BIOCHEMISTY

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GLYCOLYSIS

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- Glycolysis => a set of reactions => take place in **cytoplasm** of prokaryotes and eukaryotes.

- Glycolysis => an almost **universal central pathway** of glucose catabolism .

- major roles of glycolysis => **produce energy** and **intermediates** for biosynthetic pathways.

Glycolysis has two Phases

- **Preparatory phase**
- **Pay Off Phase**

- In **preparatory phase** of glycolysis => two molecules of **ATP** are **invested** and hexose is **cleaved** => two triose phosphates (glyceraldehyde 3 phosphate and Dihydroxy acetone phosphate).

- The **payoff phase** of glycolysis includes energy-conserving phosphorylation steps => some of the free energy of the glucose molecule is **conserved** => **ATP**.

- **one molecule** of glucose => **two molecules** of glyceraldehyde 3-phosphate => both halves of the glucose molecule follow the **same pathway** in second phase of glycolysis.

- conversion of two molecules of glyceraldehyde 3-phosphate => two molecules of pyruvate is accompanied by => formation of **four molecules of ATP** from ADP.

- net yield of ATP per molecule of glucose degraded is **only two** => because two ATP were invested in the preparatory phase of glycolysis to phosphorylate the two ends of the hexose molecule.

- For each molecule of glucose degraded => pyruvate => two molecules of ATP are generated from ADP and Pi.

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$$\text{Glucose} + 2NAD^+ \longrightarrow 2\ \text{pyruvate} + 2NADH + 2H \quad \Delta G1 = -146\ \text{kJ/mol}$$

- formation of ATP from ADP and Pi => is endergonic:

$$2ADP + 2Pi \longrightarrow 2ATP + 2H_2O \qquad \Delta G2 = +61.0\ \text{kJ/mol}$$

$$\Delta Gs = G1 + G2 \quad (-146\ \text{kJ/mol} + 61.0\ \text{kJ/mol} = -85\ \text{kJ/mol})$$

However, complete oxidation of glucose to carbon dioxide and water proceeds with a standard free-energy change of -2,840 kJ/mol.

