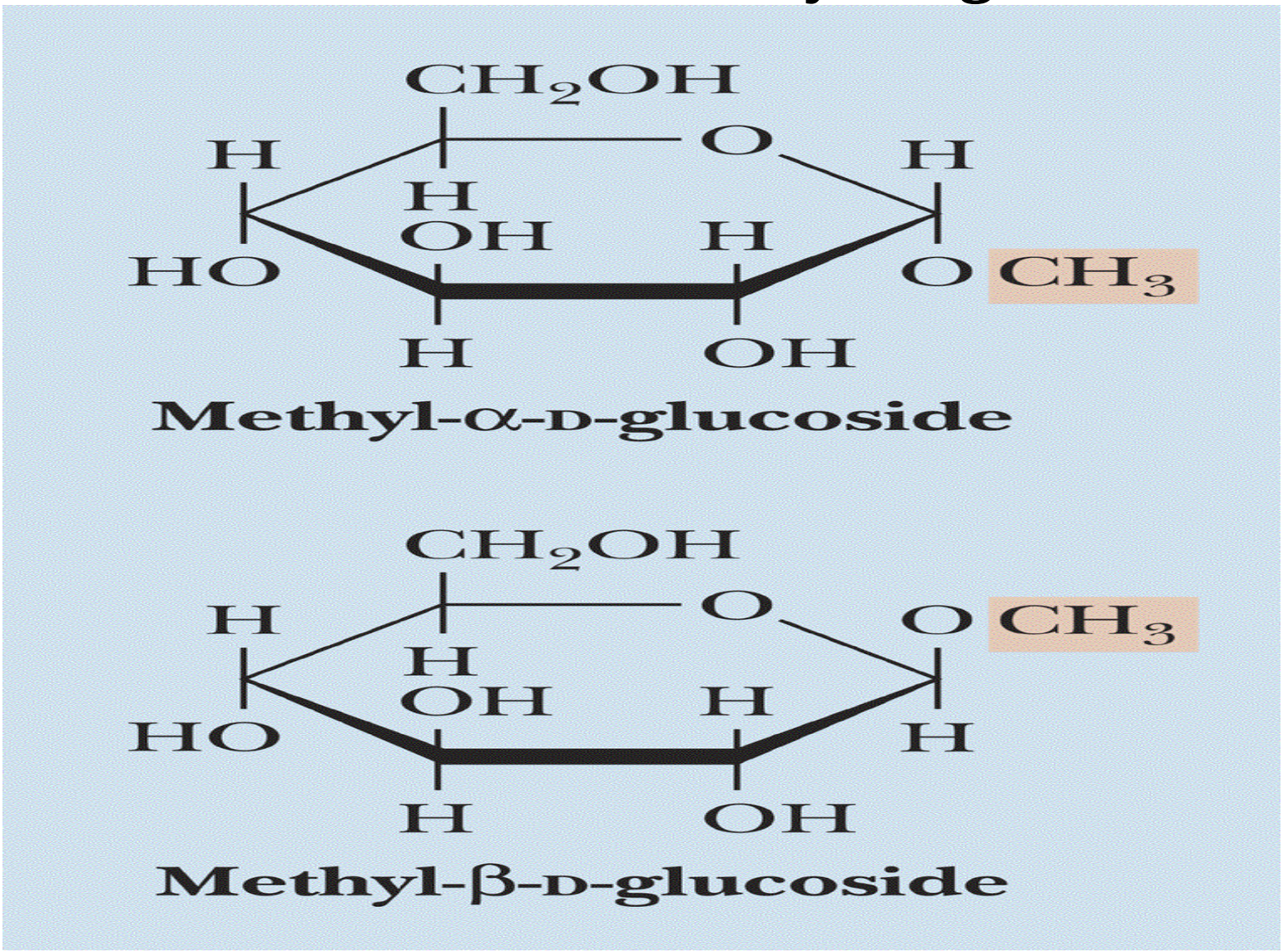
Haworth projection



Chair conformation

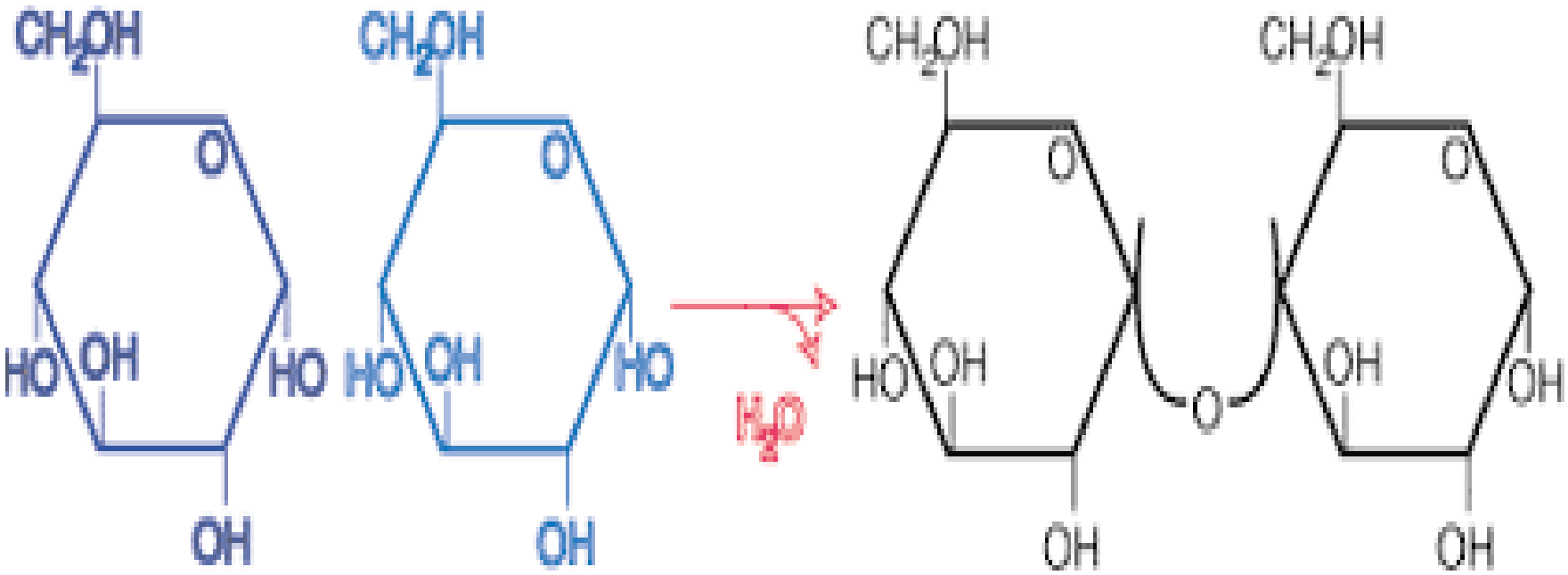
N-Acetyl-D-neuraminic acid (NeuNAc), a sialic acid

The anomeric forms of methyl-D-glucoside



Oligosaccharides

Glycosidic bond



Oligosaccharides

The most common are the disaccharides:

Sucrose, lactose & maltose

Maltose is composed of 2 molecules of D-glucose

Lactose is composed of a molecule of glucose & a molecule of galactose.

Sucrose is composed of a moledule of glucose & a molecule of fructose.

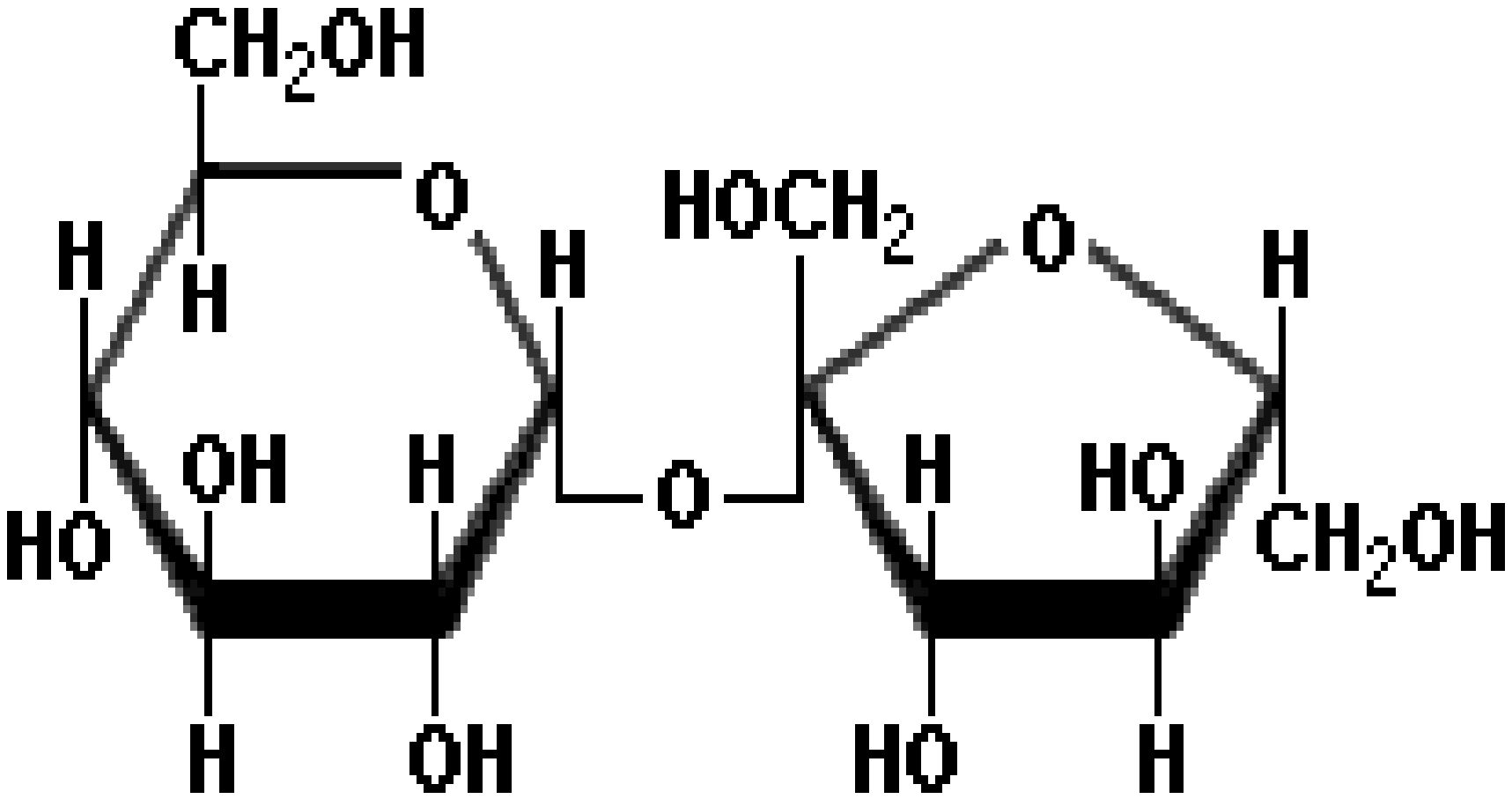
Sucrose

a-D-glucopyranosido-b-D-fructofuranoside

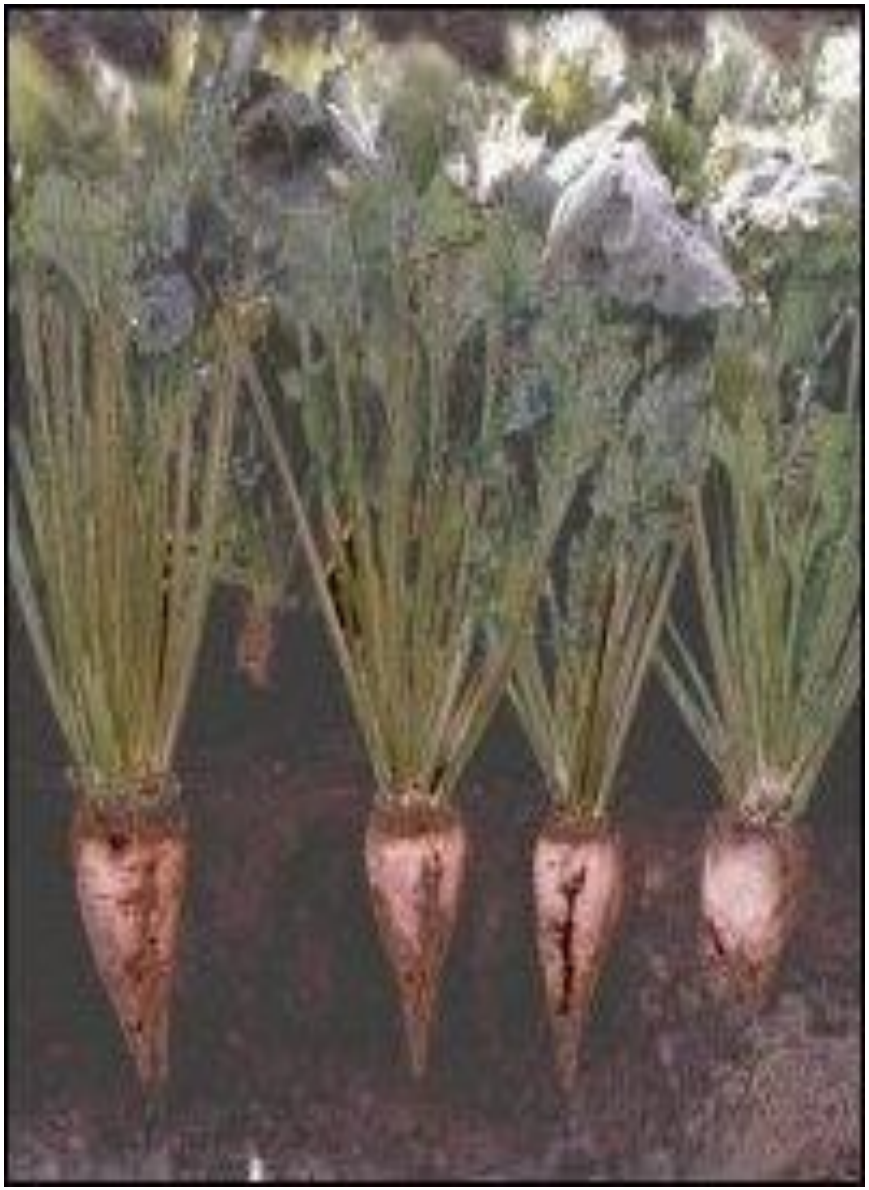
b-D-fructofuranosido-a-D-glucopyranoside

- also known as tablet sugar
- commercially obtained from sugar cane or sugar beet.

Sucrose structure



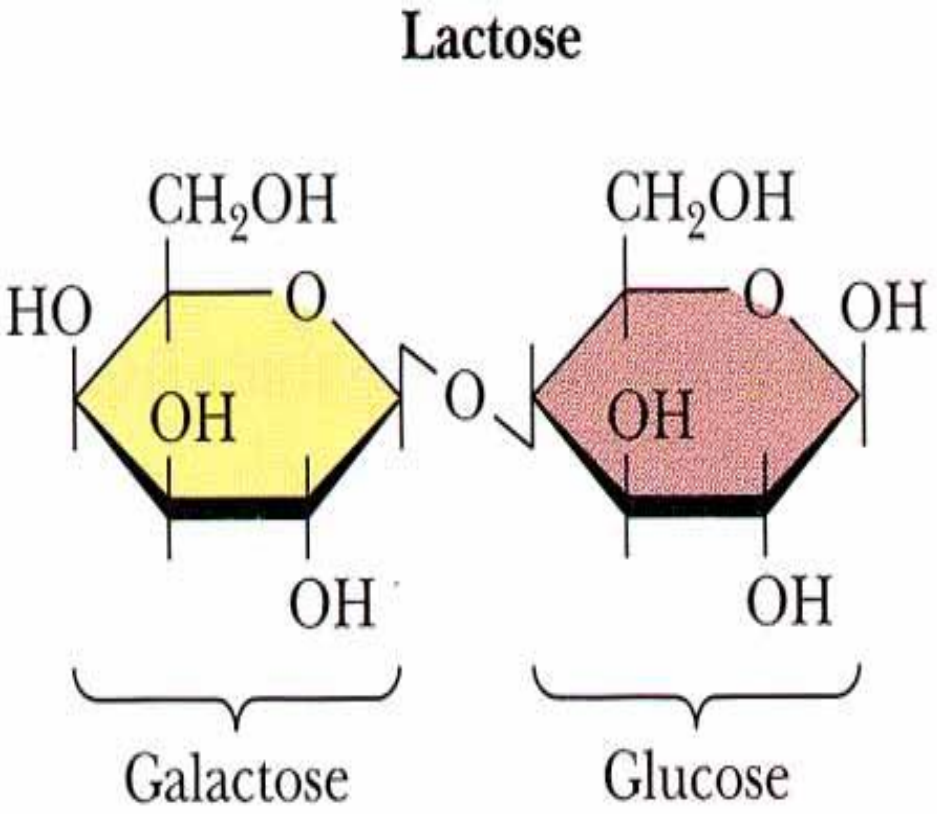
Sugar cane (canne à sucre)



Sugar beet (betterave)

Lactose

- Glucose-galactose linked by β 1-4 glycosidic bond.
- Galactose opens and closes so REDUCING sugar



Lactose

β-D-galactose joined to α–D-glucose via β (1,4) linkage

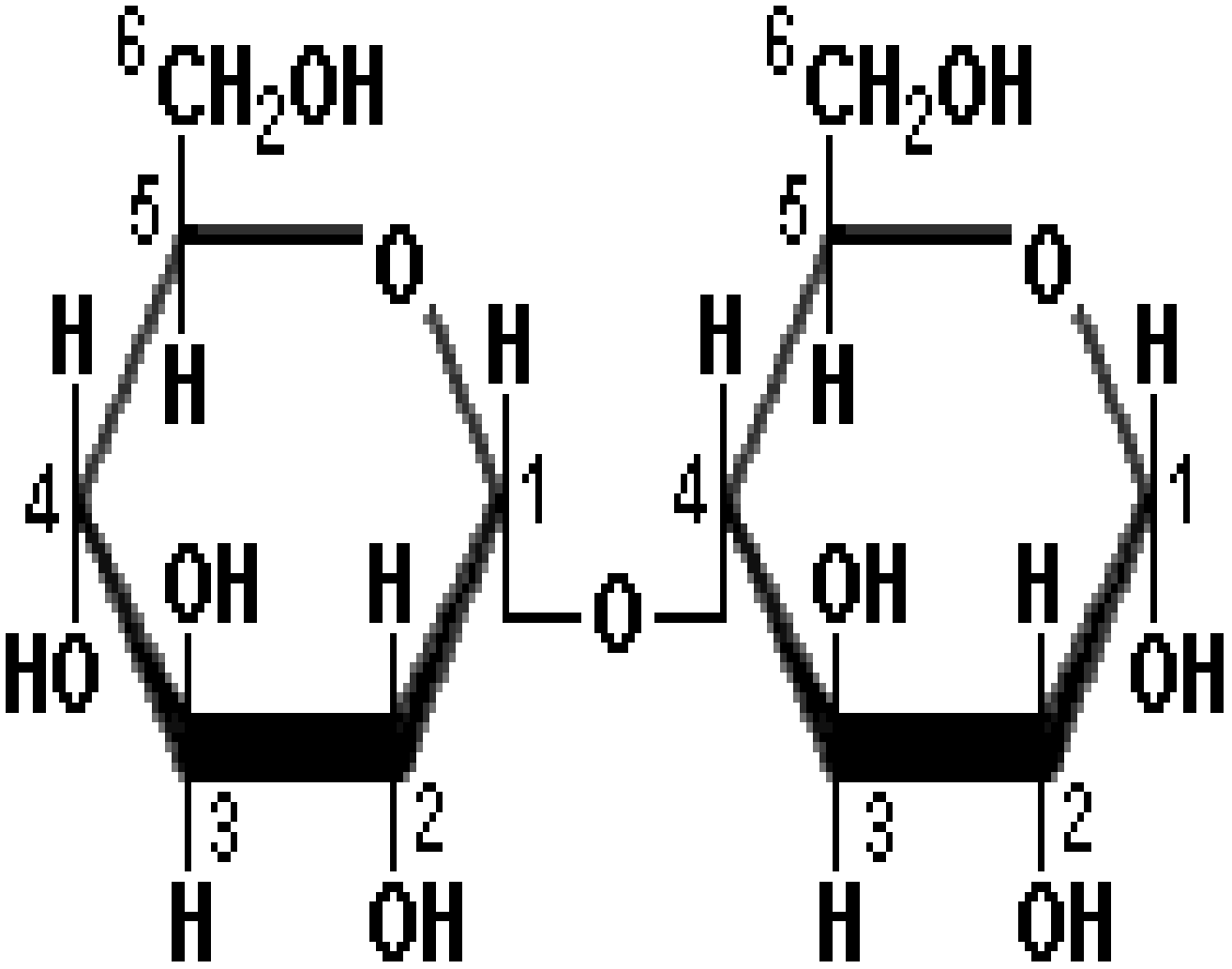
- milk contains the a and b-anomers in a 2:3 ratio

β-lactose is sweeter and more soluble than ordinary α- lactose

Maltose

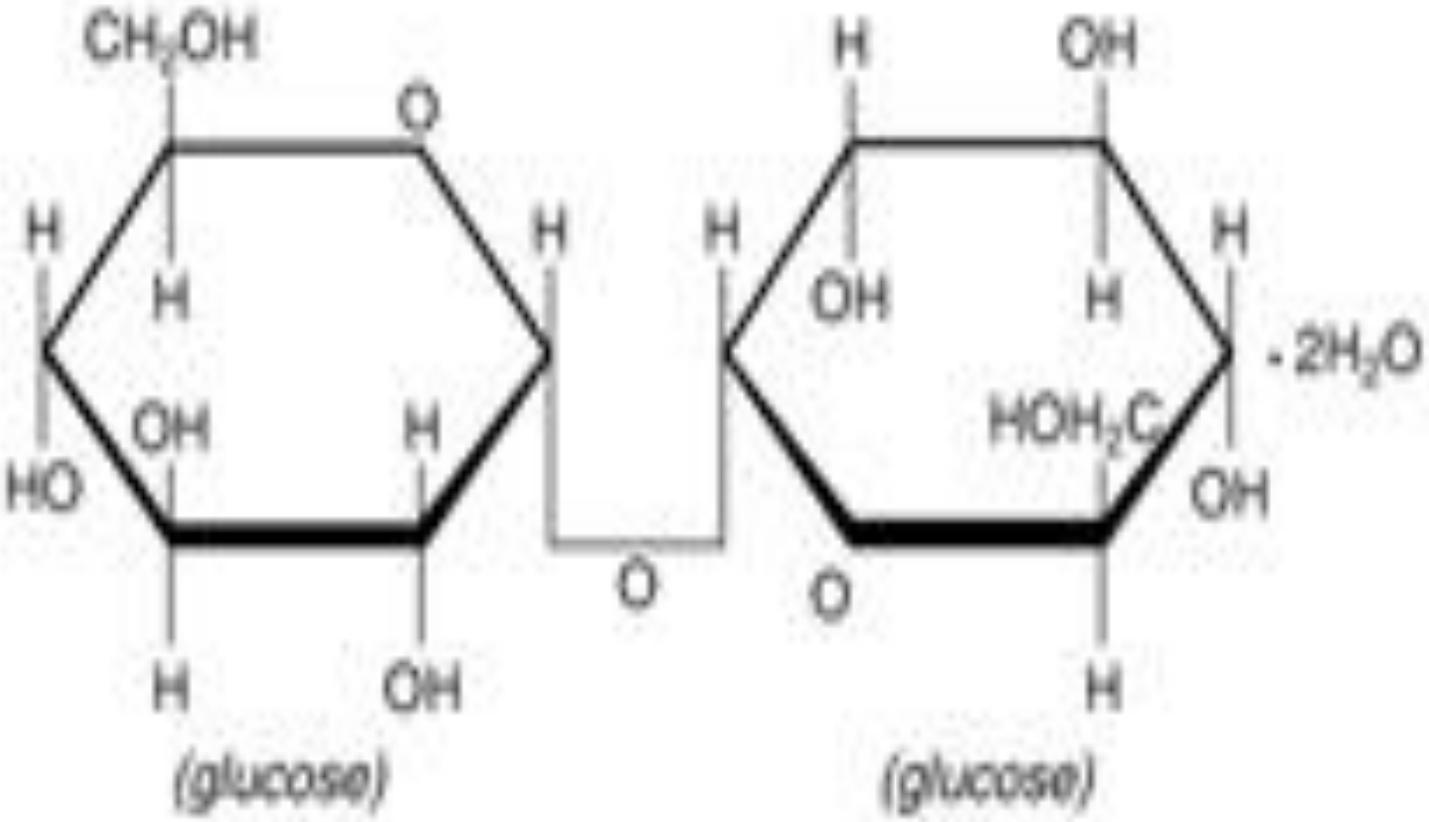
- Two glucose molecules joined via α(1,4) linkage.
- These 2 glucose pyranose rings linked by an α-1-4 bond
- produced by the partial hydrolysis of starch (either salivary amylase or pancreatic amylase).

Maltose



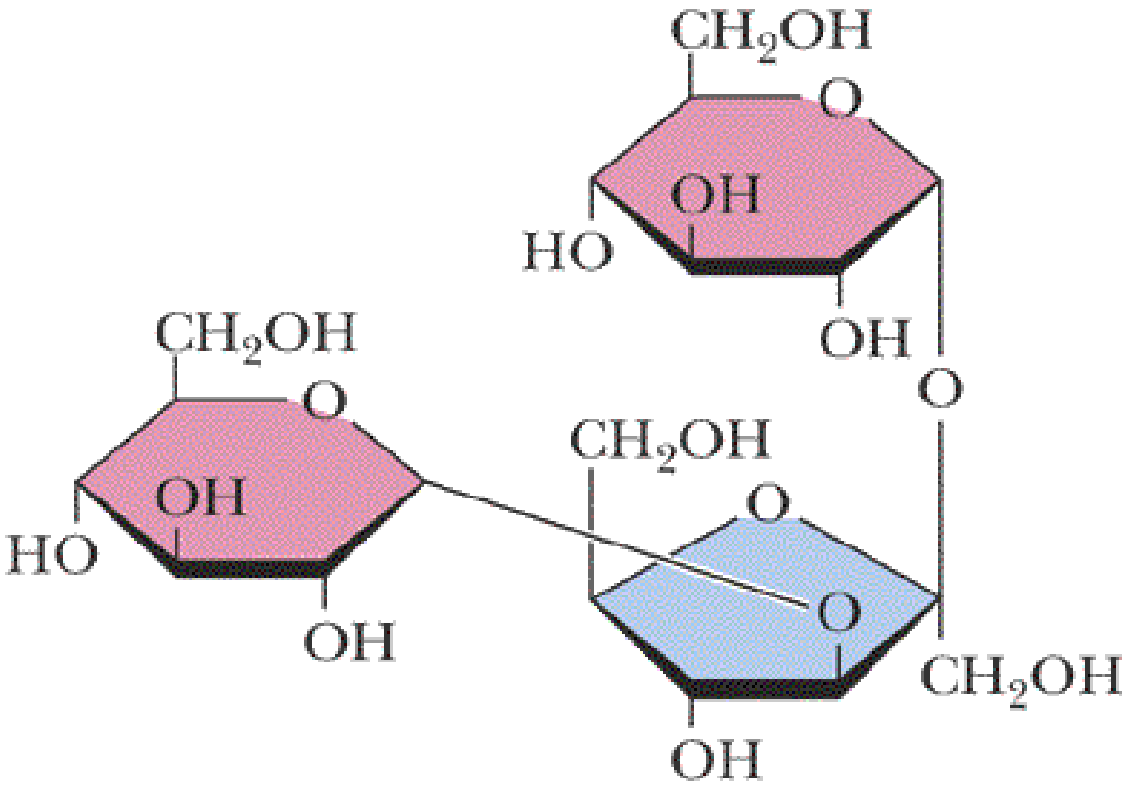
Trehalose

- Two glucose molecules with an α-1,1 linkage
- Non reducing



Melezitose

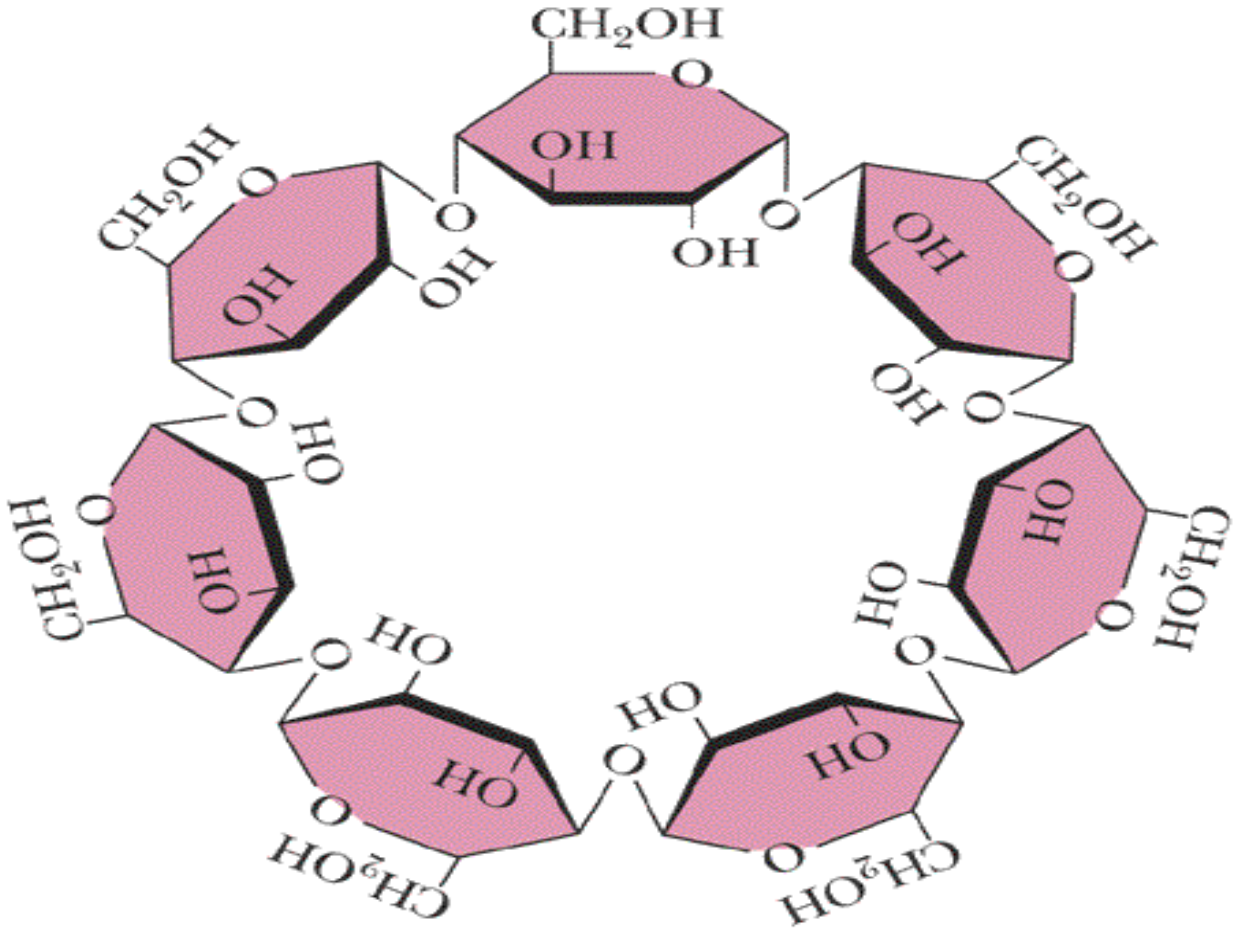
Melezitose (a constituent of honey)



Honey also contains glucose and fructose along with some volatile oils

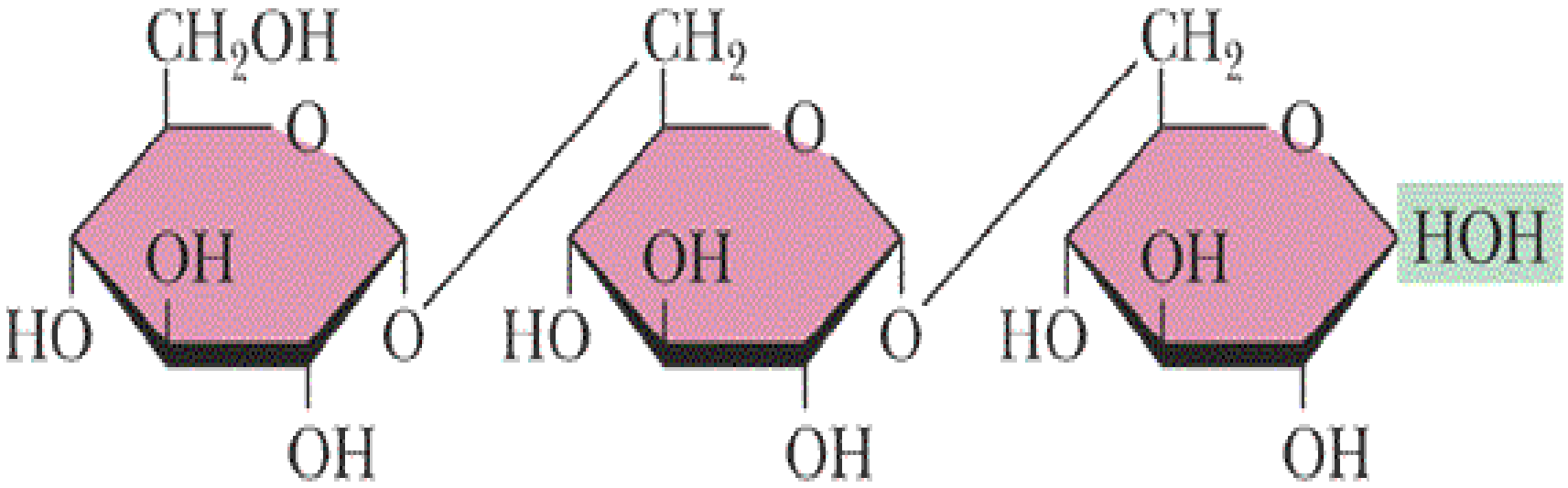
Cycloheptaamylose

Cycloheptaamylose (a breakdown product of useful in chromatographic separations)



Dextrantriose

Dextrantriose (a constituent of saké and honeydew)



Complex carbohydrates

- homoglycans (starch, glycogen, cellulose,)
- heteroglycans (gums, mucopolysaccharides)

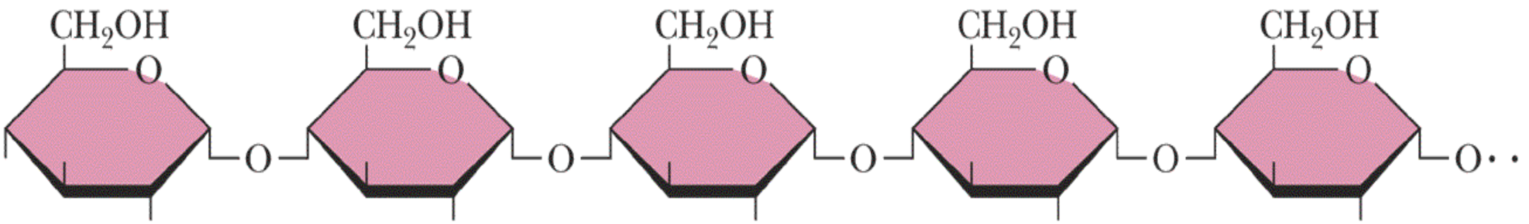
Starch

- most common storage polysaccharide in plants
- composed of 10 – 30% α–amylose and 70-90% amylopectin depending on the source
- the chains are of varying length, having molecular weights from several thousands to half a million

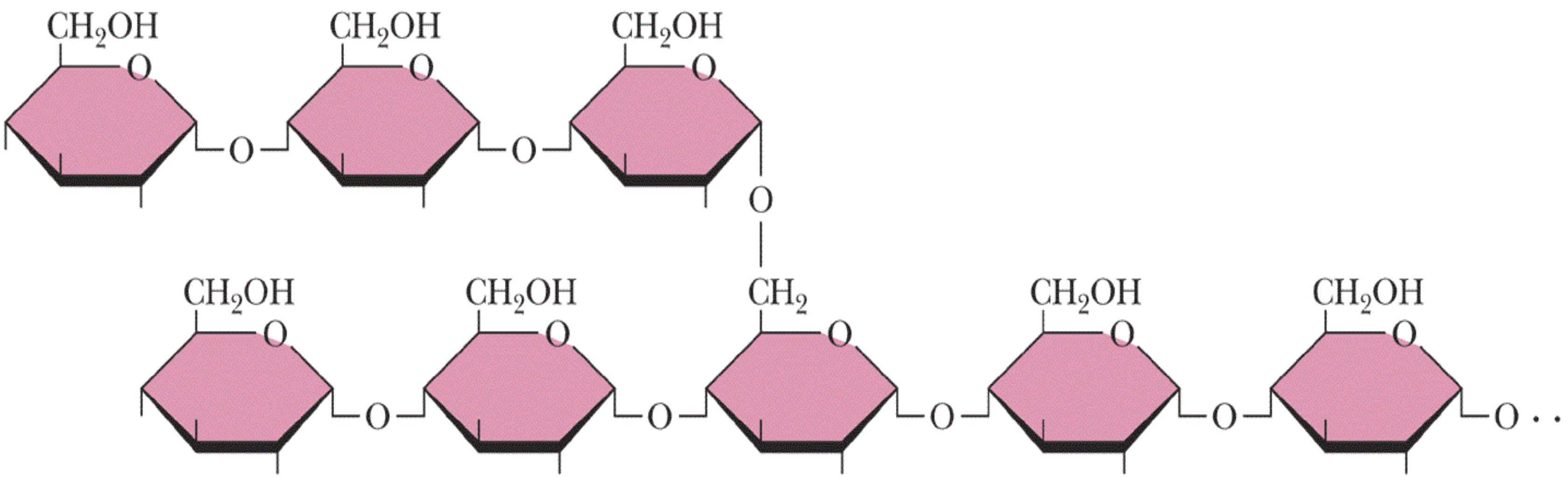
Starch

Amylose and amylopectin are the 2 forms of starch.

Amylopectin is a highly branched structure, with branches occurring every 12 to 30 residues



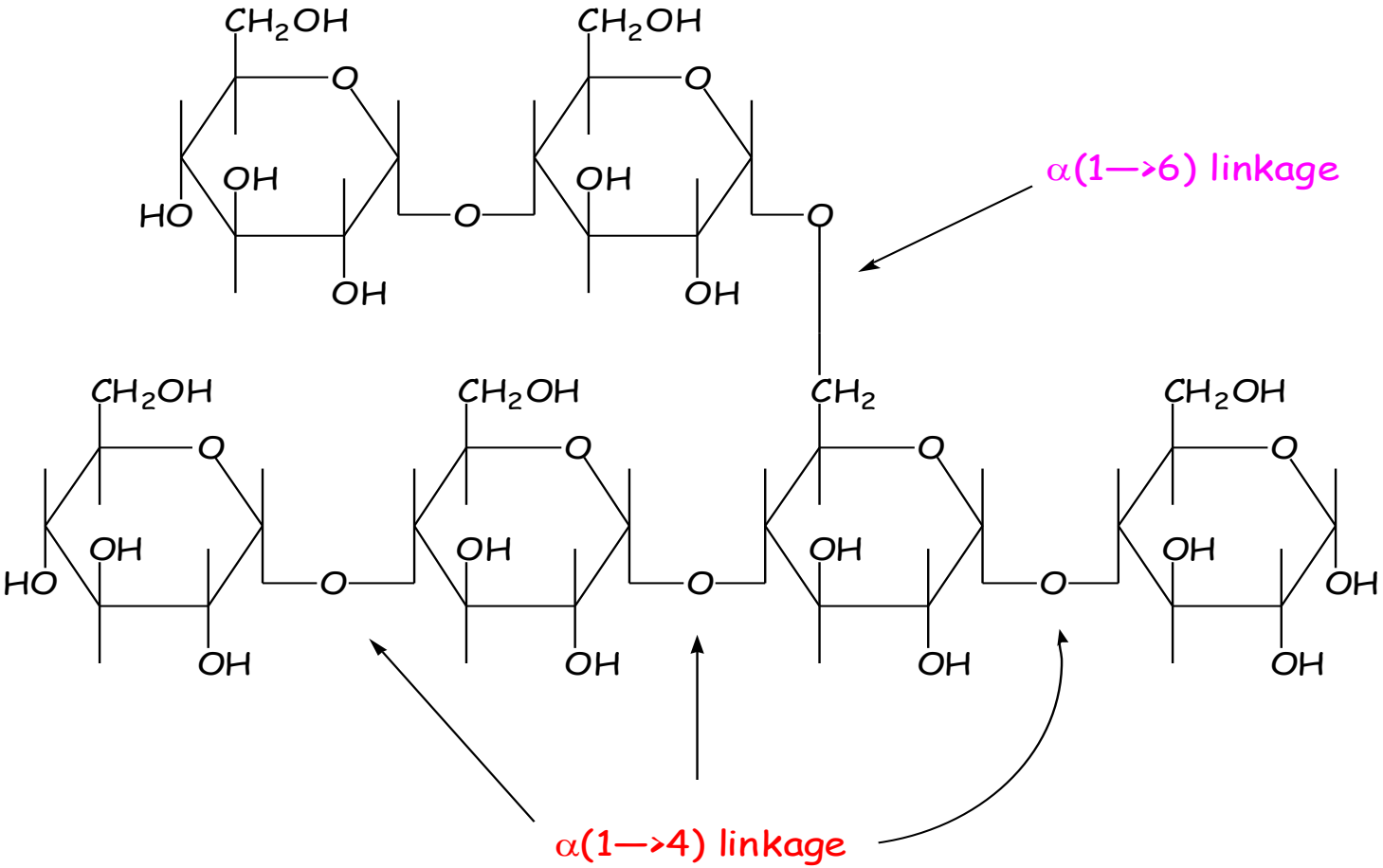
Amylose



Amylopectin

Amylopectin

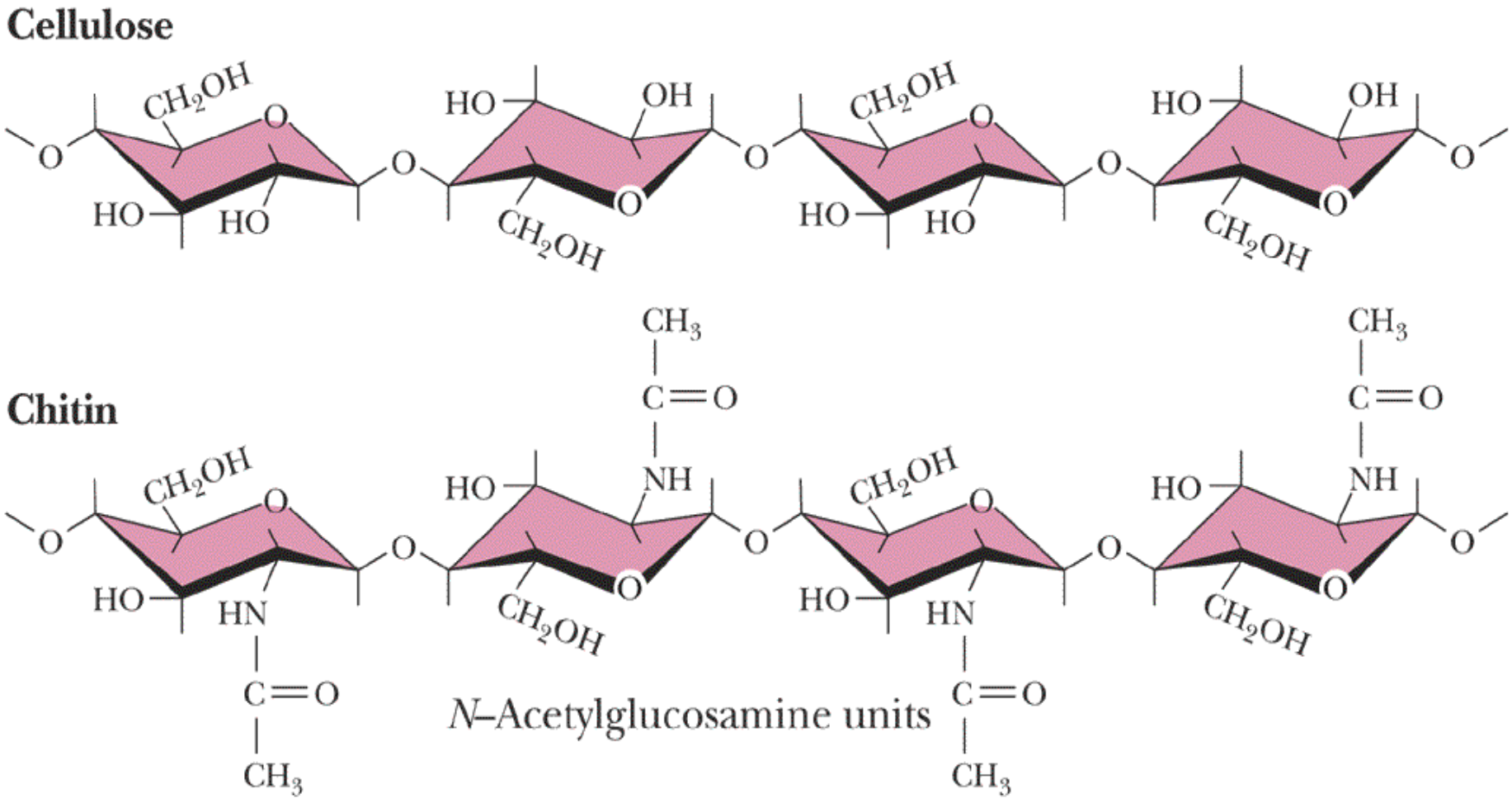
There are 2 types of glucosidic bonds inside amylopectin molecule:



Cellulose

- Polymer of β-D-glucose attached by β(1,4) glucosidic bonds.
- Yields glucose upon complete hydrolysis
- Most abundant of all carbohydrates
  - Cotton flax: 97-99% cellulose
  - Wood: ~ 50% cellulose
- Gives no color with iodine
- Held together with lignin in woody plant tissues

Linear structures of cellulose and chitin (2 most abundant polysaccharides)



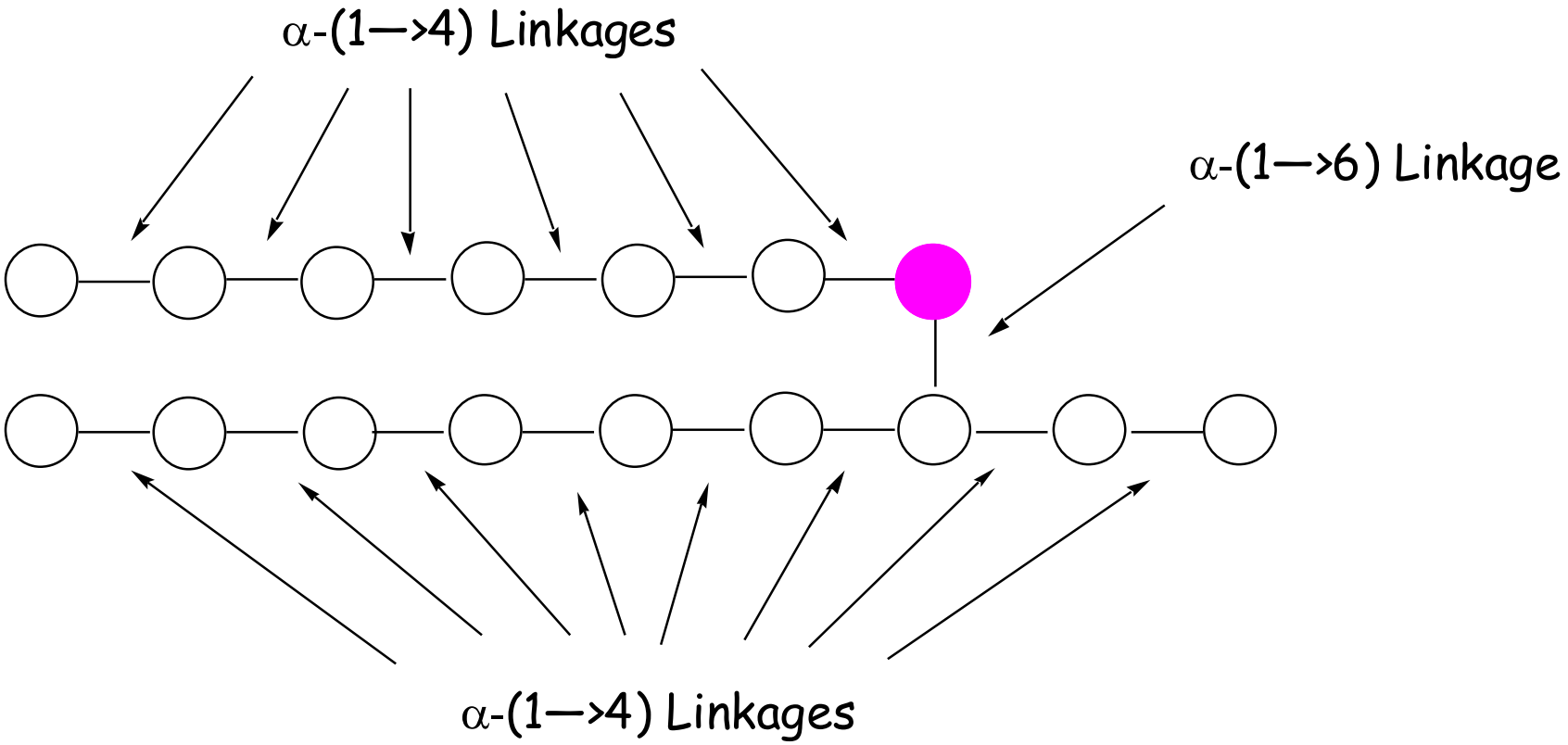
Glycogen

- also known as animal starch
- stored in muscle and liver
- present in cells as granules
- contains both α (1,4) links and α (1,6) branches at every 8 to 12 glucose units.