Irreversible / Regulatory steps in glycolysis

Hexokinase

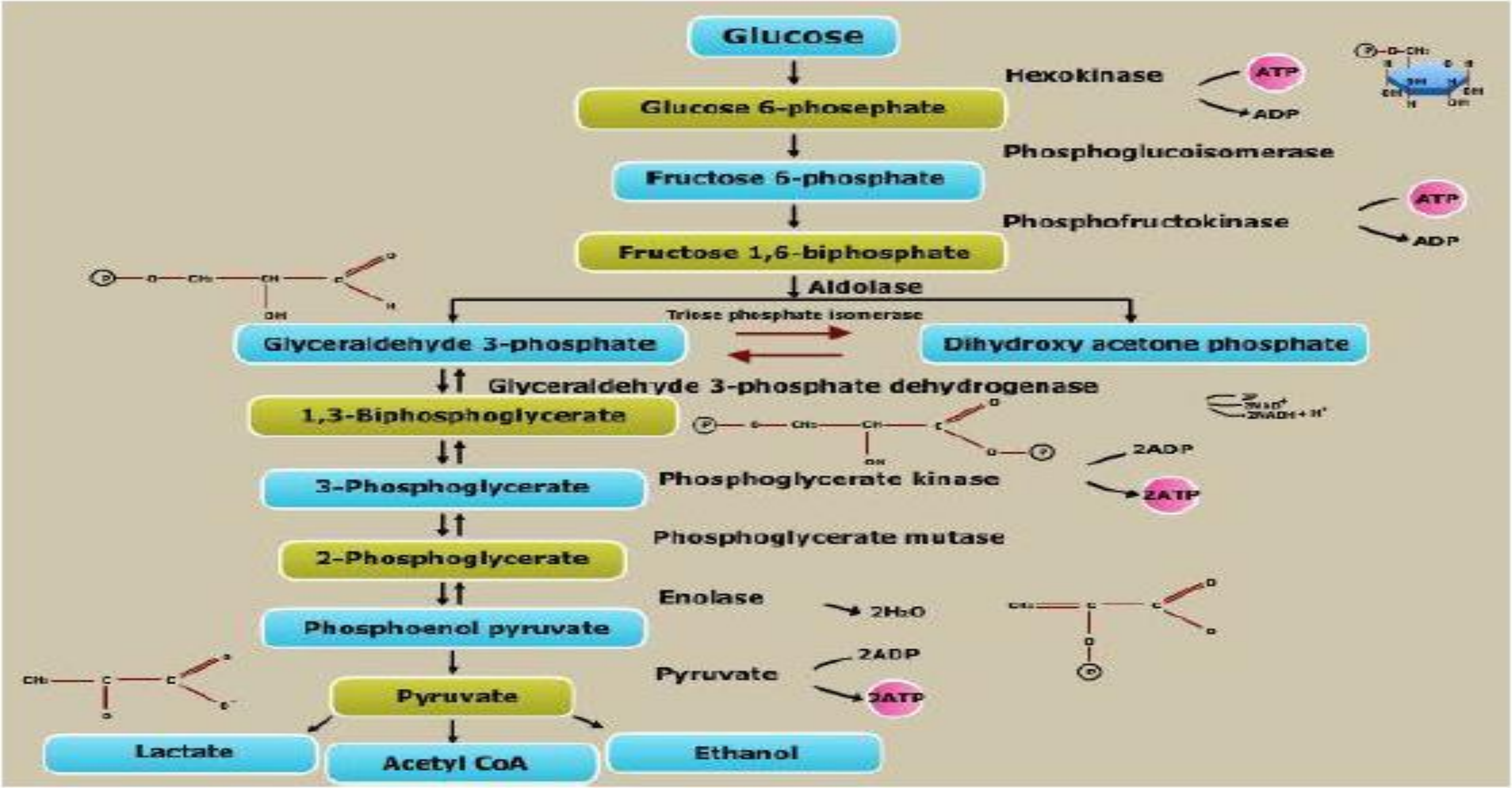
- Hexokinase => present in all cells of all organisms.
- Hepatocytes also contain a form of hexokinase called hexokinase IV or **glucokinase**, which differs from other forms of hexokinase in kinetic and regulatory properties.
- Two enzymes that catalyze the same reaction but are encoded in different genes are => called isozymes.

Phosphofructokinase

- PFK-1 reaction is essentially **irreversible** under cellular conditions
- it is **first “committed” step** in the glycolytic pathway
- glucose 6-phosphate and fructose 6-phosphate have other possible fates, but **fructose 1,6-diphosphate** is targeted => **glycolysis**.
- **Phosphofructokinase-1** is a regulatory enzyme => activity is **increased** whenever the cell’s **ATP supply is depleted** or when the ATP breakdown products => ADP and AMP are in excess.
- enzyme is **inhibited** whenever the cell has ample ATP and is well supplied by other fuels such as fatty acids.

Pyruvate kinase