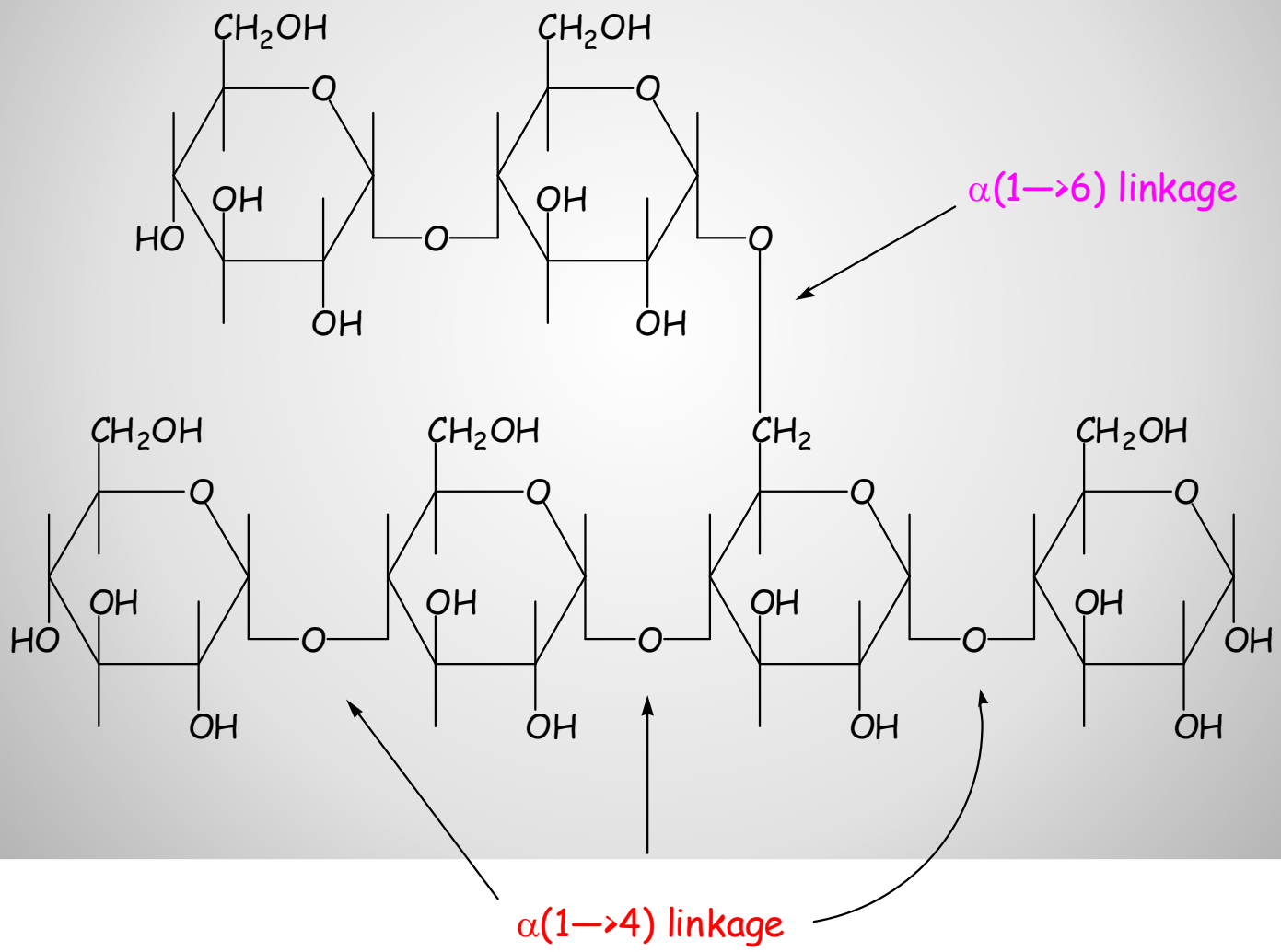
Glycogen

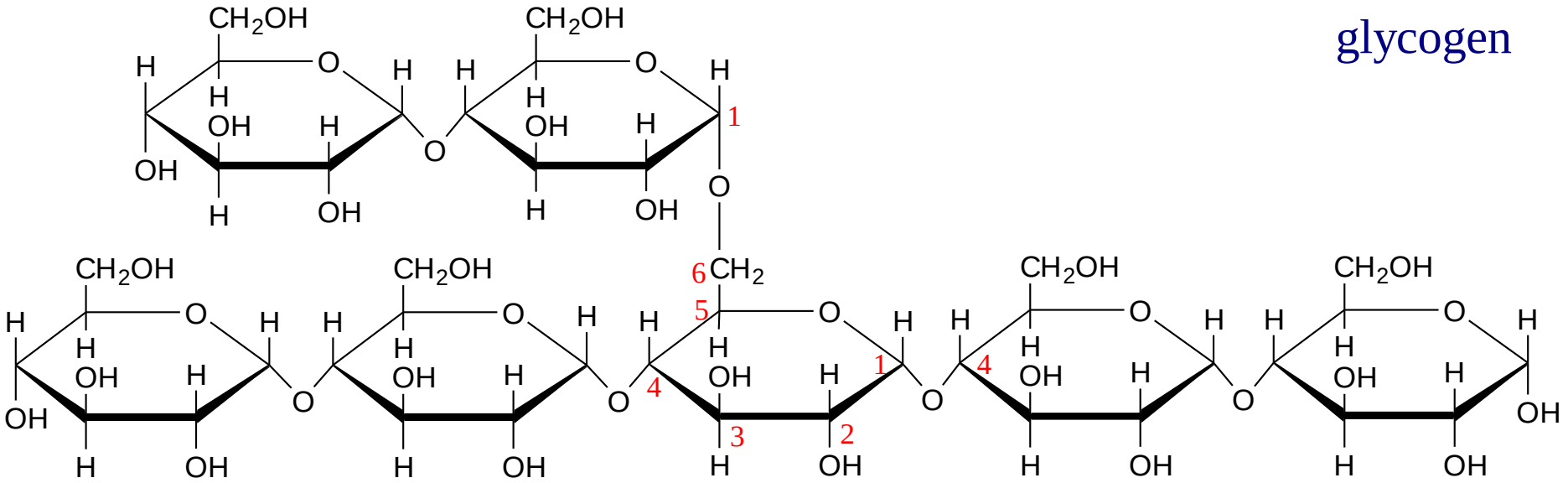
- complete hydrolysis yields glucose
- glycogen and iodine gives a red-violet color
- hydrolyzed by both α and β-amylases and by glycogen phosphorylase

Structure of Glycogen



Glycogen structure





Glycogen is a polymer of **glucose** residues linked by

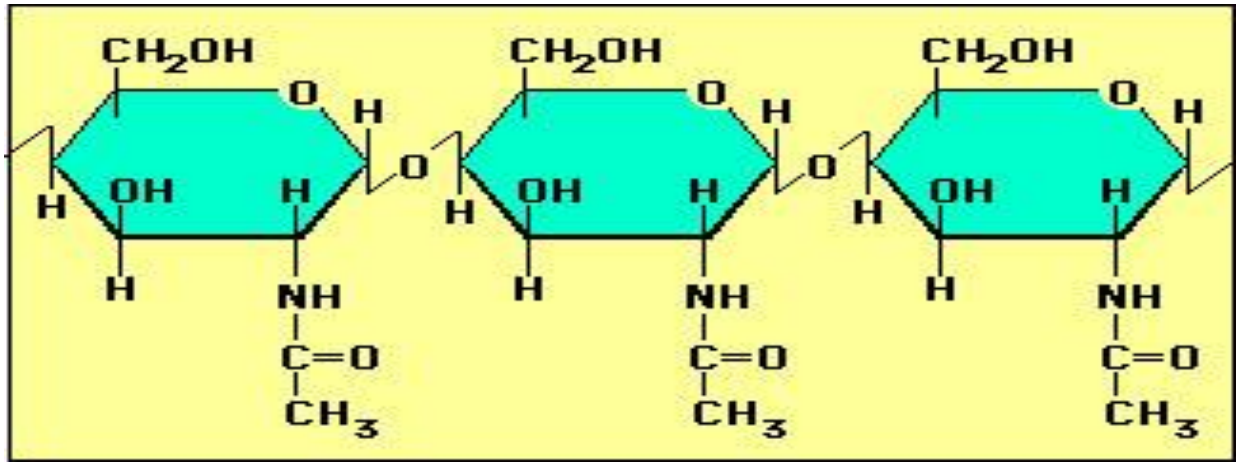
- α(1→4) glycosidic bonds, mainly
- α(1→6) glycosidic bonds, at branch points.

Glycogen chains & branches are longer than shown.

Glucose is stored as glycogen predominantly in **liver** and **muscle** cells.

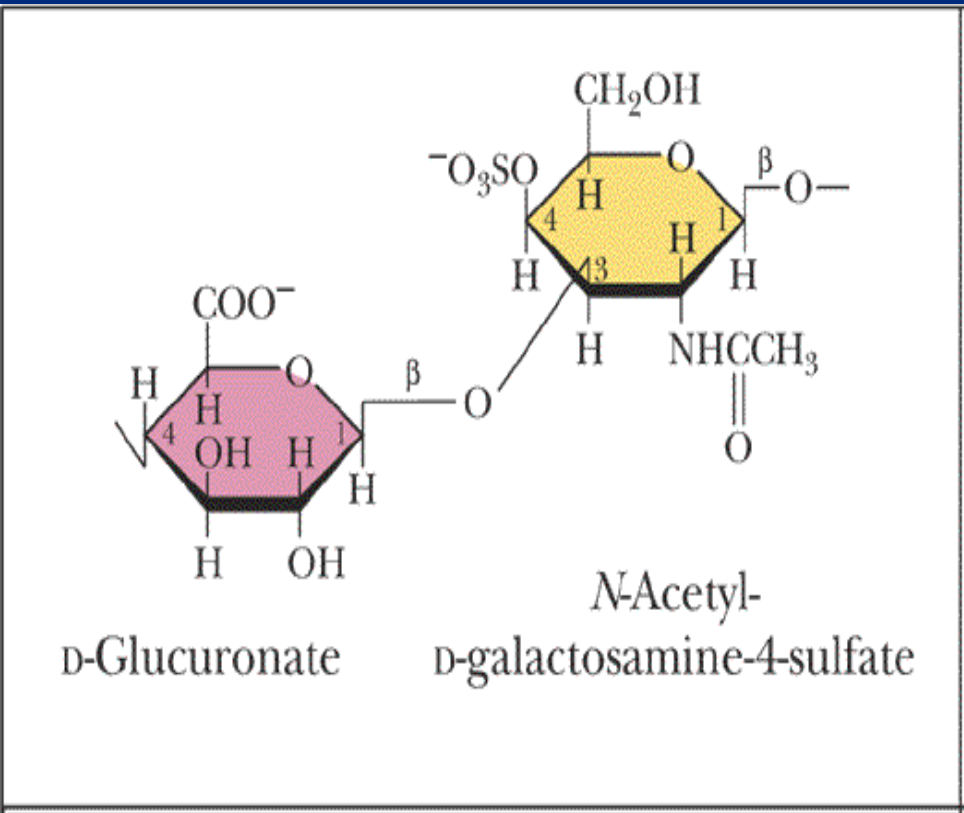
Chitin

- chitin is the second most abundant carbohydrate polymer. It is a structural polysaccharide made from chains of modified glucose.
- *present in the cell wall of fungi, exoskeletons of insects*, etc…..

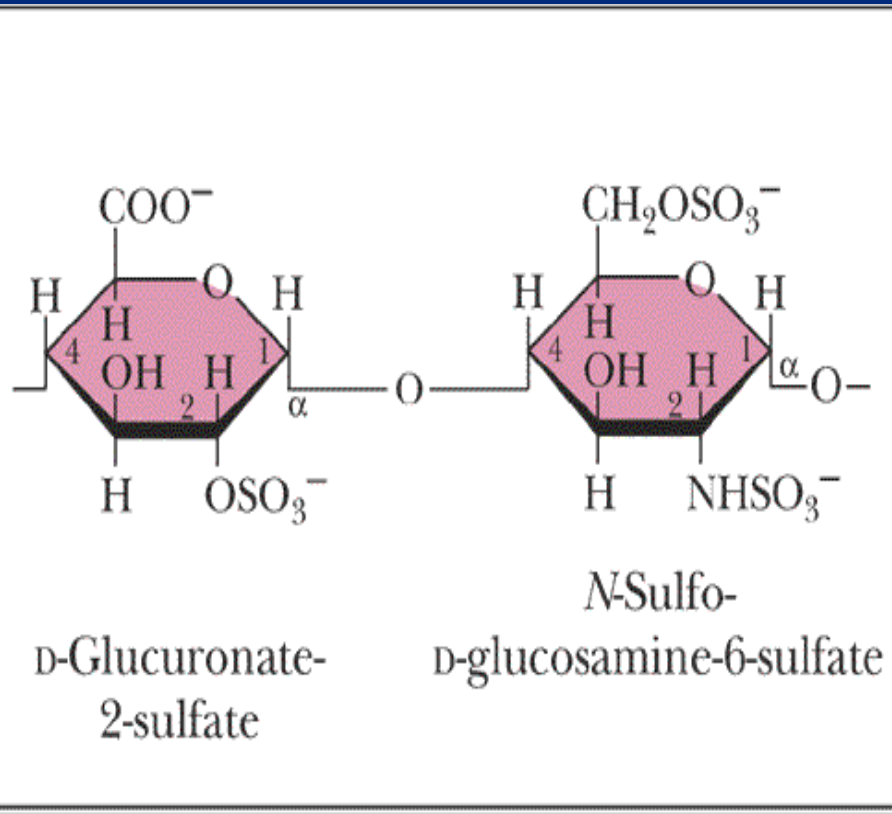


Glycosaminoglycans

Involved in a variety of extracellular functions; chondroitin is found in tendons, cartilage and other connective tissues



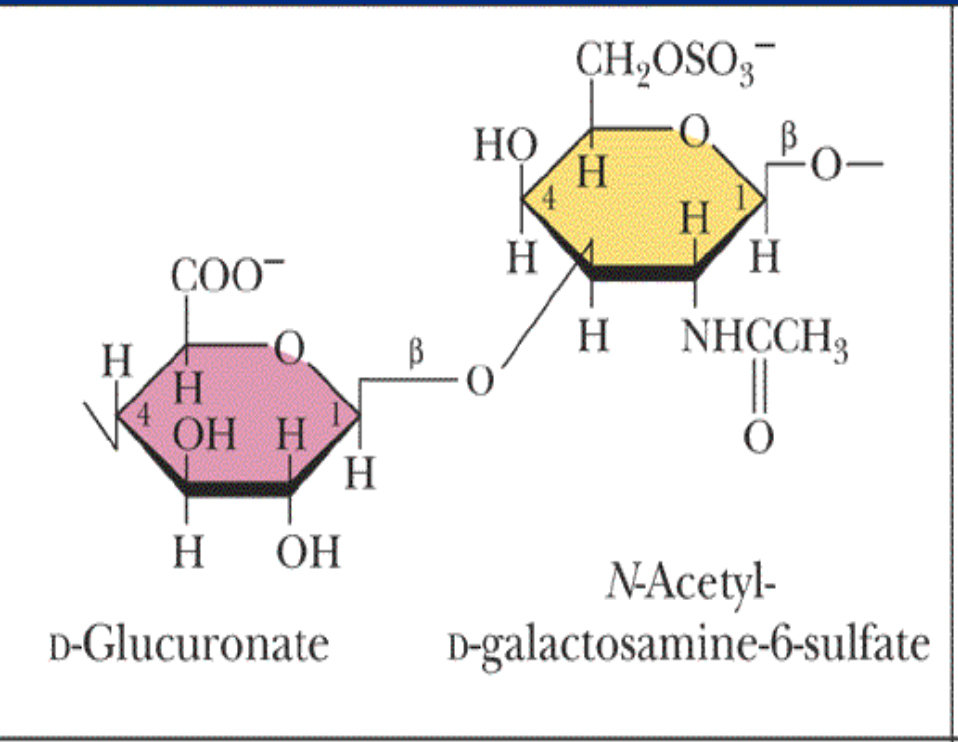
Chondroitin-4-sulfate



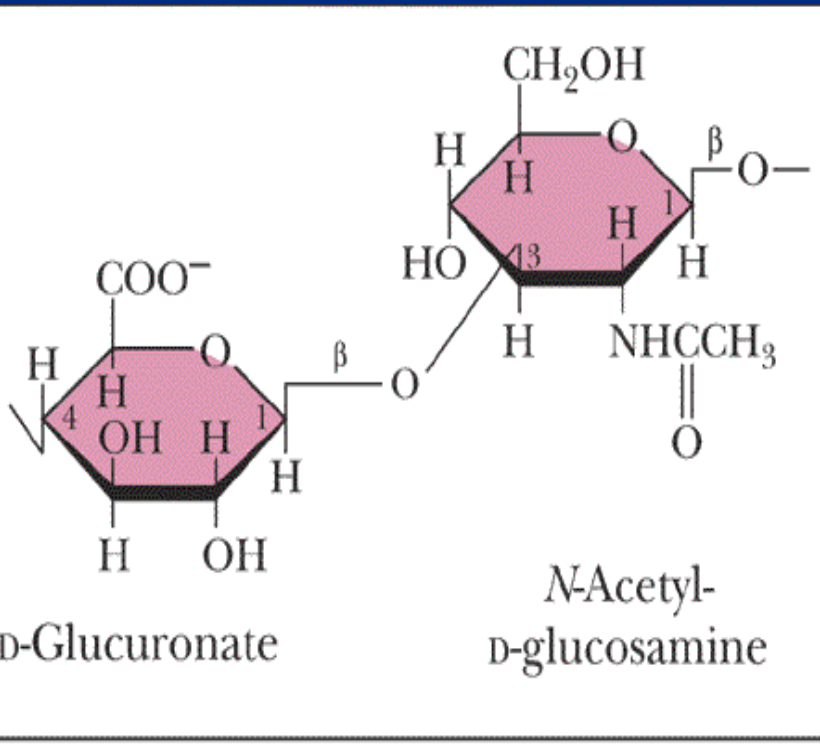
Heparin

Glycosaminoglycans

A characteristic of glycosaminoglycans is the presence of acidic functionalities (carboxylate and/or sulfates)



Chondroitin-6-sulfate

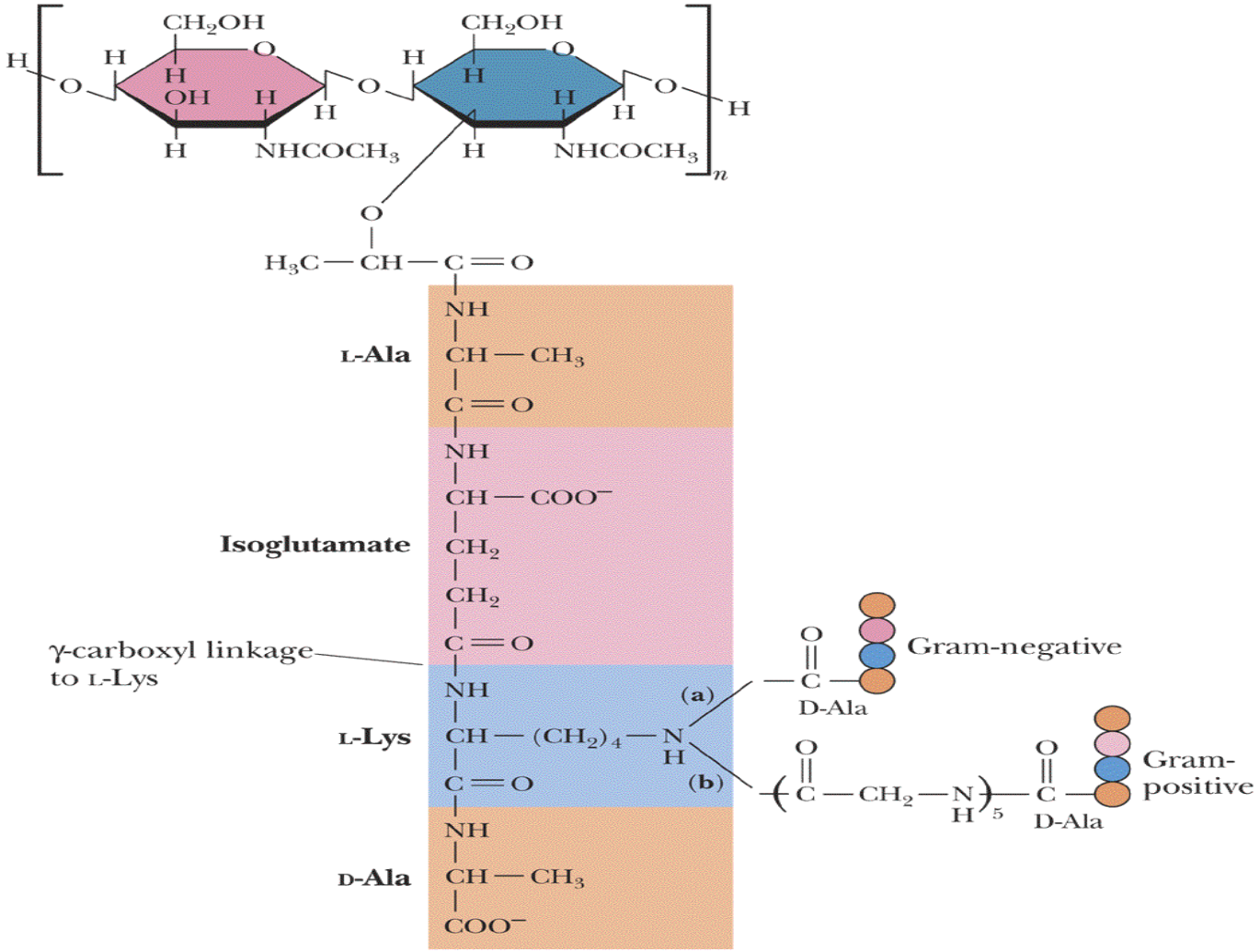


Hyaluronate

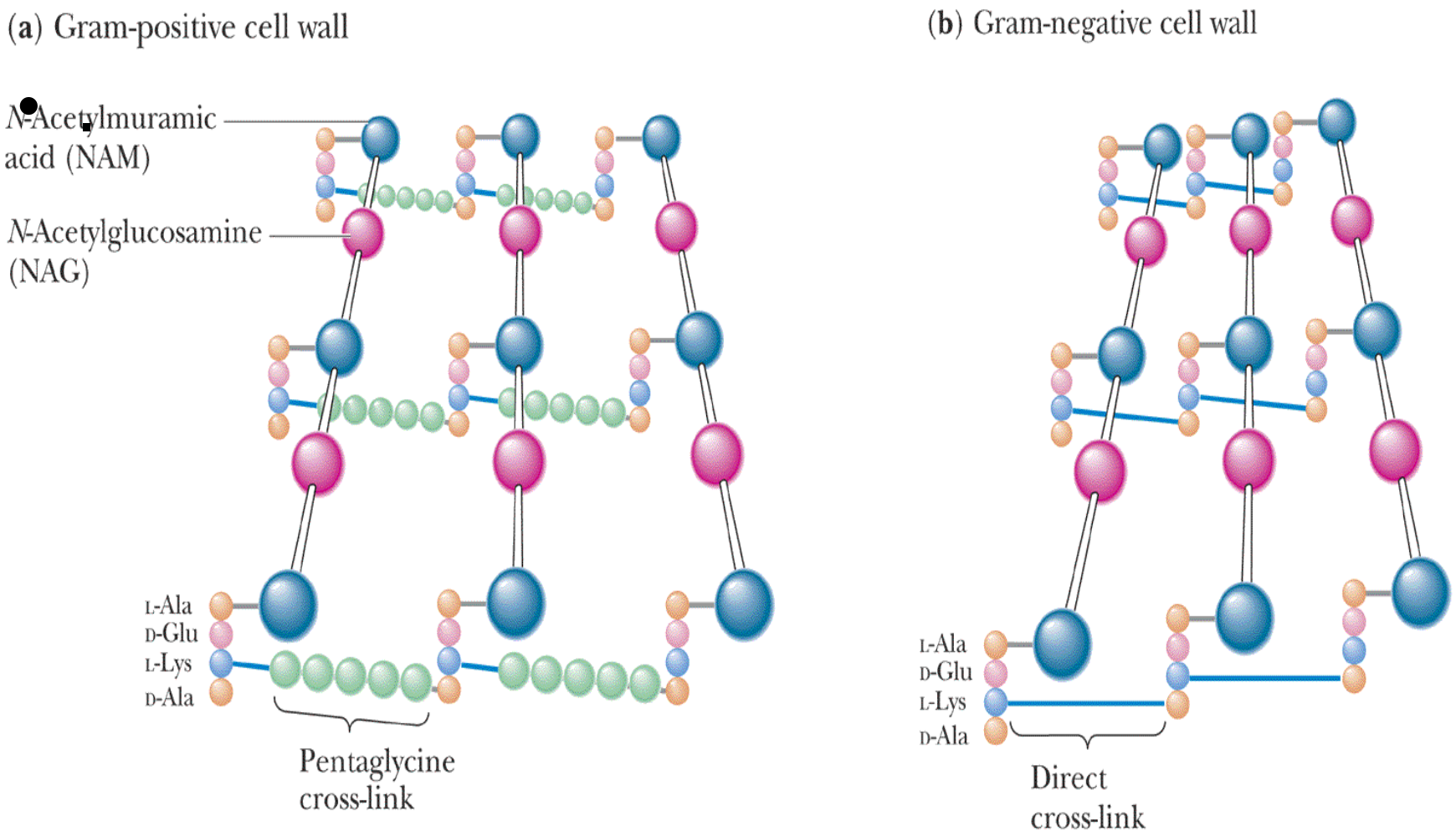
Bacterial cell wall

- provide strength and rigidity for the organism
- consists of a polypeptide-polysaccharide known as peptidoglycan or murein
- determines the Gram staining characteristic of the bacteria

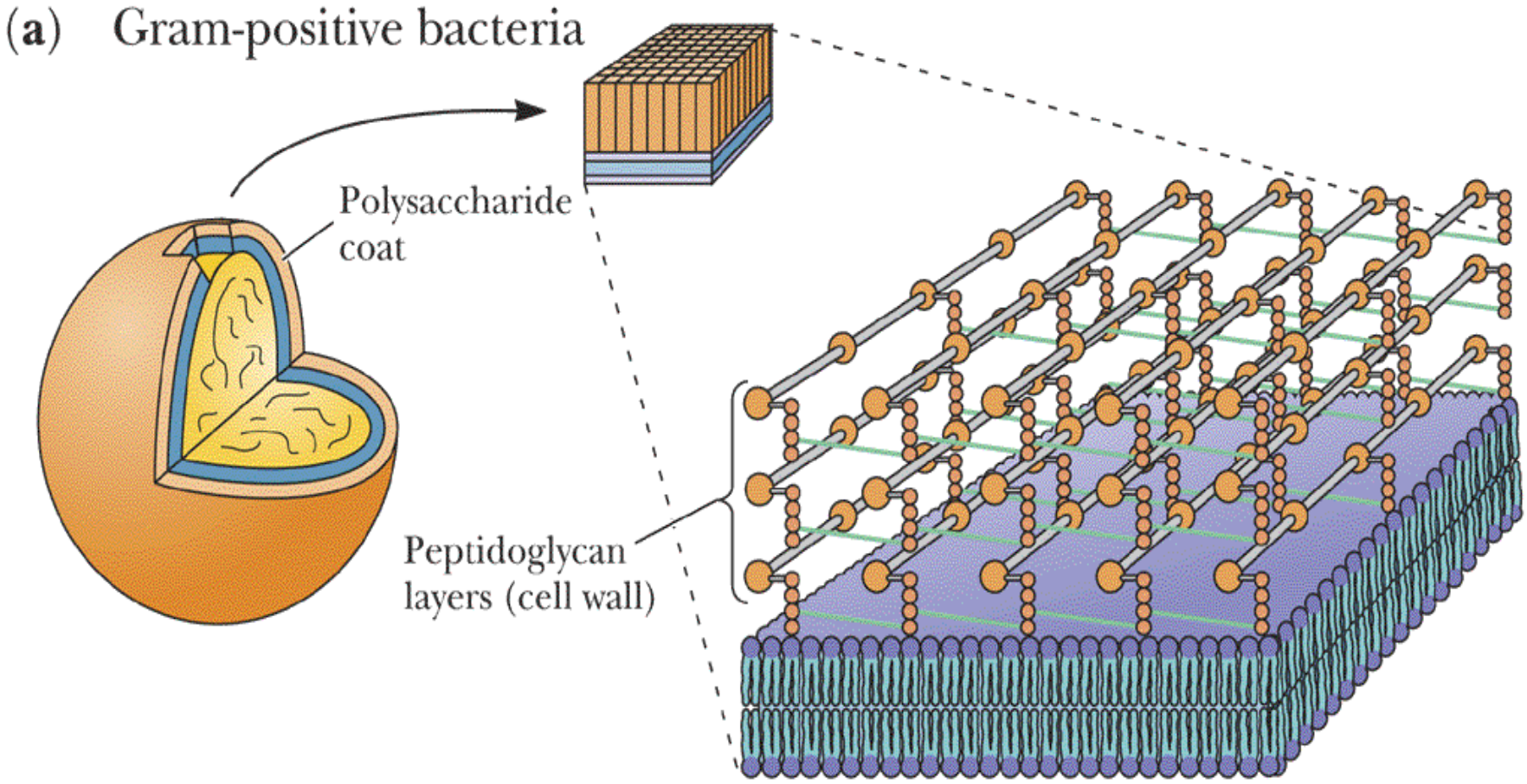
Structure of peptidoglycan



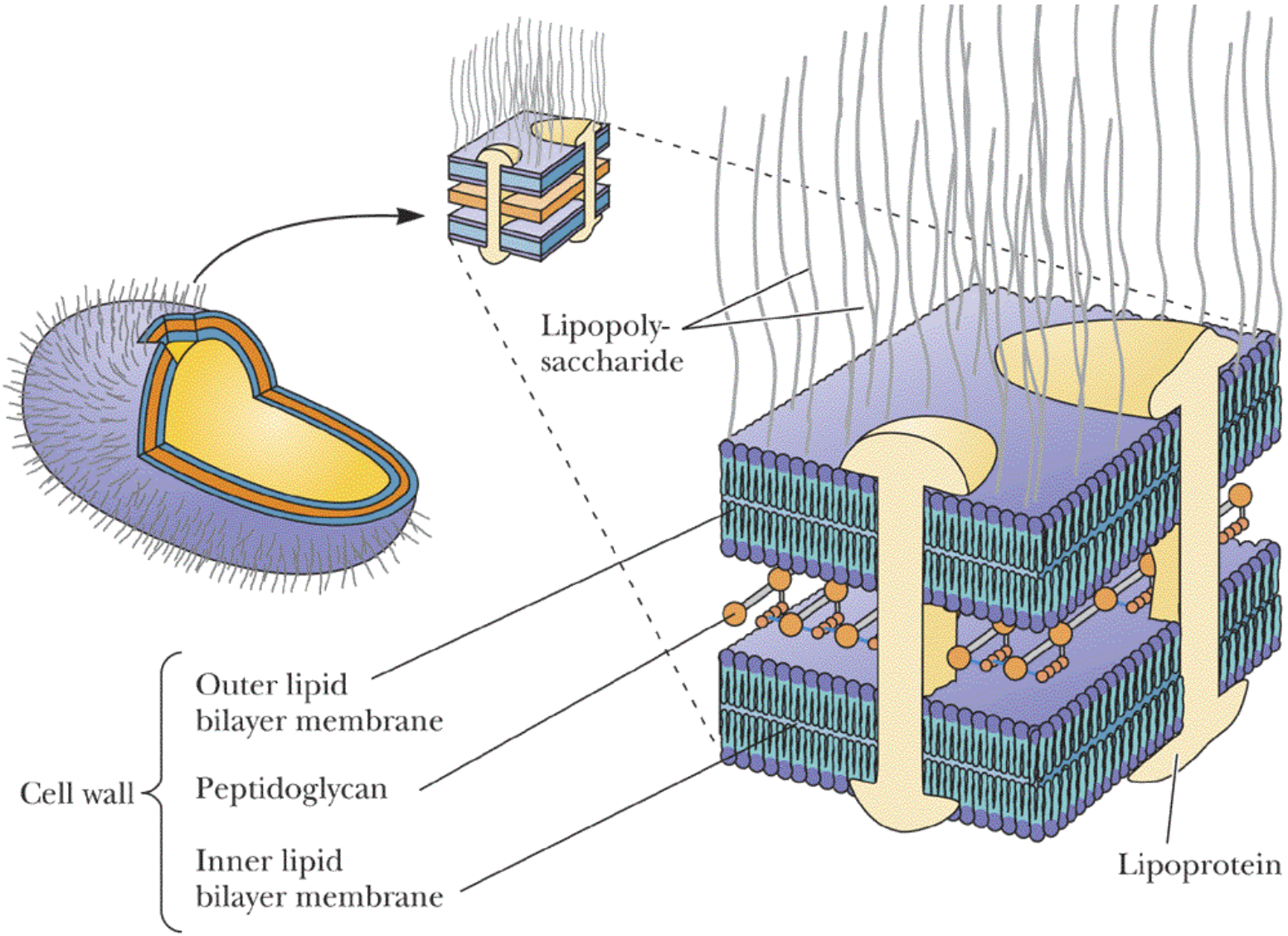
Structure of peptidoglycan



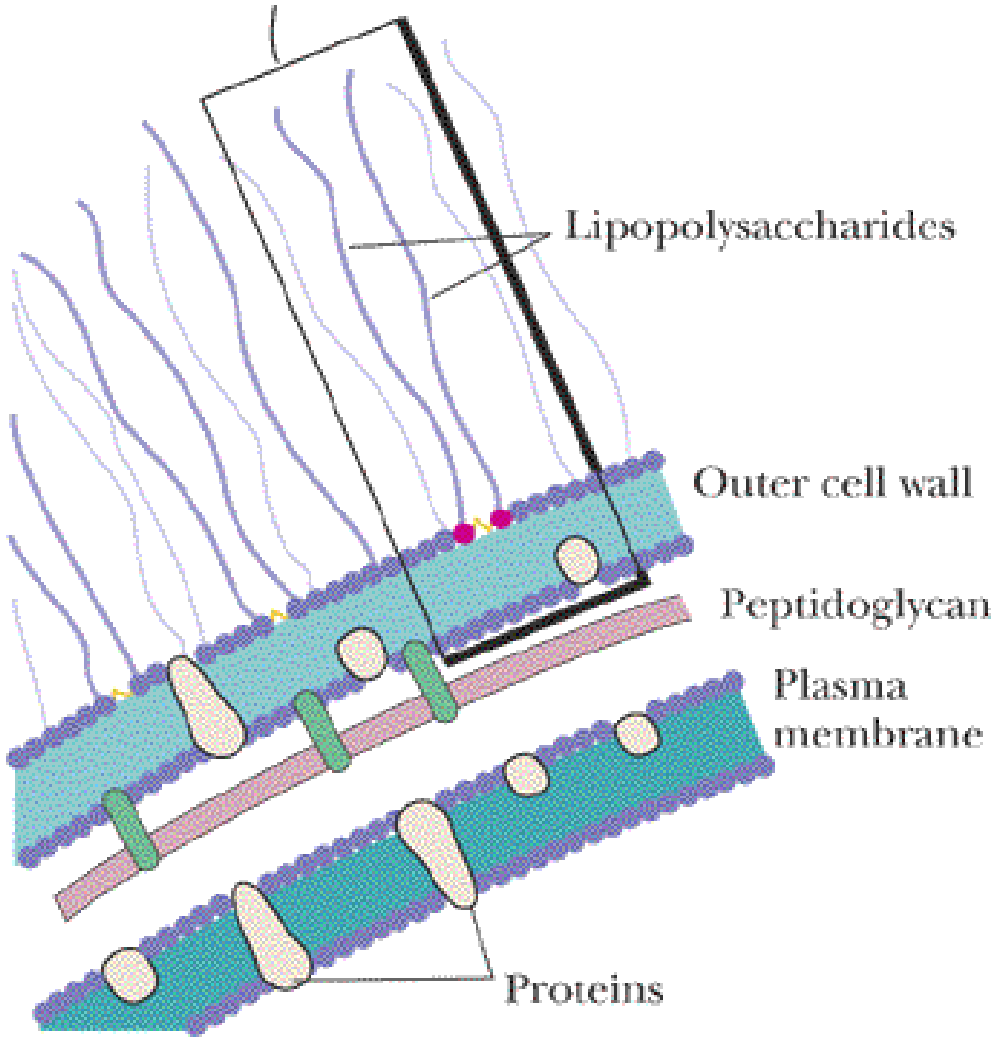
Cell wall of Gram-positive bacteria



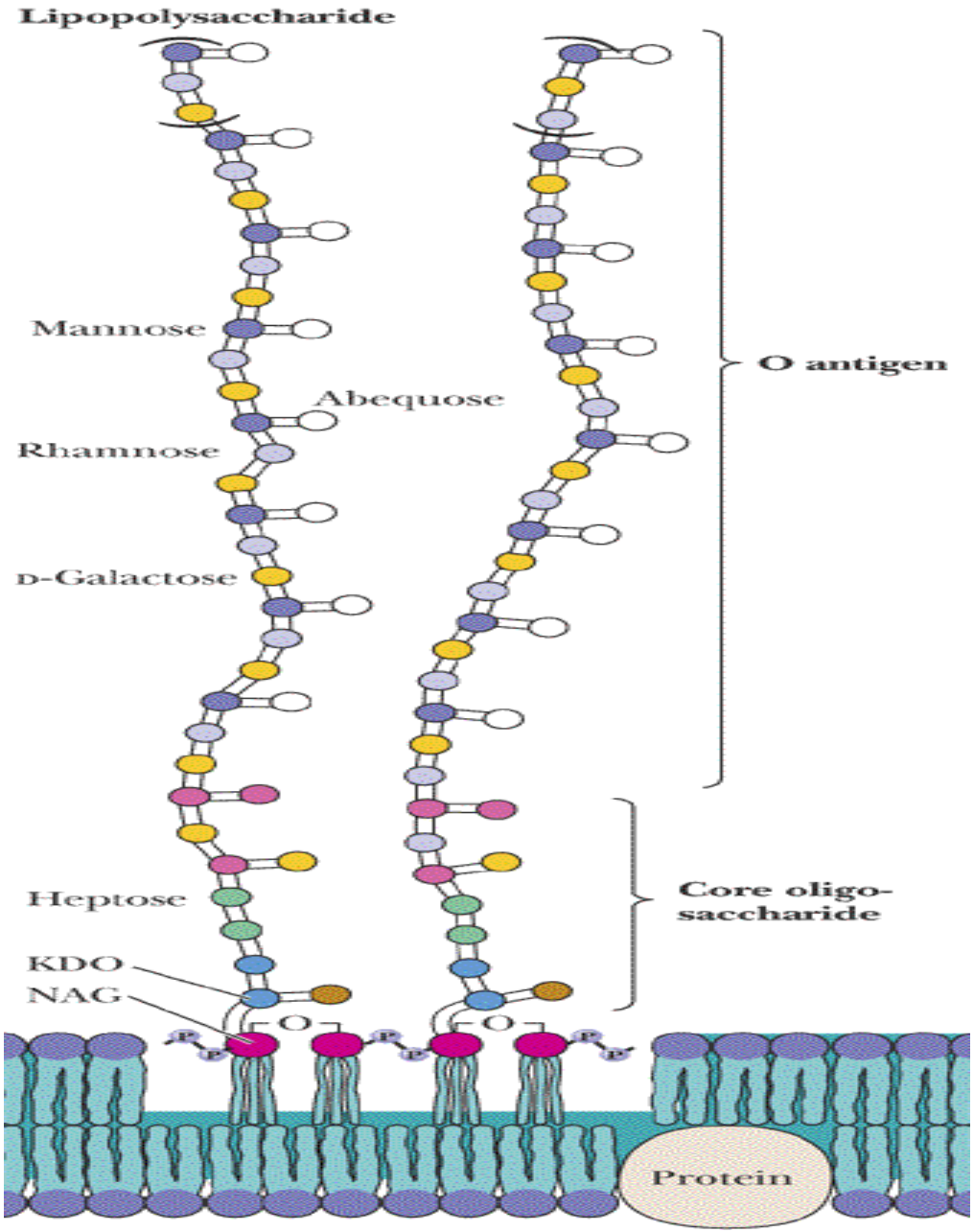
Gram-negative bacteria



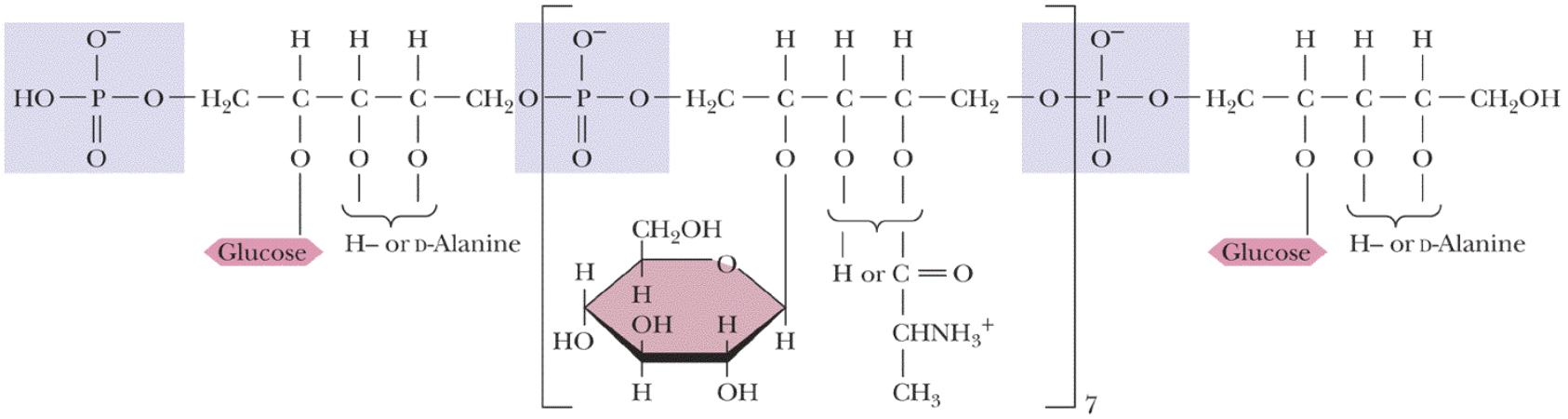
Cross-section of the cell wall of a gram-negative organism such as E.coli



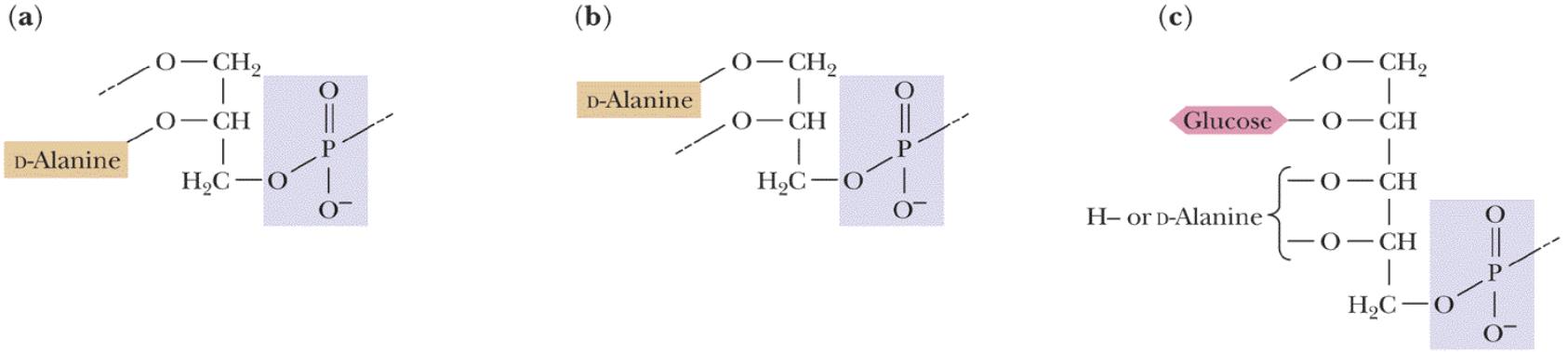
Lipopolysaccharide (LPS) coats the outer membrane of Gram-negative bacteria.
the lipid portion of the LPS is embedded in the outer membrane and is linked to
a complex polysaccharide



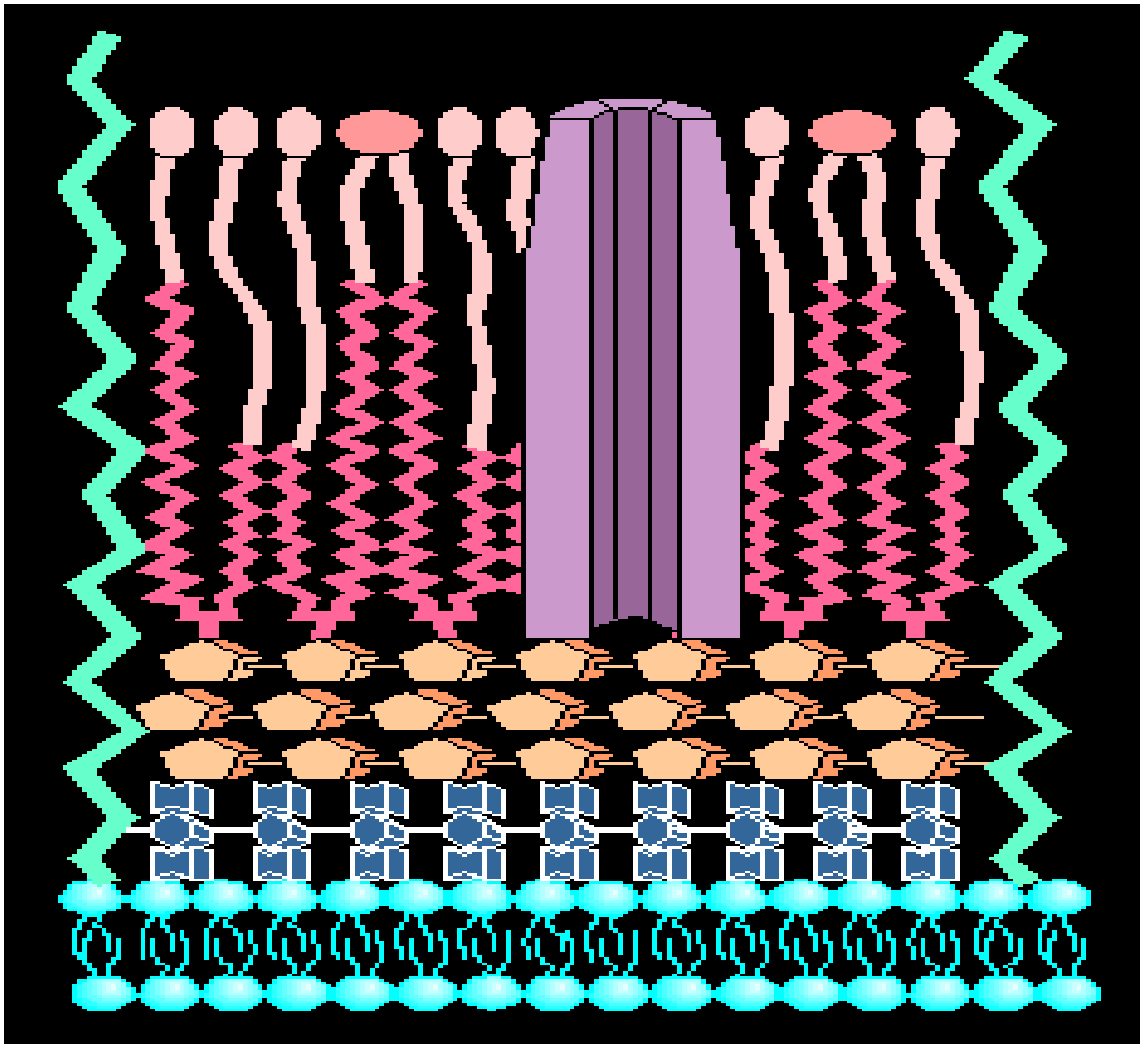
Teichoic acids are covalently linked to the peptidoglycan of gram-positive bacteria. These polymers of glycerol phosphate (a and b) or ribitol phosphate (c) are linked by phosphodiester bonds