last step in glycolysis is => transfer of phosphoryl group from phosphoenolpyruvate => to ADP, catalyzed by pyruvate kinase, which requires K^+ and either Mg^{2+} or Mn^{2+} .


Glucose
Hexokinase
ATP
ADP
Glucose 6-phosephate
Phosphoglucoisomerase
Fructose 6-phosphate
Phosphofructokinase
ATP
ADP
Fructose 1,6-biphosphate
Aldolase
Triose phosphate isomerase
Glyceraldehyde 3-phosphate
Dihydroxy acetone phosphate
Glyceraldehyde 3-phosphate dehydrogenase
1,3-Biphosphoglycerate
2ADP
Phosphoglycerate kinase
2ATP
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
2H2O
Phosphoenol pyruvate
2ADP
Pyruvate
2ATP
Pyruvate
Lactate
Acetyl CoA
Ethanol

GLYCOLYSIS

Pasteur Effect

- Louis Pasteur discovered => both the **rate** and the total amount of **glucose consumption** were => many times greater under **anaerobic** than **aerobic conditions**.
- ATP yield from glycolysis under anaerobic conditions (**2** ATP per molecule of glucose) is much smaller than that from the complete oxidation of glucose to CO_2 under aerobic conditions (**32** ATP per glucose).
- About 16 times as much glucose must therefore be consumed anaerobically as aerobically to yield the same amount of ATP.