Ribitol teichoic acid from *Bacillus subtilis*

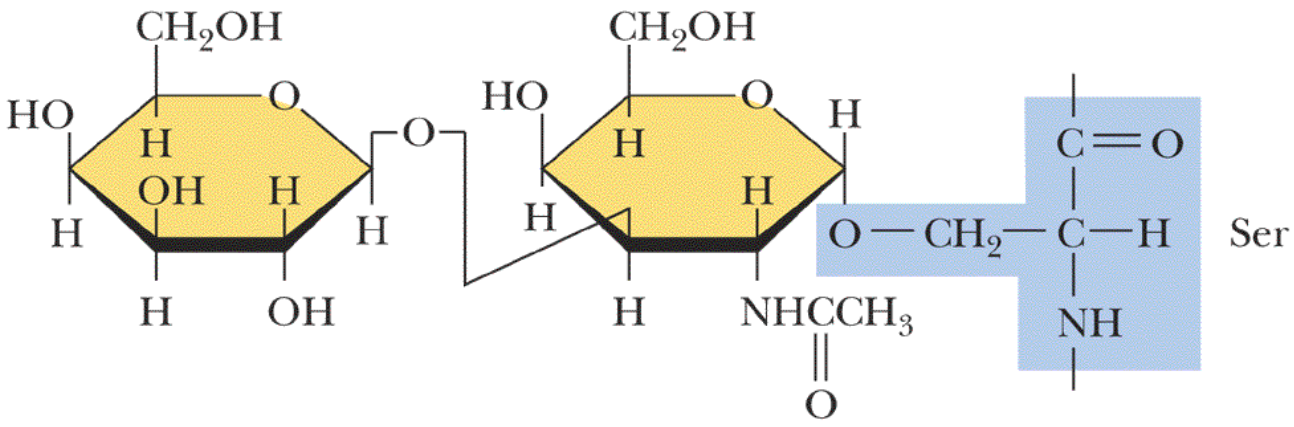


Mycobacterial cell wall

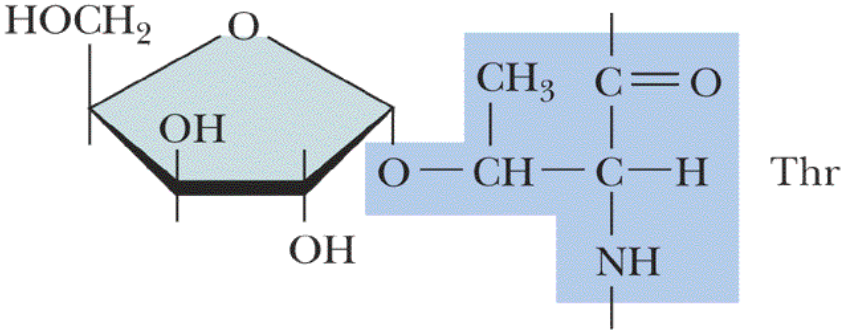


Serine or threonine O-linked saccharides

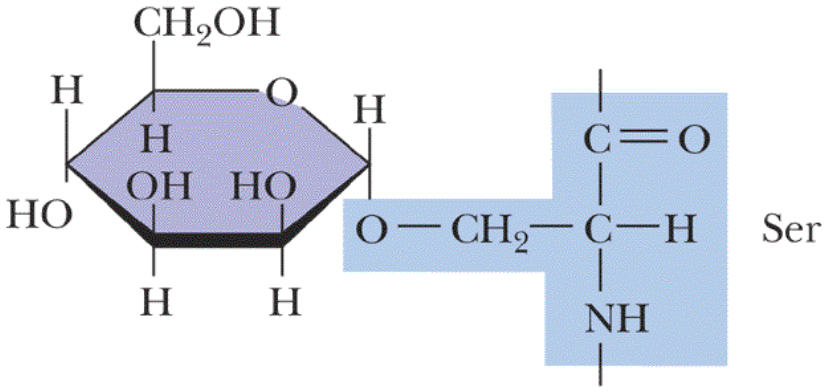
(a) O-linked saccharides



β-Galactosyl–1,3–α-*N*-acetylgalactosyl-serine

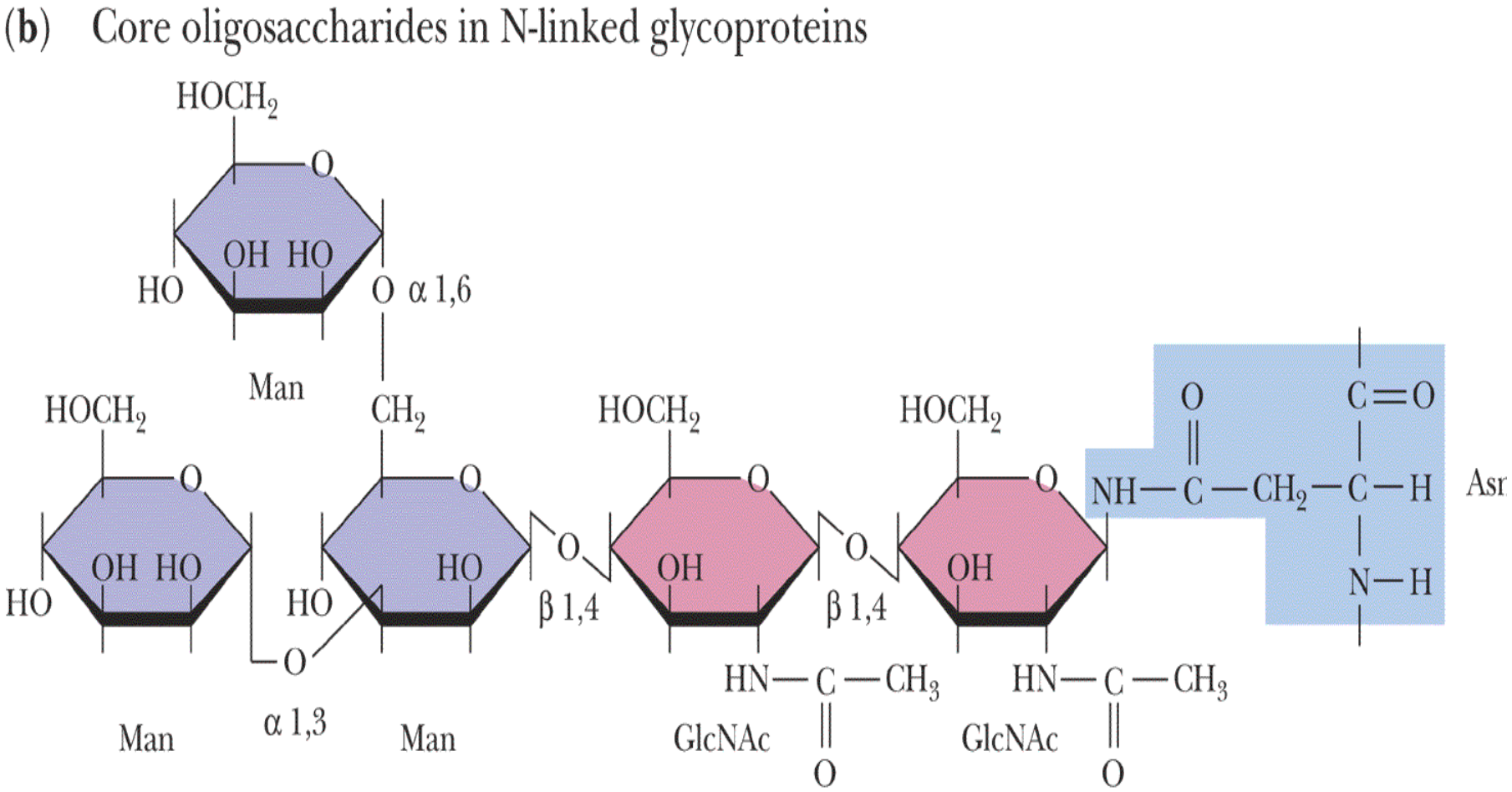


α-Xylosyl-threonine

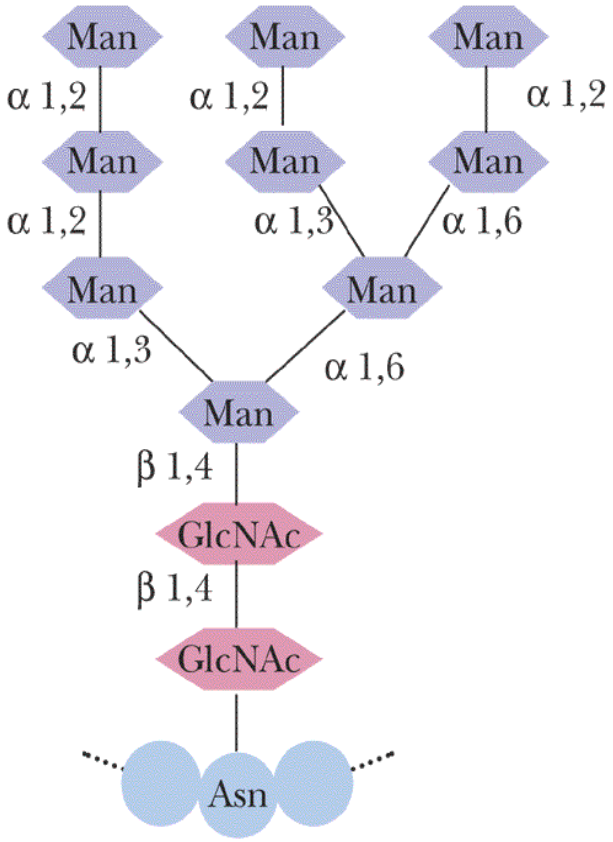


α-Mannosyl-serine

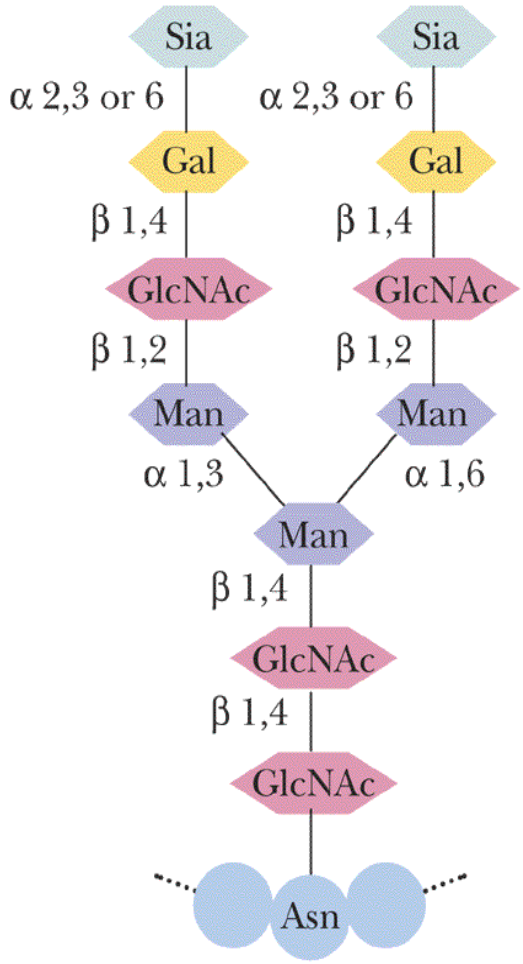
Aspargine N-linked glycoproteins



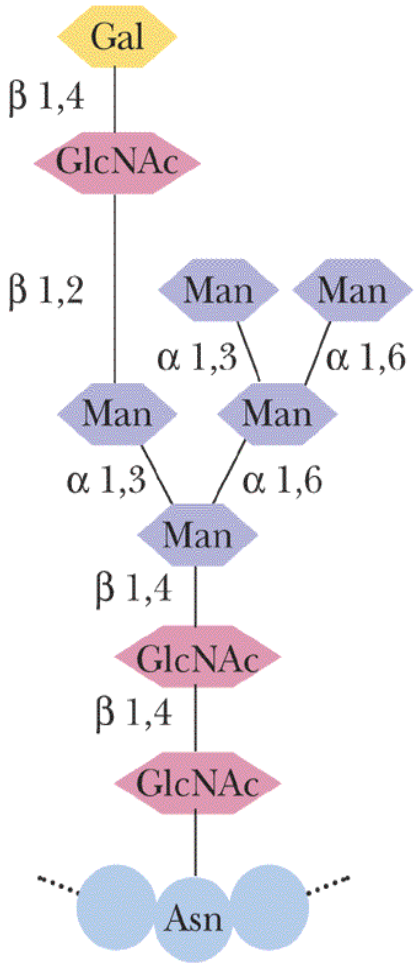
(c) N-linked glycoproteins



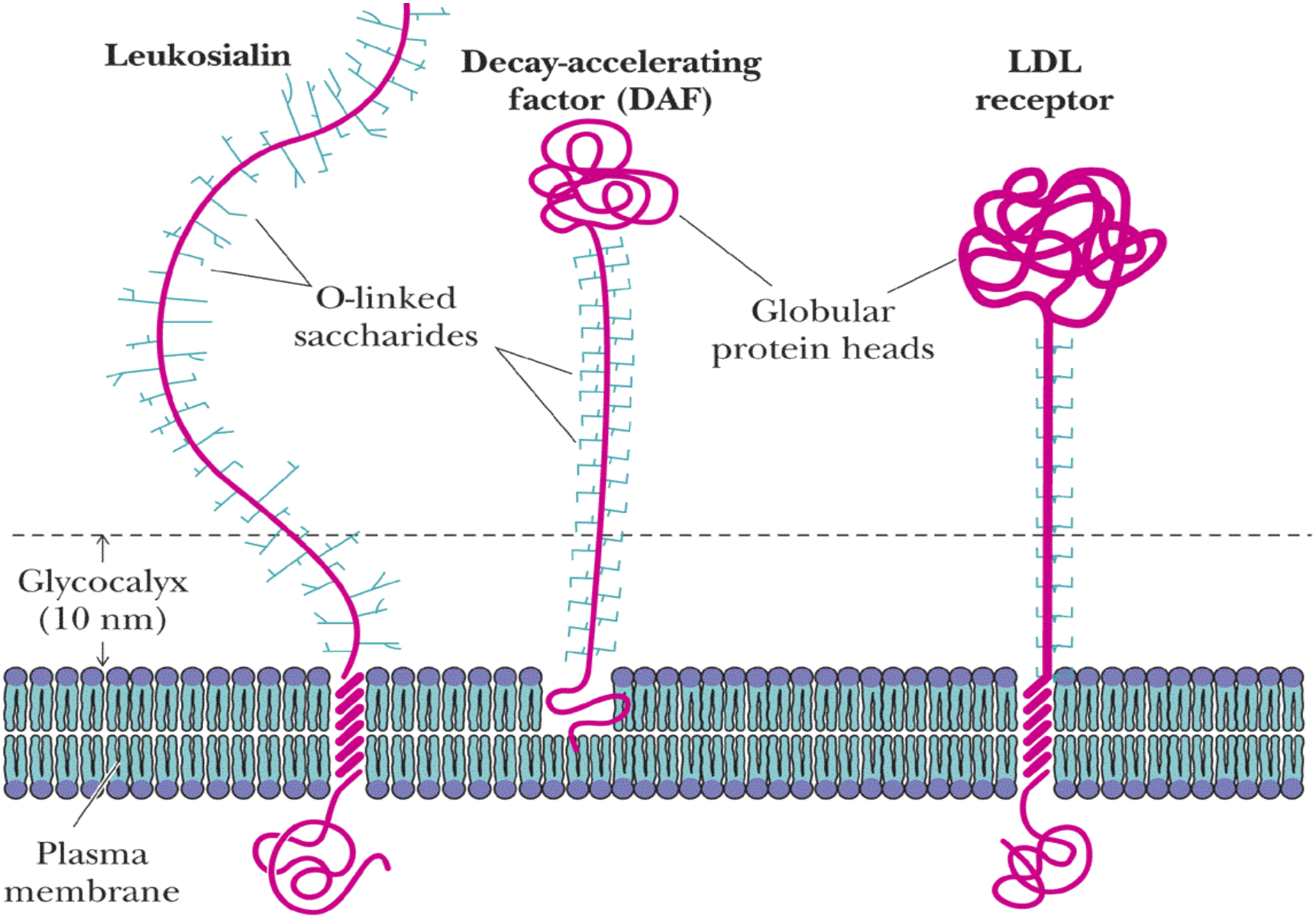
High mannose



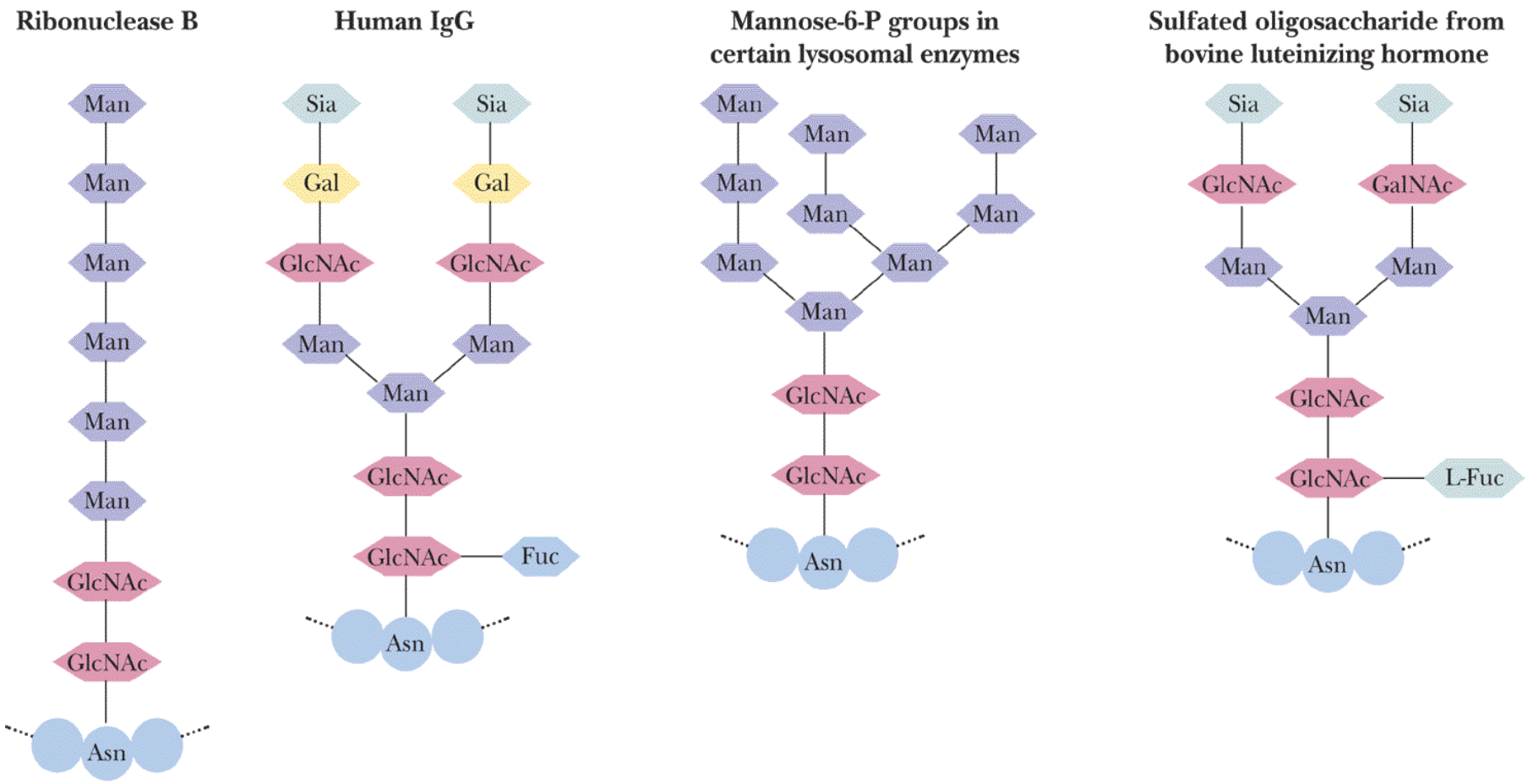
Complex



Hybrid

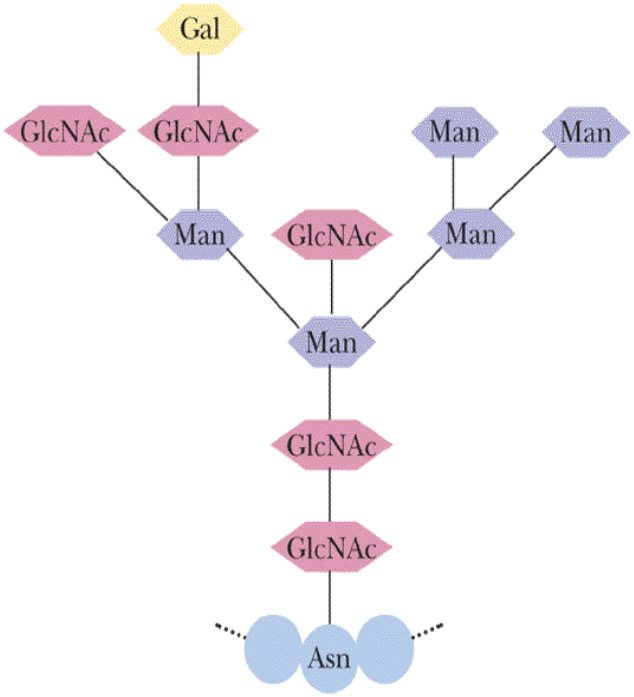

Leukosialin
Decay-accelerating factor (DAF)
LDL receptor
O-linked saccharides
Globular protein heads
Glycocalyx (10 nm)
Plasma membrane

Some of the oligosaccharides found in N-linked glycoproteins

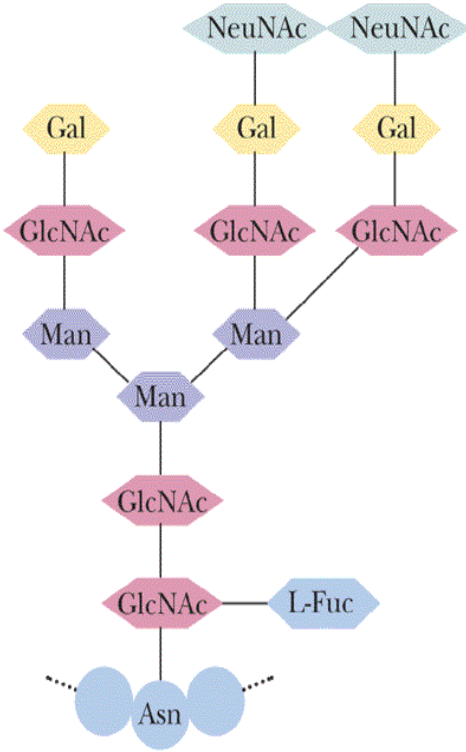


Some of the oligosaccharides found in N-linked glycoproteins

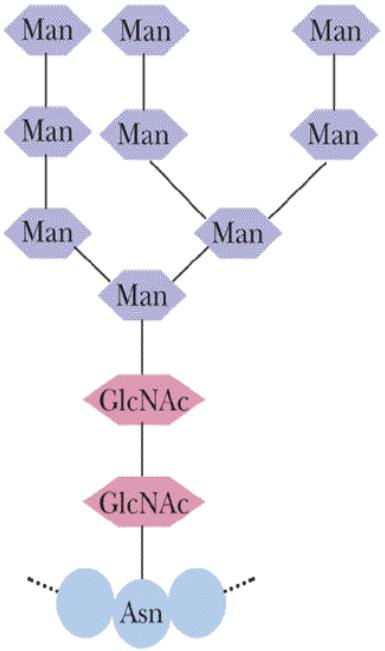
One of several from ovalbumin



Various serum glycoproteins

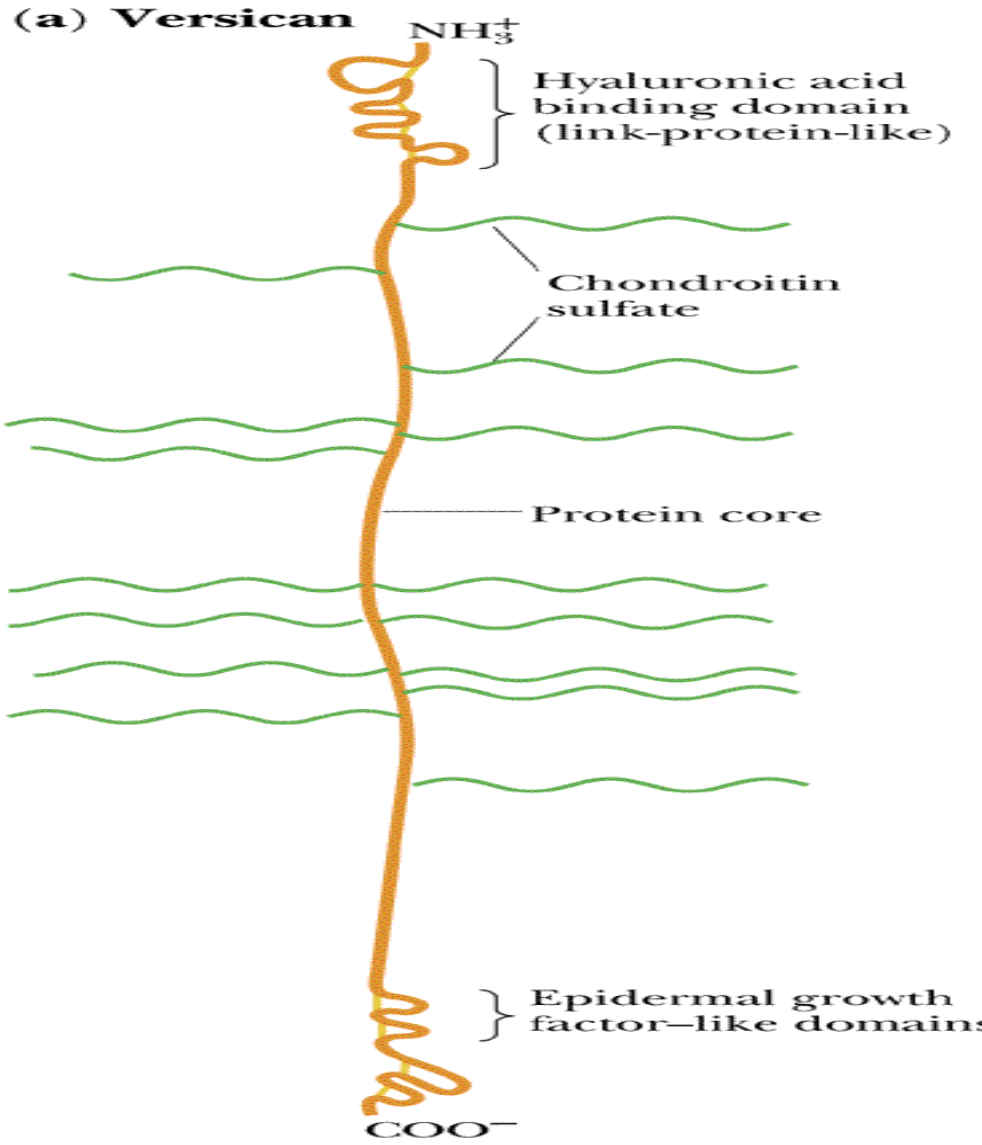


Porcine thyroglobulin
Soybean agglutinin



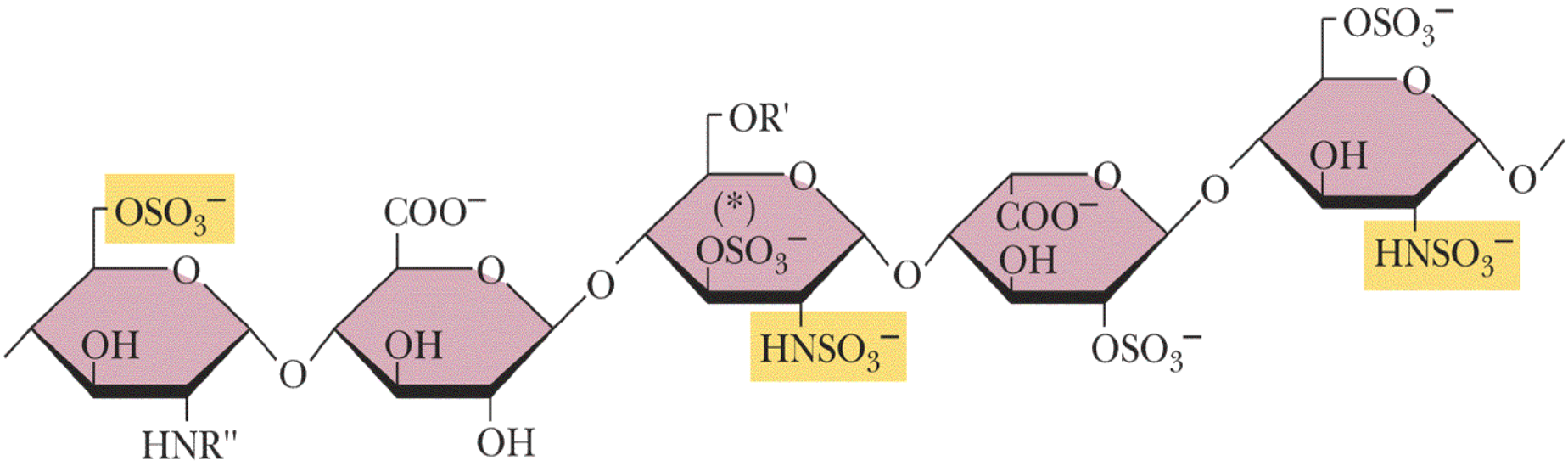
Proteoglycans are a family of glycoproteins whose carbohydrate moieties are predominantly glycosaminoglycans structures are quite diverse as are sizes
examples: versican, serglycin, decorin, syndecan

Functions:
- modulate cell growth processes
- provide flexibility and resiliency to cartilage



A portion of the structure of heparin

Heparin is a carbohydrate with anticoagulant properties. It is used in blood banks to prevent clotting and in the prevention of blood clots in patients recovering from serious injury or surgery. Numerous derivatives of heparin have been made (Fondaparinux).



GLYCOLIPIDS

Cerebrosides

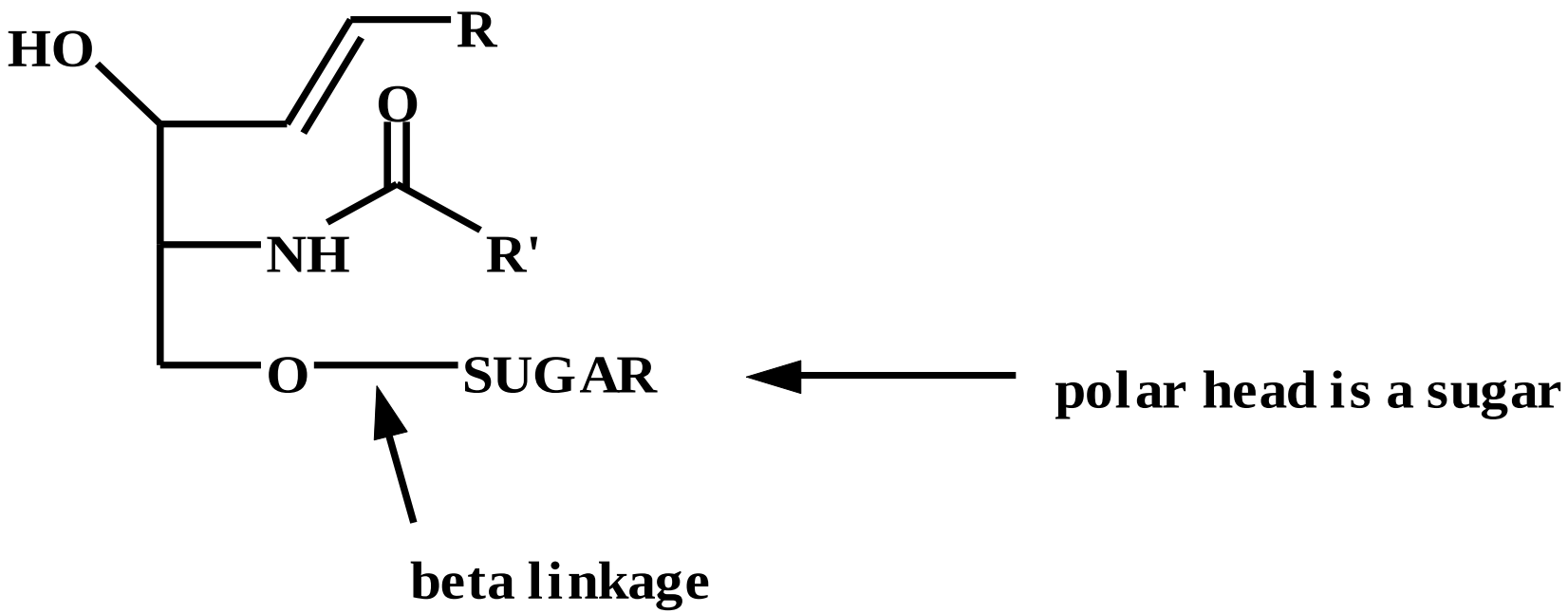
- One sugar molecule
  - Galactocerebroside – in neuronal membranes
  - Glucocerebrosides – elsewhere in the body

- Sulfatides or sulfogalactocerebrosides
  A sulfuric acid ester of galactocerebroside

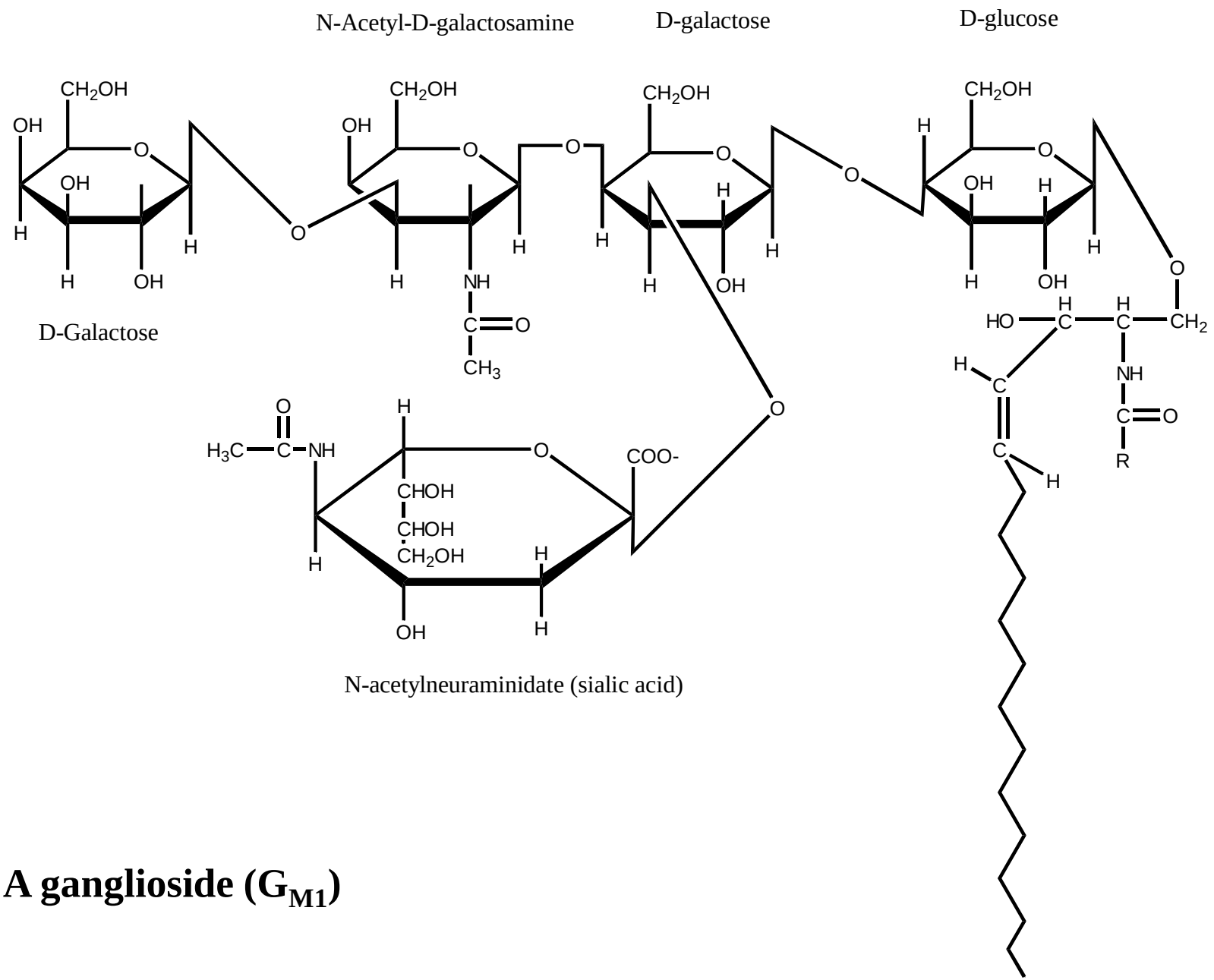
GLYCOLIPIDS

- Globosides
  ceramide oligosaccharides
  Lactosylceramide
  - 2 sugars (eg. lactose)
- Gangliosides
  - Have a more complex oligosaccharide attached.
  - Biological functions: cell-cell recognition; receptors for hormones

Glycolipids



There are different types of glycolipids: cerebrosides, gangliosides, lactosylceramides



A ganglioside (G_{M1})

Digestion of Carbohydrates

Digestion of Carbohydrates

The main food carbohydrates are:

sucrose, lactose, trehalose, starch, glycogen, cellulose.

- Trehalose: the α–(1–1) glucosidic bond is broken down by an enzyme called trehalase.

Digestion of Carbohydrates

- Sucrose: the β-(1,2) osidic bond between β-fructose and α–glucose is broken down by an enzyme called invertase (sucrase or β- fructosidase).
- Lactose: β-(1,4) galactosidic bond between β- galactose and α– or β-glucose is broken down by an enzyme called lactase (β- galactosidase)

Digestion of Carbohydrates

- Cellulose: this dietary polysaccharide is composed by molecules of glucose linked together by β-(1,4) glucosidic bonds. These bonds are usually broken down by cellulase, but this enzyme is never synthesized by the human body.

Digestion: small intestine

Enzymes associated with intestinal surface membranes

- Sucrase
- Alpha-dextrinase
- Glucoamylase (maltase)
- Lactase
- peptidases

Digestion of glycogen

It happens in the similar way like the one of starch. The following enzymes are involved:

1. α-amylase
2. amylo α-1-6 glycosidase
3. maltase

Digestion of glycogen

- **α–amylase** breaks down the α–1-4 glucosidic bonds releasing maltose and maltotriose
- **Amylo-α–1,6- glycosidase** breaks α–1-6 glucosidic bonds
- **Maltase** will degrade maltose releasing two molecules of glucose.

Metabolism of carbohydrates

The main monosaccharides obtained after digestion of dietary carbohydrates are glucose, fructose, galactose

These monomers enter into cytoplasm of living cells by absorption.

Metabolism of Carbohydrates

The main metabolic processes in which the monosaccharides are involved include:

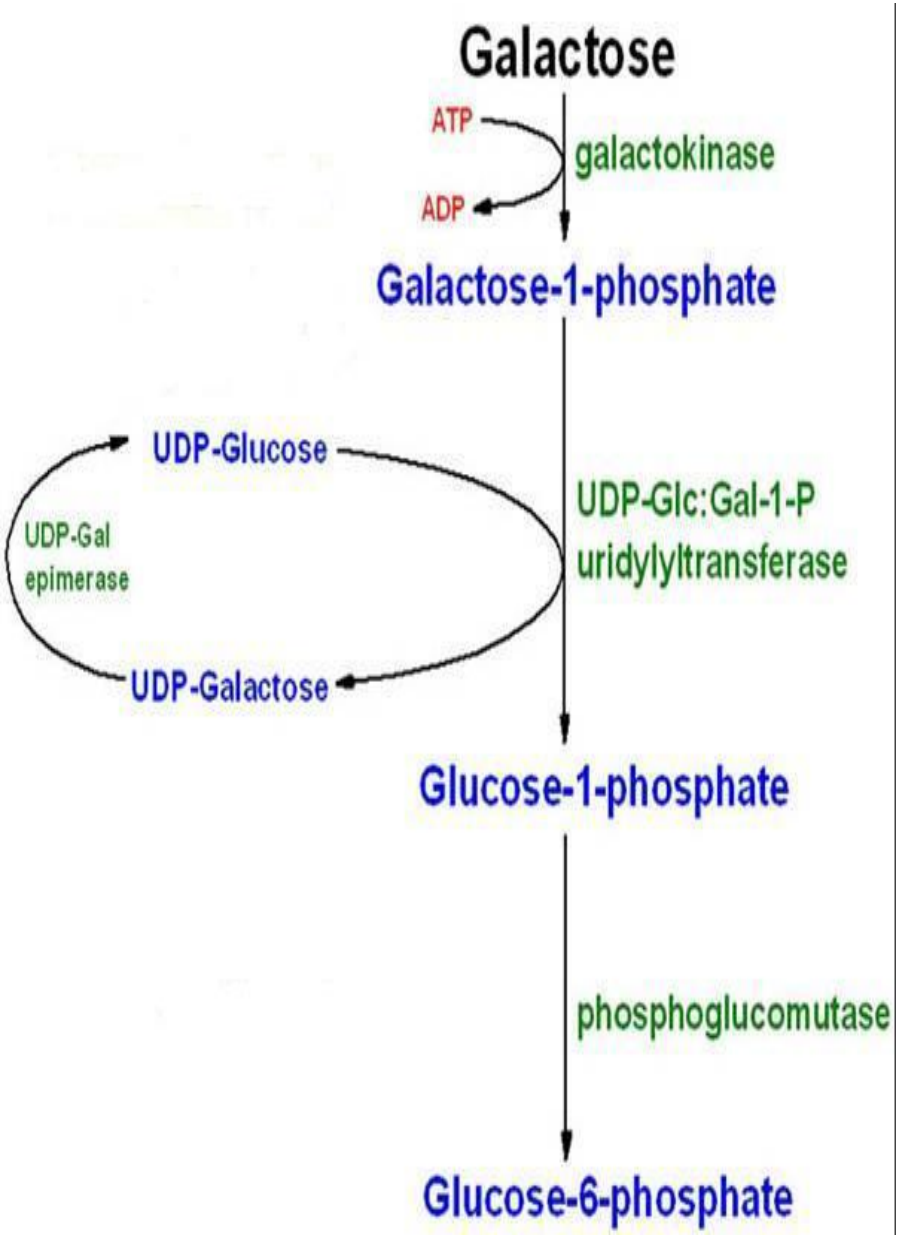
- **Glycogenesis**
- **Glycogenolysis**
- **Glycolysis**
- **Neoglycogenesis**
- **Krebs cycle**
- **Electron transport chain**
- **Cellular aerobic respiration**
- **Pentose-phosphate path way**

Metabolism of monosaccharides

. Before they enter different metabolic pathways, all monosaccharides must be phosphoprylated by attaching a phosphate group on the hydroxylic function of monosaccharide. In general the phosphprylation of monosaccharides occurs on the 5^{th} carbon for pentoses, on the 6^{th} carbon for the hexoses and on the 7^{th} carbon for heptoses.

Conversion of Galactose into glucose

Before it enters different metabolic pathways, galactose must be converted ito glucose. This process undergoes within a series of reactions.



At the final step

Glc-6-P can yield glucose by the action of “Glc-6-phosphatase”

Water is added and inorganic phosphate is released.

METABOLISM OF GALACTOSE

Galactose is metabolized from the milk sugar, lactose (a disaccharide of glucose and galactose) and enters glycolysis by its conversion to glucose-1-phosphate. This occurs through a series of steps. First the galactose is phosphorylated by galactokinase to yield galactose-1-phosphate.

METABOLISM OF GALACTOSE

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.

METABOLISM OF GALACTOSE

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.

Metabolism of galactose

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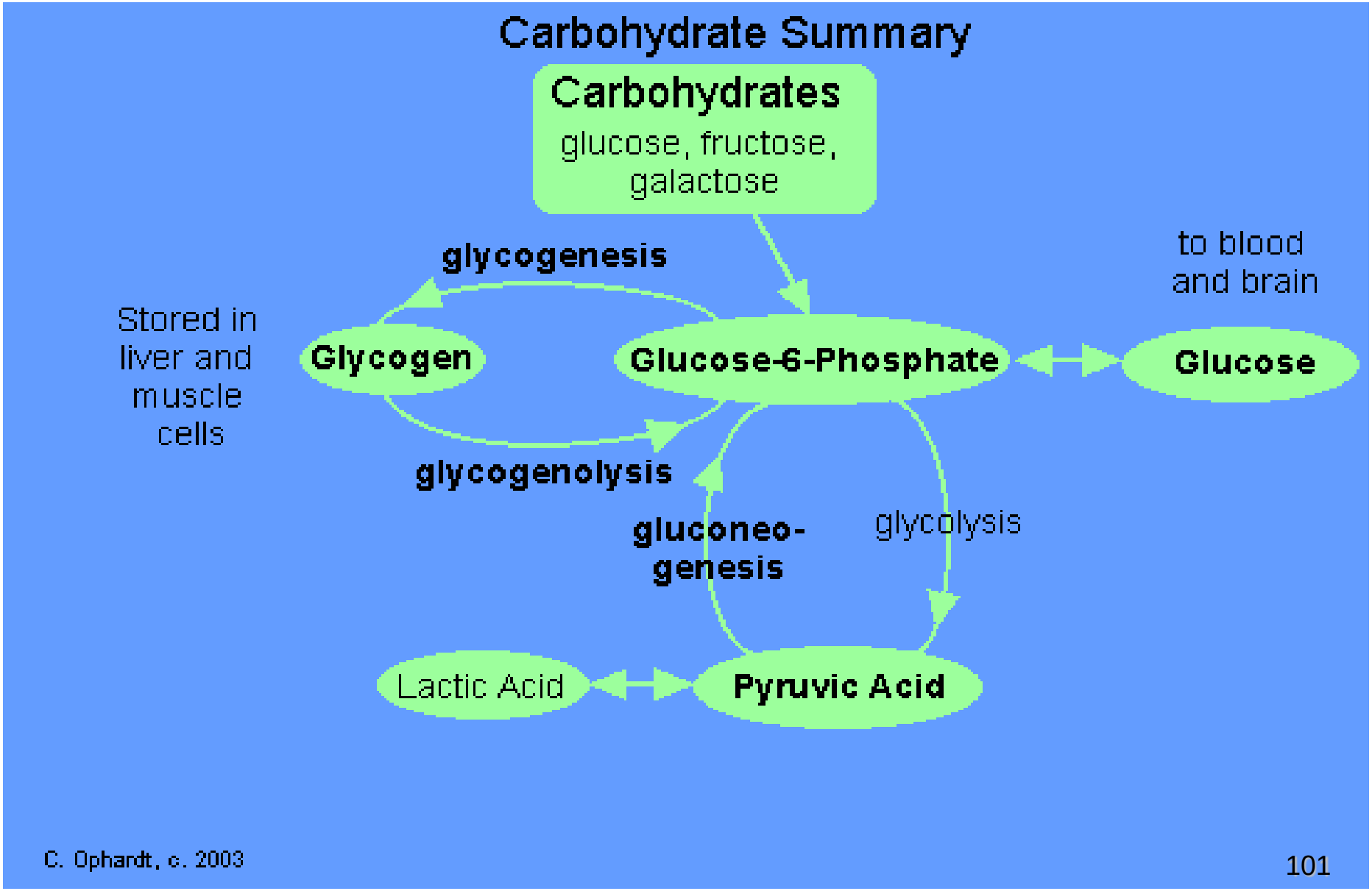
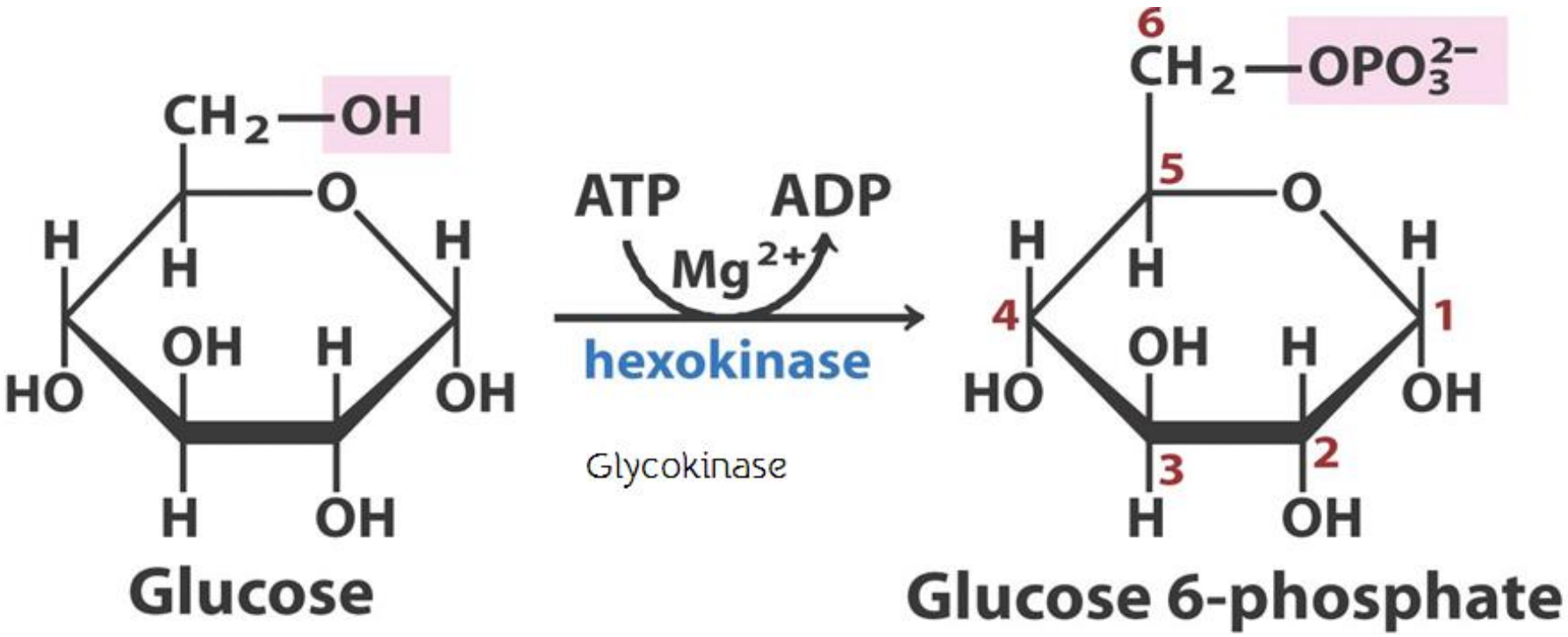
Metabolism of carbohydrates: summary



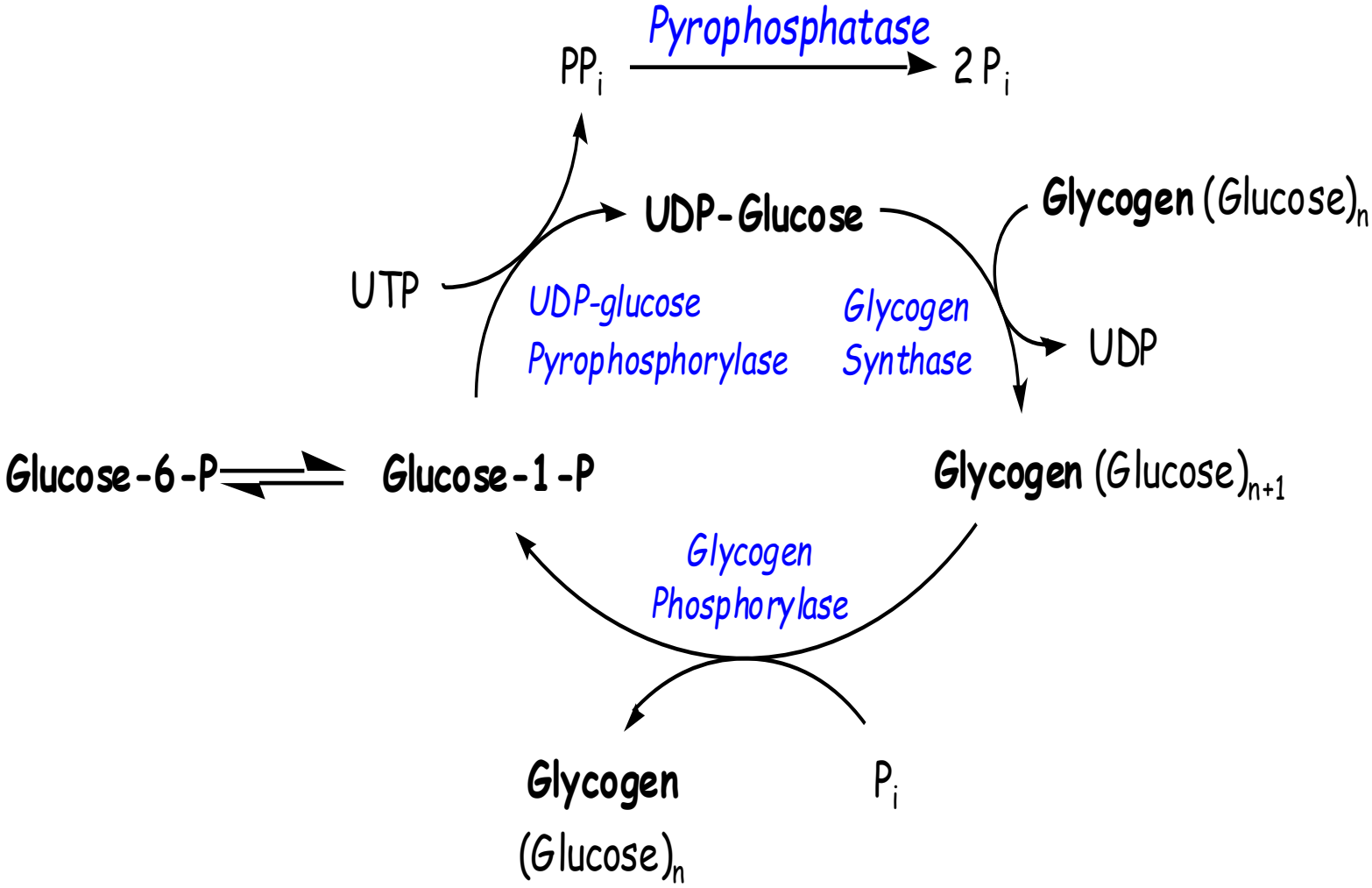
1. Phosphorylation of glucose



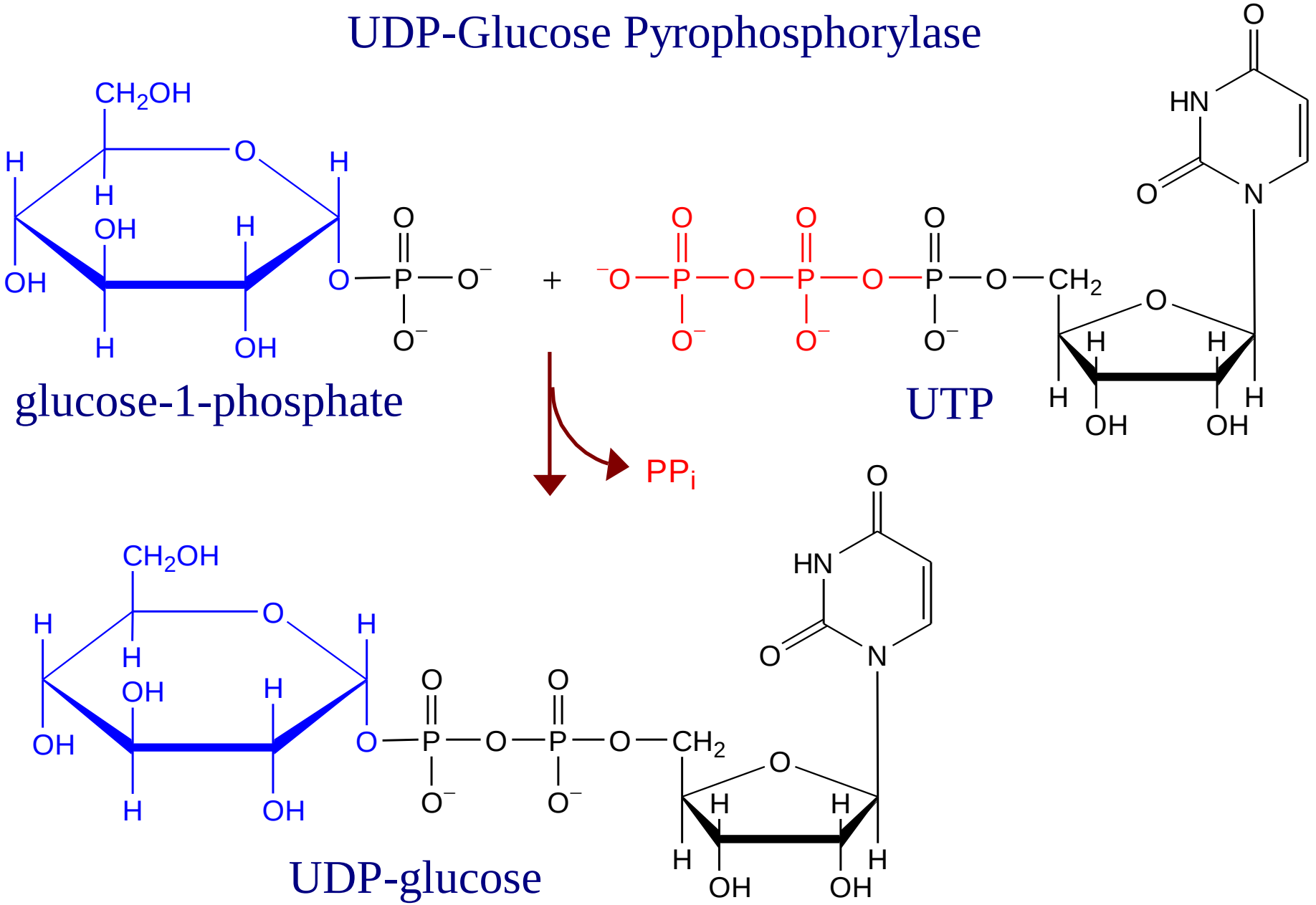
METABOLISM OF GLYCOGEN

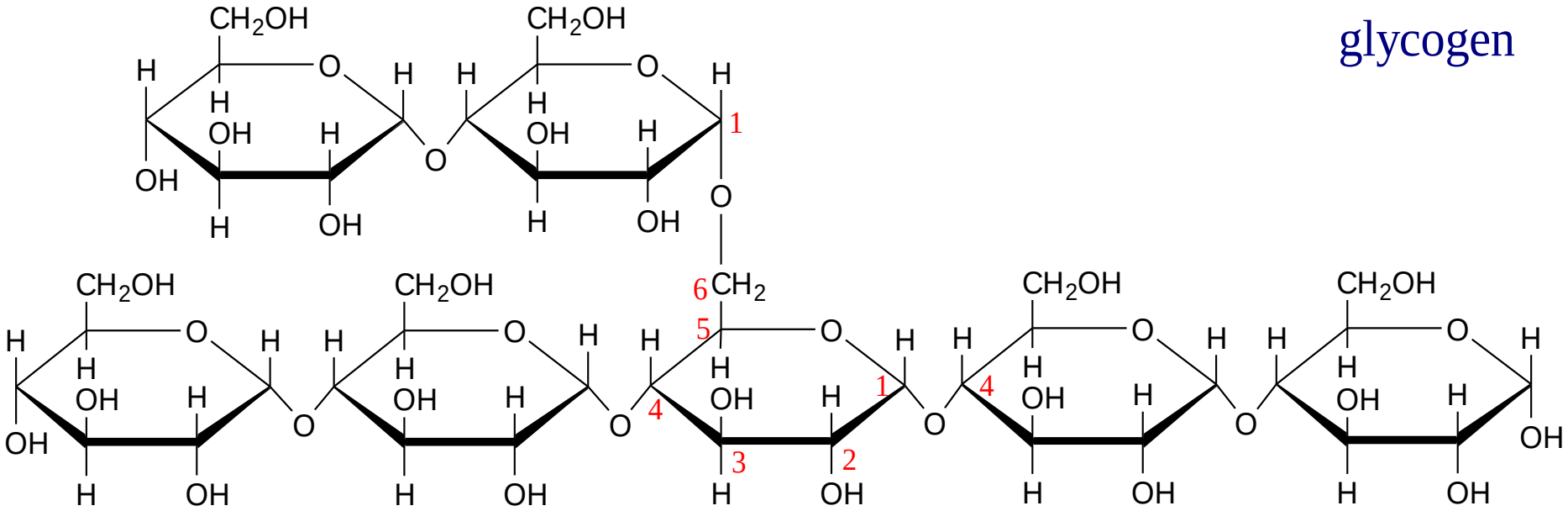
Glycogen forms an energy reserve that can be quickly mobilized to meet a sudden need for glucose, but one that is less compact than the energy reserves of triglycerides. In the liver hepatocytes, glycogen can compose up to 8% of the fresh weight (100–120 g in an adult) soon after a meal.

Glycogenesis & Glycogenolysis: overview



UDP-Glucose Pyrophosphorylase





Glycogen is a polymer of **glucose** residues linked by:

- α(1→4) glycosidic bonds, mainly
- α(1→6) glycosidic bonds, at branch points.

Glycogen chains & branches are longer than shown.

Glucose is stored as glycogen predominantly in **liver** and **muscle** cells.

Metabolism of glycogen

Only the glycogen stored in the liver can be made accessible to other organs.

In the muscles, glycogen is found in a much lower concentration (1% to 2% of the muscle mass), but the total amount exceeds that in the liver. However the amount of glycogen in the blood and muscles depends on physical training.

Metabolism of glycogen

As a meal containing carbohydrates is eaten and digested, blood glucose levels rise, and the pancreas secretes insulin. Glucose from the hepatic portal vein enters the liver cells (hepatocytes).

Insulin acts on the hepatocytes to stimulate the action of several enzymes, including glycogen synthase.

Metabolism of glycogen

Glucose molecules are added to the chains of glycogen as long as both insulin and glucose remain great.

In this "fed" state, the liver takes in more glucose from the blood than it releases.

Metabolism of glycogen

After a meal has been digested and glucose levels begin to fall, insulin secretion is reduced, and glycogen synthesis stops.

About four hours after a meal, glycogen begins to be broken down and converted again to glucose.

Metabolism of glycogen: Glycogenolysis

Glycogen phosphorylase is the primary enzyme of glycogen breakdown. For the next 8–12 hours, glucose derived from liver glycogen will be the primary source of blood glucose to be used by the rest of the body for fuel.

Metabolism of glycogen: Glycogenolysis

Glucagon (liver) and epinephrine (muscle) are the other hormones produced by the pancreas, which in many respects serve as the counter-signal to insulin. When the blood sugar begins to fall below normal, glucagon is secreted in increasing amounts. It stimulates glycogen breakdown into glucose even when insulin levels are abnormally high.

Metabolism of glycogen

Muscle cell glycogen appears to function as an immediate reserve source of available glucose for muscle cells. Other cells that contain small amounts use it locally as well. Muscle cells lack glucose-6-phosphatase enzyme, so they lack the ability to pass glucose into the blood, so the glycogen they store internally is destined for internal use and is not shared with other cells, unlike liver cells.

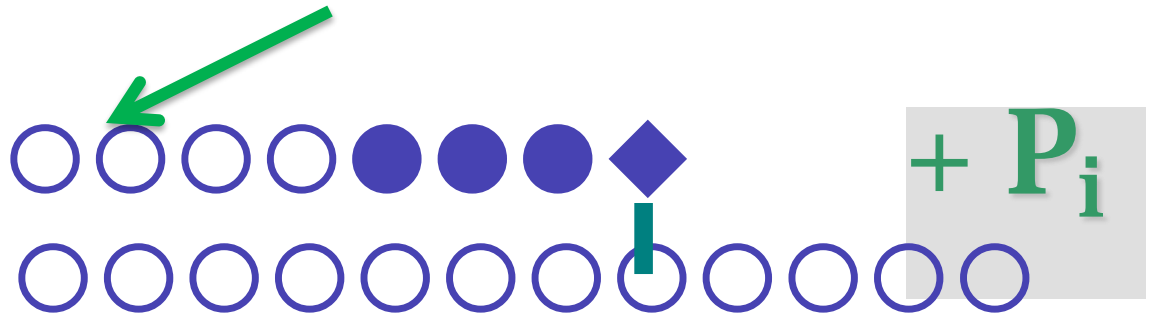
GLYCOGENOLYSIS

DEGRADATION OF GLYCOGEN INTO GLUCOSES IN THE LIVER AND MUSCLES

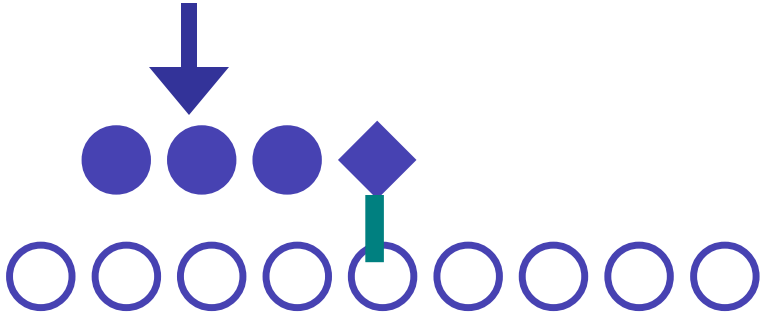
1. Release of glucose-1-phosphate

Enzyme = ***glycogen phosphorylase***

non-reducing ends



glucose-1-phosphate +



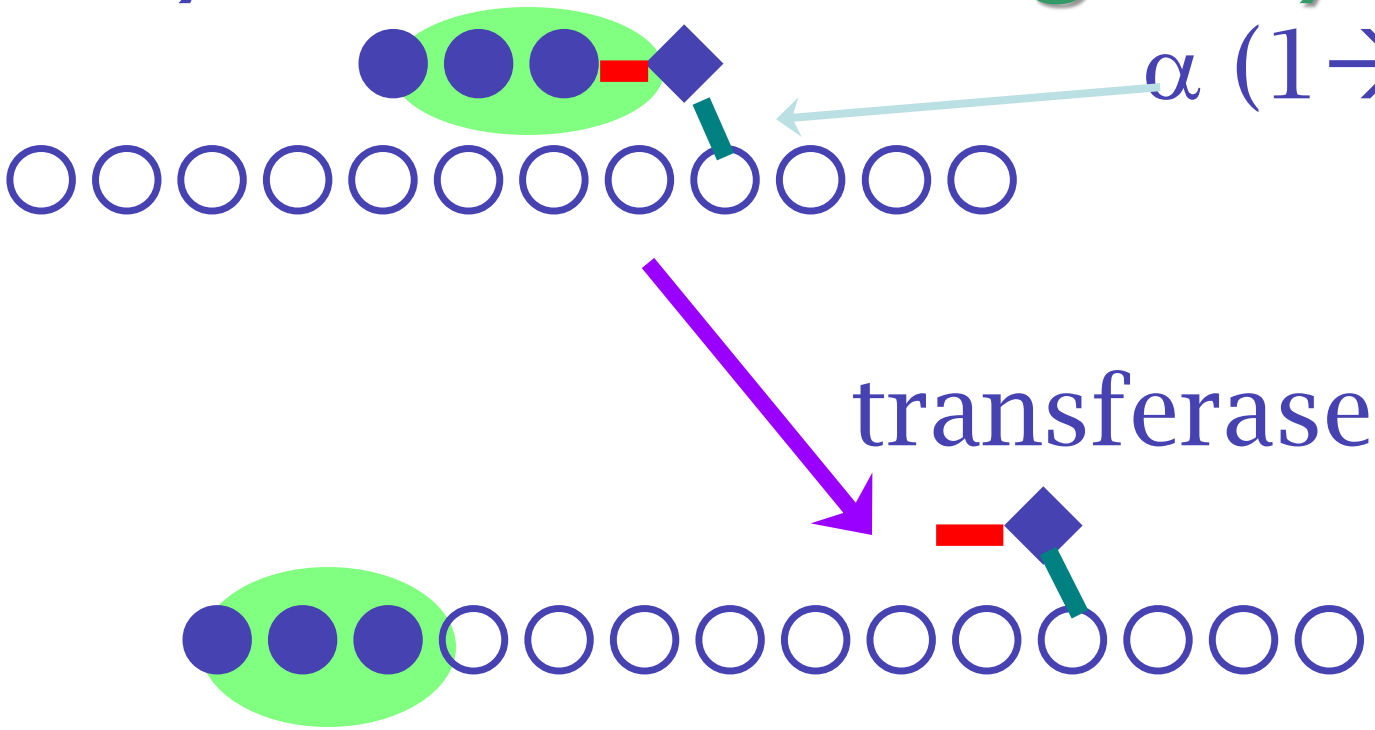
- ***stops*** at fourth glucose from a 1,6 branch point

- contrast with enzymes acting on starch and glycogen in the gut, which yield sugars, *not* sugar phosphates, as products.

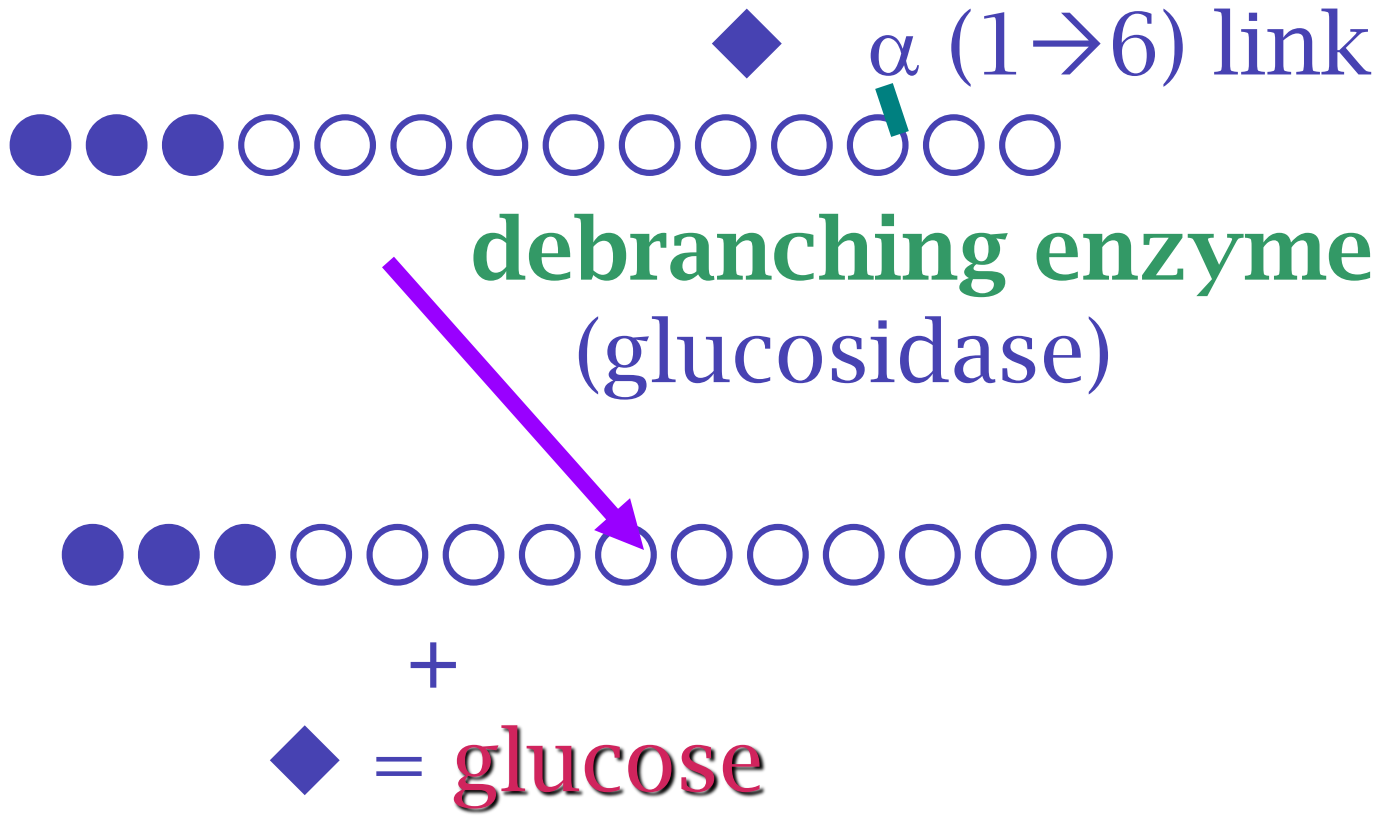
- *activated* by phosphorylation, regulated by glucagon and epinephrine

2. Debranching - two parts

Enzyme = **debranching enzyme** (both)

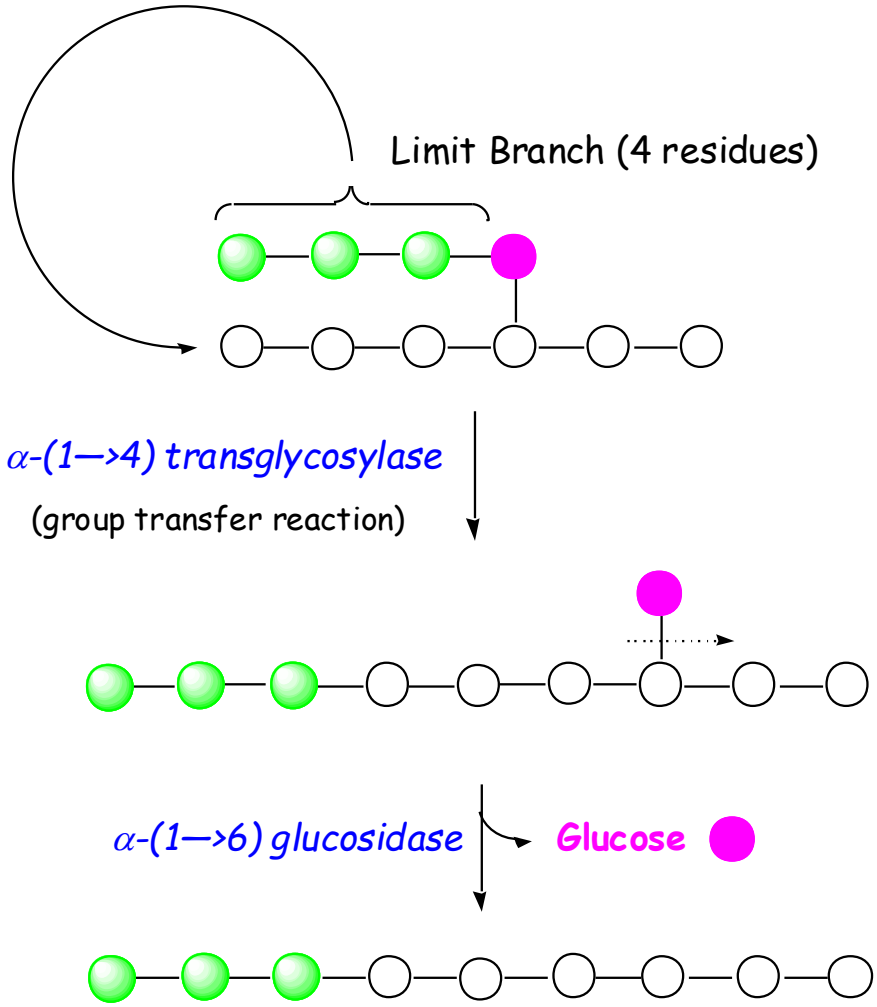


Transfers chain of three glucoses to ***any*** nonreducing end



1,6 linkage cleaved

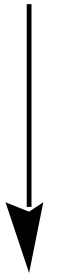
Glycogen Debranching Enzyme



Glycogen Debranching Enzyme

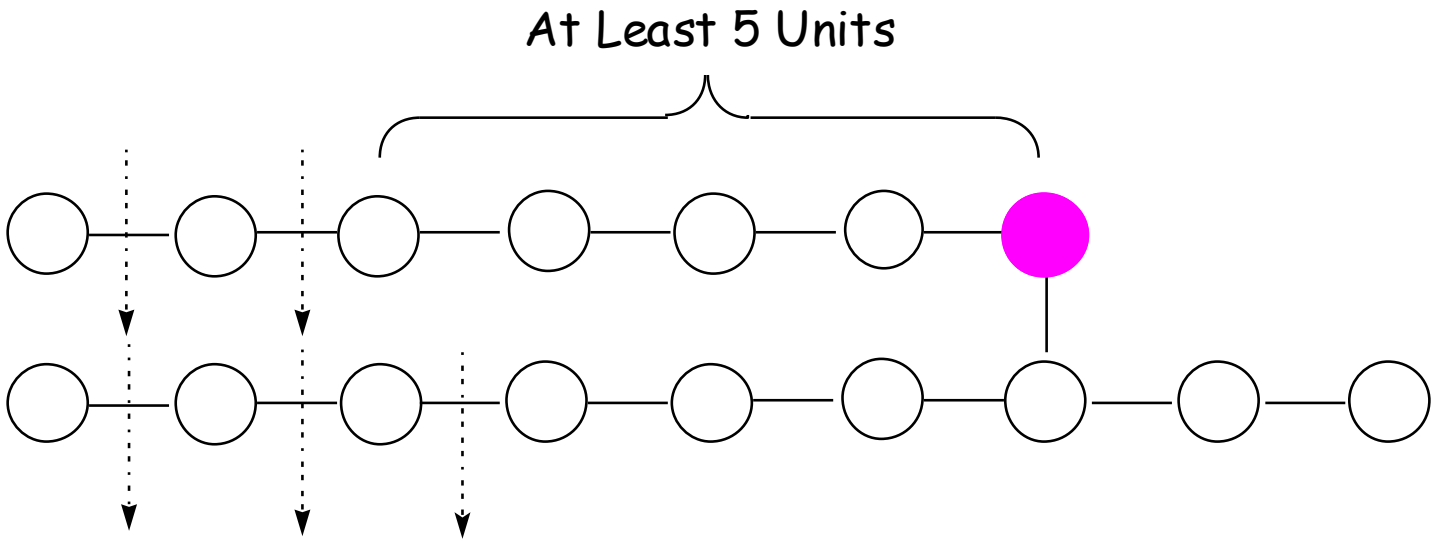
[α(1 —> 6) Linkages]

$(Glucose)_n$

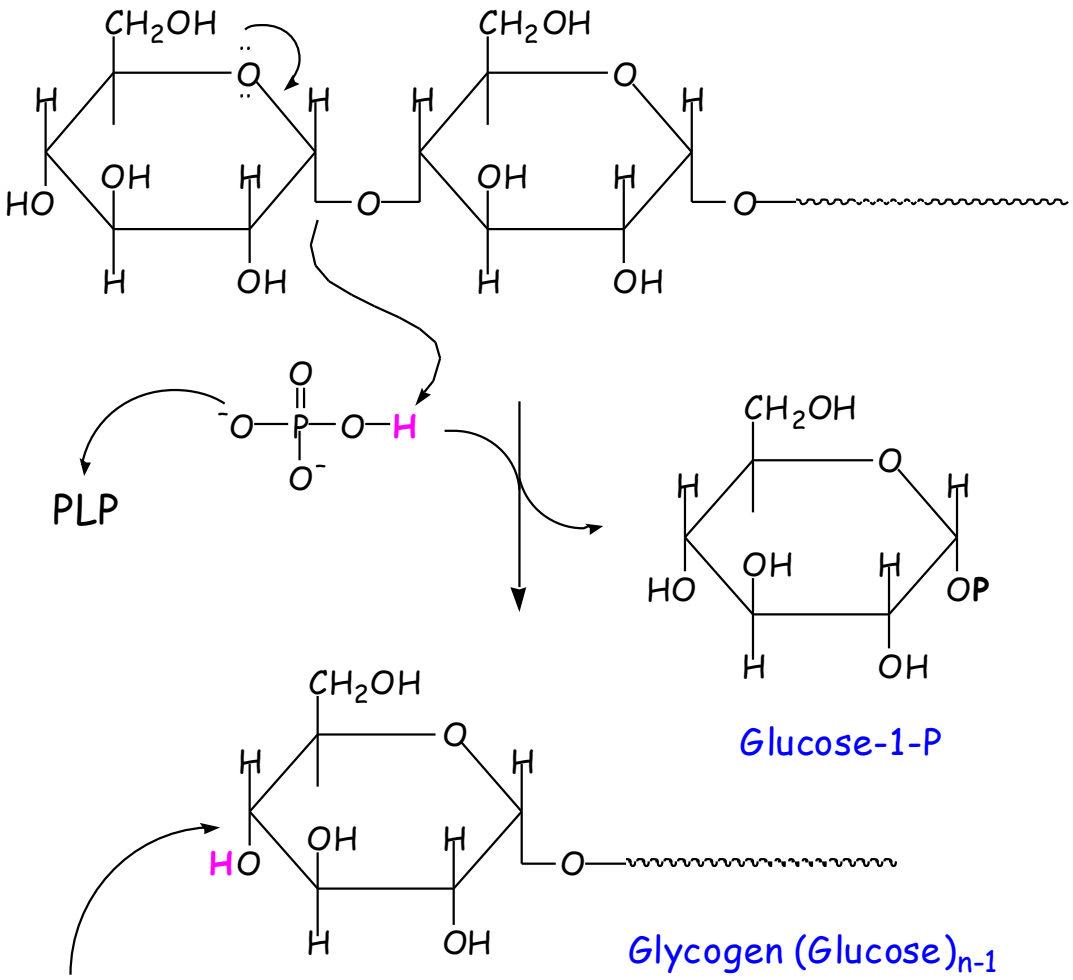


$(Glucose)_{n-1}$ + Glucose

Glycogen Phosphorylase



Reaction of *Glycogen Phosphorylase*



NOTE: Retention of Configuration

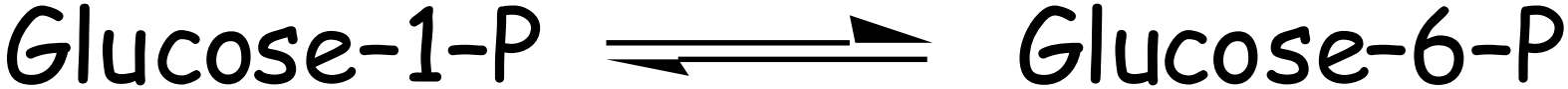
Glycogen Phosphorylase

[α(1 —> 4) Linkages]

$(Glucose)_n + P_i$

$(Glucose)_{n-1} + Glucose\text{-}1\text{-}P$

Phosphoglucomutase



Glycogenolysis

Debranching enzyme has 2 independent active sites, consisting of residues in different segments of a single polypeptide chain:

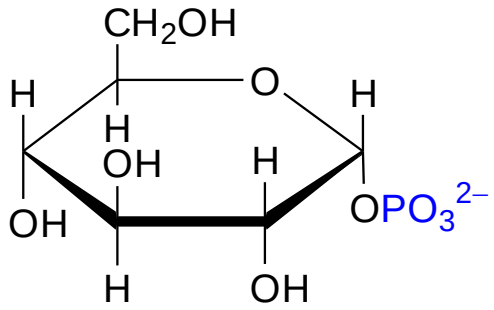
- The **transferase** of the debranching enzyme transfers 3 glucose residues from a 4-residue limit branch to the end of another branch, diminishing the limit branch to a single glucose residue.

Glycogenolysis

- The **α(1→6) glucosidase** moiety of the debranching enzyme then catalyzes hydrolysis of the **α(1→6)** linkage, yielding free **glucose**. This is a minor fraction of glucose released from glycogen.
- View an animation

The major product of glycogen breakdown is **glucose-1-phosphate**, from Phosphorylase activity.

Glycogen catabolism (breakdown):



glucose-1-phosphate

Glycogen Phosphorylase catalyzes phosphorolytic cleavage of the **α(1→4)** glycosidic linkages of glycogen, releasing glucose-1-phosphate as reaction product.

$glycogen_{(n\ residues)} + P_i \rightarrow$

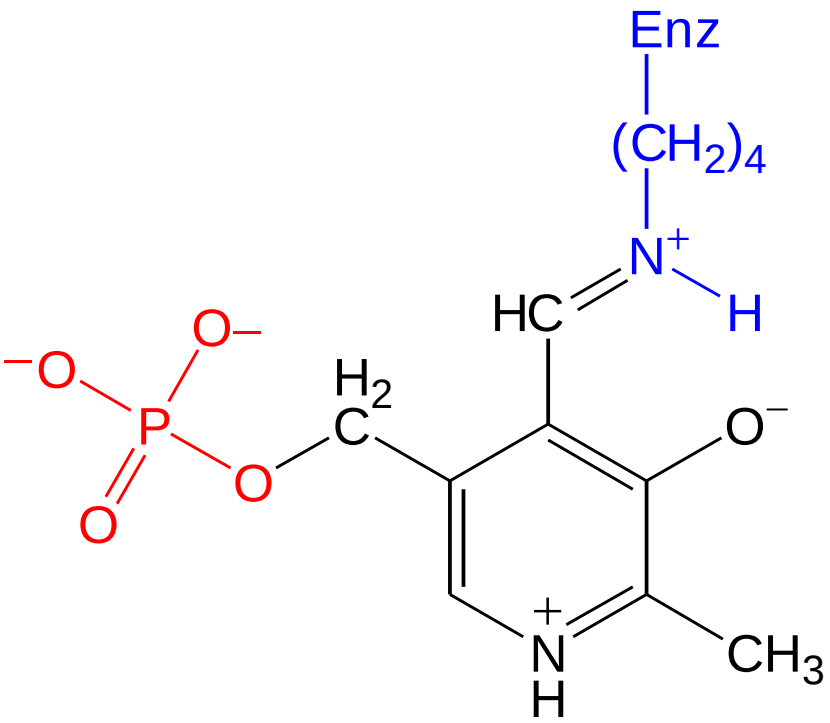
$glycogen_{(n-1\ residues)}$ + glucose-1-phosphate

This **phosphorolysis** may be compared to hydrolysis:

Hydrolysis: **R-O-R' + HOH → R-OH + R'-OH**

Phosphorolysis: **R-O-R' + $HO\text{-}PO_3^{2-}$ → R-OH + $R'\text{-}O\text{-}PO_3^{2-}$**

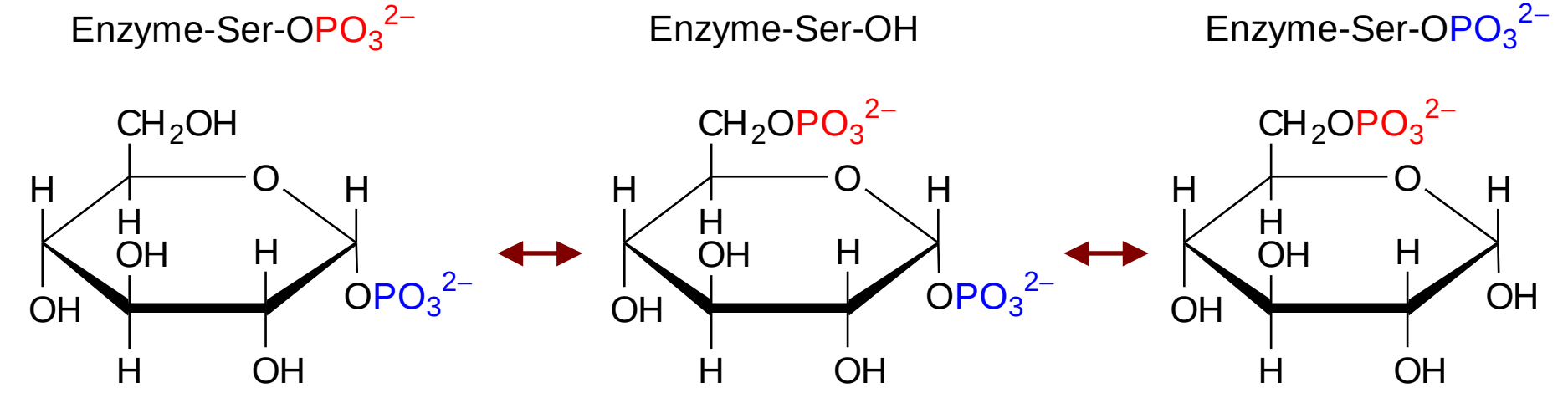
The **P_i substrate** binds between the phosphate of PLP and the glycosidic O linking the terminal glucose residue of the glycogen.



Enzyme (Lys)-PLP Schiff base

After the phosphate substrate donates **H^+** during cleavage of the glycosidic bond, it receives H^+ from the phosphate moiety of PLP.

PLP then takes back the H^+ as the phosphate O attacks C1 of the cleaved glucose to yield glucose-1-phosphate



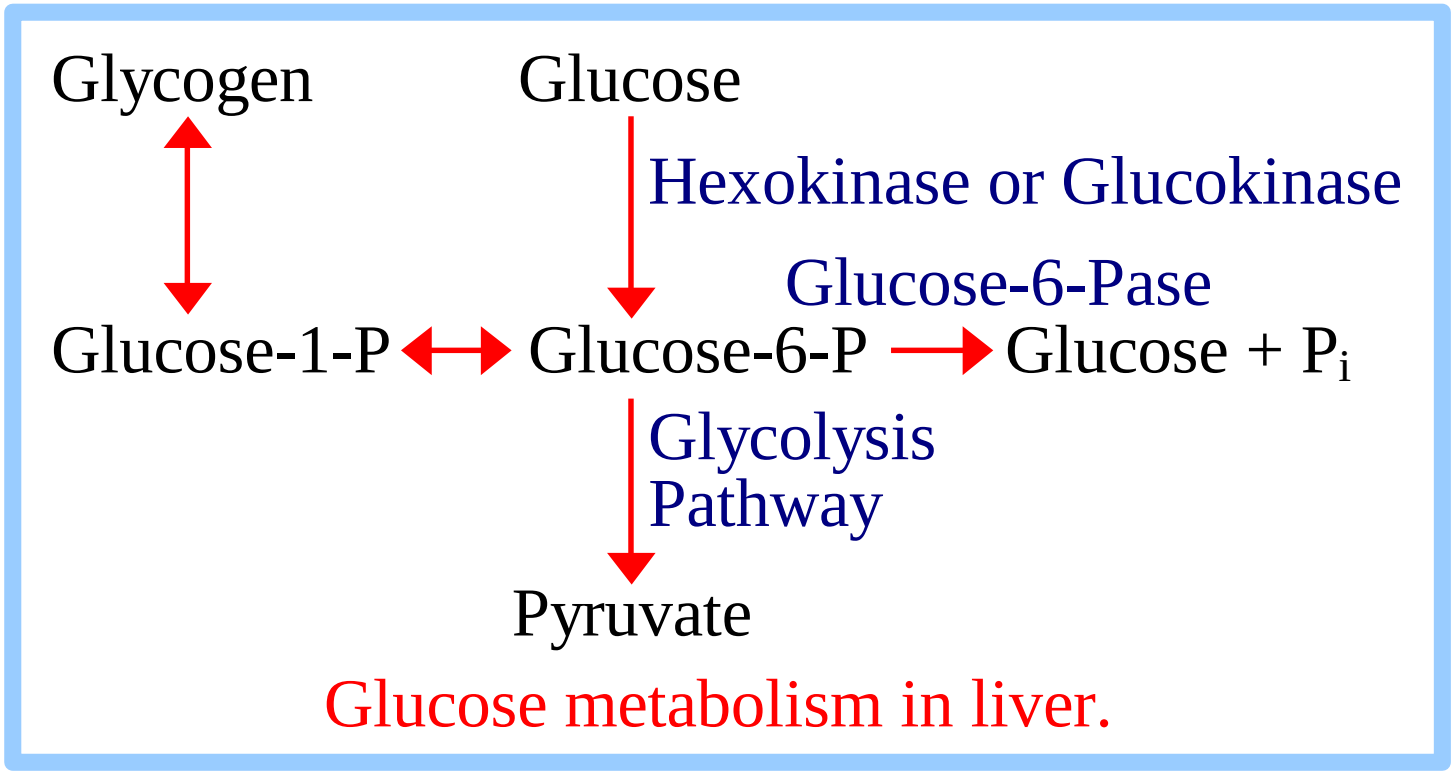
Phosphoglucomutase catalyzes the reversible reaction:

glucose-1-phosphate ←→ glucose-6-phosphate

A **serine OH** at the active site donates & accepts P_i.

The bisphosphate is not released.

Phosphoglycerate Mutase has a similar mechanism, but instead uses His for P_i transfer.



Glucose metabolism in liver.

Glucose-6-phosphate may enter Glycolysis or (mainly in liver) be dephosphorylated for release to the blood.

Liver **Glucose-6-phosphatase** catalyzes the following, essential to the liver's role in maintaining blood glucose:

glucose-6-phosphate + H_2O → glucose + P_i

Most other tissues lack this enzyme.

Glycogenesis

Glycogenesis is the synthesis of glycogen.

It mainly takes place in: liver, muscles, brain and stomach

Glycogenesis

= GLYCOGEN BIOSYNTHESIS

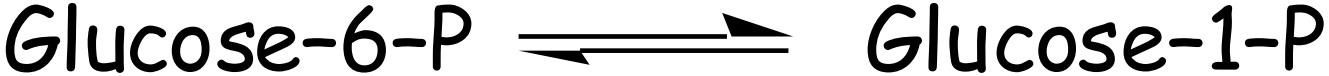
==========

☺Glucose is transported into the liver cell by a specific glucose transporter and immediately phosphorylated.

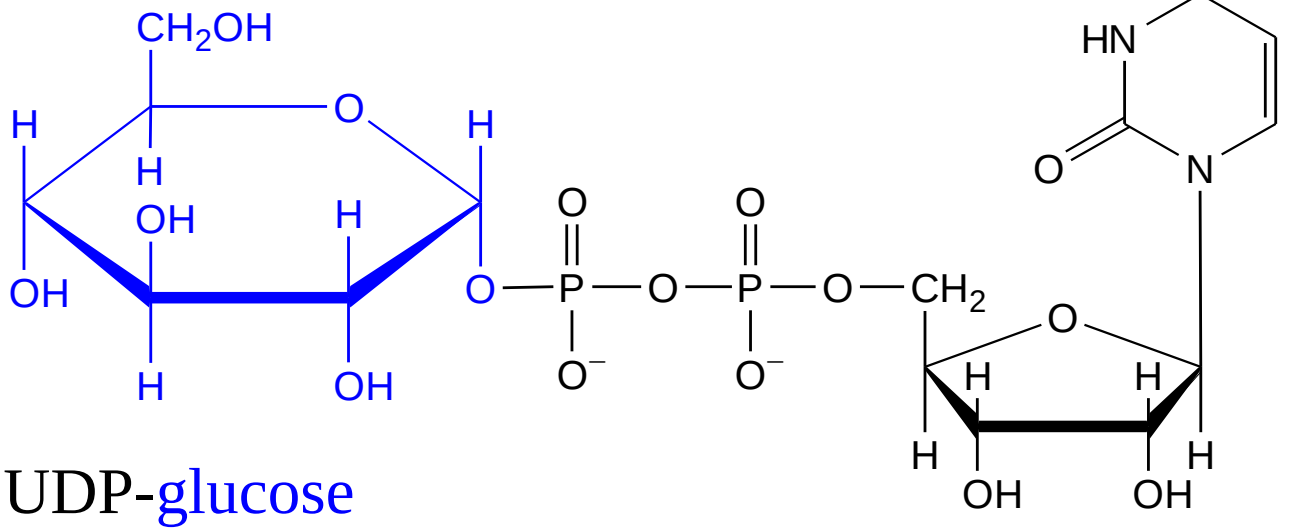
==========

-- Most of the glucose in a cell is in the form of glucose-6-phosphate.

Phosphoglucomutase



Glycogen synthesis



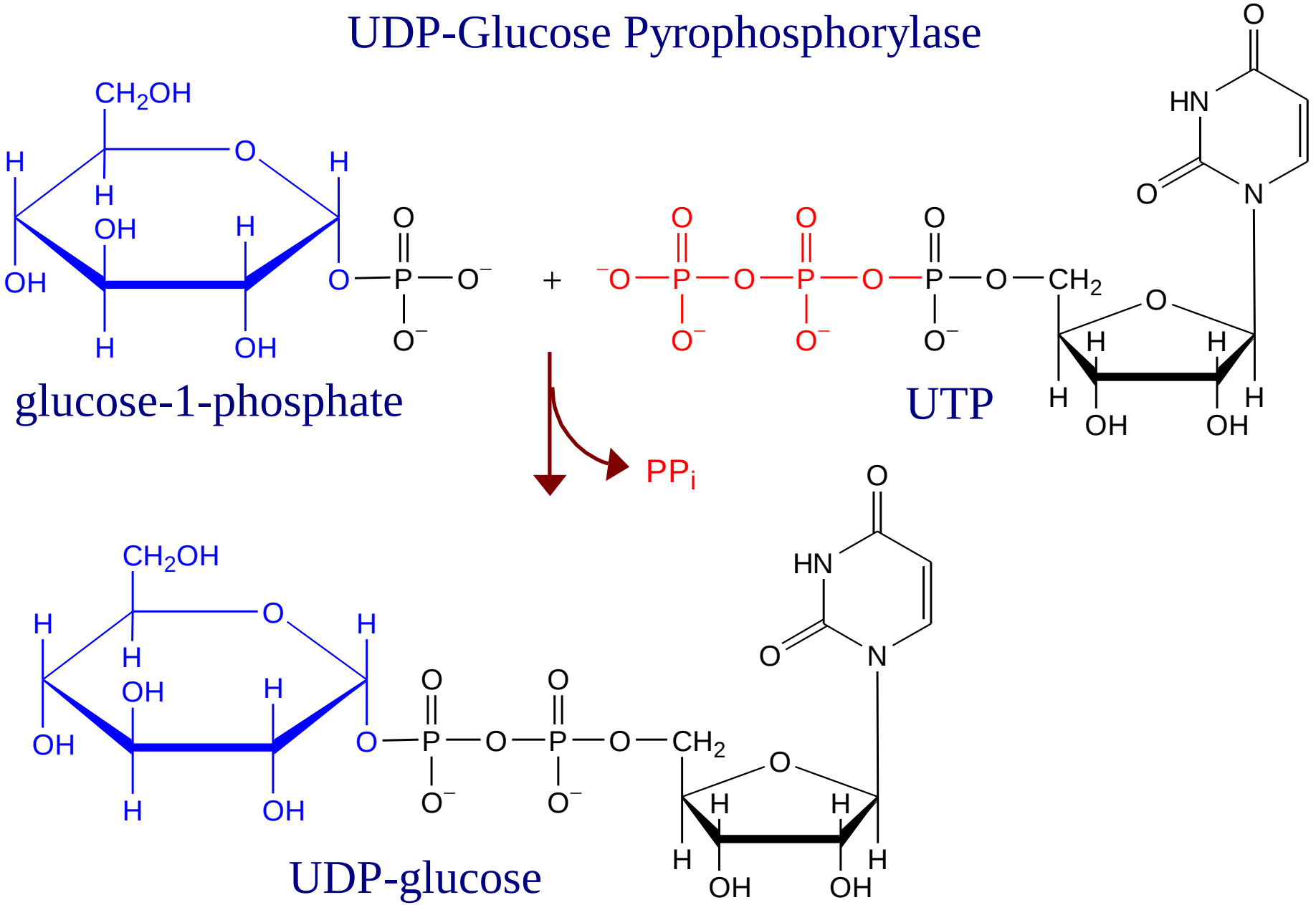
UDP-glucose

Uridine diphosphate glucose (UDP-glucose) is the immediate precursor for **glycogen synthesis**.

As glucose residues are added to glycogen, UDP-glucose is the substrate and UDP is released as a reaction product.

Nucleotide diphosphate sugars are precursors also for synthesis of other complex carbohydrates, including oligosaccharide chains of glycoproteins, etc.