Substrate-level phosphorylation

enzyme phosphoglycerate kinase transfers the high-energy phosphoryl group from the carboxyl group of 1,3-bisphosphoglycerate to ADP => forming ATP and 3- phosphoglycerate. Thus by consuming the product of 1,3-bisphosphoglycerate of previous step, keeps [1,3-bisphosphoglycerate] relatively low in the steady state. The outcome of these coupled reactions, both reversible under cellular conditions, is that the energy released on oxidation of an aldehyde to a carboxylate group is conserved by the coupled formation of ATP from ADP and Pi. The **formation of ATP by phosphoryl group transfer from a substrate such as 1,3 bisphosphoglycerate is referred to as a substrate-level phosphorylation**, to distinguish this mechanism from respiration-linked phosphorylation. Substrate-level phosphorylations involve soluble enzymes and chemical intermediates (1,3-bisphosphoglycerate in this case). **Respiration-linked phosphorylations**, on the other hand, involve membrane-bound enzymes and transmembrane gradients of protons

$$\text{Glucose} + 2\text{ATP} + 2\text{NAD}^{+} + 4\text{ADP}\_+2\text{Pi} \longrightarrow 2\ \text{pyruvate} + 2\text{ADP} + 2\text{NADH} + 2\text{H} + 4\text{ATP} + 2\text{H}_2\text{O}$$

In the overall glycolytic process, **one molecule of glucose is converted => two molecules of pyruvate** (the pathway of carbon).

Two molecules of ADP and two of Pi are converted => two molecules of ATP (the pathway of phosphoryl groups).

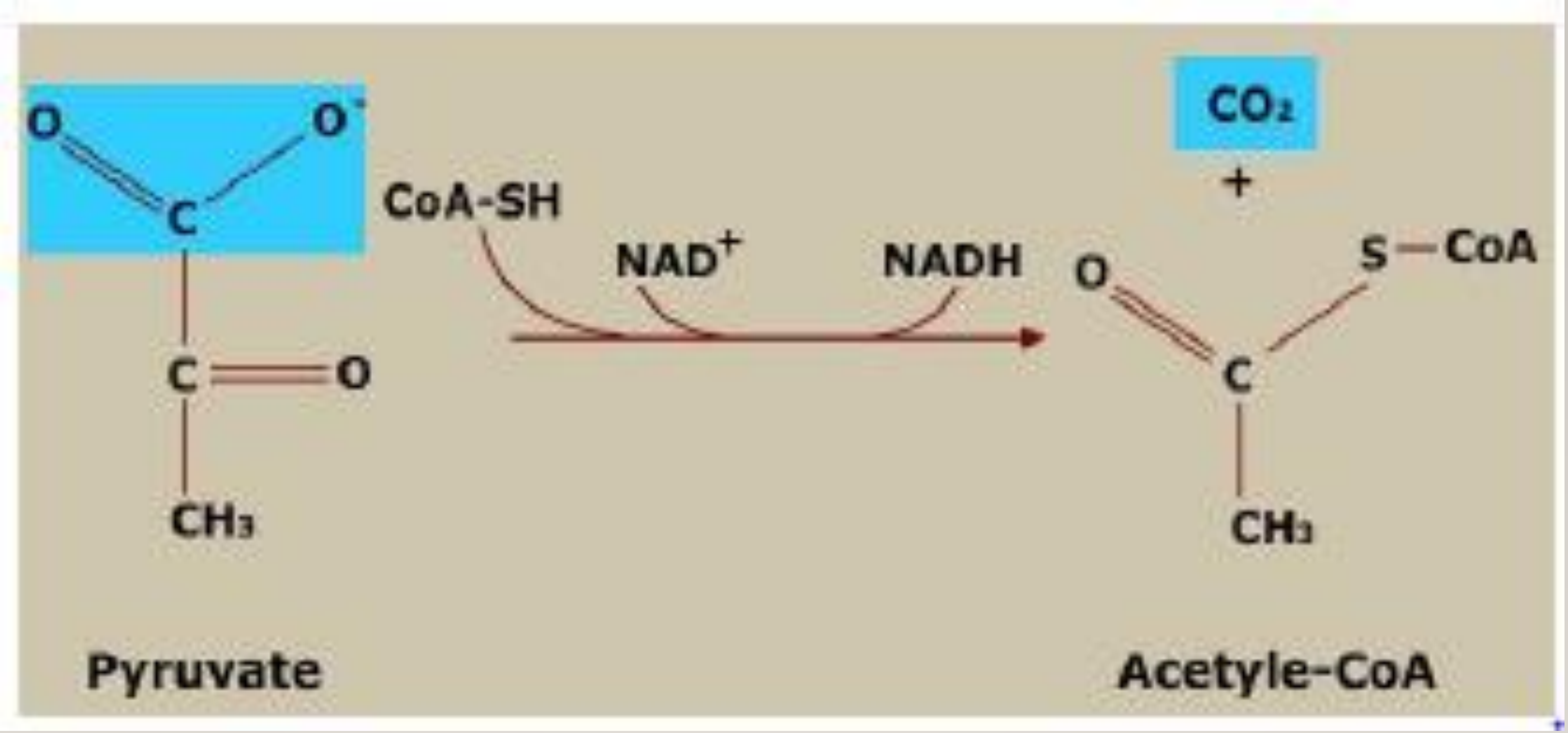
Four electrons => as two hydride ions, are transferred from two molecules of glyceraldehyde 3-phosphate => two of NAD+ (the pathway of electrons).

Fate of Pyruvate
Entry into citric acid cycle

Glycolysis releases => relatively little of the **energy** present in a glucose molecule

much more is released by => subsequent operation of citric acid cycle and oxidative phosphorylation

Under **aerobic conditions => pyruvate** is converted => **acetyl Co-A** by the enzyme **pyruvate dehydrogenase** which enters => **citric acid cycle**.



Entry of Pyruvate (PDH) into citric acid cycle

Conversion to fatty acids or ketone bodies

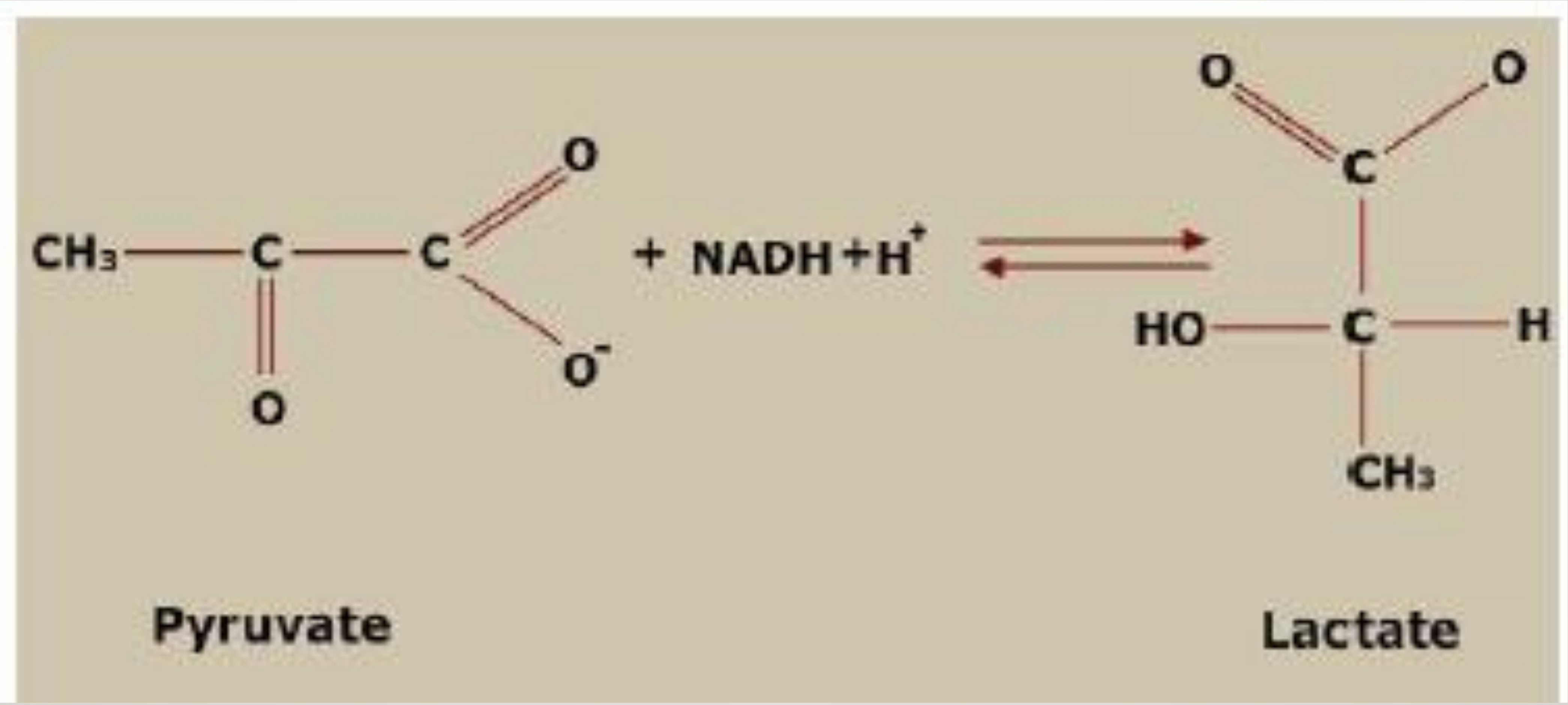
When cellular energy level is high (ATP in excess)
=> rate of citric acid cycle decreases, and
acetyl CoA begins to accumulate and is used for
=> **fatty acid** or **ketone body synthesis** .

Conversion to lactate

- **NAD+** used during glycolysis in the formation of 1,3 diphosphoglycerate, by glyceraldehyde 3- phosphate dehydrogenase must be **regenerated** if glycolysis has to continue.

- Under **aerobic conditions,** NAD+ is regenerated by reoxidation of NADH via electron transport chain.

- when oxygen is limiting as in muscle **during exercise** reoxidation of NADH to NAD+ by ETC is insufficient to maintain glycolysis . Hence NAD+ is **regenerated** by conversion of the pyruvate => lactate by lactate dehydrogenase.