UDP-Glucose Pyrophosphorylase



UDP-glucose is formed from glucose-1-phosphate:

- **glucose-1-phosphate + UTP → UDP-glucose + PP_i**
- **PP_i + H_2O → 2 P_i**

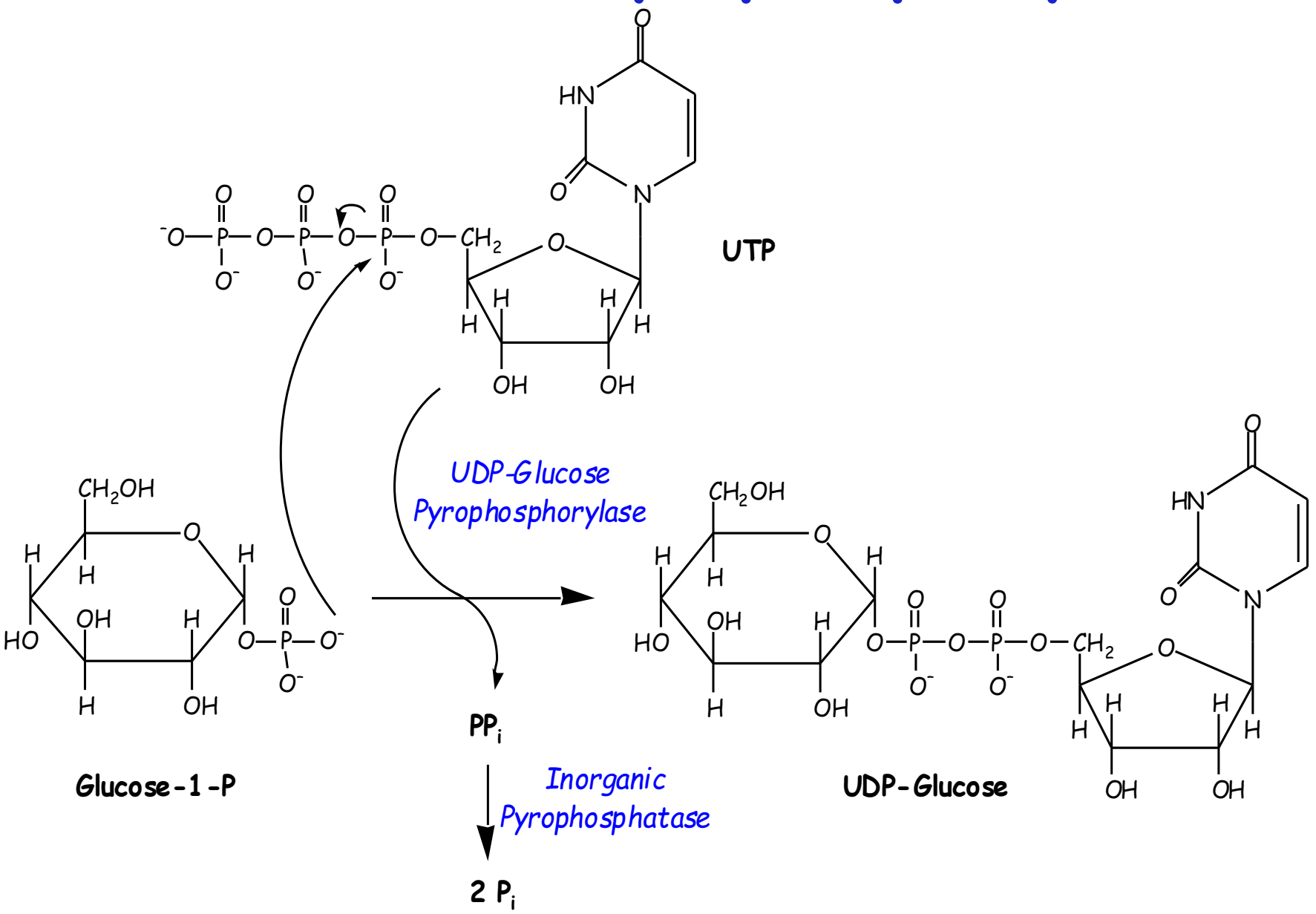
Overall:

- **glucose-1-phosphate + UTP → UDP-glucose + 2 P_i**

Spontaneous hydrolysis of the ~P bond in PP_i (P~P) drives the overall reaction.

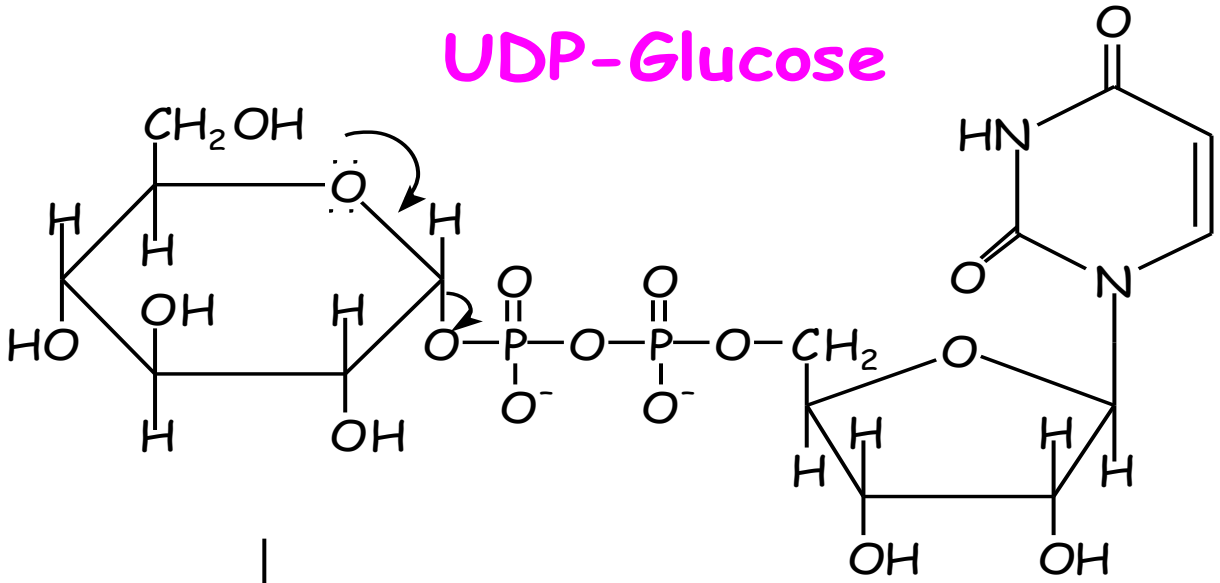
Cleavage of PP_i is the only energy cost for glycogen synthesis (<u>one</u> ~P bond per glucose residue).

UDP-Glucose Pyrophosphorylase

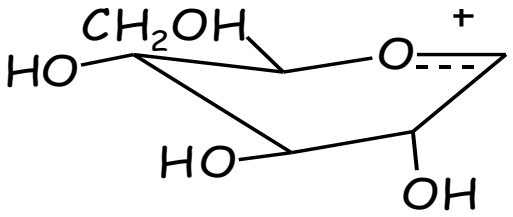


Glycogen Synthase I

UDP-Glucose

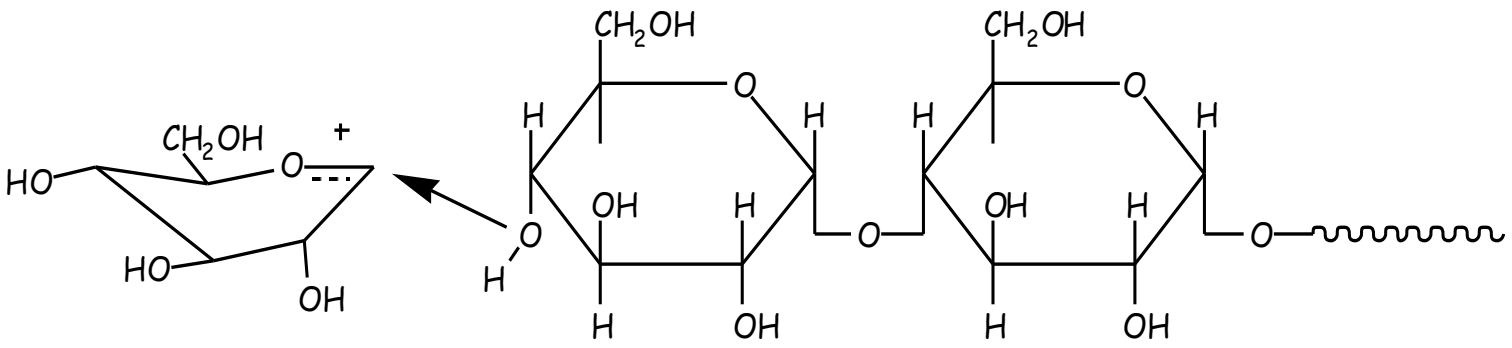


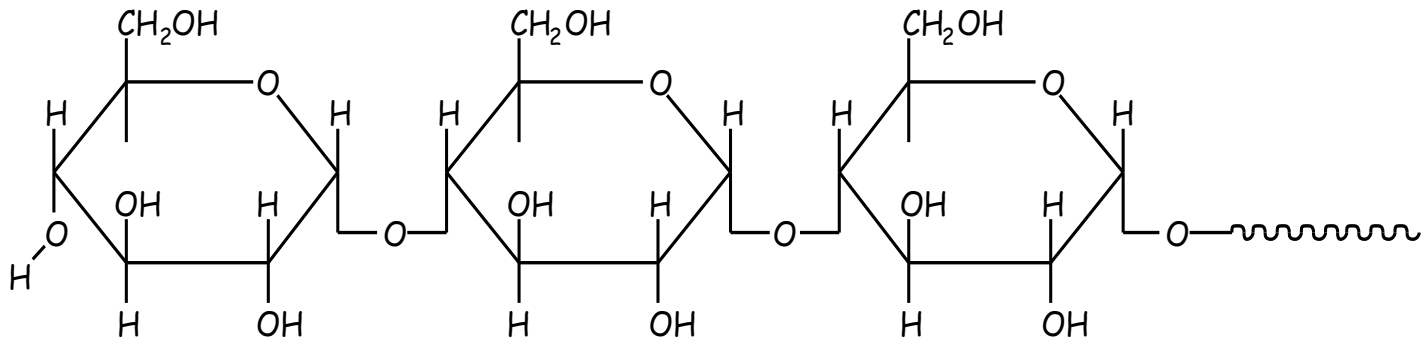
UDP

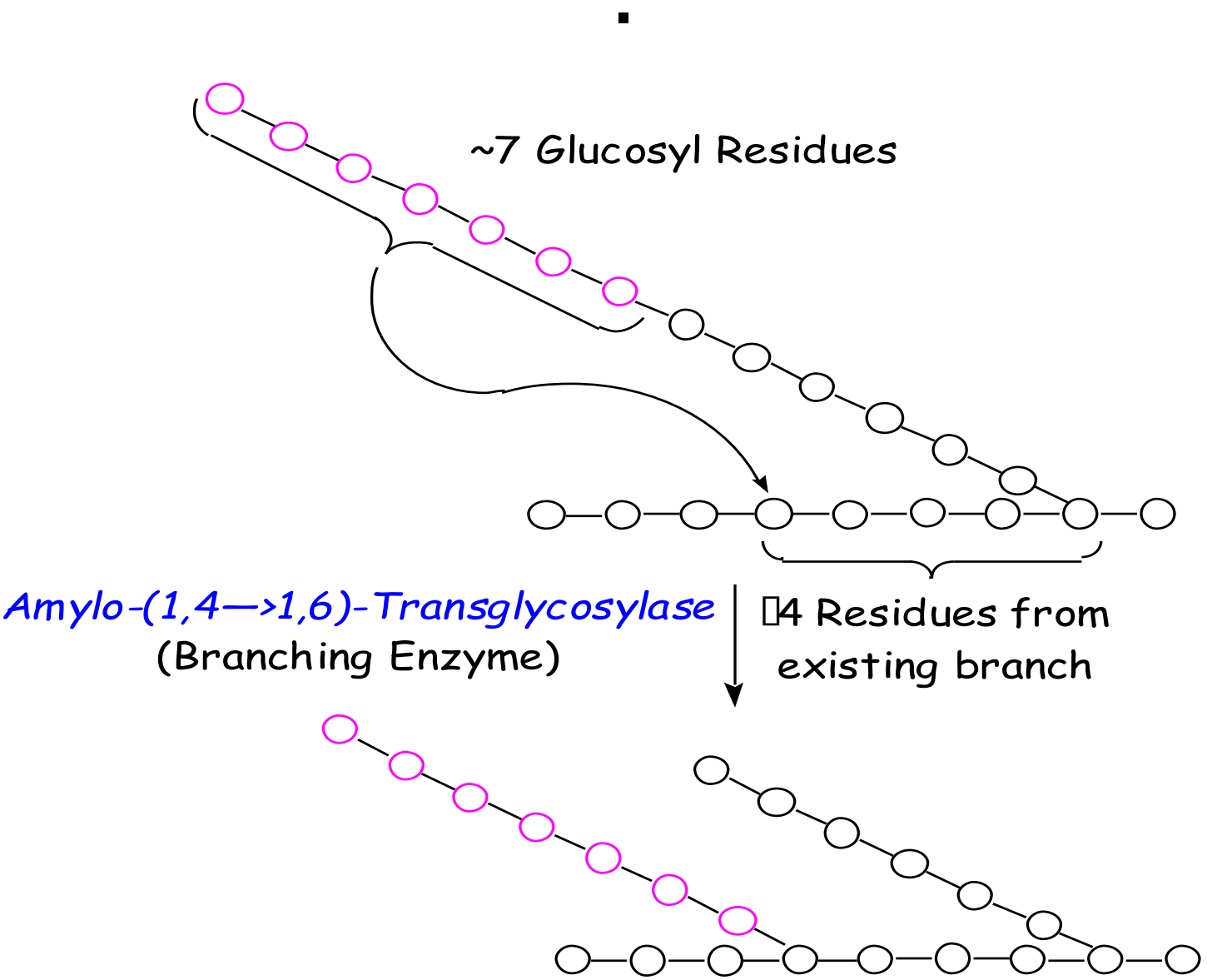


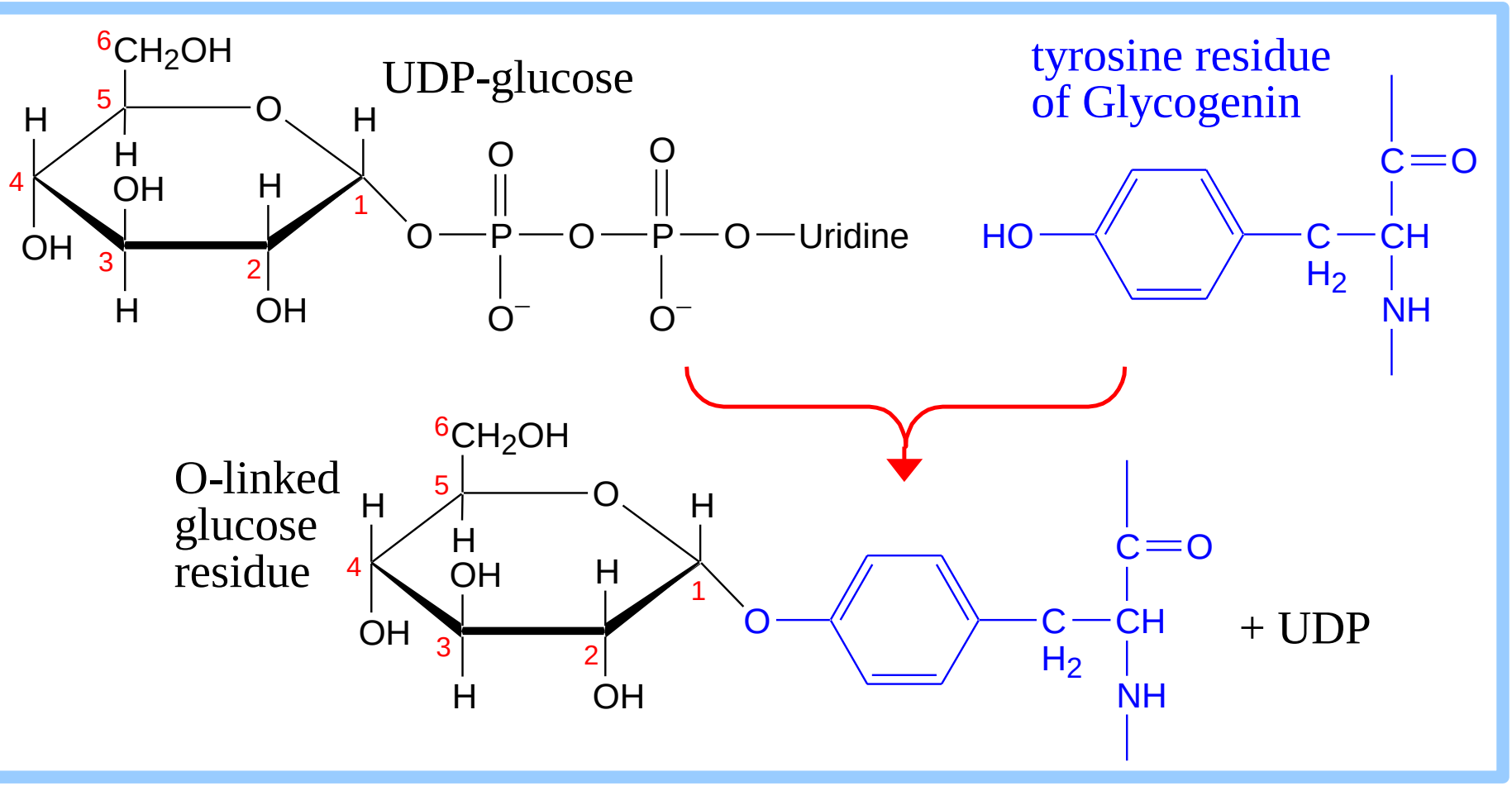
Oxonium Ion

Glycogen Synthase II






~7 Glucosyl Residues
Amylo-(1,4—>1,6)-Transglycosylase
(Branching Enzyme)
4 Residues from
existing branch



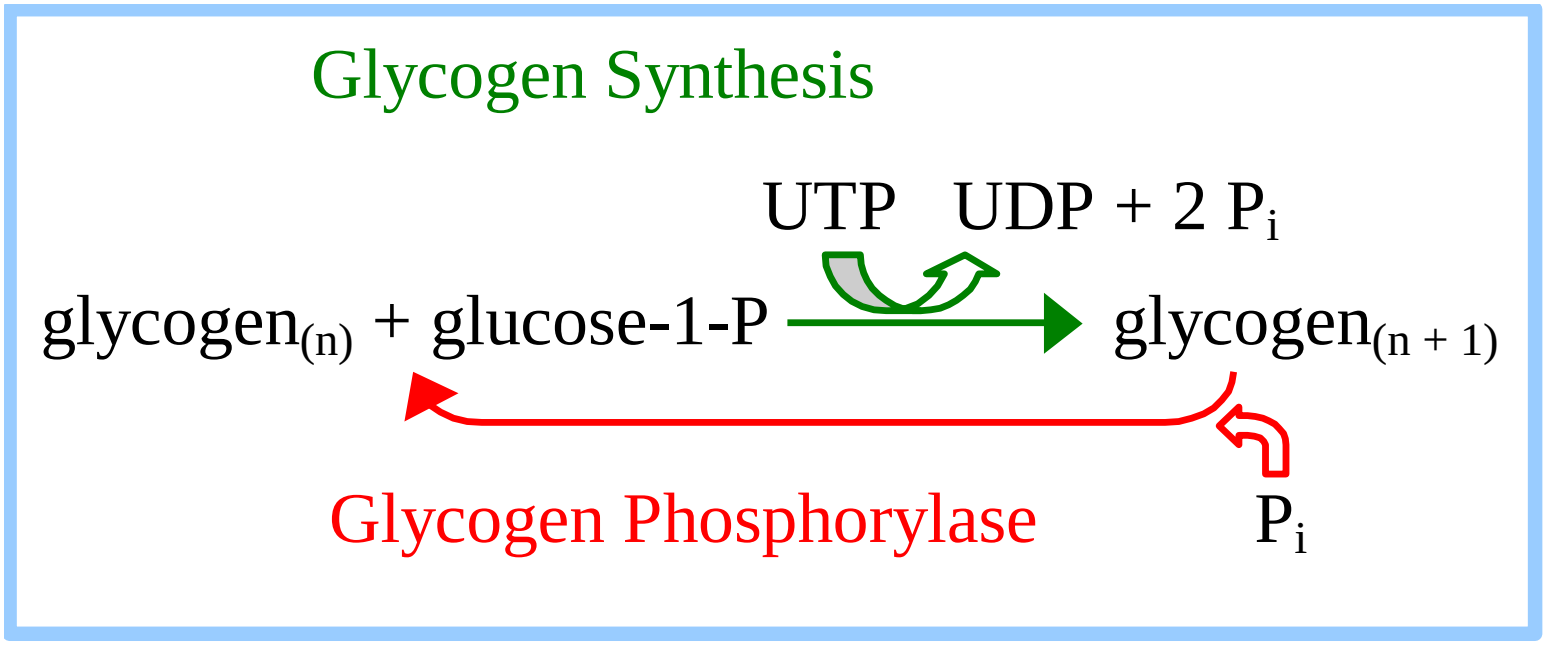
A **glycosidic bond** is formed between the anomeric C1 of the glucose moiety derived from UDP-glucose and the hydroxyl oxygen of a **tyrosine** side-chain of **Glycogenin**.

UDP is released as a product.

Glycogen Synthase catalyzes transfer of the glucose moiety of UDP-glucose to the hydroxyl at C4 of the terminal residue of a glycogen chain to form an **α(1→ 4)** glycosidic linkage:

$$\text{glycogen}_{(n\ \text{residues})} + \text{UDP-glucose} \rightarrow \text{glycogen}_{(n+1\ \text{residues})} + \text{UDP}$$

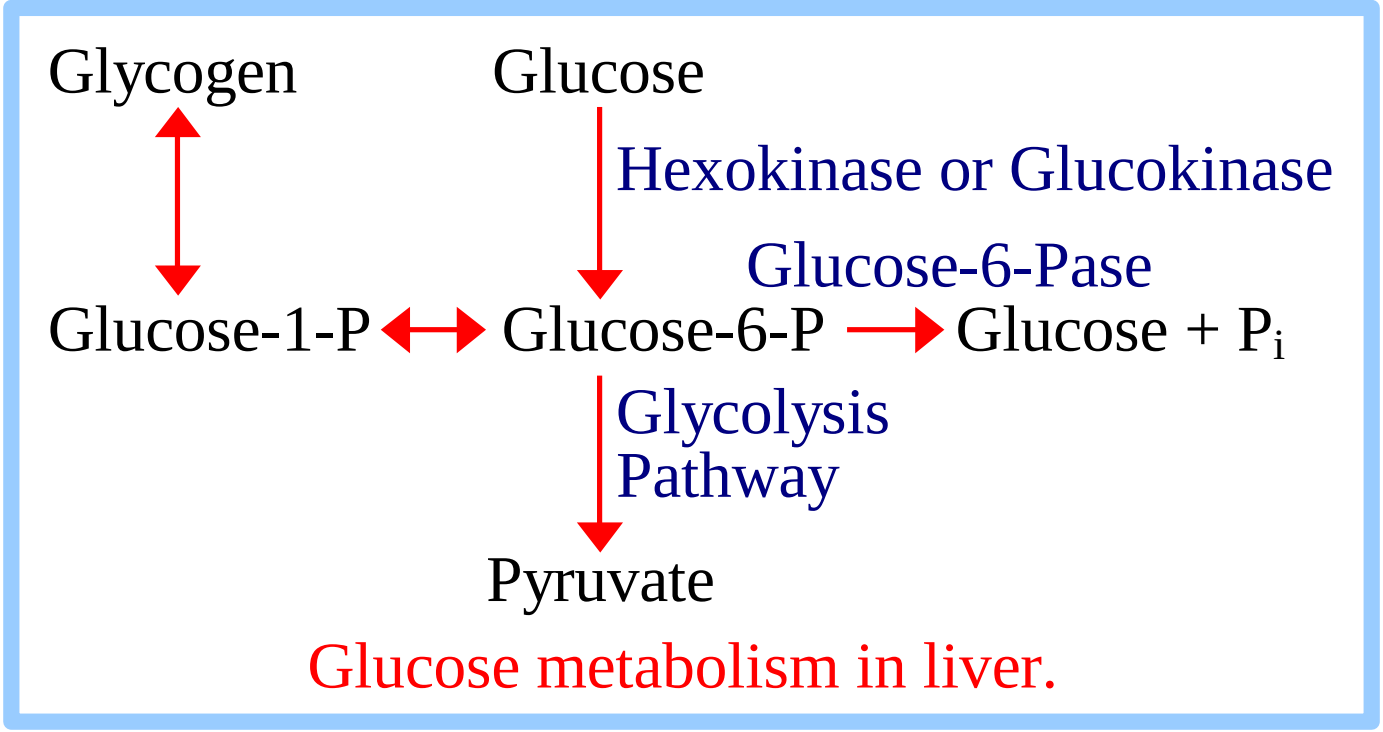
A **branching enzyme** transfers a segment from the end of a glycogen chain to the C6 hydroxyl of a glucose residue of glycogen to yield a branch with an **α(1→6)** linkage.



Both synthesis & breakdown of glycogen are spontaneous.

If both pathways were active simultaneously in a cell, there would be a "**futile cycle**" with cleavage of **one ~P bond per cycle** (in forming UDP-glucose).

To prevent such a futile cycle, Glycogen Synthase and Glycogen Phosphorylase are **reciprocally regulated**, by allosteric effectors and by phosphorylation.

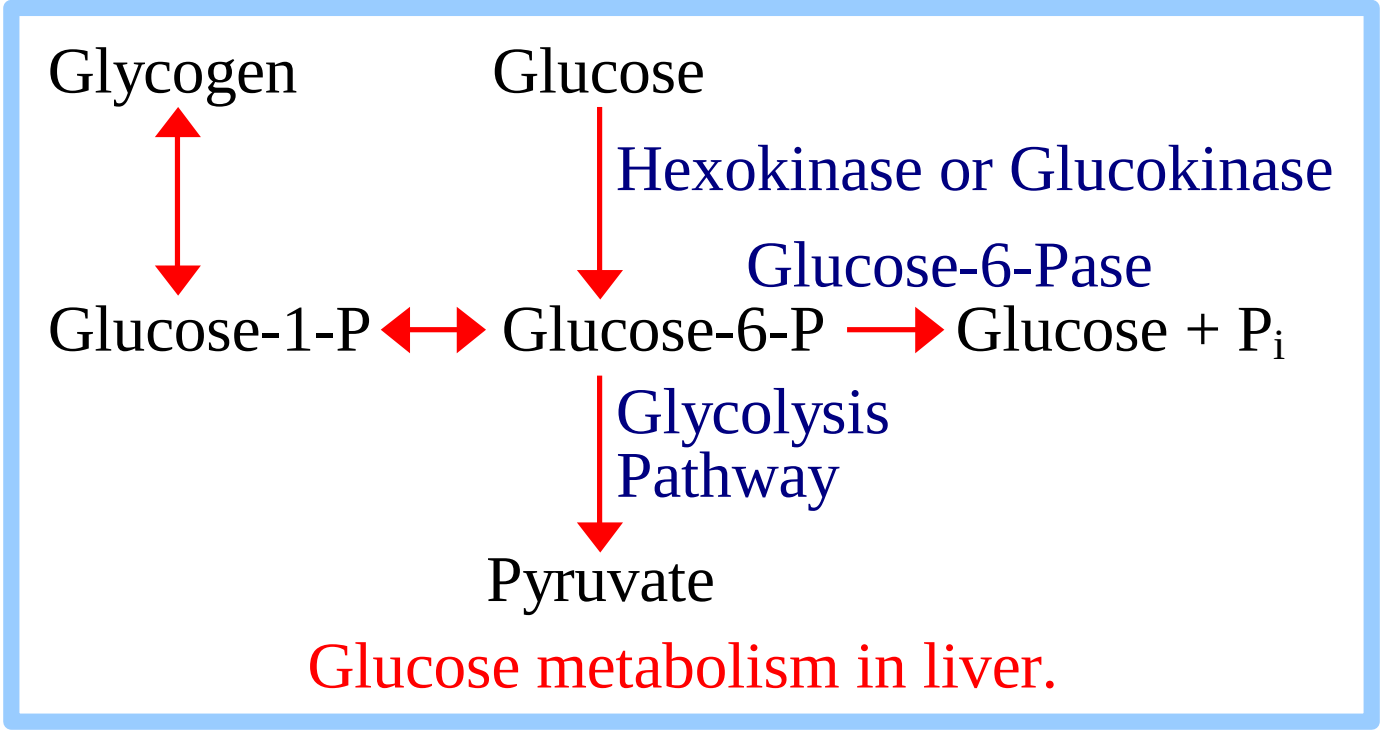


Glucose metabolism in liver.

Glycogen Synthase is allosterically **activated** by **glucose-6-P** (opposite of effect on Phosphorylase).

Thus Glycogen Synthase is active when high blood glucose leads to elevated intracellular glucose-6-P.

It is useful to a cell to store glucose as glycogen when the input to Glycolysis (glucose-6-P), and the main product of Glycolysis (ATP), are adequate.



Glucose metabolism in liver.

High cytosolic glucose-6-phosphate, which would result when blood glucose is high, turns off the signal with regard to glycogen synthesis.

The conformation of Glycogen Synthase induced by the allosteric activator glucose-6-phosphate is susceptible to dephosphorylation by Protein Phosphatase.

◆Glucose stored in polymeric form as glycogen mostly in the liver and skeletal muscle.

◆ Glucose can be rapidly delivered to the blood stream when needed upon degradation of glycogen.
= **glycogenolysis**

◆ Enough glucose and energy triggers synthesis of glycogen.
= **glycogenesis**

4 Glycogen synthesis

Enzyme = ***glycogen synthase***

UDP-glucose + $(glucose)_n$ → UDP + $(glucose)_{n+1}$

Insulin

-- ***High levels of glucose*** induce release of insulin from β-cells of islets of Langerhan in the pancreas.
-- Insulin is polypeptide hormone.
-- Detected by receptors at surface of ***muscle*** cells.
-- Increases glycogenesis in muscle.
-- Intracellular signal pathway involves complex sequential phosphorylations and dephosphorylations.

Physiological importance of glycogenesis

- Reserve of glucose molecules
- There is no *hypoglyccemia* when there is enough reserve of glucose.

Glycogenolysis

Glycogen is cleaved from the non reducing ends of the chain by the enzyme glycogen phosphorylase to produce monomers of glucose-1-phosphate that is then converted to glucose-6-phosphate. A special debranching enzyme is needed to remove the alpha(1-6) branches in branched glycogen and reshape the chain into linear polymer.

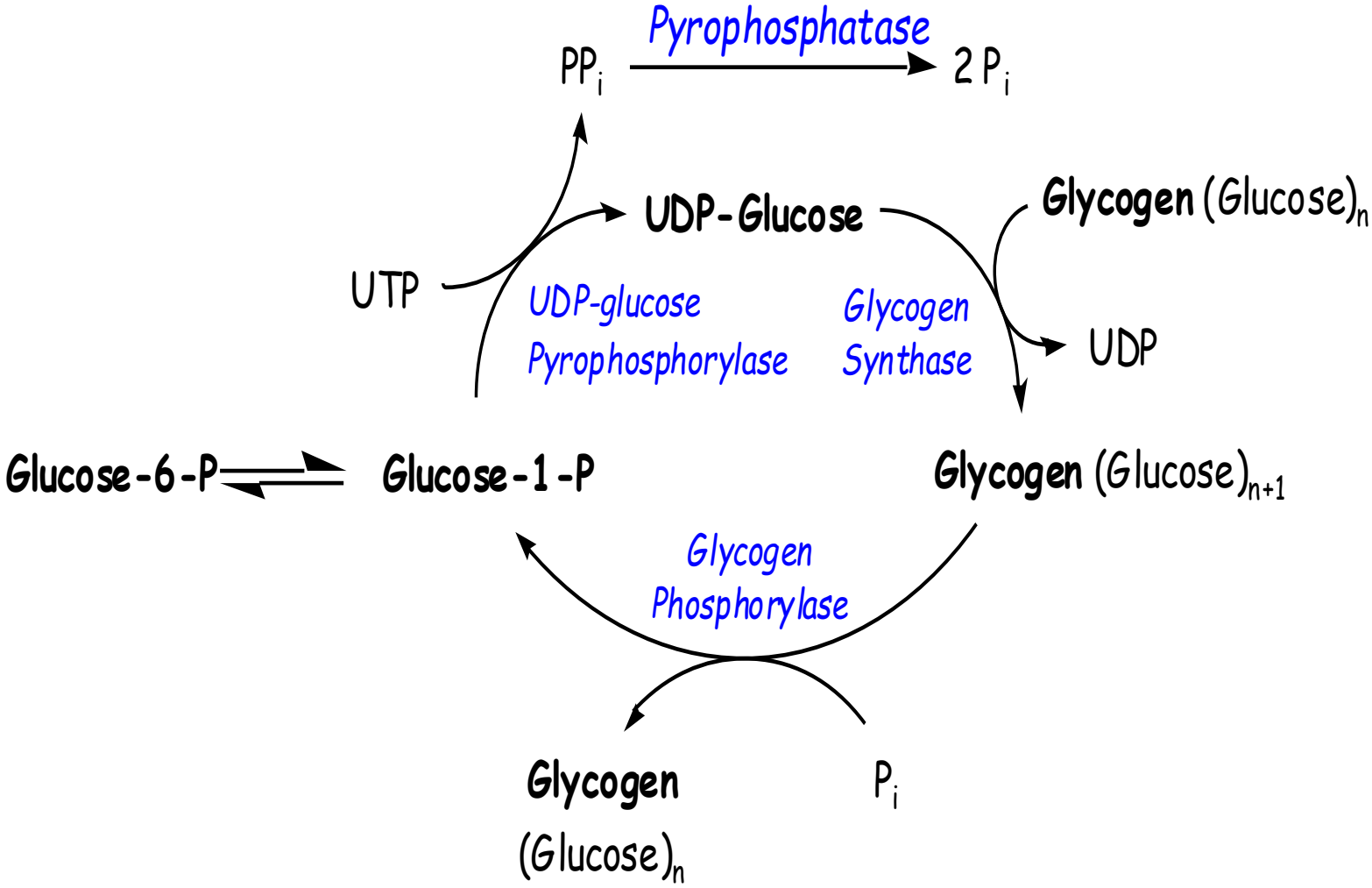
Glycogenolysis

- The G-6-P monomers produced have three possible fates:
- G-6-P can continue on the glycolysis pathway and be used as fuel.
- G-6-P can enter the PPPW via the enzyme glucose-6-phosphate dehydrogenase to produce NADPH and 5-carbon sugars.

Glycogenolysis

- In the liver and kidney, G-6-P can be dephosphorylated back to glucose by the enzyme glucose-6-phosphatase. This is the final step in the gluconeogenesis pathway.

Glycogenesis & Glycogenolysis: summary



Cellular aerobic respiration

The cellular aerobic respiration (CAR) is a biochemical pathway the living cells use to synthesize a maximum number of energy (ATP molecules) needed in different cell activities.

The CAR summary:

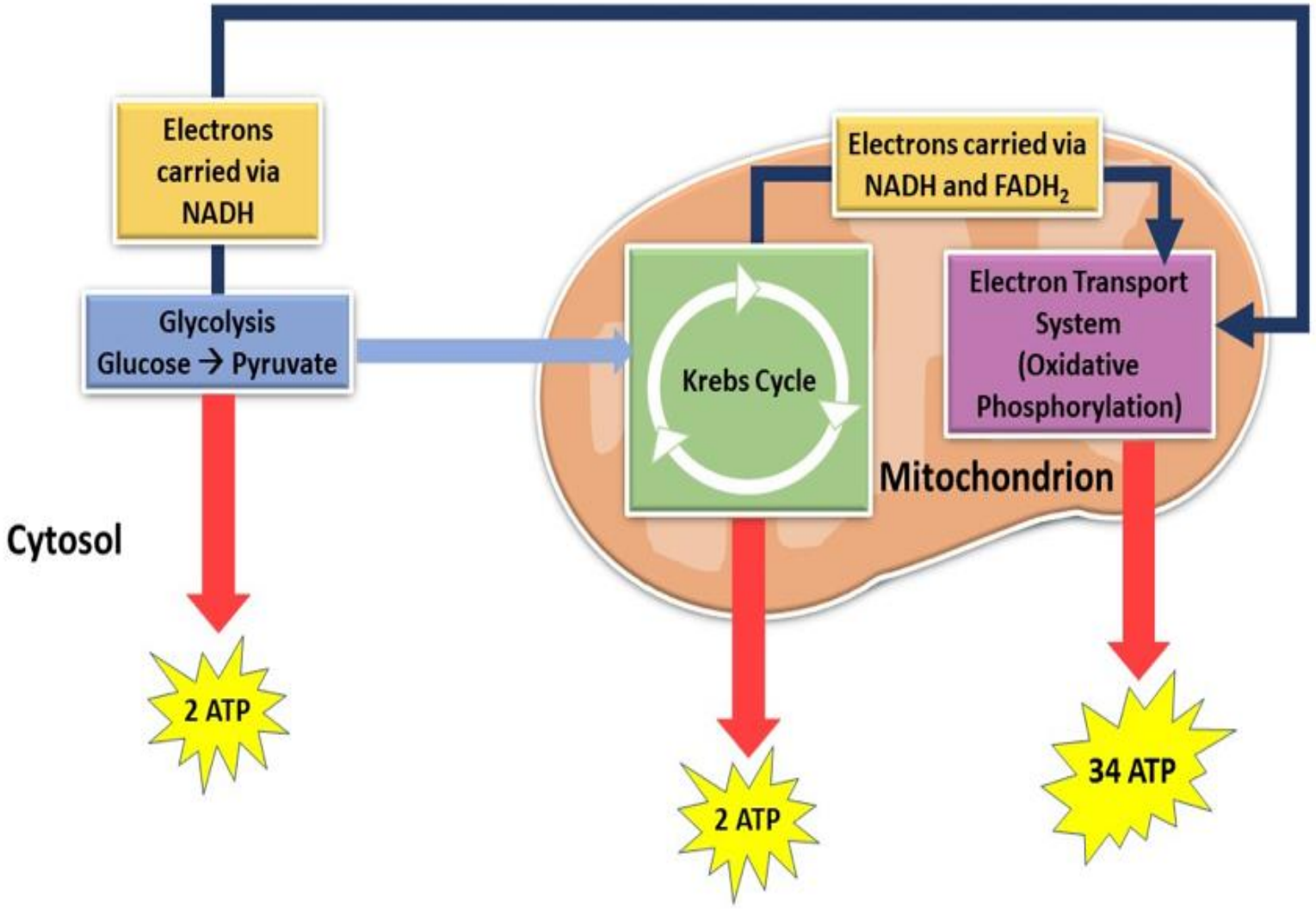
$$C_6H_{12}O_6 + O_2 \rightarrow 6CO_2 + H_2O + E\ (ATP)$$

Cellular aerobic respiration

The cellular aerobic respiration (CAR) includes the following pathways:

- *aerobic glycolysis*
- *Krebs cycle*
- *electron transport chain.*

CELLULAR AEROBIC RESPIRATION

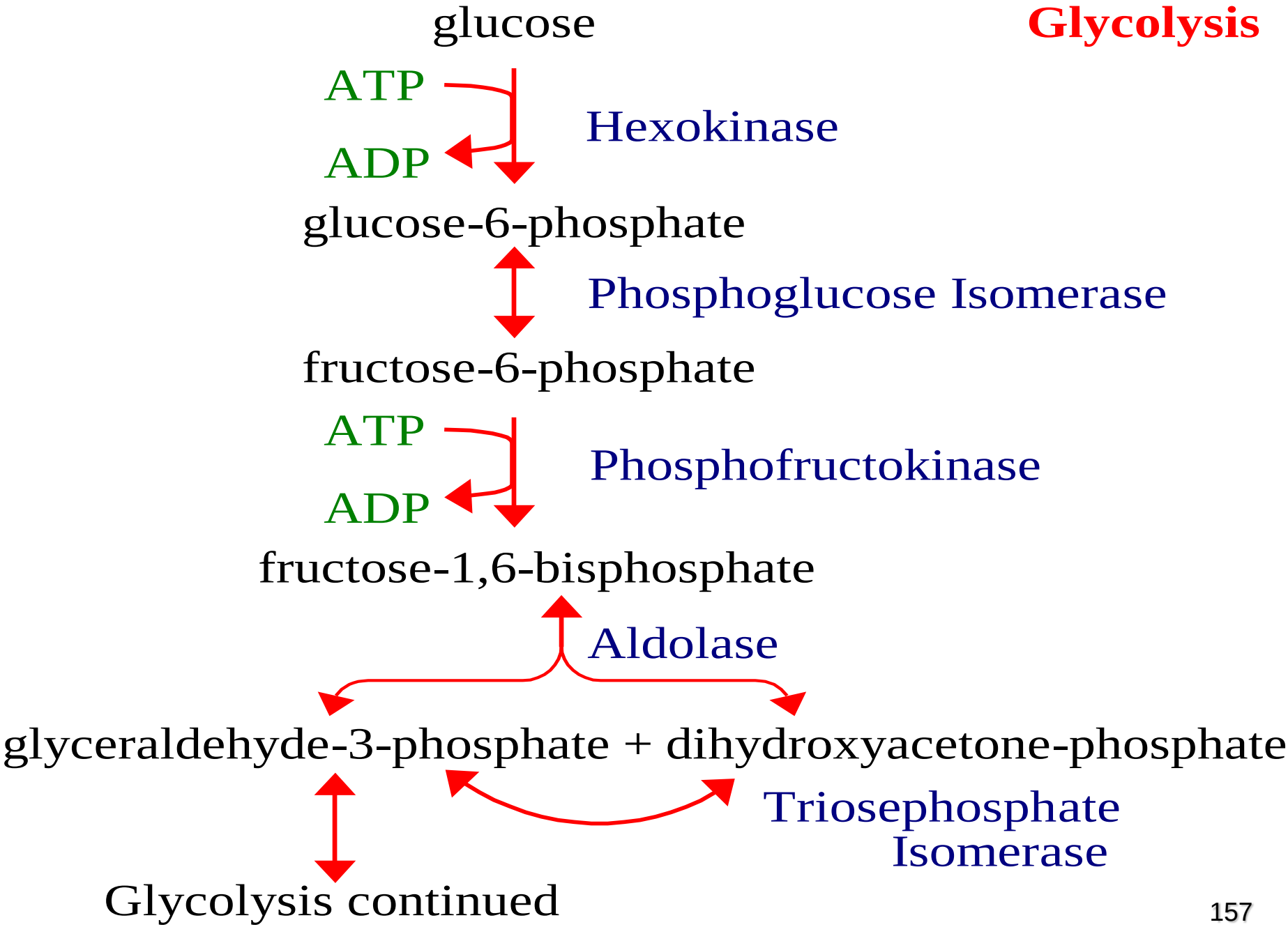


Glycolysis

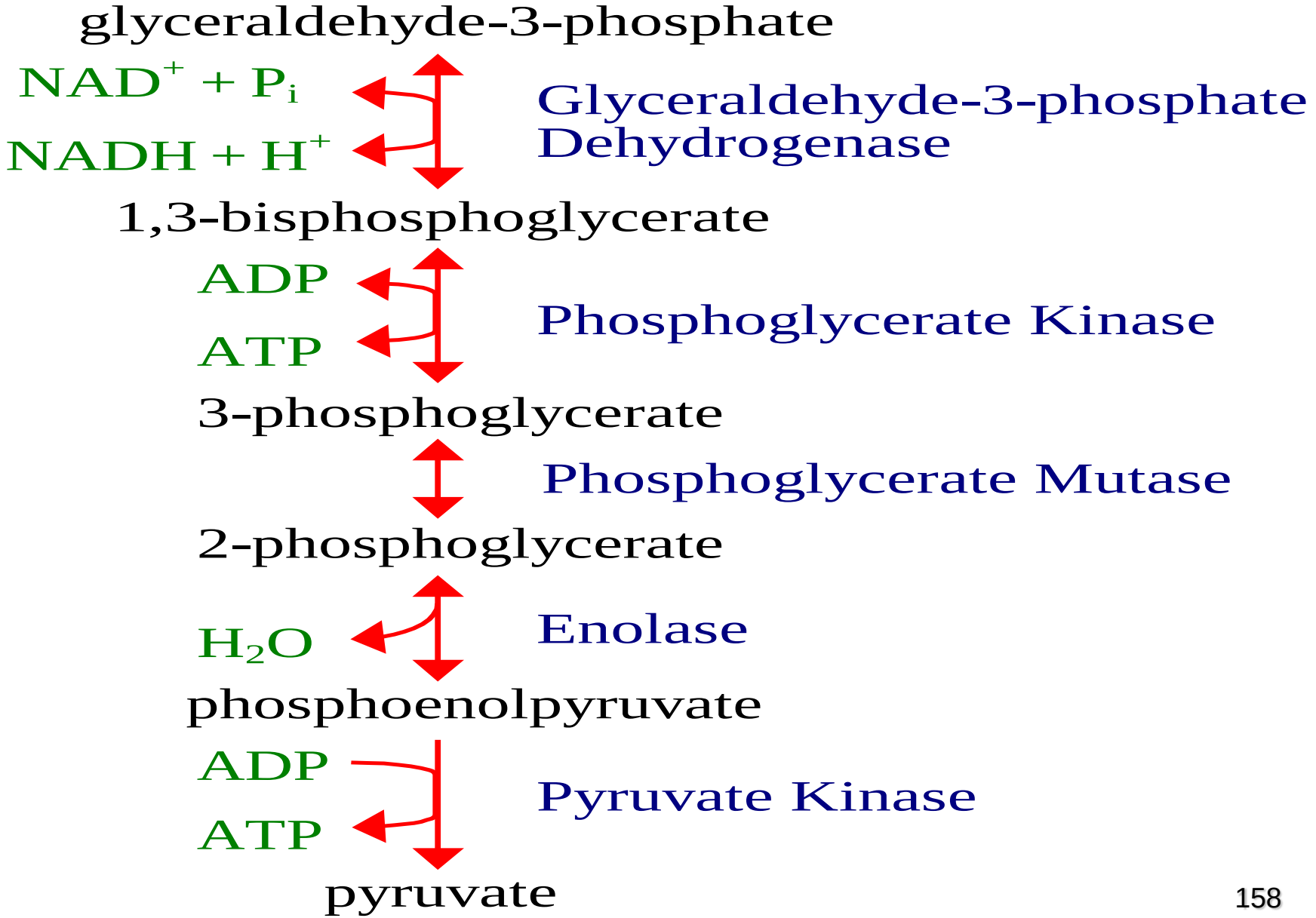
Glycolysis is the breakdown of a molecule of glucose to produce 2 molecules of pyruvate, ATP and $NADH_2$.

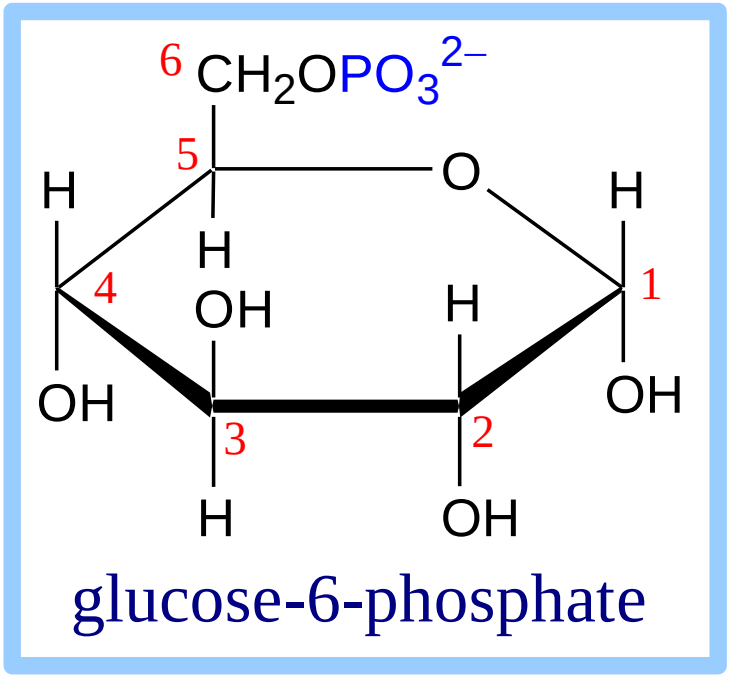
Glycolysis takes place in the cytoplasm of a cell and involves the steps shown on the next slides:

Glycolysis


glucose
ATP
ADP
Hexokinase
glucose-6-phosphate
Phosphoglucose Isomerase
fructose-6-phosphate
ATP
ADP
Phosphofructokinase
fructose-1,6-bisphosphate
Aldolase
glyceraldehyde-3-phosphate + dihydroxyacetone-phosphate
Triosephosphate Isomerase
Glycolysis continued

Glycolysis

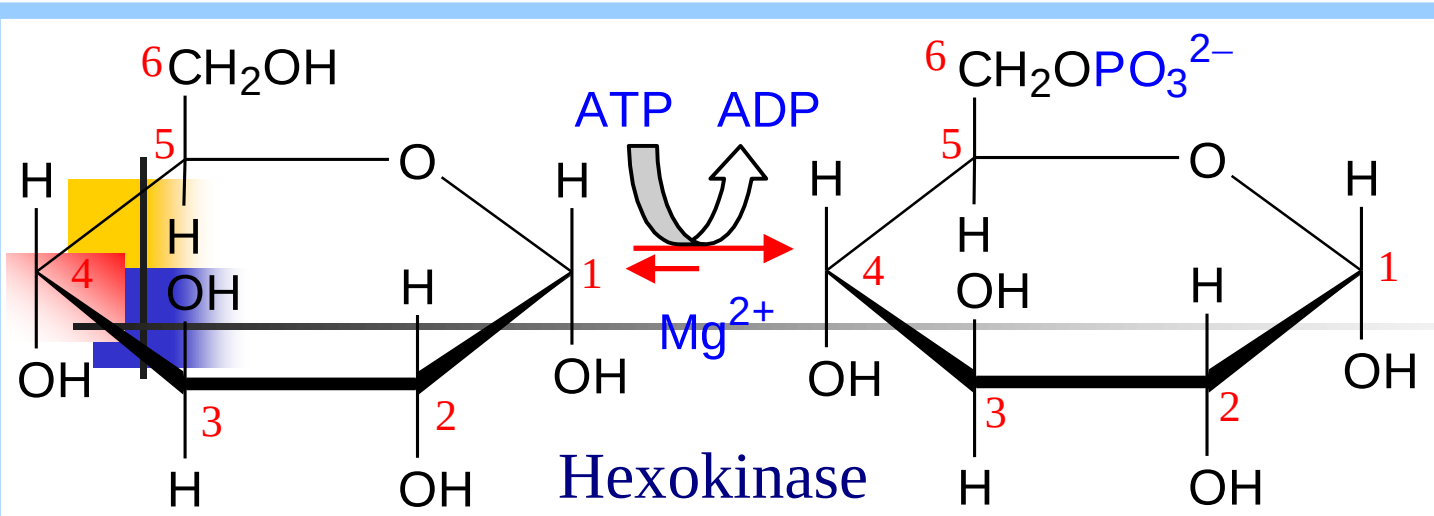

glyceraldehyde-3-phosphate
NAD+ + Pi
NADH + H+
Glyceraldehyde-3-phosphate Dehydrogenase
1,3-bisphosphoglycerate
ADP
ATP
Phosphoglycerate Kinase
3-phosphoglycerate
Phosphoglycerate Mutase
2-phosphoglycerate
H2O
Enolase
phosphoenolpyruvate
ADP
ATP
Pyruvate Kinase
pyruvate



glucose-6-phosphate

Glucose enters the Glycolysis pathway by conversion to **glucose-6-phosphate**.

Initially there is energy input corresponding to cleavage of two ~P bonds of ATP.

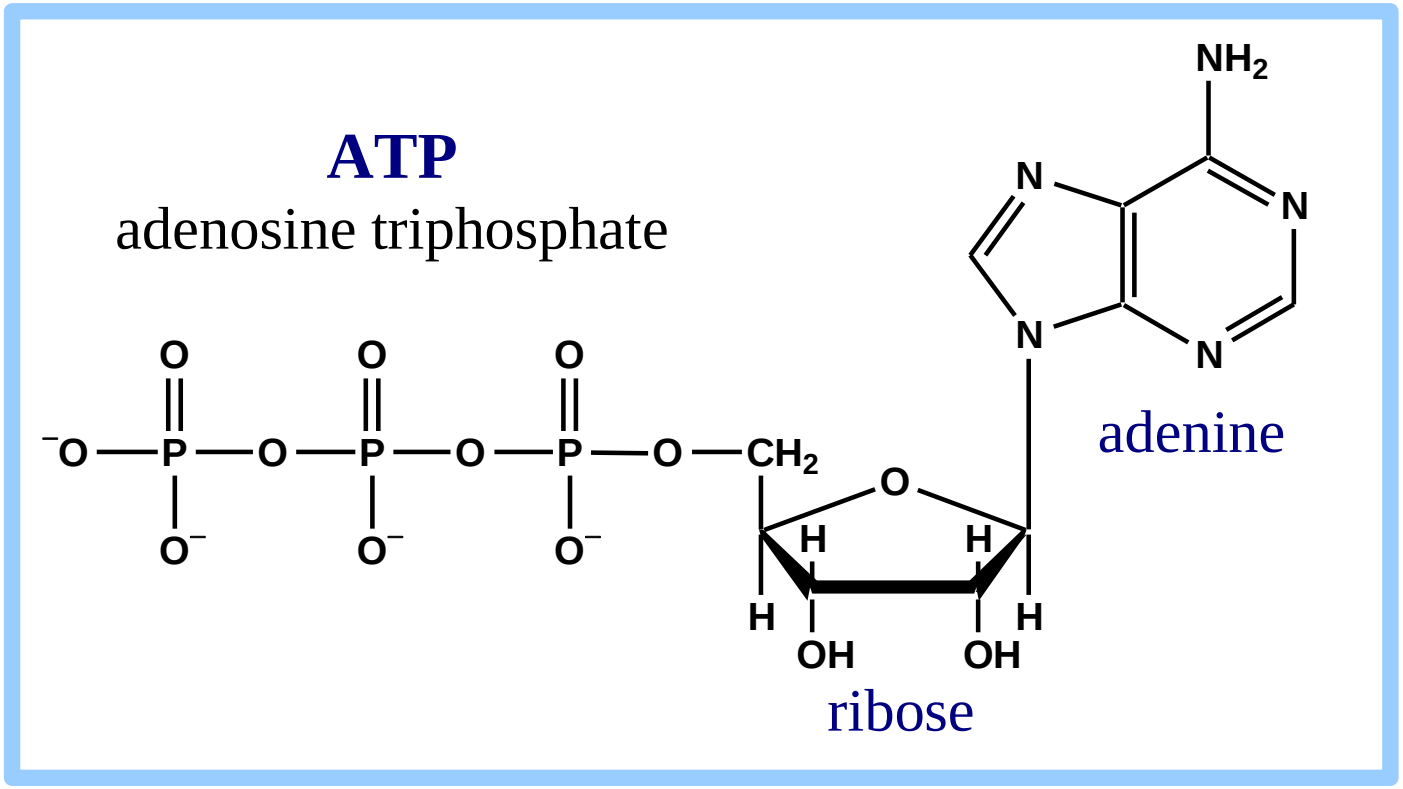


1. Hexokinase catalyzes:

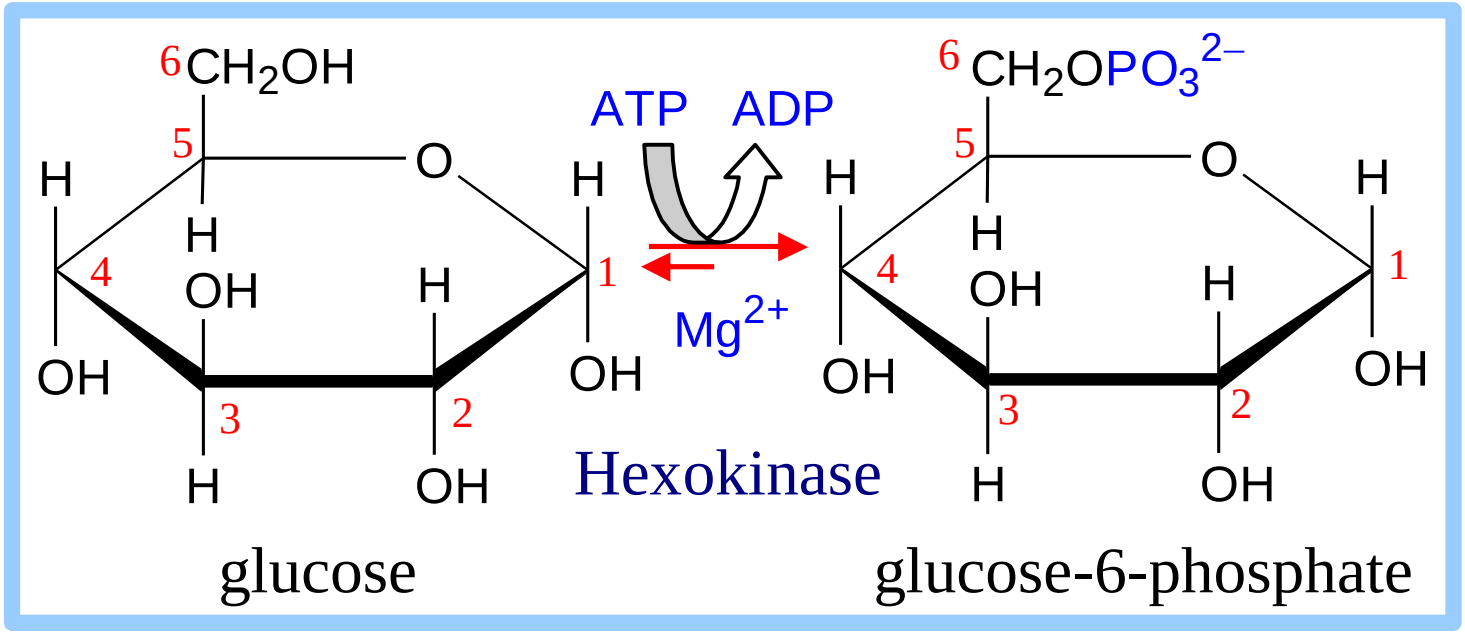
Glucose + ATP → glucose-6-P + ADP

The reaction involves nucleophilic attack of the C6 hydroxyl O of glucose on P of the terminal phosphate of ATP.

ATP binds to the enzyme as a complex with **Mg^{++}**.



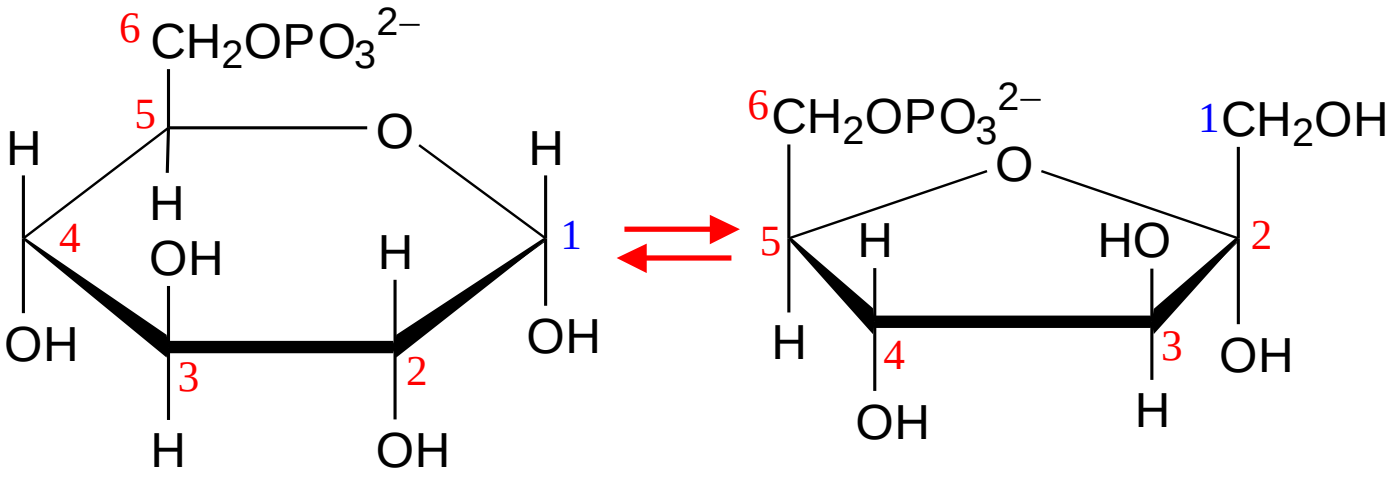
Mg^{++} interacts with negatively charged phosphate oxygen atoms, providing charge compensation & promoting a favorable conformation of ATP at the active site of the Hexokinase enzyme.



The reaction catalyzed by Hexokinase is highly **spontaneous**.

A phosphoanhydride bond of ATP (**~P**) is cleaved.

The phosphate ester formed in glucose-6-phosphate has a lower ΔG of hydrolysis.



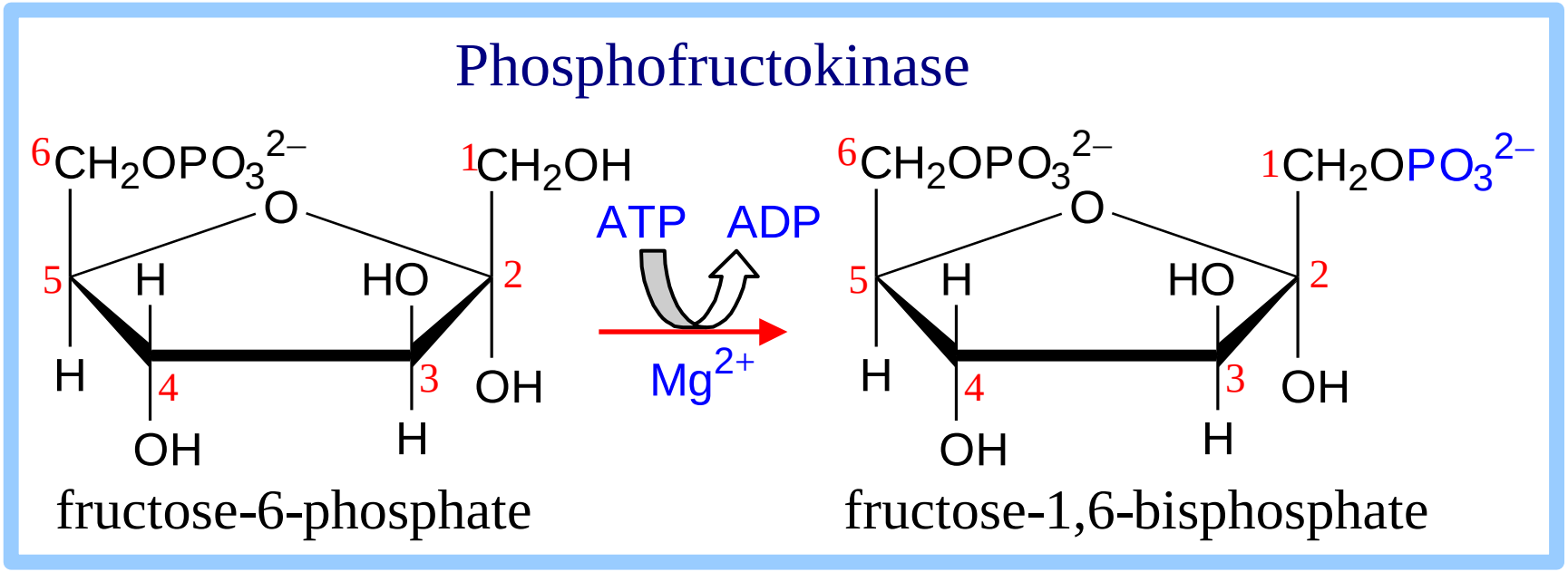
Phosphoglucose Isomerase

glucose-6-phosphate fructose-6-phosphate

2. Phosphoglucose Isomerase catalyzes:

glucose-6-P (aldose) ←→ **fructose-6-P** (ketose)

The mechanism involves acid/base catalysis, with ring opening, isomerization via an **enediolate intermediate**, and then ring closure. A similar reaction catalyzed by Triosephosphate Isomerase



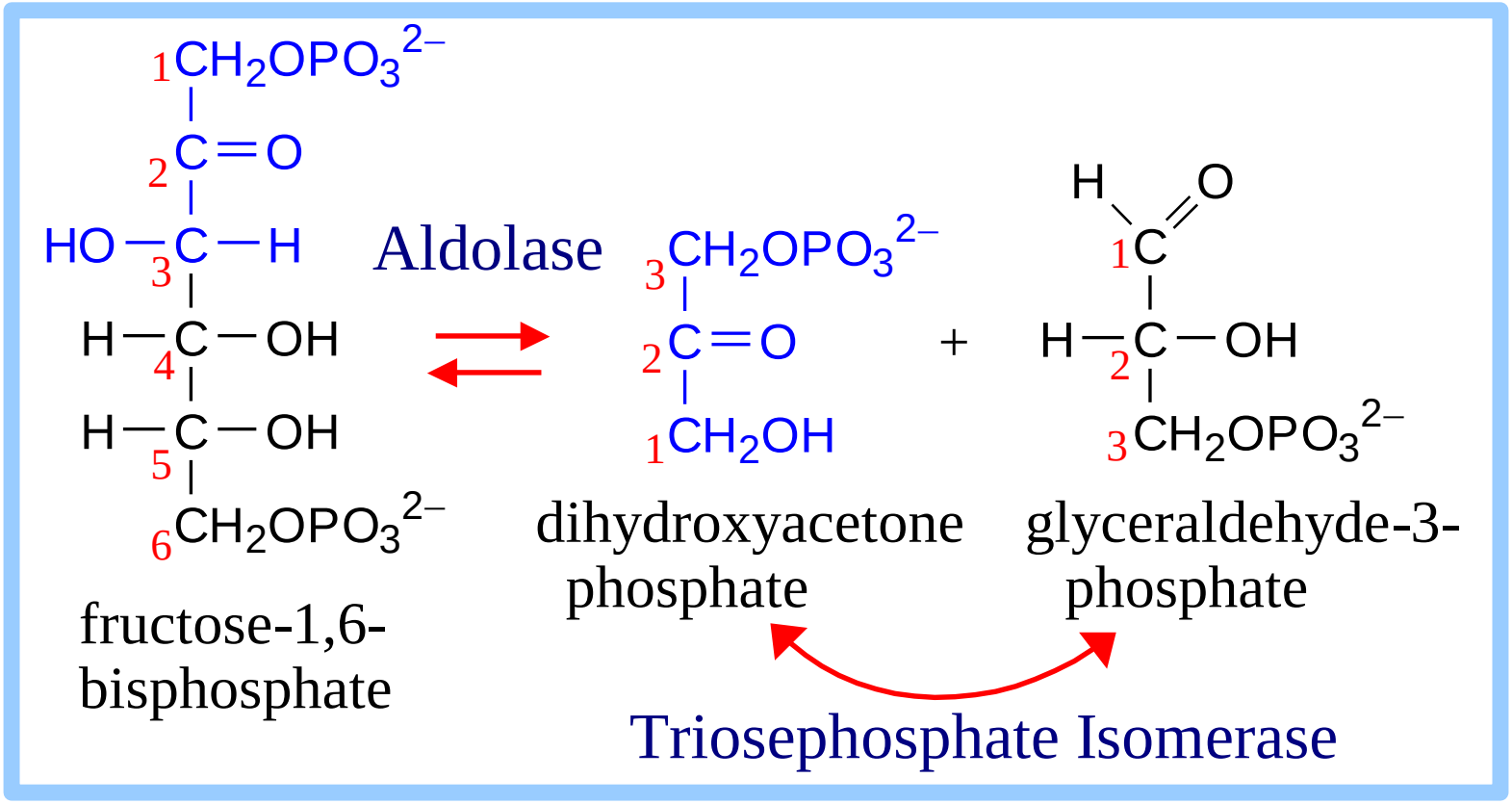
3. Phosphofructokinase catalyzes:

fructose-6-P + ATP → fructose-1,6-bisP + ADP

This highly **spontaneous** reaction has a mechanism similar to that of Hexokinase.

The Phosphofructokinase reaction is the **rate-limiting step** of Glycolysis.

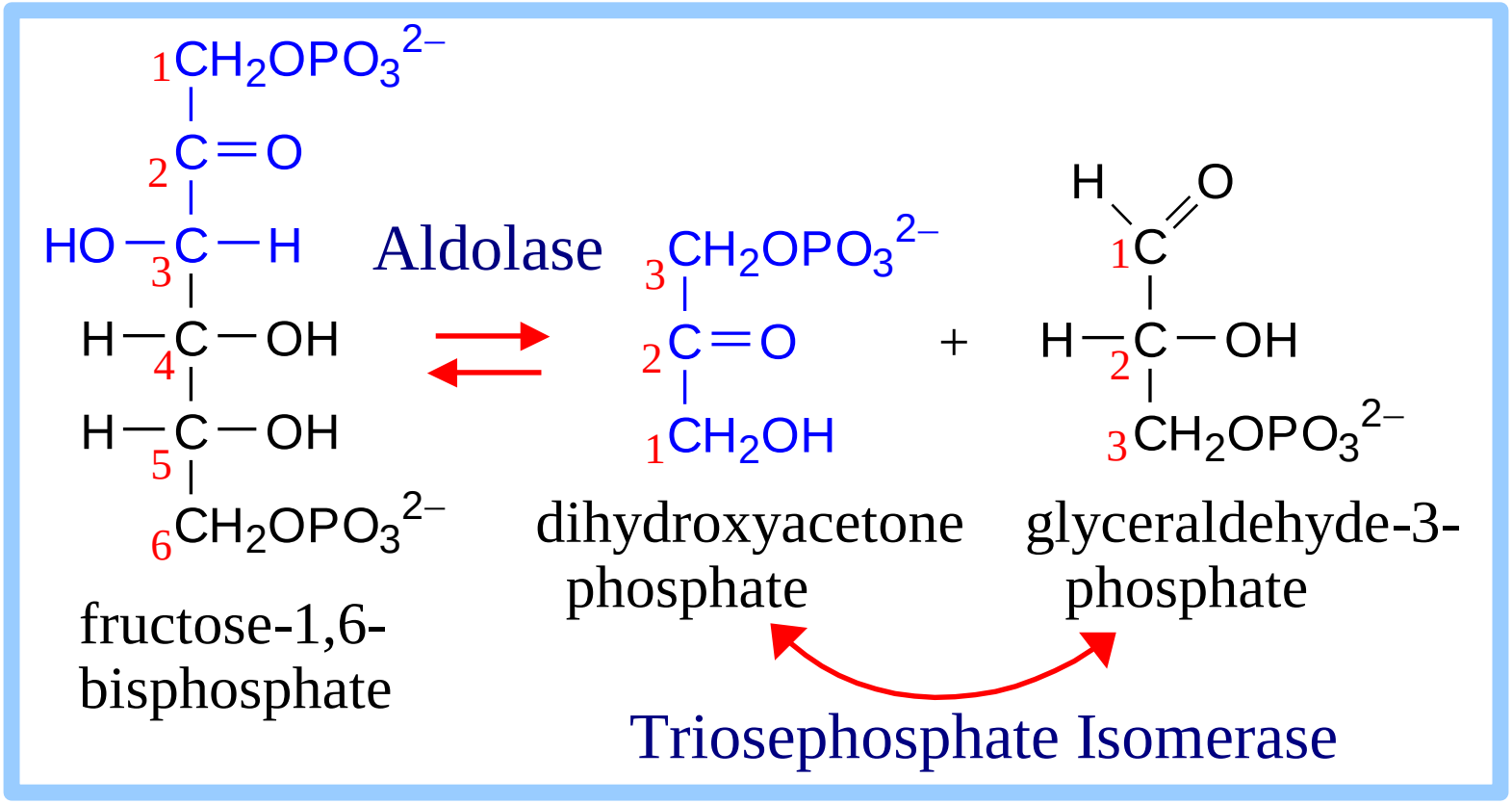
The enzyme is highly **regulated**, as will be discussed later.



4. Aldolase catalyzes: **fructose-1,6-bisphosphate ←→ dihydroxyacetone-P + glyceraldehyde-3-P**

The reaction is an **aldol cleavage**, the reverse of an aldol condensation.

Note that C atoms are renumbered in products of Aldolase.

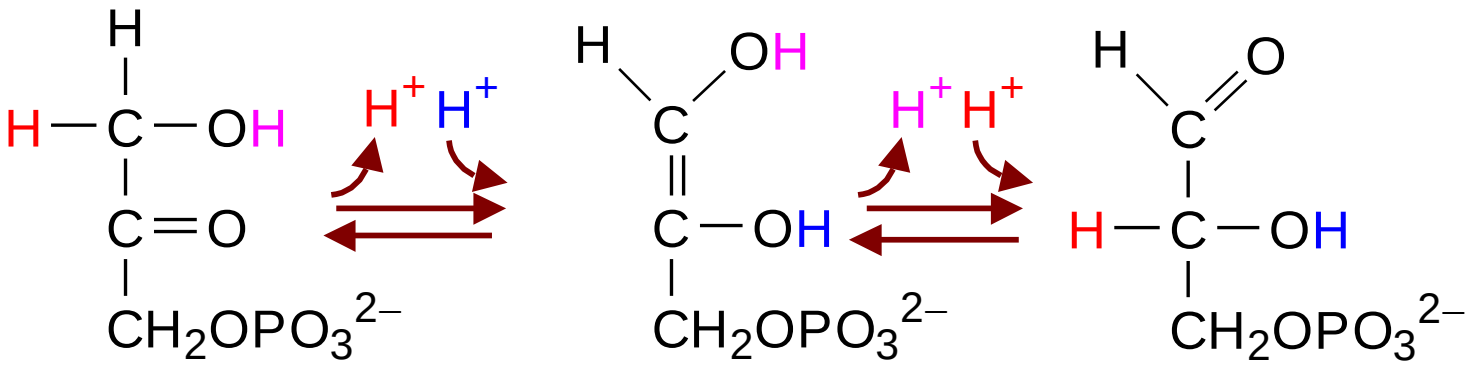


5. Triose Phosphate Isomerase (TIM) catalyzes:

dihydroxyacetone-P ←→ glyceraldehyde-3-P

Glycolysis continues from glyceraldehyde-3-P. TIM's K_{eq} favors dihydroxyacetone-P. Removal of glyceraldehyde-3-P by a subsequent spontaneous reaction allows throughput.

Triosephosphate Isomerase



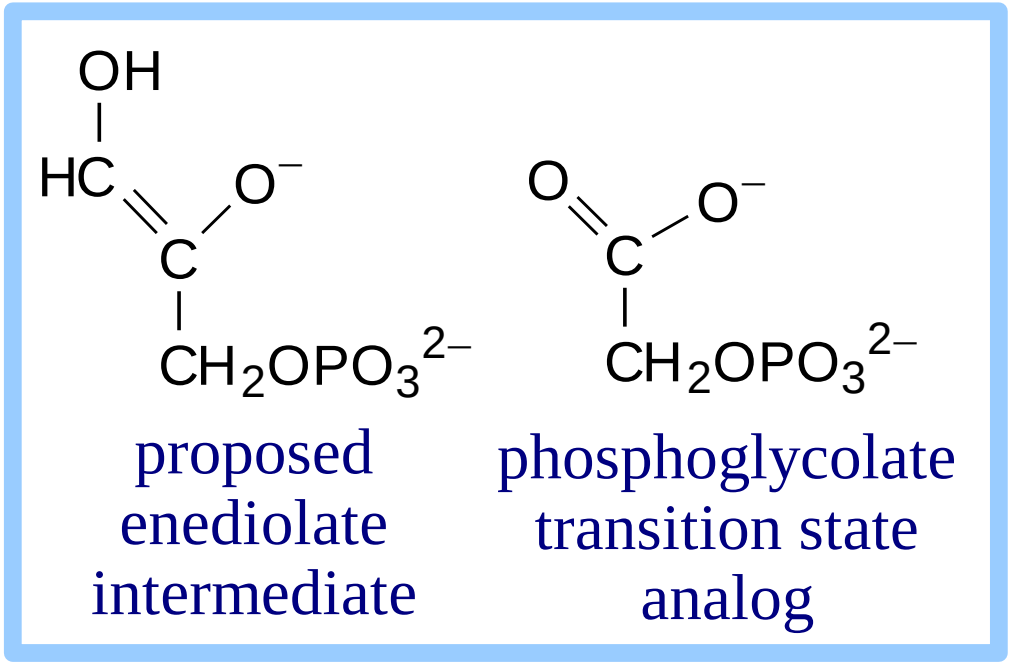
dihydroxyacetone phosphate

enediol intermediate

glyceraldehyde-3-phosphate

The ketose/aldose conversion involves **acid/base catalysis**, and is thought to proceed via an **enediol** intermediate, as with Phosphoglucose Isomerase.

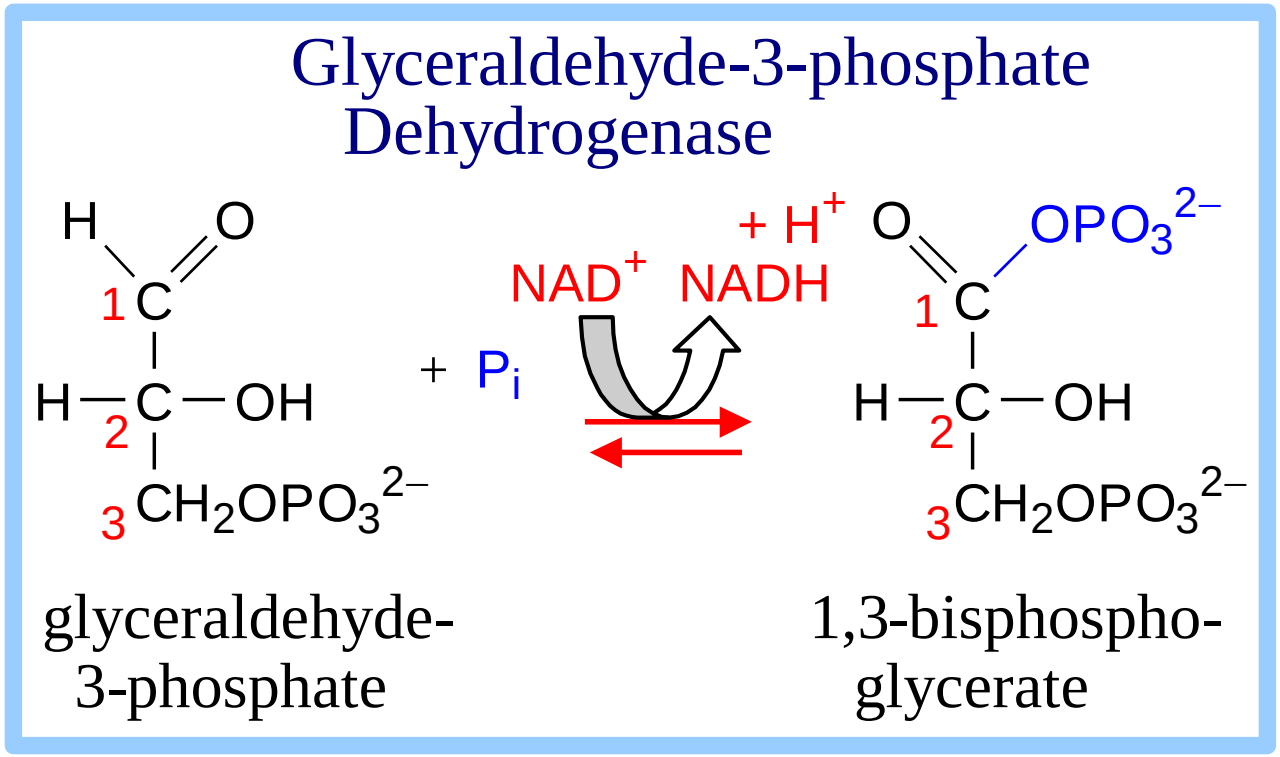
Active site Glu and His residues are thought to extract and donate protons during catalysis.



2-Phosphoglycolate is a **transition state analog** that binds tightly at the active site of Triose Phosphate Isomerase (TIM).

This inhibitor of catalysis by TIM is similar in structure to the proposed enediolate intermediate.

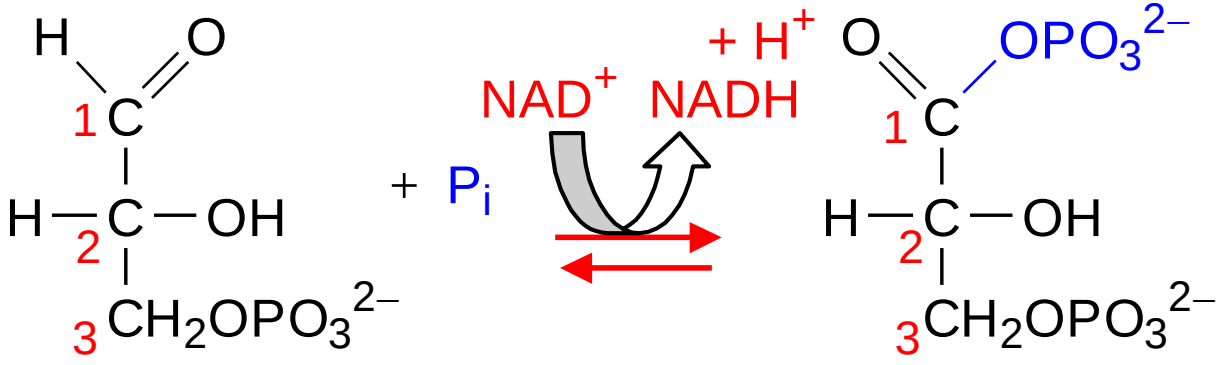
TIM is judged a "perfect enzyme." Reaction rate is limited only by the rate that substrate collides with the enzyme.



6. Glyceraldehyde-3-phosphate Dehydrogenase catalyzes:

glyceraldehyde-3-P + NAD^+ + P_i ←→ 1,3-bisphosphoglycerate + NADH + H^+

Glyceraldehyde-3-phosphate Dehydrogenase



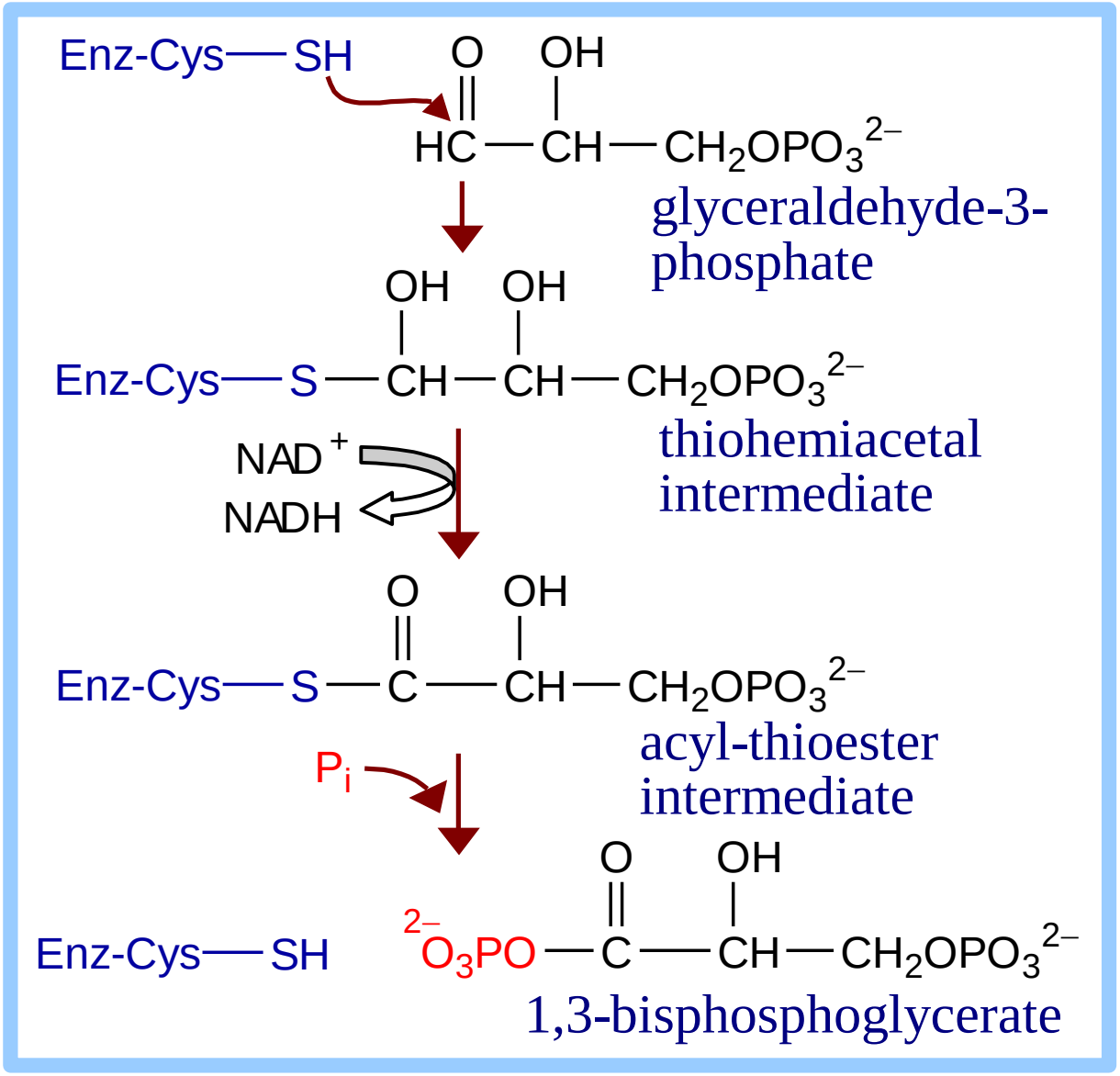
glyceraldehyde-3-phosphate

1,3-bisphospho-glycerate

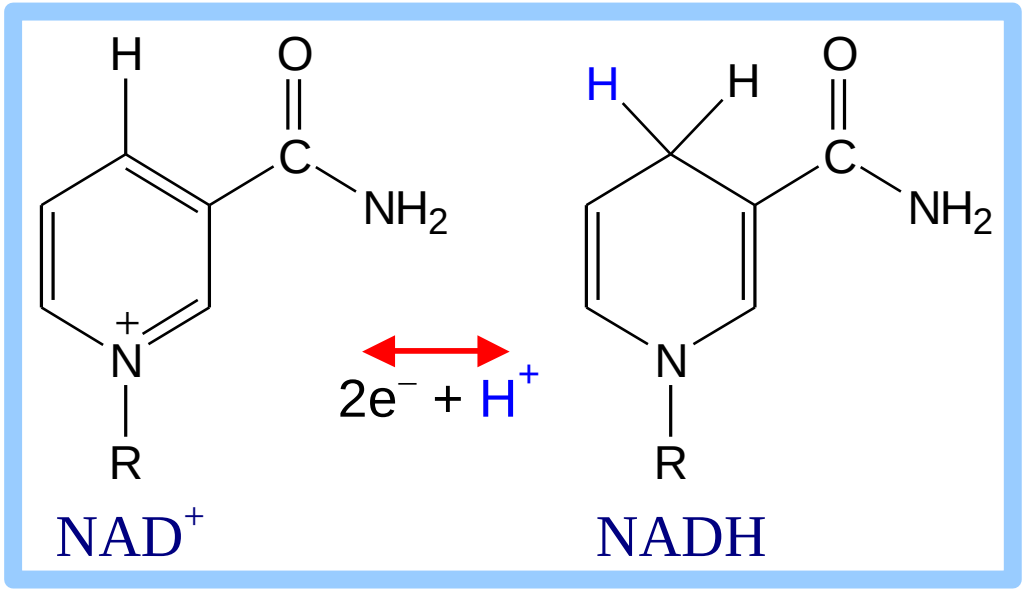
The oxidation of the aldehyde in glyceraldehyde-3-phosphate, to a carboxylic acid, drives formation of an acyl phosphate, a "high energy" bond (~P).

This is the only step in Glycolysis in which NAD^+ is reduced to NADH.

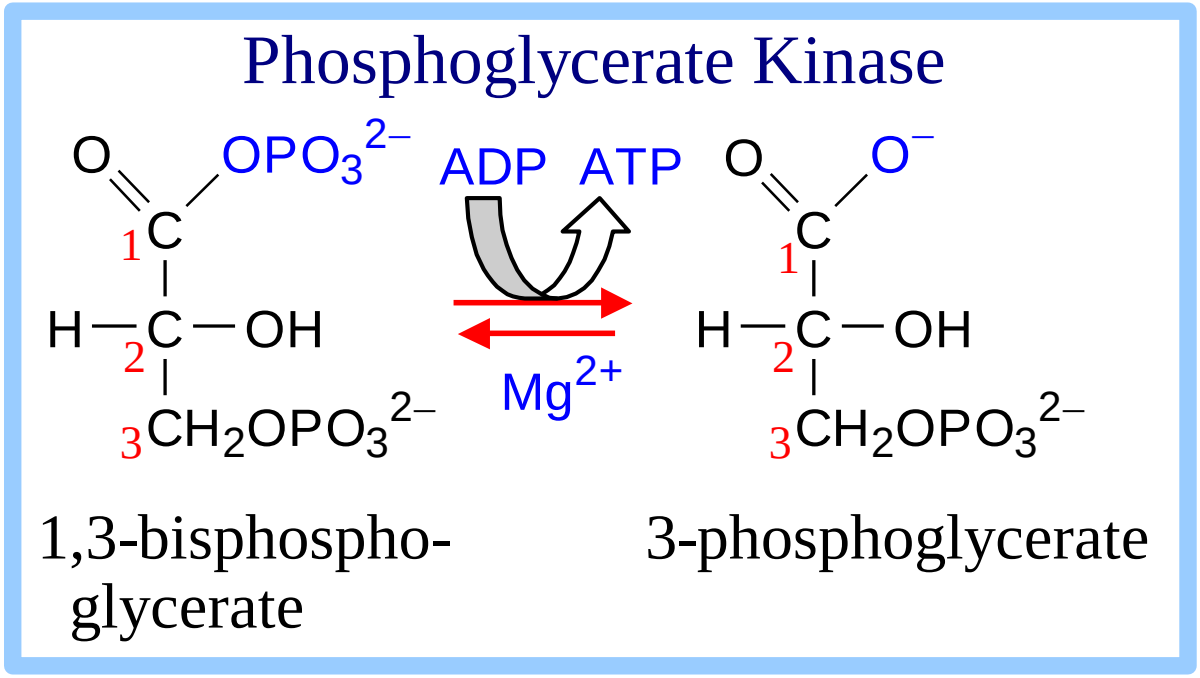
Oxidation to a carboxylic acid (in a ~ **thioester**) occurs, as NAD^+ is reduced to **NADH**.



The "high energy" acyl thioester is attacked by P_i to yield the acyl phosphate (~P) product.



Recall that NAD^+ accepts 2 e^- plus one H^+ (a hydride) in going to its reduced form.



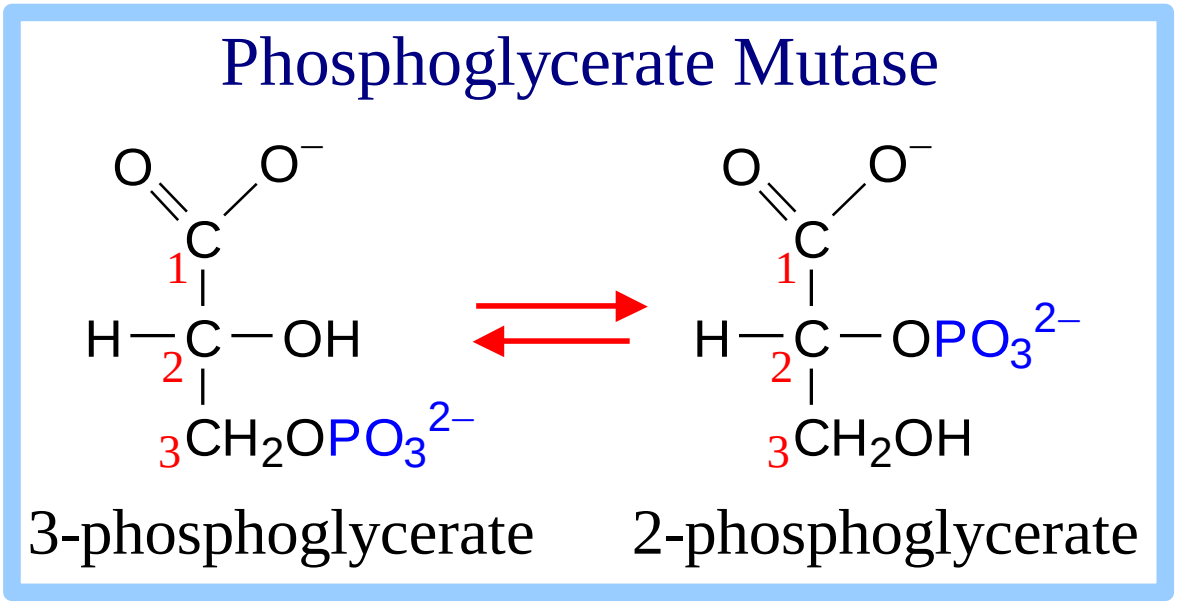
7. Phosphoglycerate Kinase catalyzes:

1,3-bisphosphoglycerate + ADP ←→

3-phosphoglycerate + ATP

This phosphate transfer is reversible (low ΔG), since one **~P** bond is cleaved & another synthesized.

The enzyme undergoes substrate-induced conformational change similar to that of Hexokinase.

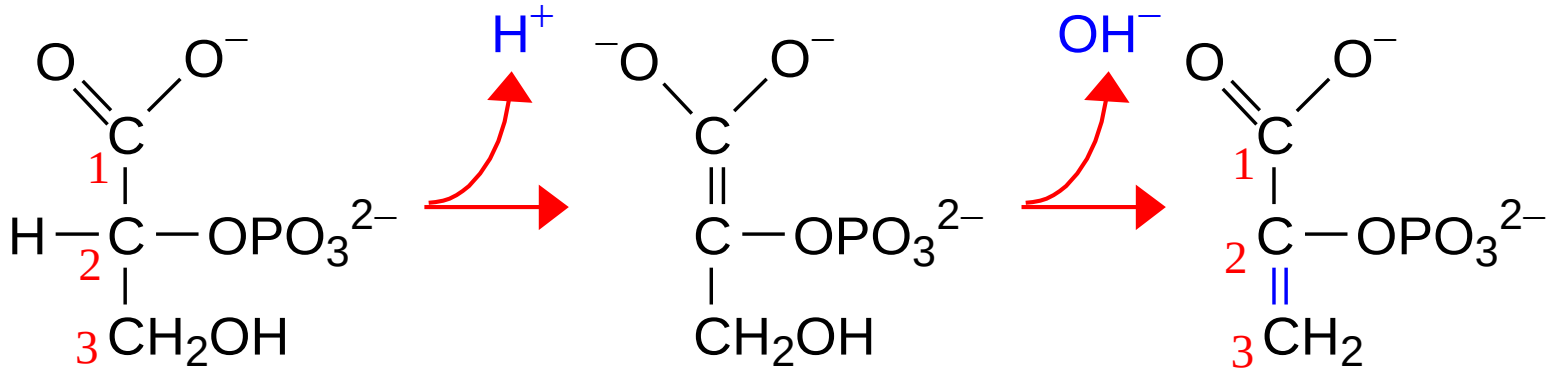


8. Phosphoglycerate Mutase catalyzes:

3-phosphoglycerate ←→ 2-phosphoglycerate

Phosphate is shifted from the OH on C3 to the OH on C2.

Enolase



2-phosphoglycerate enolate intermediate phosphoenolpyruvate

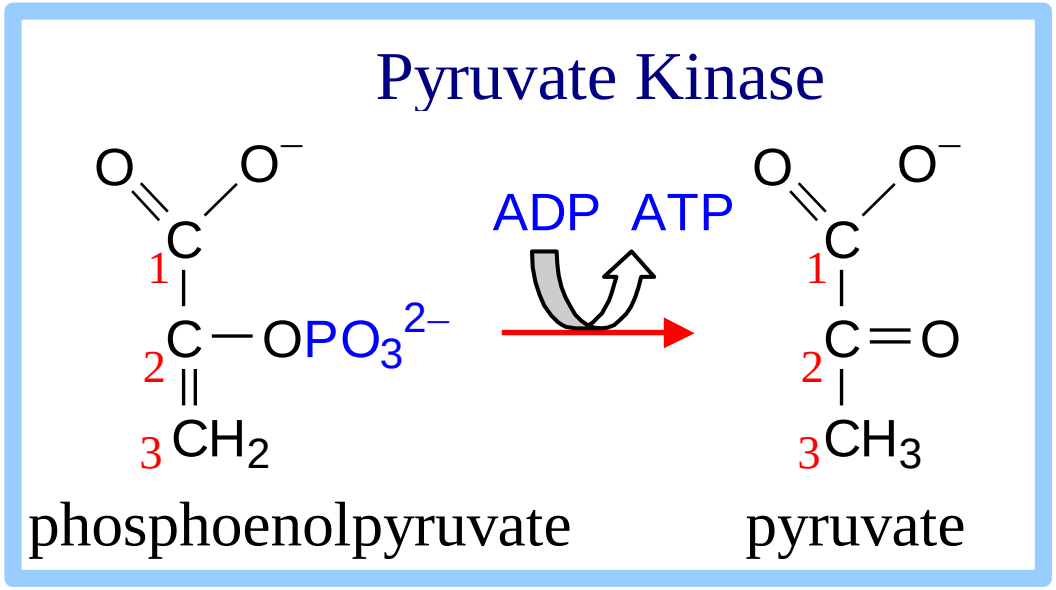
9. Enolase catalyzes:

2-phosphoglycerate ←→ phosphoenolpyruvate + H_2O

This dehydration reaction is **Mg^{++}-dependent**.

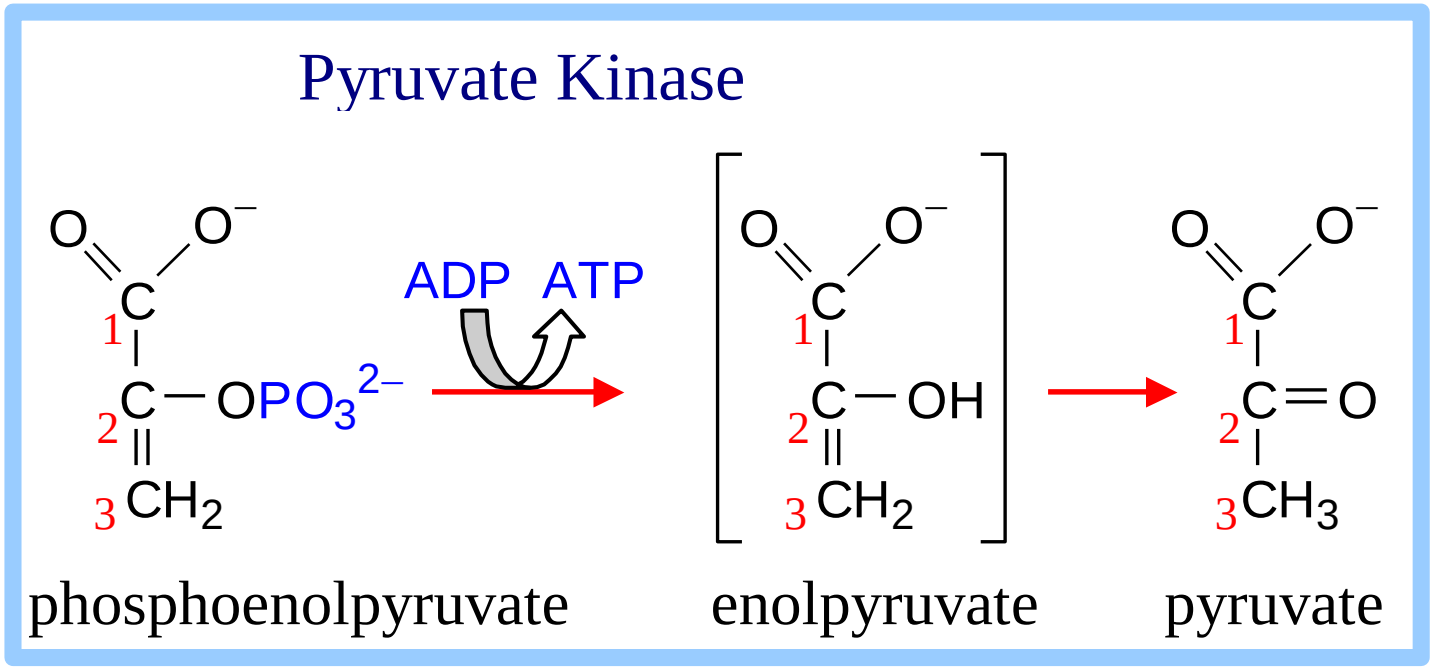
2 Mg^{++} ions interact with oxygen atoms of the substrate **carboxyl** group at the active site.