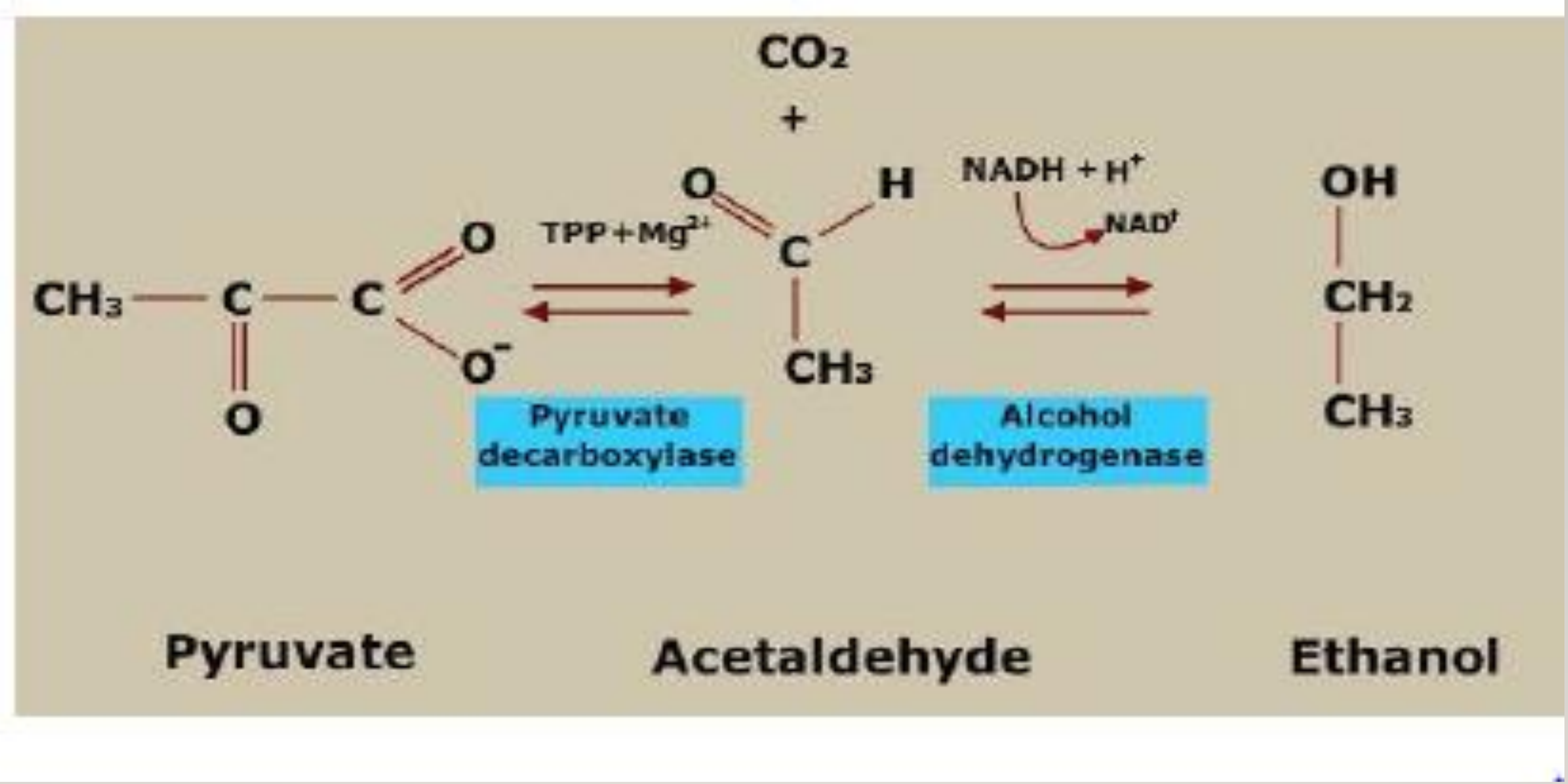
Conversion of Pyruvate to lactate

Alcoholic fermentation

In microbes, NAD+ is required for continuation of glycolysis under anaerobic conditions.

So, pyruvate is converted => **acetaldehyde** by pyruvate decarboxylase and then to **ethanol** by alcohol dehydrogenase.

The last reaction simultaneously reoxidizes, the NADH to NAD+.



Involvement of Pyruvate into Alcoholic fermentation

Entry of other Carbohydrates in Glycolysis

Many carbohydrates besides glucose meet their **catabolic fate** in glycolysis => after being transformed => one of the **glycolytic intermediates**.

most significant are

polysaccharides - glycogen and starch;

Disaccharides - maltose, lactose, and sucrose;