The Mg^{++} ions help to stabilize the enolate anion intermediate that forms when a Lys extracts H^+ from C #2.



10. Pyruvate Kinase catalyzes:

phosphoenolpyruvate + ADP → pyruvate + ATP



This phosphate transfer from PEP to ADP is **spontaneous**.

- PEP has a larger ΔG of phosphate hydrolysis than ATP.
- Removal of P_i from PEP yields an unstable enol, which spontaneously converts to the keto form of pyruvate.

Required inorganic **cations** K^+ and Mg^{++} bind to anionic residues at the active site of Pyruvate Kinase.

Glycolysis

Balance sheet for **~P** bonds of ATP:

- How many ATP ~P bonds expended? 2 _____
- How many ~P bonds of ATP produced? (Remember there are two 3C fragments from glucose.) 4 _____
- Net production of **~P bonds of ATP per glucose**: 2 _____

Balance sheet for **~P** bonds of ATP:

- 2 ATP expended
- 4 ATP produced (2 from each of two 3C fragments from glucose)
- Net production of **2 ~P** bonds of **ATP** per glucose.

Glycolysis - total pathway, omitting H^+:

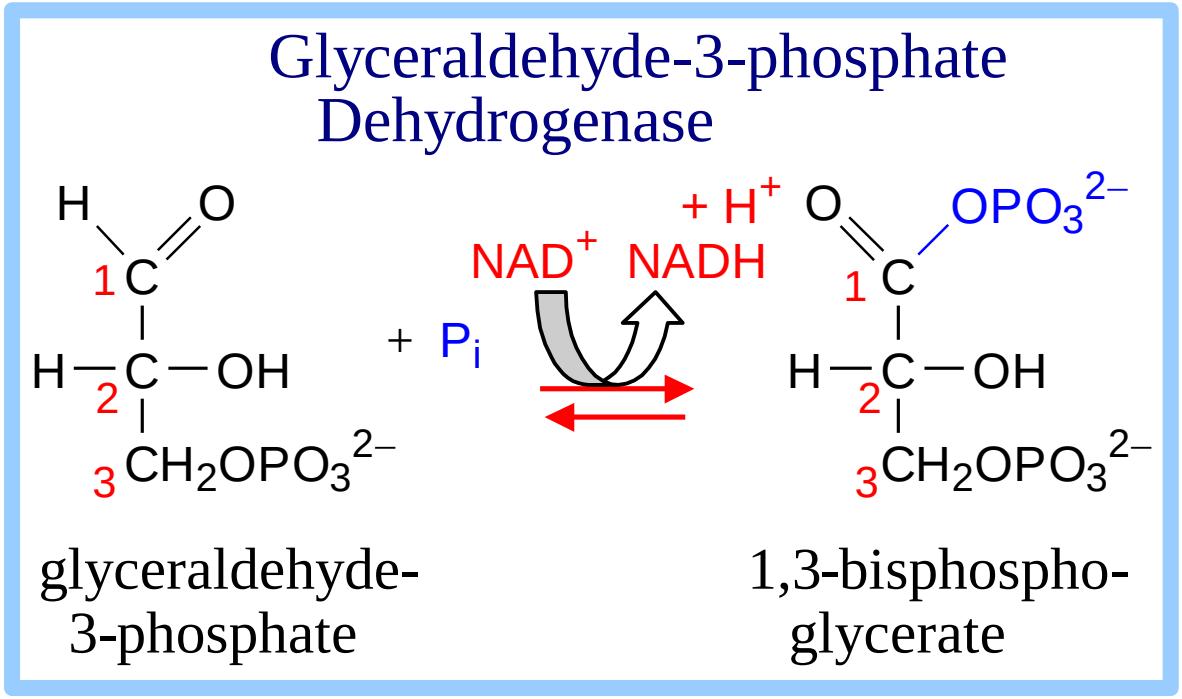
glucose + 2 NAD^+ + 2 ADP + 2 P_i → 2 pyruvate + 2 NADH + 2 ATP

In **aerobic organisms**:

- **pyruvate** produced in Glycolysis is oxidized to CO_2 via Krebs Cycle
- **NADH** produced in Glycolysis & Krebs Cycle is reoxidized via the respiratory chain, with production of much additional ATP.

Fermentation:

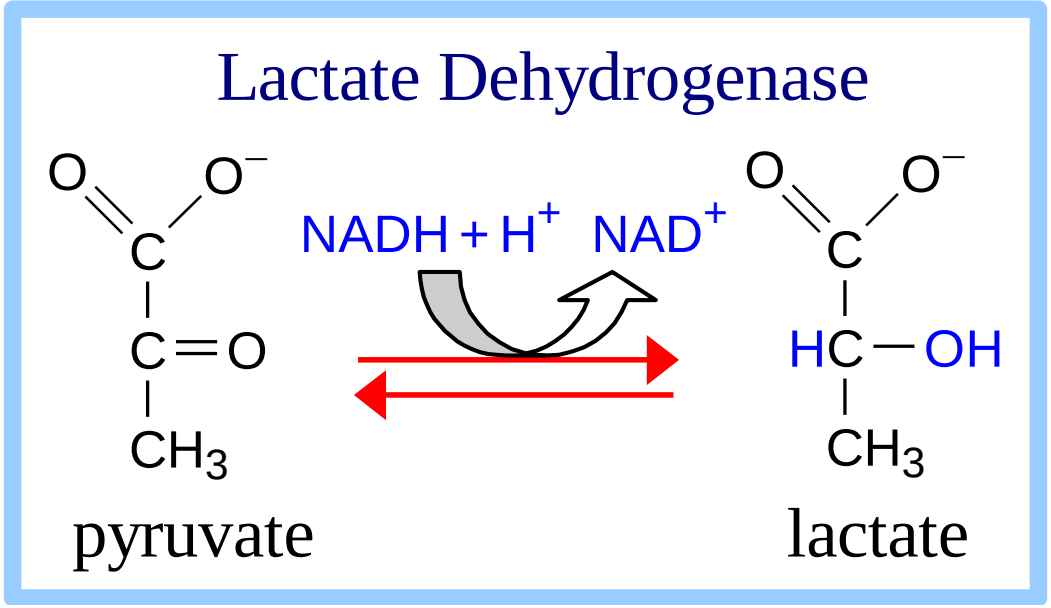
Anaerobic organisms lack a respiratory chain.



They **must reoxidize NADH** produced in Glycolysis through some other reaction, because **NAD^+** is needed for the Glyceraldehyde-3-phosphate Dehydrogenase reaction.

Usually NADH is reoxidized as **pyruvate** is converted to a **more reduced** compound.

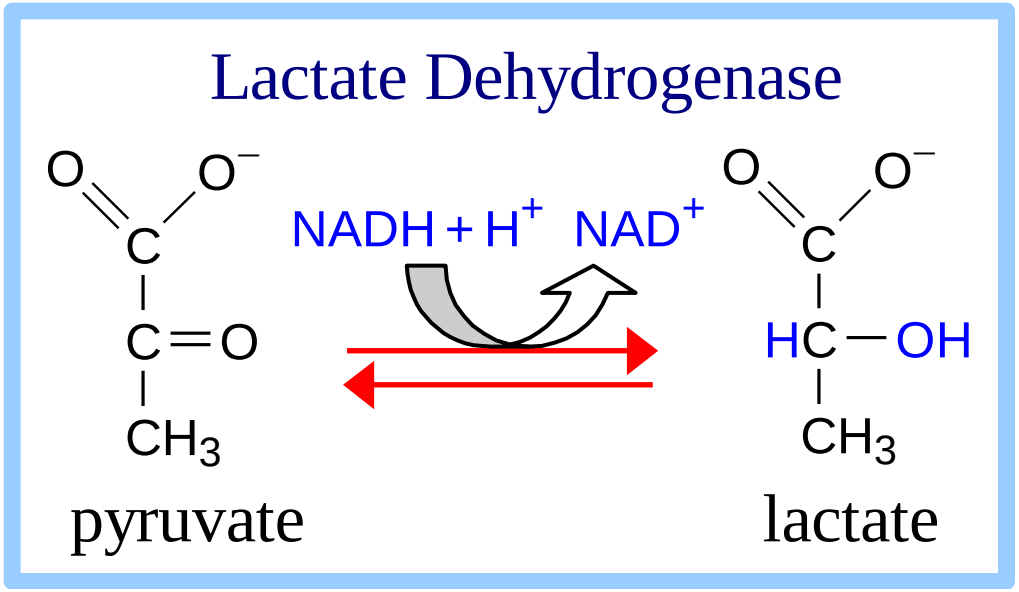
The complete pathway, including Glycolysis and the reoxidation of NADH, is called **fermentation**.



E.g., **Lactate Dehydrogenase** catalyzes **reduction** of the keto in **pyruvate** to a hydroxyl, yielding **lactate**, as NADH is oxidized to NAD^+.

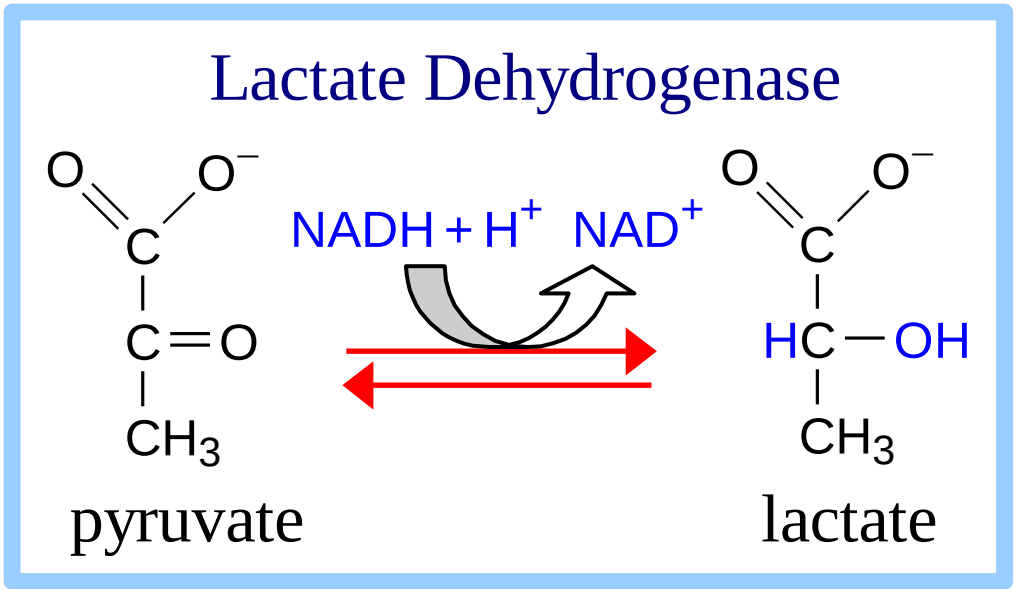
Lactate, in addition to being an end-product of fermentation, serves as a **mobile** form of **nutrient energy**, & possibly as a **signal** molecule in mammalian organisms.

Cell membranes contain **carrier** proteins that facilitate transport of lactate.



Skeletal muscles ferment glucose to **lactate** during exercise, when the exertion is brief and intense.

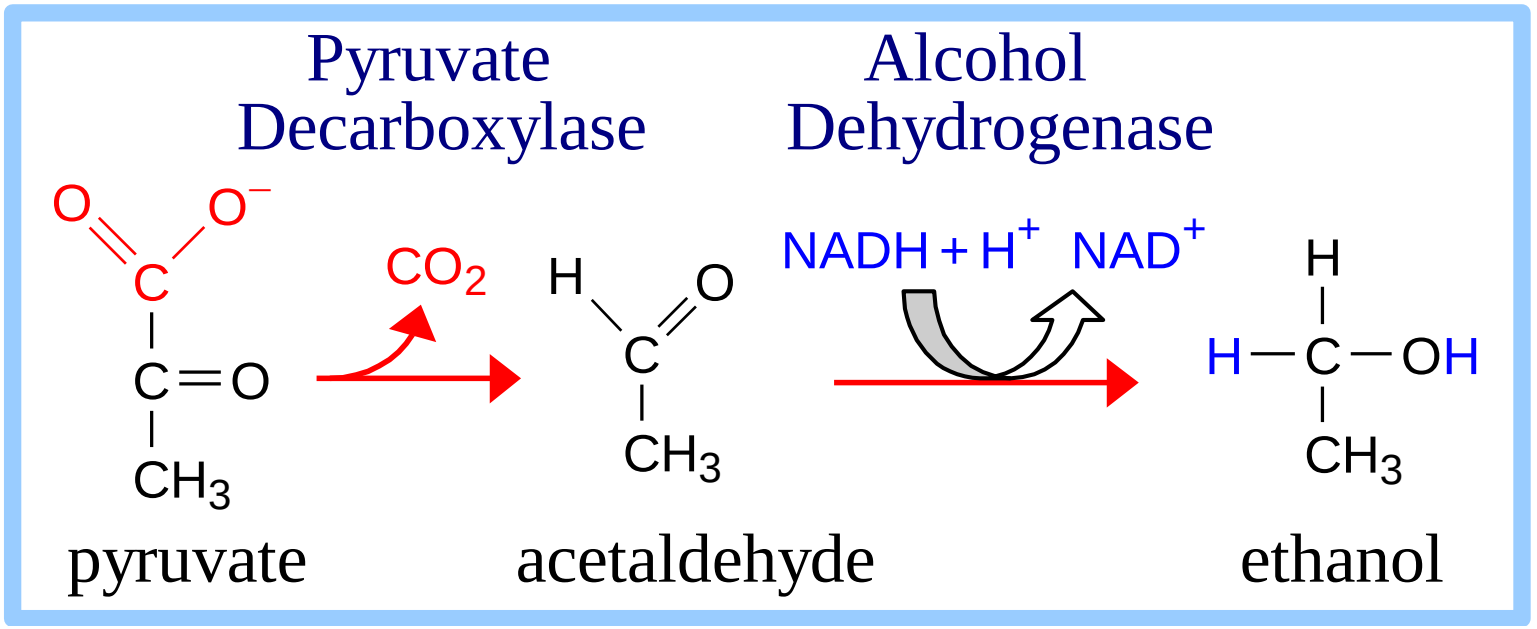
Lactate released to the **blood** may be taken up by other tissues, or by skeletal muscle after exercise, and converted via Lactate Dehydrogenase back to **pyruvate**, which may be oxidized in **Krebs Cycle** or (in liver) converted to back to **glucose** via gluconeogenesis



Lactate serves as a **fuel** source for **cardiac muscle** as well as **brain neurons**.

Astrocytes, which surround and protect neurons in the brain, **ferment glucose** to **lactate** and release it.

Lactate taken up by adjacent neurons is converted to pyruvate that is oxidized via Krebs Cycle.



Some anaerobic organisms metabolize pyruvate to **ethanol**, which is excreted as a waste product.

NADH is converted to **NAD⁺** in the reaction catalyzed by Alcohol Dehydrogenase.

Glycolysis, omitting H^+:

glucose + 2 NAD^+ + 2 ADP + 2 P_i → 2 pyruvate + 2 NADH + 2 ATP

Fermentation, from glucose to lactate:

glucose + 2 ADP + 2 P_i → 2 lactate + 2 ATP

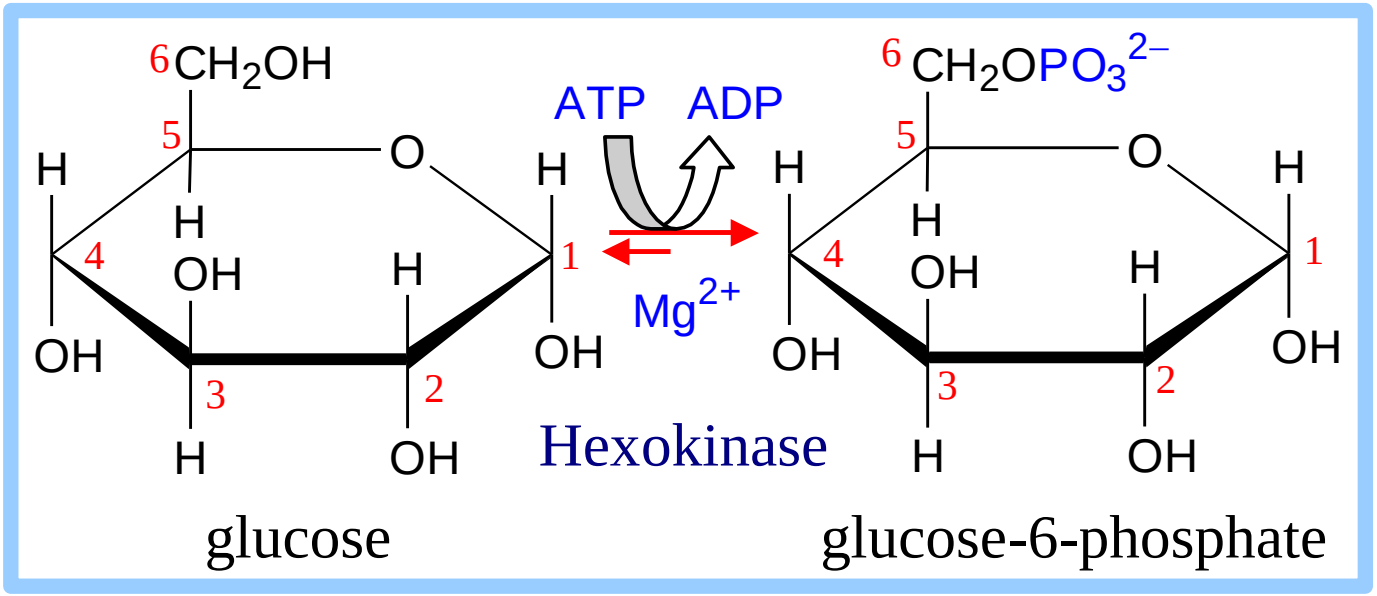
Anaerobic catabolism of glucose yields only 2 “high energy” bonds of ATP.

Flux through the Glycolysis pathway is **regulated** by control of 3 enzymes that catalyze **spontaneous** reactions:

Hexokinase, Phosphofructokinase & Pyruvate Kinase.

- **Local control** of metabolism involves regulatory effects of varied concentrations of pathway **substrates** or **intermediates**, to benefit the cell.
- **Global control** is for the benefit of the whole organism, & often involves **hormone-activated signal cascades**.

  Liver cells have major roles in metabolism, including maintaining blood levels various of nutrients such as glucose. Thus global control



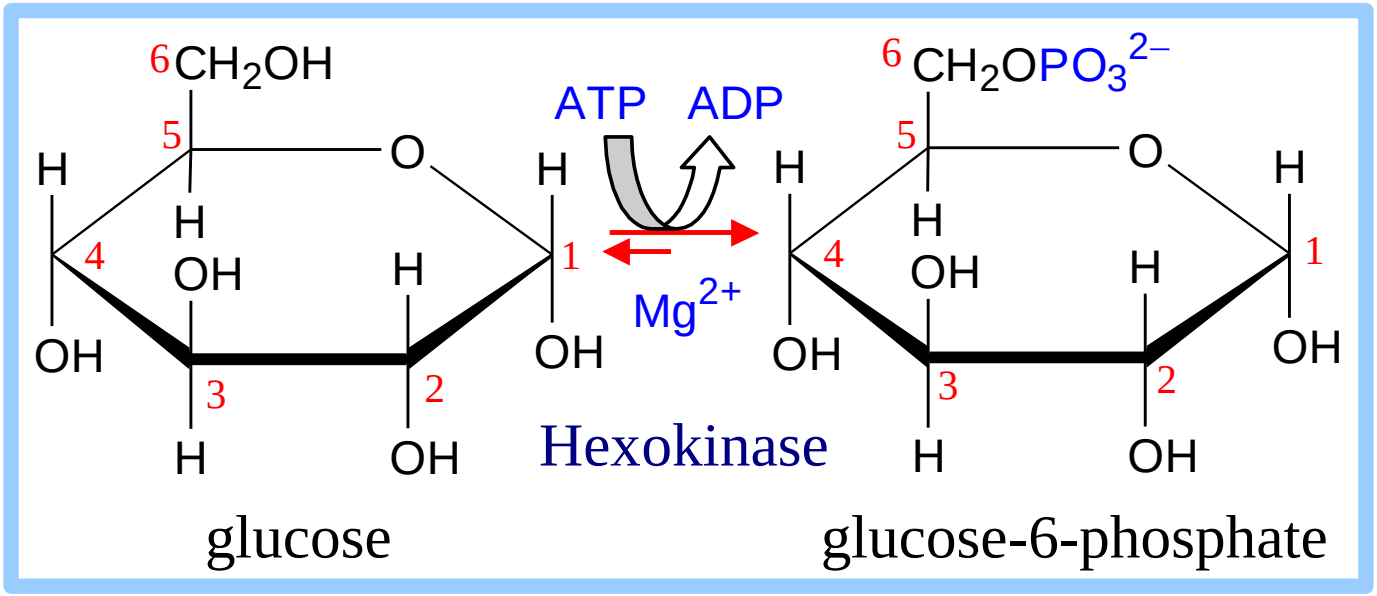
Hexokinase is **inhibited** by **product glucose-6-phosphate**:

- by **competition** at the **active site**
- by **allosteric** interaction at a **separate** enzyme site.

Cells **trap glucose** by **phosphorylating** it, preventing exit on glucose carriers.

Product inhibition of Hexokinase ensures that cells

Glucokinase is a variant of Hexokinase found in **liver**.

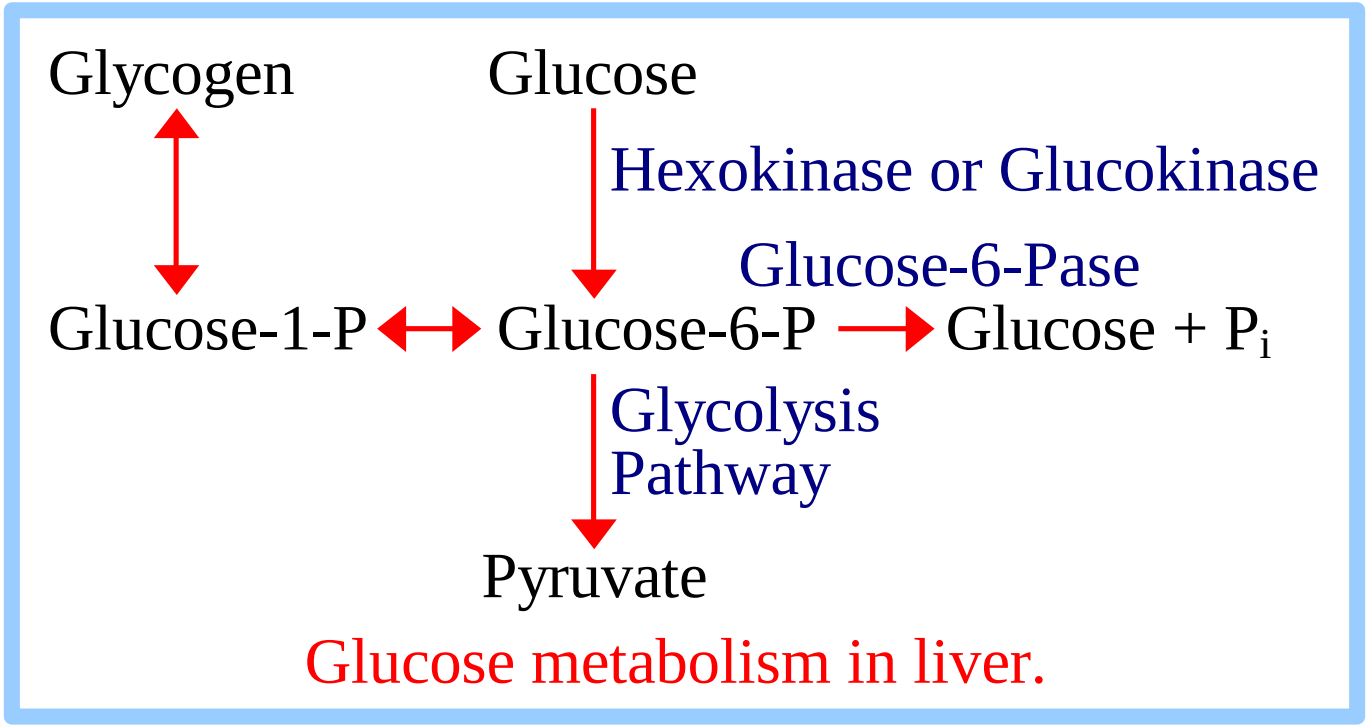


- **Glucokinase** has a **high K_M** for **glucose**. It is **active** only **at high [glucose]**.
- One effect of **insulin**, a hormone produced when blood glucose is high, is **activation** in liver of **transcription** of the gene that encodes the **Glucokinase** enzyme.
- Glucokinase is **not subject to product inhibition** by glucose-6-phosphate. Liver will take up &

- Glucokinase is subject to **inhibition** by **glucokinase regulatory protein** (**GKRP**).

  The ratio of Glucokinase to GKRP in liver changes in different metabolic states, providing a mechanism for modulating glucose phosphorylation.

Glucokinase, with high K_M for glucose, allows liver to store glucose as glycogen in the fed state when blood [glucose] is high.

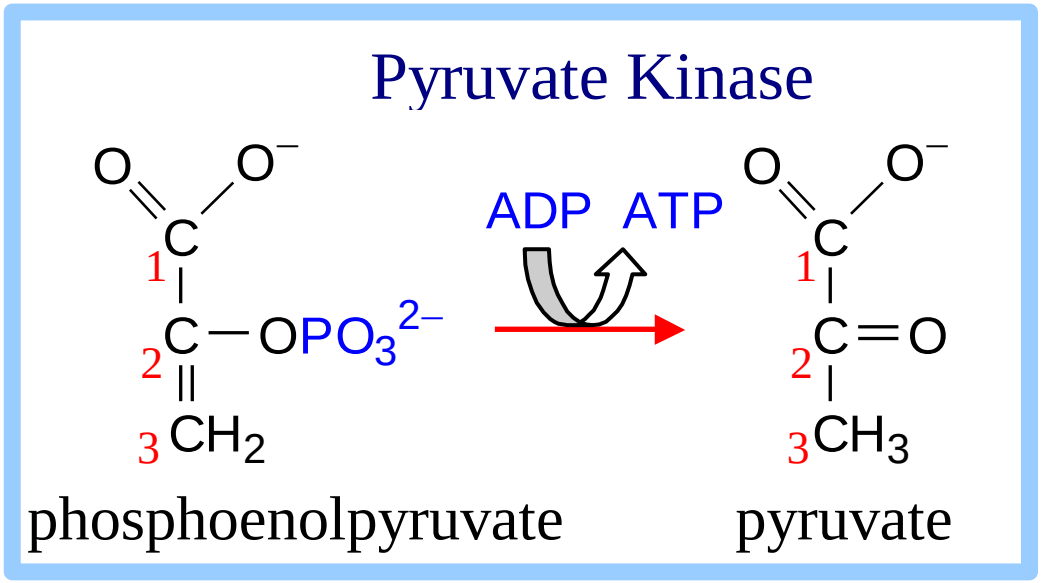


Glucose metabolism in liver.

Glucose-6-phosphatase catalyzes hydrolytic release of P_i from glucose-6-P. Thus **glucose** is **released** from the liver to the blood as needed to maintain blood [glucose].

The enzymes Glucokinase & Glucose-6-phosphatase, both found in **liver** but not in most other body cells, allow the liver to control blood [glucose]

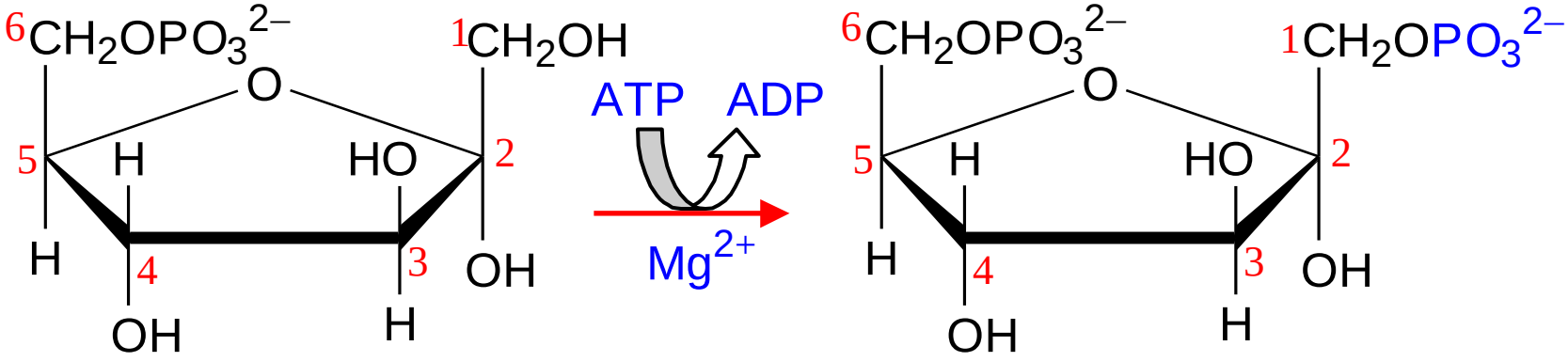
Pyruvate Kinase, the last step Glycolysis, is **controlled** in **liver** partly by modulation of the **amount** of **enzyme**.



High [glucose] within liver cells causes a transcription factor **carbohydrate responsive element binding protein** (**ChREBP**) to be transferred into the nucleus, where it activates **transcription** of the gene for Pyruvate Kinase.

This facilitates converting **excess glucose** to **pyruvate**, which is metabolized to **acetyl-CoA**, the main precursor for synthesis of **fatty acids**, for long

Phosphofructokinase



fructose-6-phosphate

fructose-1,6-bisphosphate

Phosphofructokinase is usually the **rate-limiting step** of the Glycolysis pathway.

Phosphofructokinase is **allosterically inhibited by ATP**.

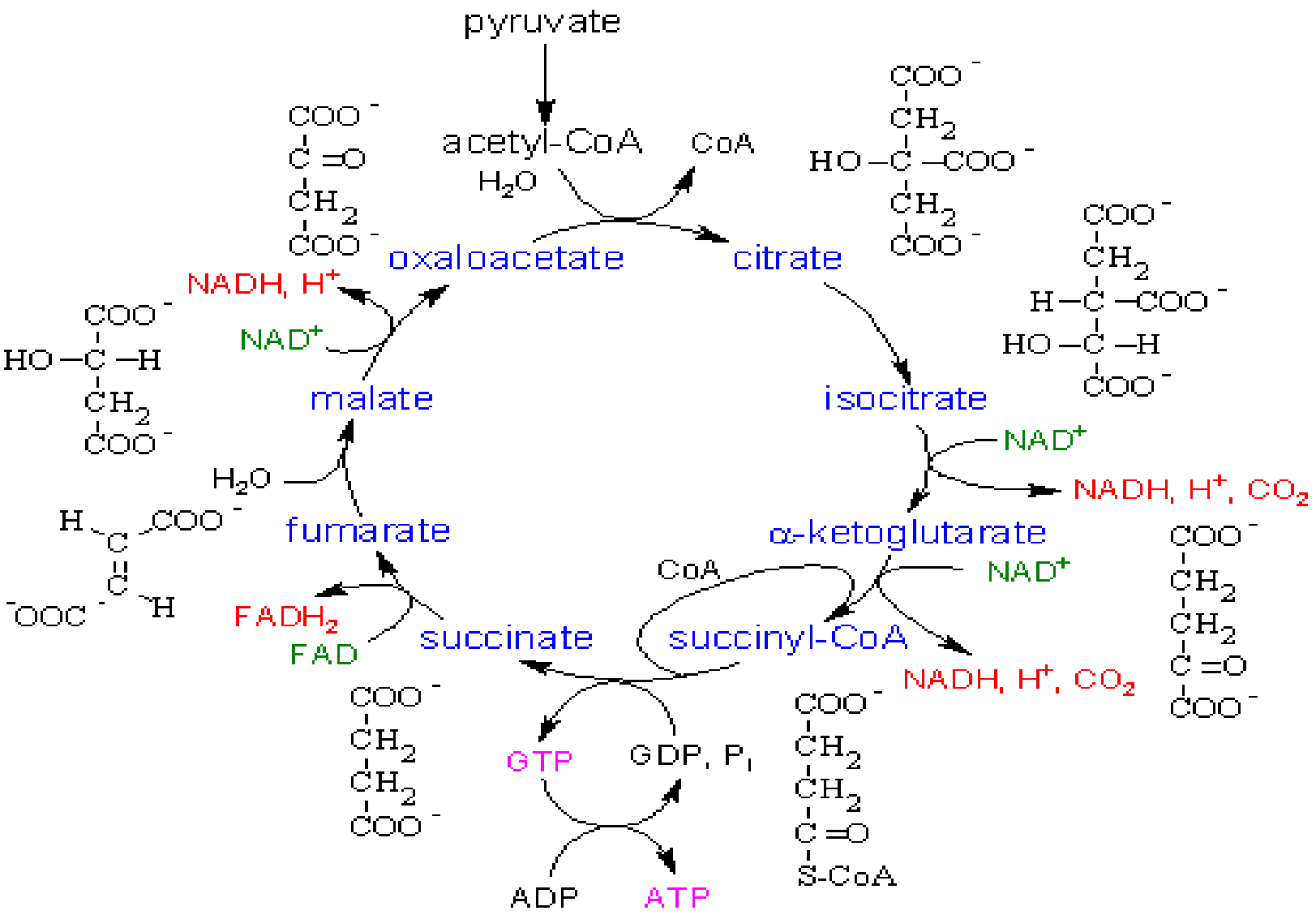
- At **low** concentration, the substrate **ATP** binds **only** at the **active site**.
- At **high** concentration, ATP binds **also** at a low-

Krebs cycle

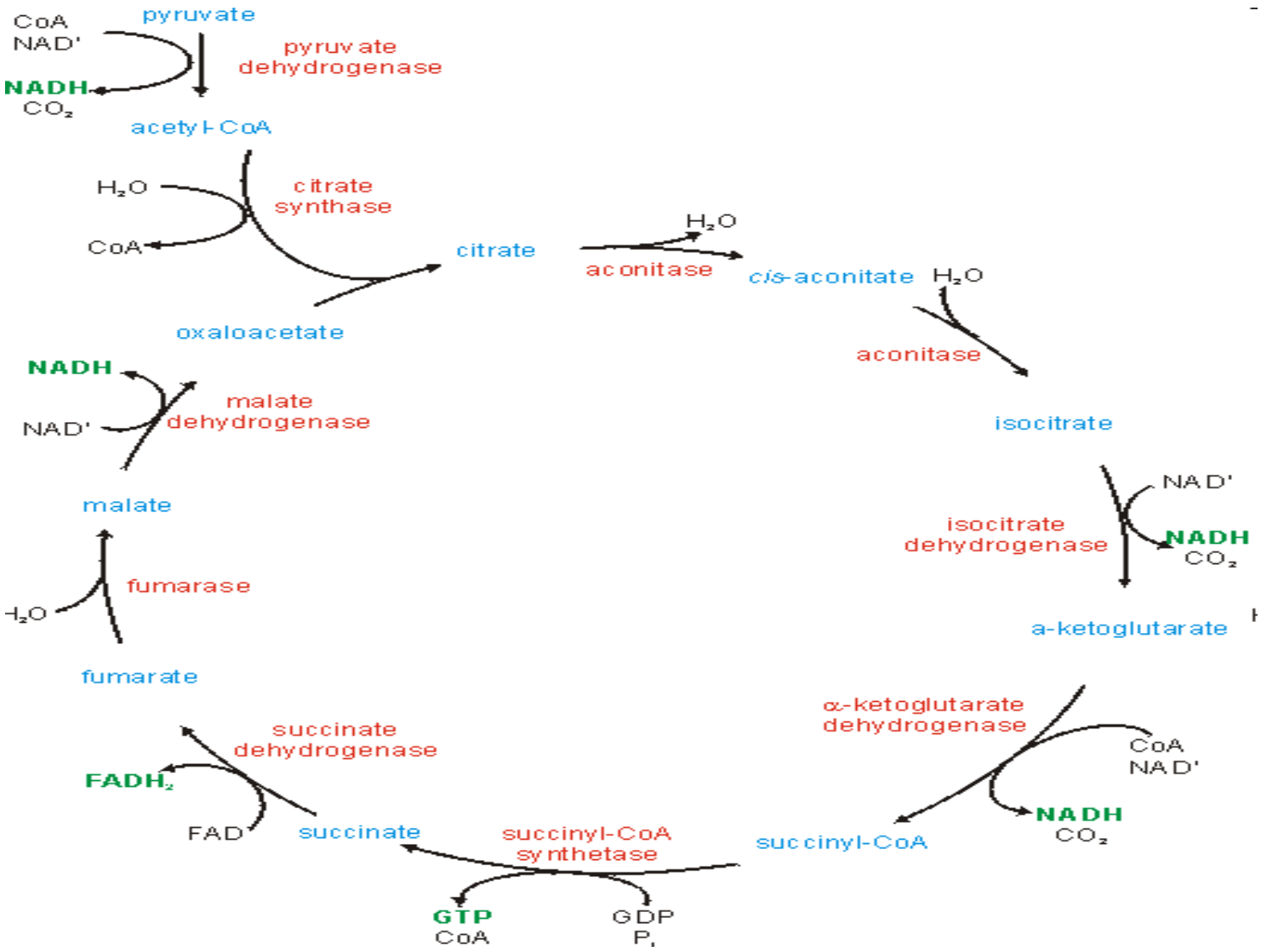
Before moving into Krebs cycle the pyruvate from glycolysis is decarboxylized to form acetyl.

This acetyl is then attached to CoA to form Acetyl-CoA which enters Krebs cycle.

KREBS CYCLE


pyruvate
acetyl-CoA
CoA
H_2O
oxaloacetate
citrate
isocitrate
NADH, H^+
NAD^+
malate
H_2O
fumarate
$FADH_2$
FAD
succinate
CoA
succinyl-CoA
NAD^+
$NADH, H^+, CO_2$
α-ketoglutarate
NAD^+
$NADH, H^+, CO_2$
GTP
GDP, P_i
ADP
ATP
S-CoA

KREBS CYCLE


CoA
NAD'
pyruvate
pyruvate dehydrogenase
NADH
CO_2
acetyl-CoA
H_2O
CoA
citrate synthase
citrate
oxaloacetate
H_2O
aconitase
cis-aconitate
H_2O
aconitase
isocitrate
NAD'
isocitrate dehydrogenase
NADH
CO_2
a-ketoglutarate
α-ketoglutarate dehydrogenase
CoA
NAD'
NADH
CO_2
succinyl-CoA
succinyl-CoA synthetase
GTP
CoA
GDP
P_i
succinate
FAD
succinate dehydrogenase
$FADH_2$
fumarate
H_2O
fumarase
malate
NADH
NAD'
malate dehydrogenase

CELLULAR AEROBIC RESPIRATION

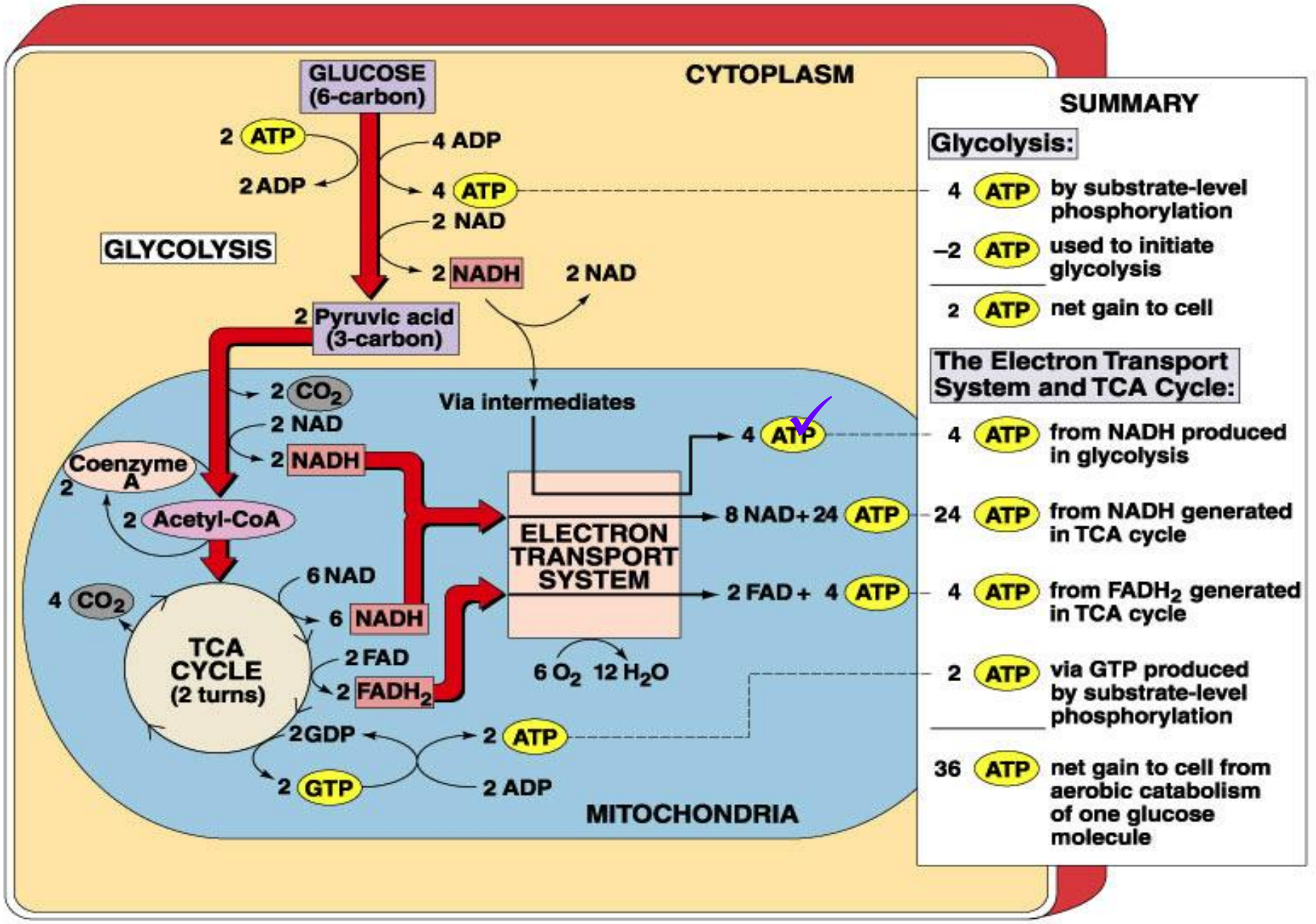
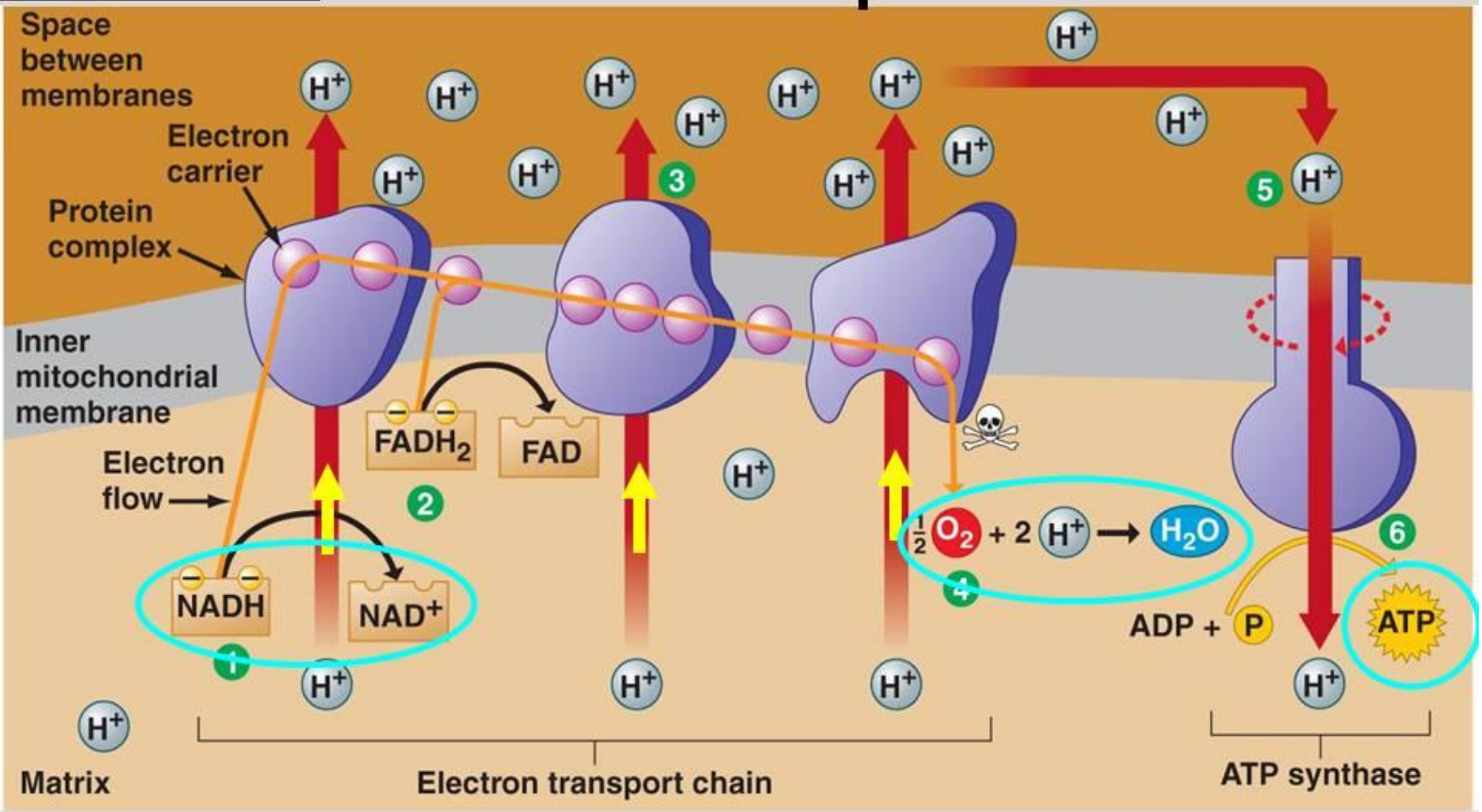