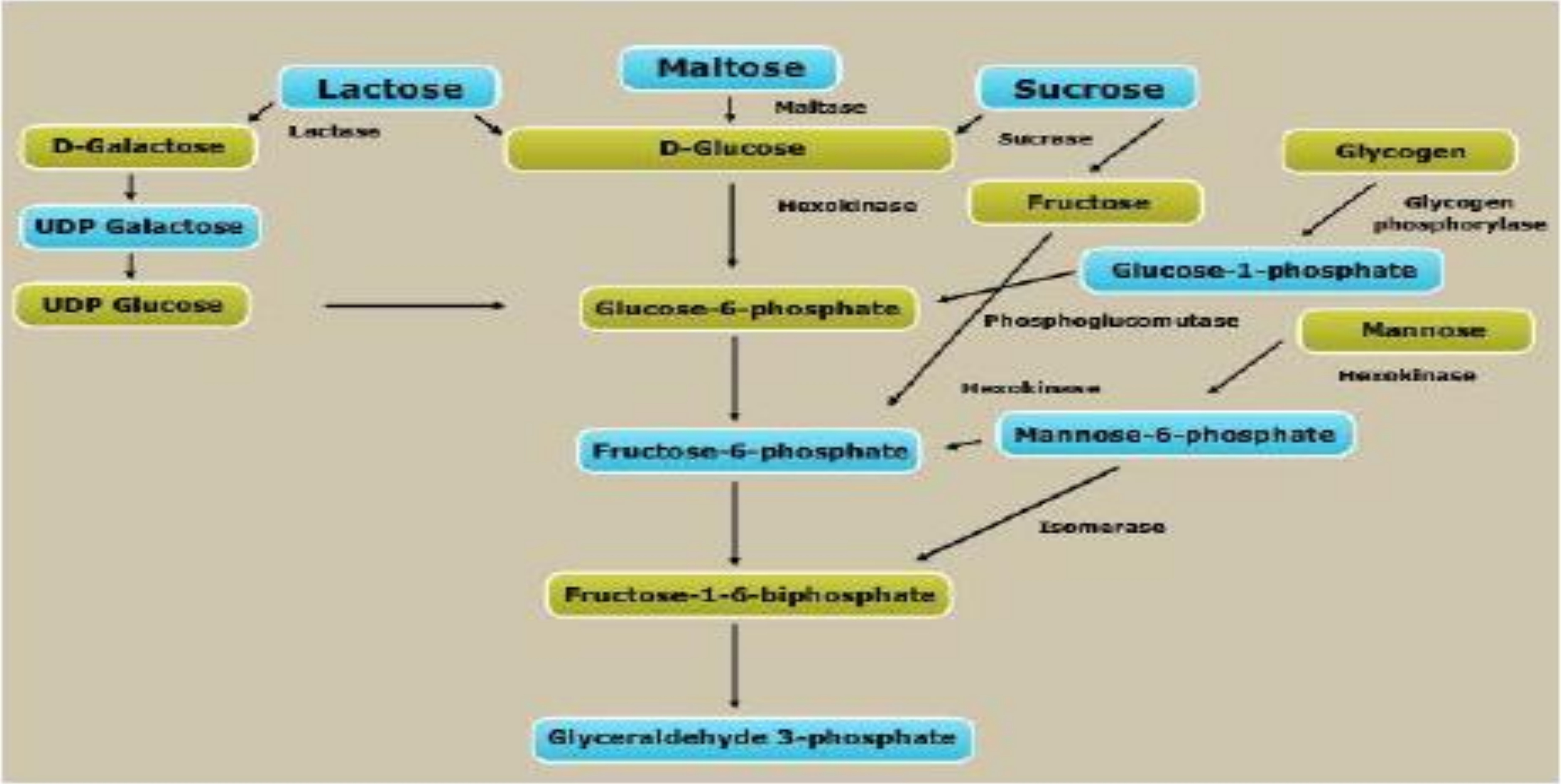
Monosaccharides - fructose, mannose, and galactose.

- **Glycogen** in animal tissues can be mobilized => use within same cell by a phosphorolytic reaction catalyzed by **glycogen phosphorylase**.

- This enzyme catalyzes an attack by Pi on the (α1-4) glycosidic linkage that joins the last two glucose residues at a nonreducing end => generating glucose 1-phosphate and a polymer one glucose unit shorter.

- A debranching enzyme removes the branches α1-6 glucosidic linkage.

PGM



Entry of other Carbohydrates in Glycolysis

THANKS