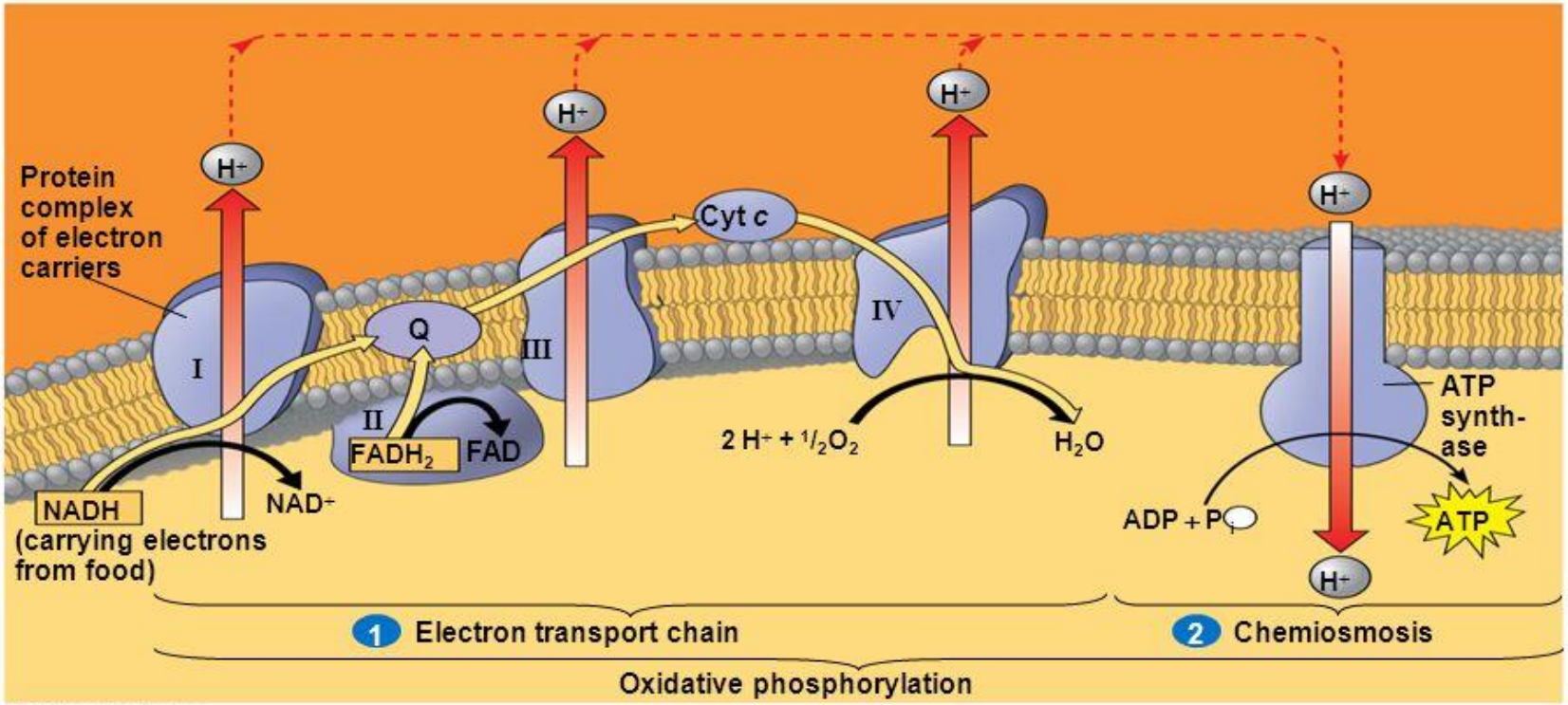
Figure 6.11

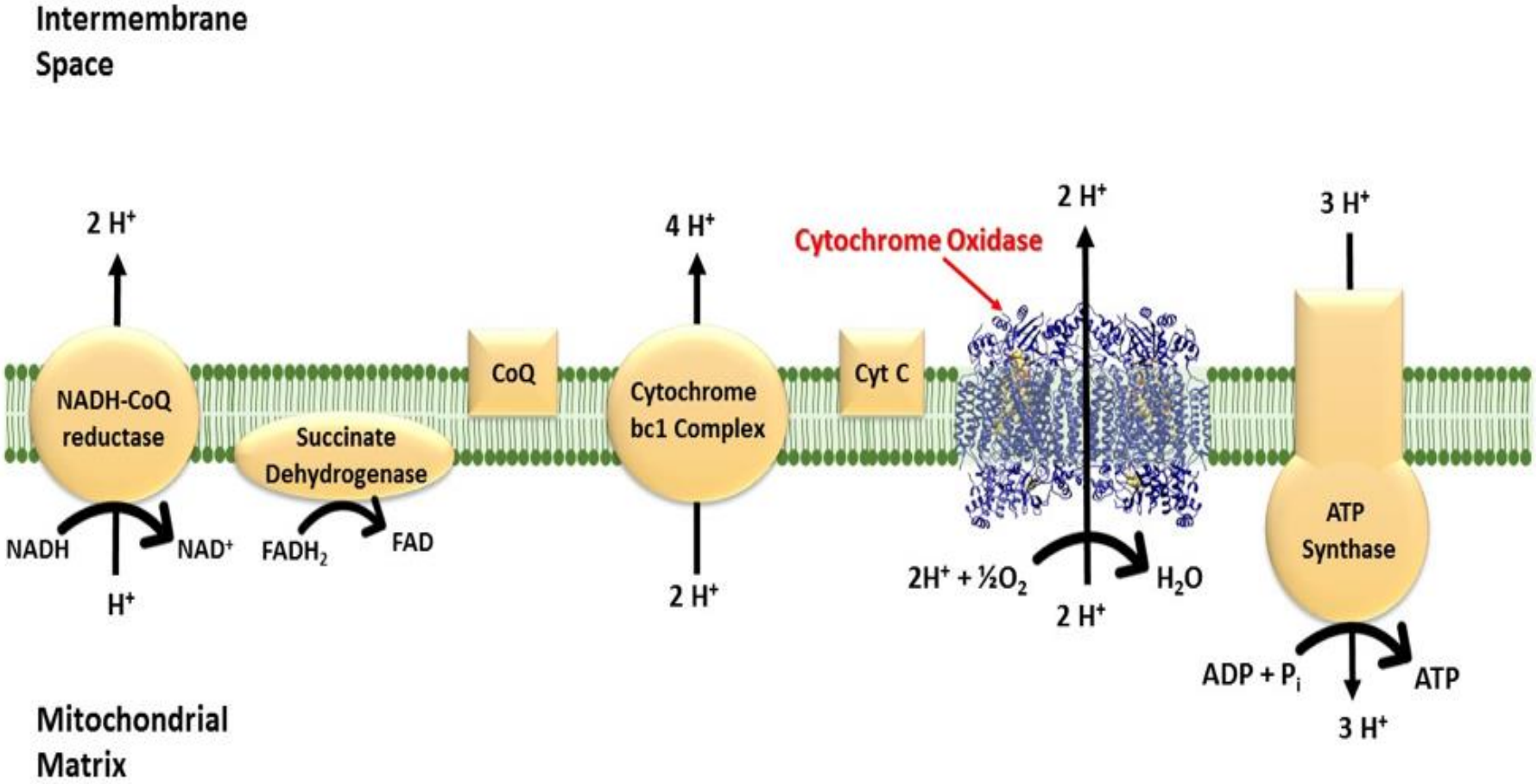
Electron transport chain

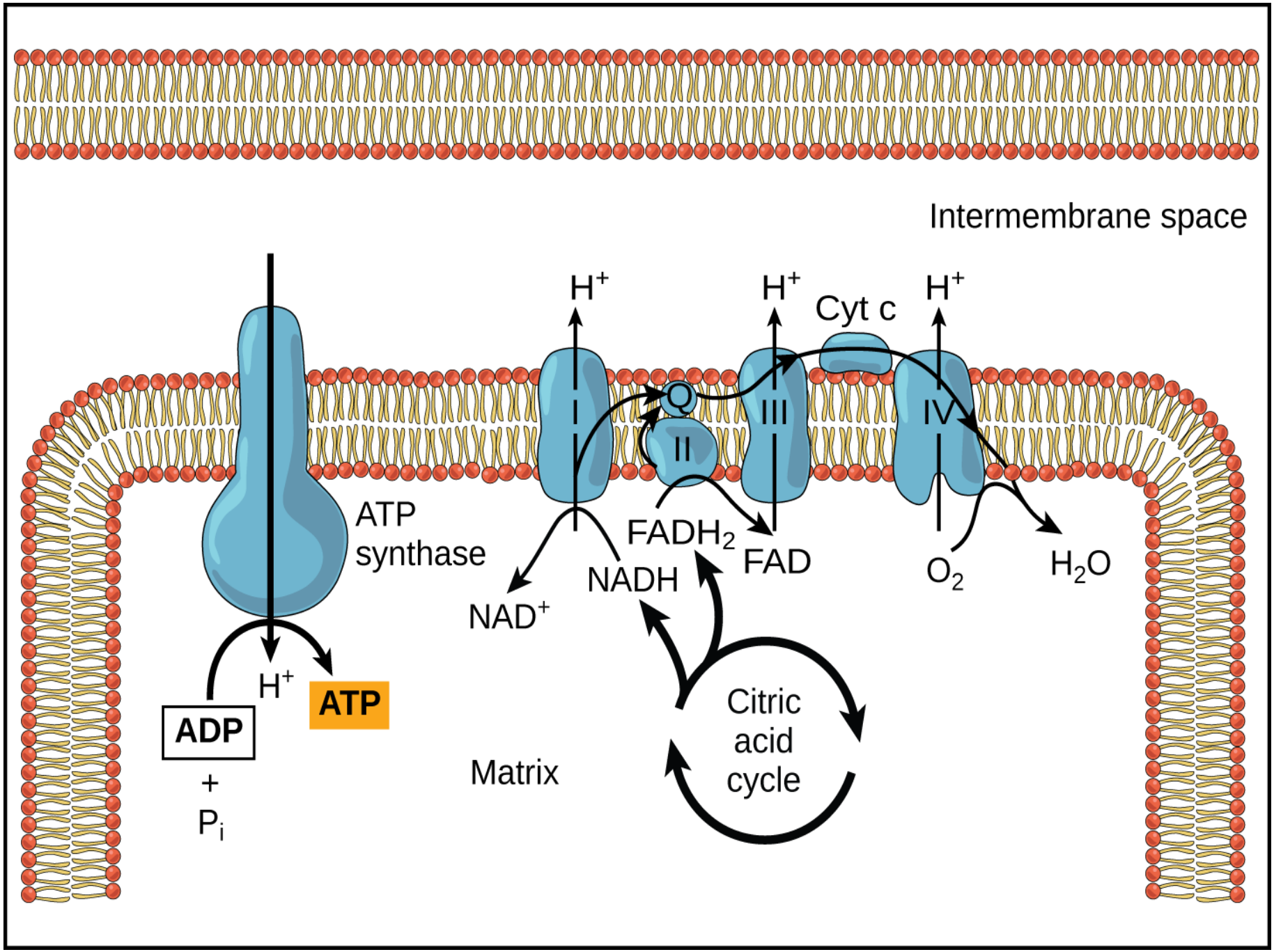


4-5 is sometimes called chemi-osmosis, kinetic energy of H^+ flowing back through ATP synthase powers the synthesis of ATP from ADP (also called oxidative phosphorylation in your book)

- The energy stored in a H^+ gradient across a membrane couples the redox reactions of the electron transport chain to ATP synthesis
- The H^+ gradient is referred to as a **proton-motive force**, emphasizing its capacity to do work




Intermembrane
Space
2 H+
NADH-CoQ
reductase
NADH
NAD+
H+
Succinate
Dehydrogenase
FADH2
FAD
CoQ
4 H+
Cytochrome
bc1 Complex
2 H+
Cyt C
Cytochrome Oxidase
2 H+
2H+ + ½O2
H2O
2 H+
3 H+
ATP
Synthase
ADP + Pi
ATP
3 H+
Mitochondrial
Matrix


Intermembrane space
H+
H+
H+
Cyt c
Q
I
II
III
IV
ATP
synthase
FADH2
FAD
NADH
NAD+
O2
H2O
H+
ATP
ADP
+
Pi
Matrix
Citric
acid
cycle

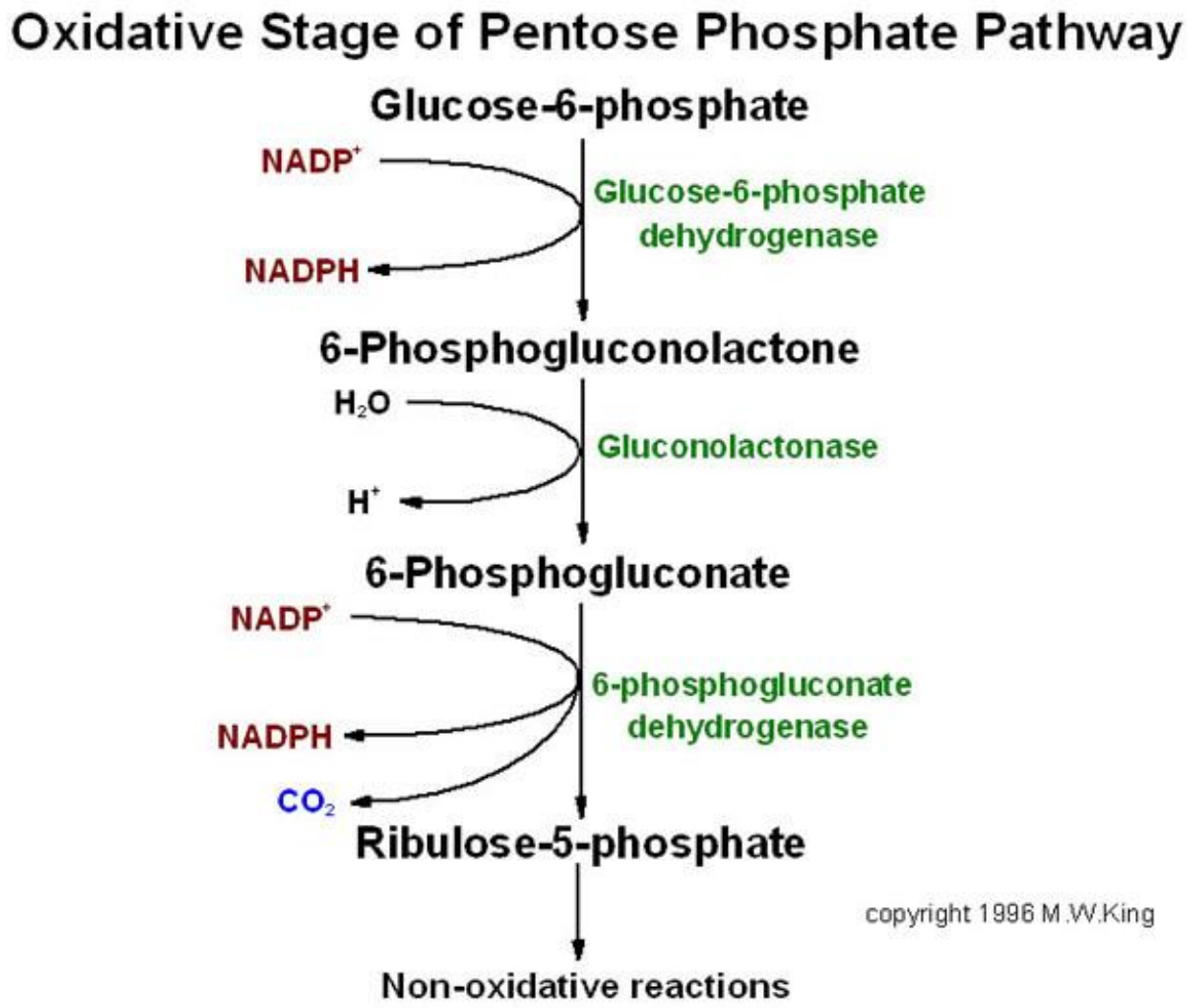
Pentose Phosphate Pathway (PPPW)

Pentose Phosphate Pathway

PPPW has 2 stages:
Oxidative & non-oxidative

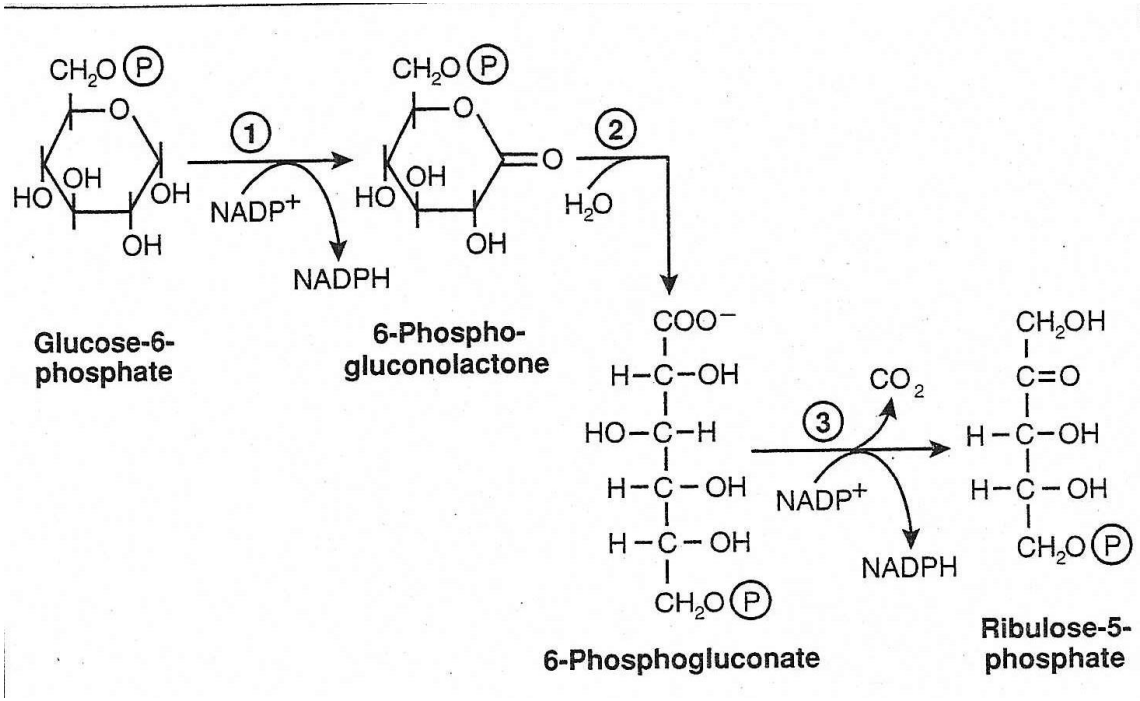
PPPW generates NADPH & Pentoses

Pentose-phosphate path way

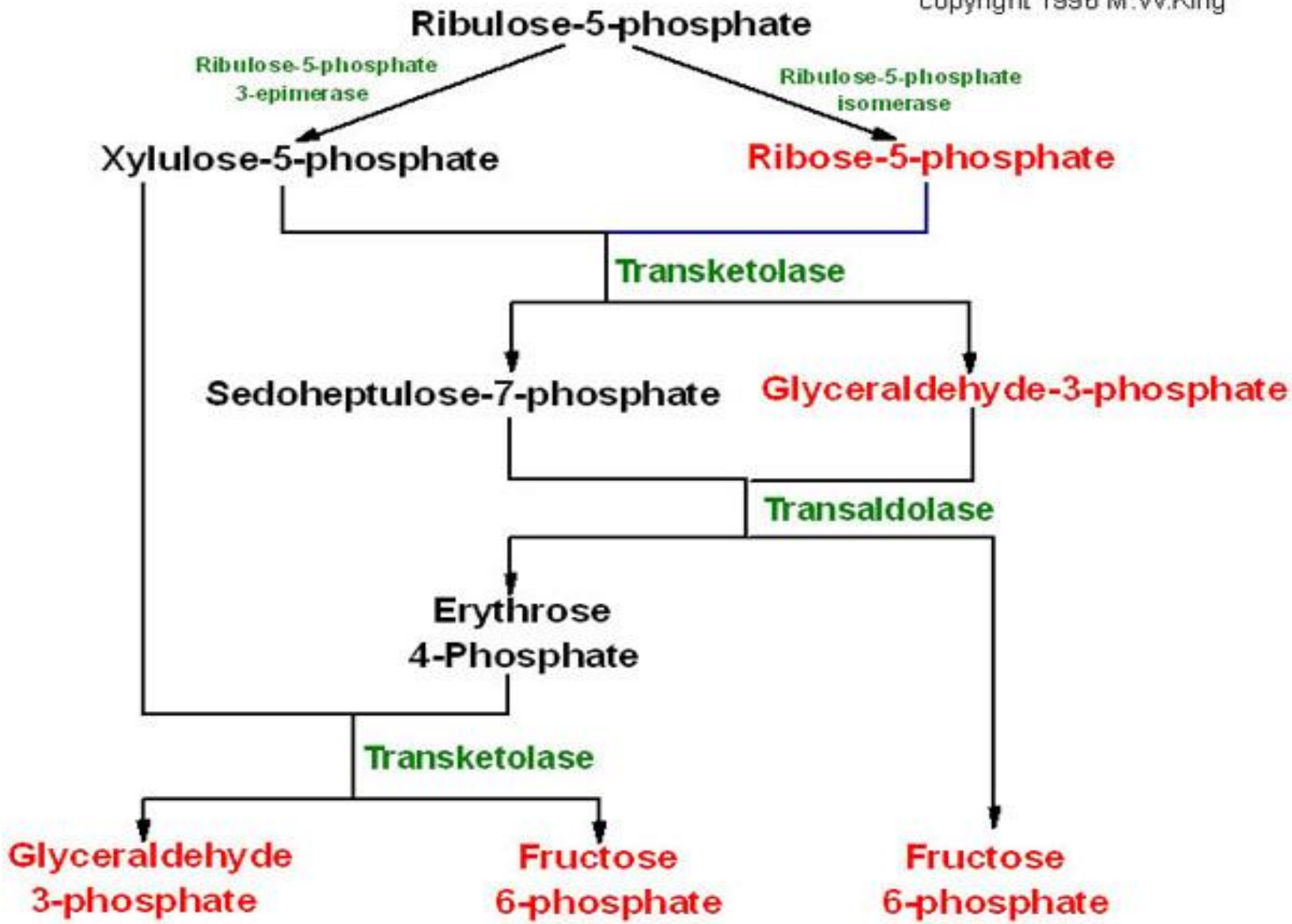


NADPH producing reactions

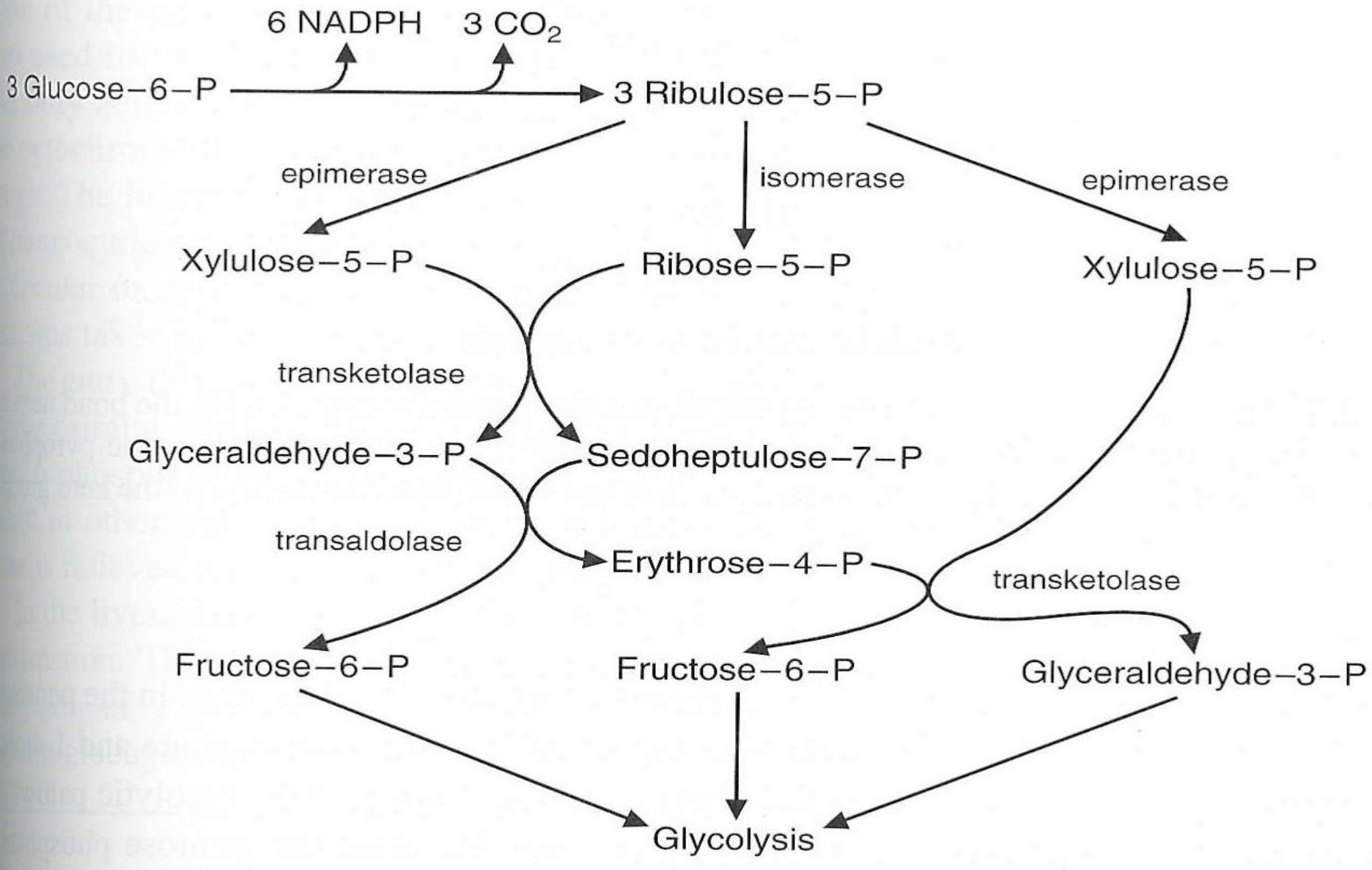
- Glucose-6-P dehydrogenase
- 6-P-gluconate dehydrogenase



Non-Oxidative Stage of Pentose Phosphate Pathway



PPPW: Summary



PPPW: physiological importance

1. Generation of reduced coenzymes NADPH, for reductive biosynthesis reactions within the cells. (e.g. fatty acid synthesis)

2. Energy production by transferring the hydrogen atoms from NADPH to electron transport system.

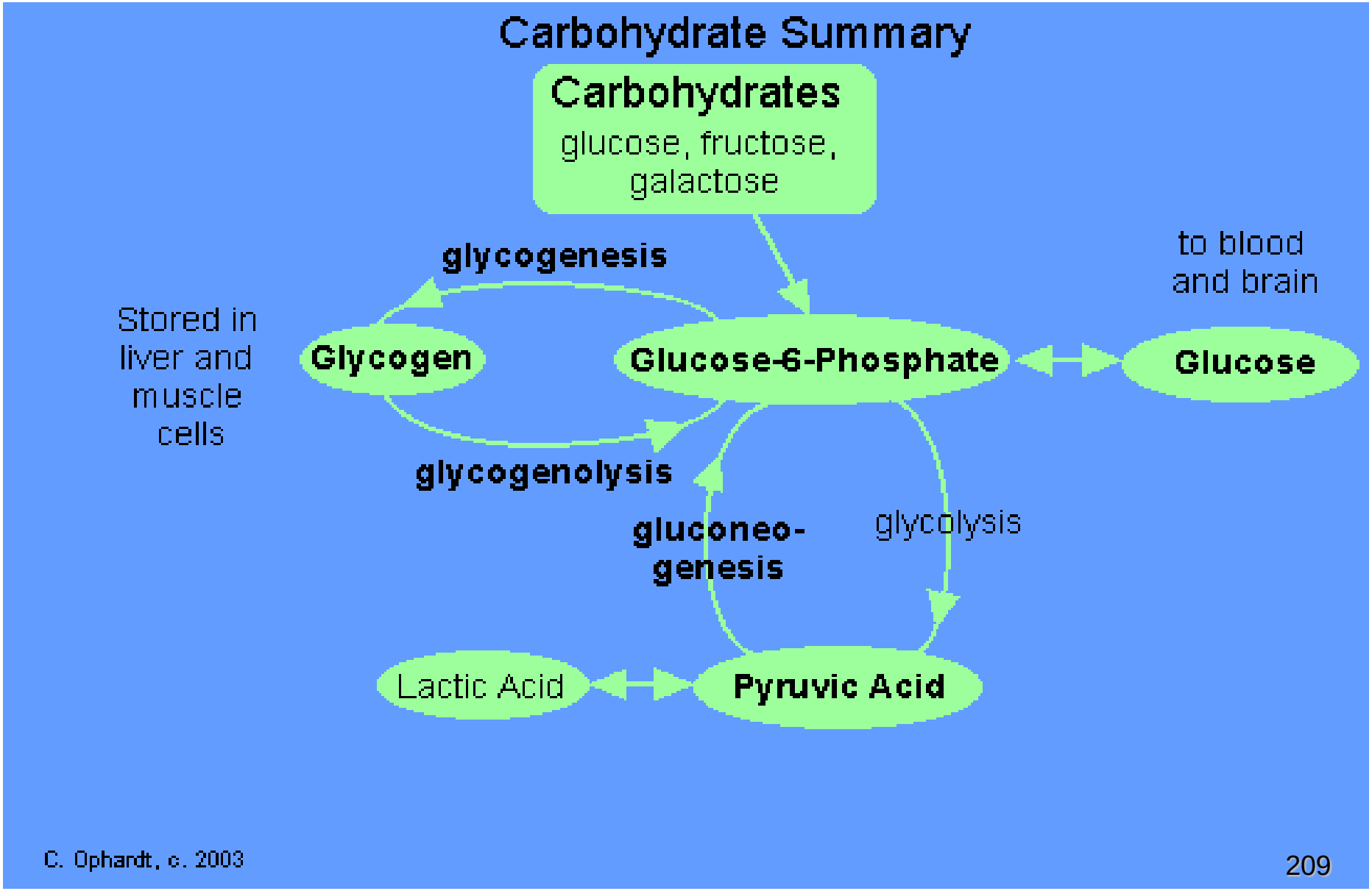
3. Production of ribose-5-phosphate used in the synthesis of nucleotides & nucleic acids.

PPPW: physiological importance

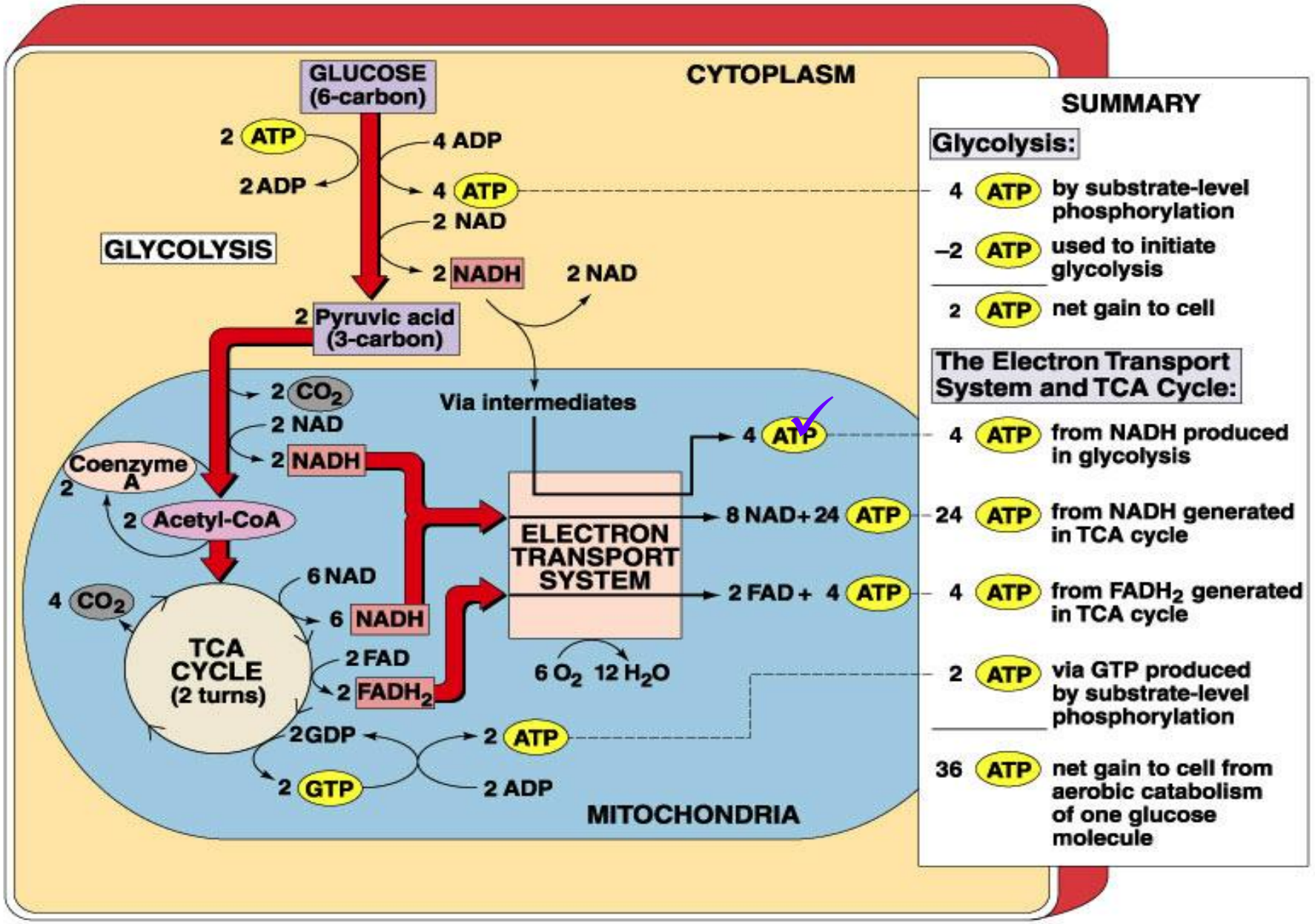
4. it can operate to metabolize dietary pentose sugars derived from the digestion of nucleic acids as well as to rearrange the carbon skeletons of dietary carbohydrates into glycolytic/gluconeogenic intermediates.

5. Production of erythrose-4-phosphate used in the synthesis of aromatic amino acids.

Metabolism of carbohydrates: summary



CELLULAR AEROBIC RESPIRATION



Gluconeogenesis conversion process

Gluconeogenesis

- Gluconeogenesis (also know as Neoglucogenesis) is defined as the *biosynthesis* of glucose from simple non-carbohydrate molecules, primarily pyruvate.

- The liver is the major location for gluconeogenesis.

Gluconeogenesis

- Gluconeogenesis pathway is *similar to the reverse* way of glycolysis but *differs* at critical steps.
- Control of these opposing pathways is *reciprocal* so that physiological conditions favoring one disfavor the other and vice versa.

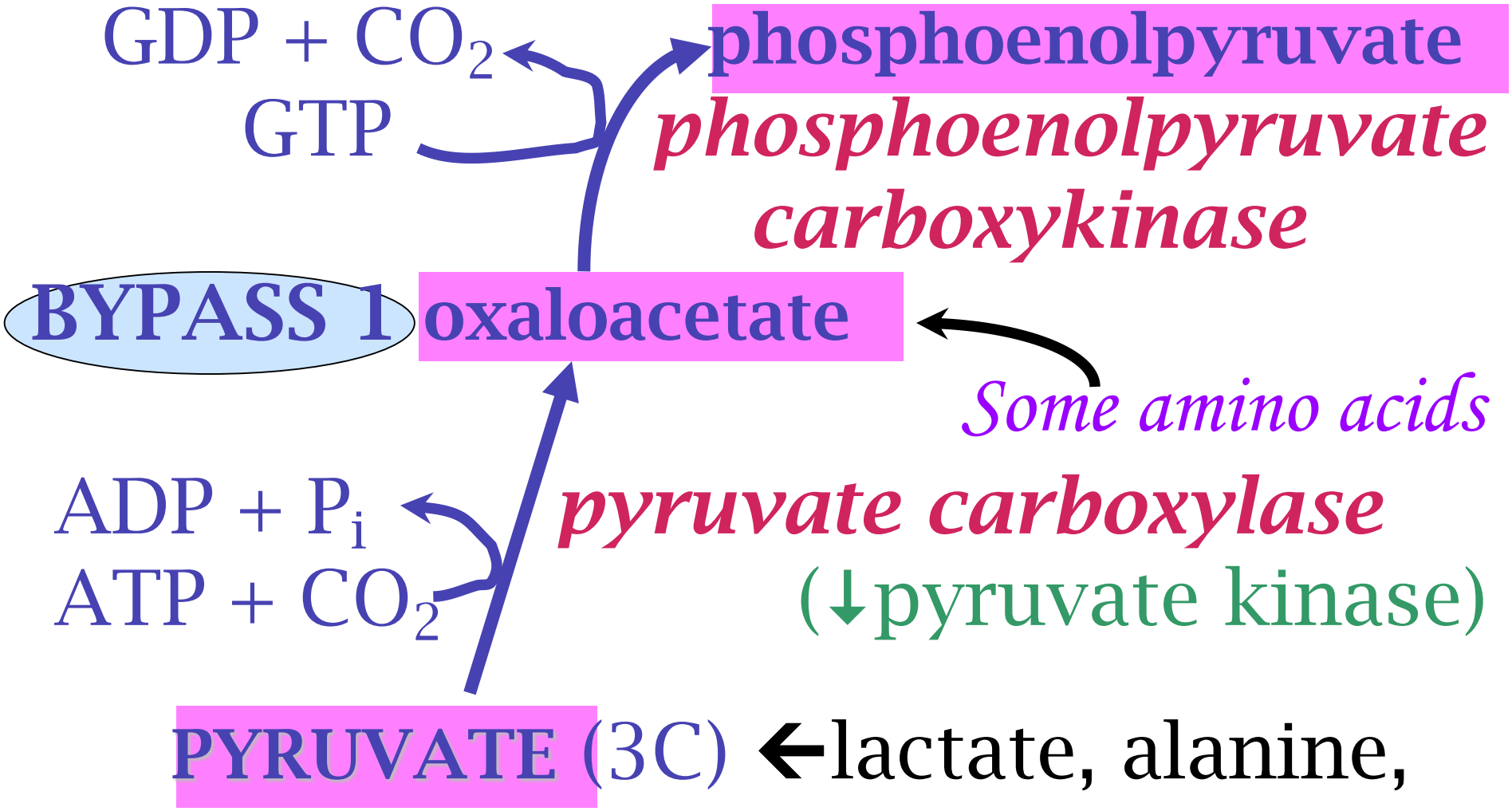
Gluconeogenesis vs. Glycolysis

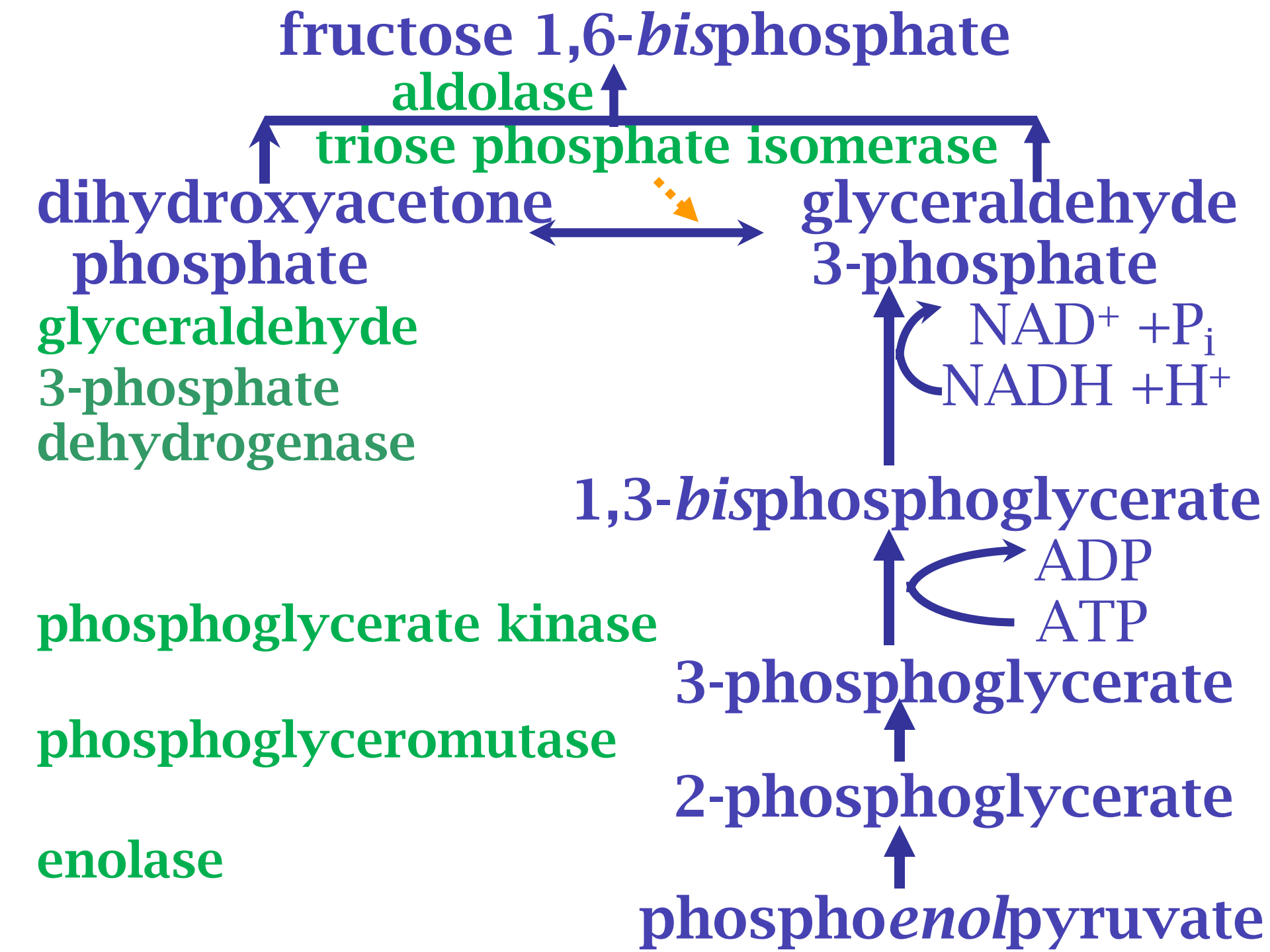
- Gluconeogenic enzymes
  - Glucose 6 phosphatase
  - Fructose bisphosphatase
  - PEP carboxykinase
  - Pyruvate carboxylase
- Glycolytic Enzymes
  - Glucokinase
  - Phosphofructokinase
  - Pyruvate Kinase

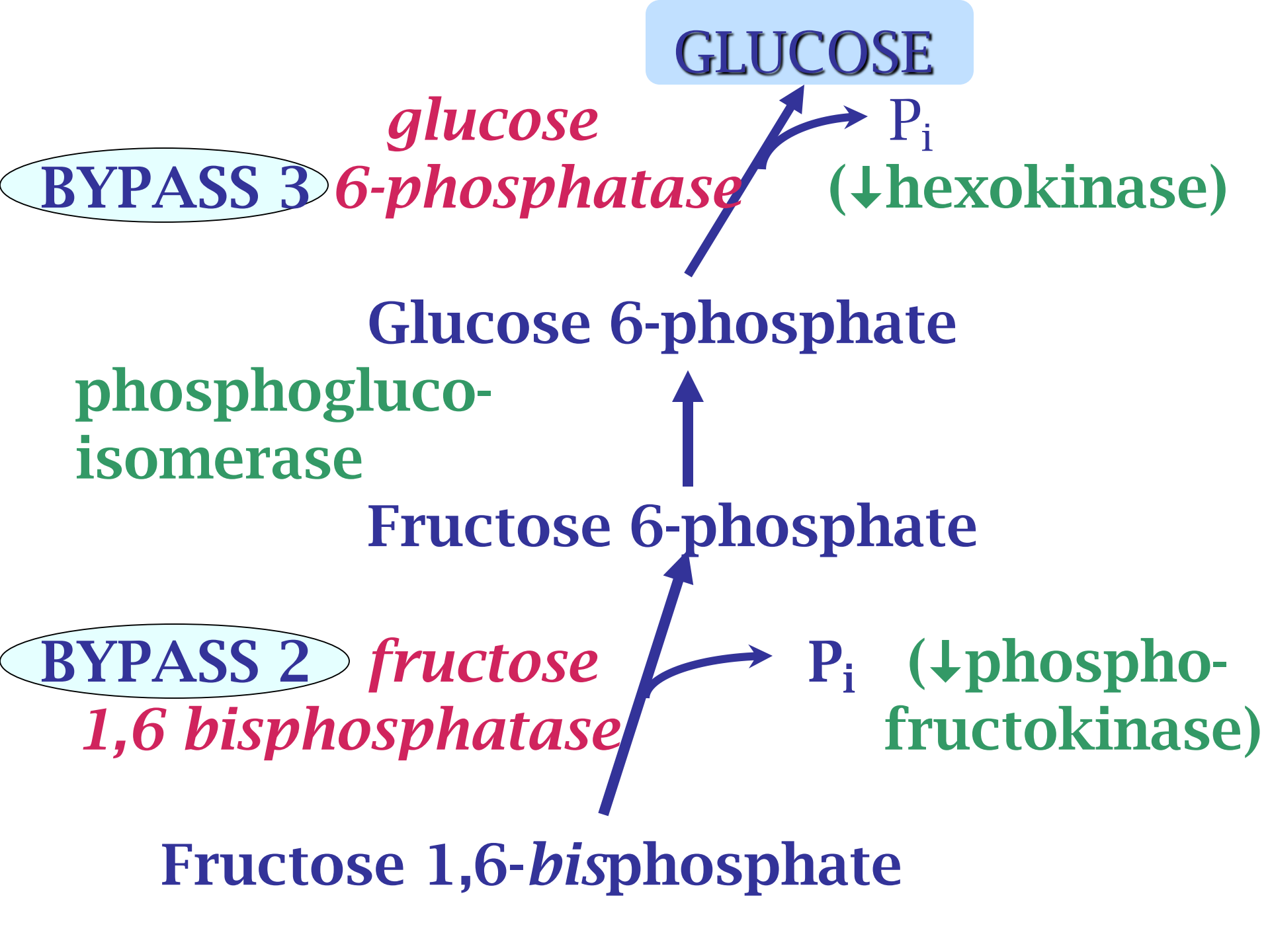
In glycolysis, there are three *irreversible* kinase reactions at *control points* involving:

- *glucokinase,*
- *phosphofructokinase*
- *pyruvate kinase*

Beginning of gluconeogenesis




fructose 1,6-*bis*phosphate
aldolase
triose phosphate isomerase
dihydroxyacetone phosphate
glyceraldehyde 3-phosphate
glyceraldehyde 3-phosphate dehydrogenase
NAD+ +Pi
NADH +H+
1,3-*bis*phosphoglycerate
phosphoglycerate kinase
ADP
ATP
3-phosphoglycerate
phosphoglyceromutase
2-phosphoglycerate
enolase
phospho*enol*pyruvate


GLUCOSE
glucose
6-phosphatase
P_i
BYPASS 3
(↓hexokinase)
Glucose 6-phosphate
phosphogluco-
isomerase
Fructose 6-phosphate
BYPASS 2
fructose
1,6 bisphosphatase
P_i
(↓phospho-
fructokinase)
Fructose 1,6-*bis*phosphate

Gluconeogenesis

Cost: The production of glucose is energy *expensive*.

Input:

2 pyruvate + 4 ATP + 2 GTP + 2 NADH

Output:

glucose + 4 ADP + 2 GDP + 2 NAD^+ + 6 P_i

Purpose of gluconeogenesis

- Need to maintain glucose levels in a limited range in blood.
- Some tissues (brain, erythrocytes, and muscles) in exercise use glucose at a rapid rate and sometimes require glucose in addition to dietary glucose.

Purpose of gluconeogenesis

- The brain uses mostly glucose and erythrocytes can use *only* glucose as a source of energy.

Gluconeogenesis: precursors

- pyruvate: major precursor
- lactate: from muscle, forms pyruvate
- some amino acid carbon skeletons (most important is alanine)
- Krebs cycle intermediates
- propionate from breakdown of fatty acids and amino acids.
- glycerol from certain lipids.

Muscle lactate: major source of pyruvate

Lactate is the primary source for pyruvate. In muscles, lactate is produced in great quantities during intense physical exercise.
This excess lactate cannot be further oxidized in muscles.

Muscle lactate: major source of pyruvate

Lactate is released from the muscles to the blood stream and travels to the *liver* for conversion to pyruvate and, ultimately to glucose.

Gluconeogenesis: control

- Gluconeogenesis serves as an alternative source of glucose when supplies are low and is largely controlled by diet.

- High carbohydrate in meal reduces gluconeogenesis and fasting increases.

Hormonal regulation

Major Hormones that regulate Metabolism

Hormone	Type of Reaction	Control of carbohydrate metabolism
Insulin	Anabolic	Stimulates glycogenesis
Glucagon	Catabolic	Stimulates glycogenolysis
Epinephrine	Catabolic	Stimulates glycogenolysis
Cortisol	Anabolic	Stimulates gluconeogenesis

Hormonal regulation: Insulin

Insulin-

High levels of glucose induce release of insulin from β-cells of the pancreas.

- Insulin is polypeptide hormone.
- Increases glycogenesis in muscle.

Hormonal regulation: Glucagon

Glucagon- low glucose levels

- A polypeptide hormone produced in α-cells of the pancreas.
- It acts primarily on liver cells.
- It stimulates glycogen breakdown & inhibits glycogenesis.
- It also blocks glycolysis & stimulates gluconeogenesis.

Hormonal regulation: Epinephrine

Epinephrine - *low glucose levels*

- Acts primarily on skeletal muscle.
- Stimulates glycogen breakdown& inhibits glycogenesis.
- Glucagon and epinephrine bothstimulate intracellular pathway via increasing levels of cAMP.

Glycogen storage diseases

A family of serious, although not necessarily fatal, diseases caused by mutations in the enzymes involved in glycogen storage and breakdown.

Types of Glycogen Storage Disease

Some forms of GSDs are life-threatening while others cause little in the way of illness. These *genetic diseases* are caused by mutations in the enzymes involved in glycogen storage and breakdown.

Type	Enzyme Deficiency	Name	Tissue	Characteristics
I	glucose-6-phosphatase	Von Gierke's disease	liver, kidney	Enlarged liver, liver loaded with glycogen, severe hypoglycemia, ketosis, hyperlipemia
II	α-glucosidase(lysosome)		liver, heart, muscle	fatal; glycogen accumulates in lysosomes
III	debranching enzyme	Pompe's disease	liver, muscle	short-chained glycogen, some hypoglycemia
IV	branching enzyme	Cori's disease	liver	fatal; long unbranched glycogen
V	phosphorylase	Andersen's disease McArdle's disease	muscle	severe cramps upon exercise; little glycogen in muscle
VI	phosphorylase	Hers' disease	liver	similar to I, but milder
VII	phosphofructokinase	Tarui's disease	muscle	similar to V; high G6P activates glycogen synthase; more glycogen accumulates in muscle; some erythrocyte involvement
VIII	phosphorylase kinase		liver	similar to I but milder
IX	glycogen synthase		liver	less glycogen in liver

Glycogen Storage Disease	**Symptoms**, in addition to glycogen accumulation
Type I, liver deficiency of **Glucose-6-phosphatase** (von Gierke's disease)	**hypoglycemia** (low blood glucose) when fasting, liver enlargement.
Type IV, deficiency of **branching enzyme** in various organs, including liver (Andersen's disease)	**liver dysfunction** and early death.
Type V, muscle deficiency of **Glycogen Phosphorylase** (McArdle's disease)	**muscle cramps** with exercise.
Type VII, muscle deficiency of **Phosphofructokinase**.	**inability to exercise**.

Metabolic disorders

The most common disease in which *glycogen metabolism becomes abnormal is diabetes*, in which, because of abnormal amounts of insulin, liver glycogen can be abnormally accumulated. Restoration of normal glucose metabolism usually normalizes glycogen metabolism as well.

Metabolic disorders

In hypoglycemia caused by excessive insulin, liver glycogen levels are high, but the high insulin level prevents glycogenolysis necessary to maintain normal blood sugar levels. Glucagon is a common treatment for this type of hypoglycemia.

TANK YOU