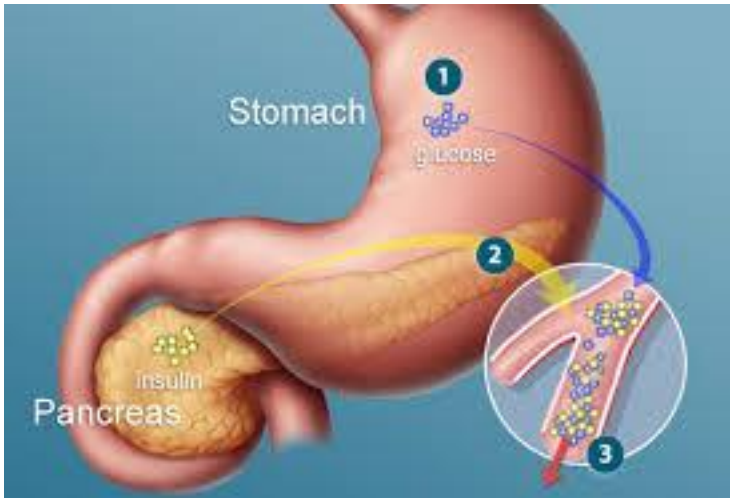
Glycolysis II



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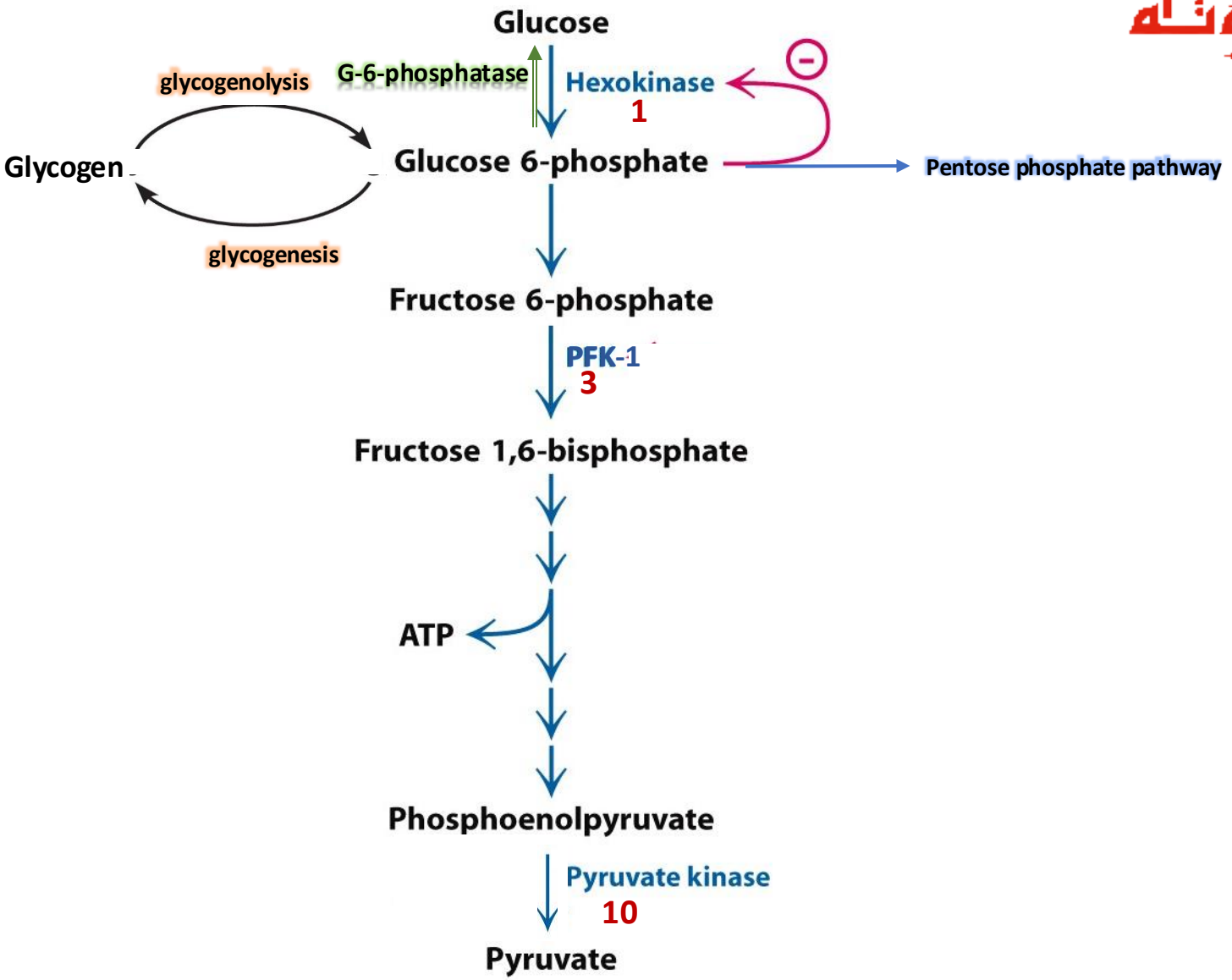
Glycolysis Regulation



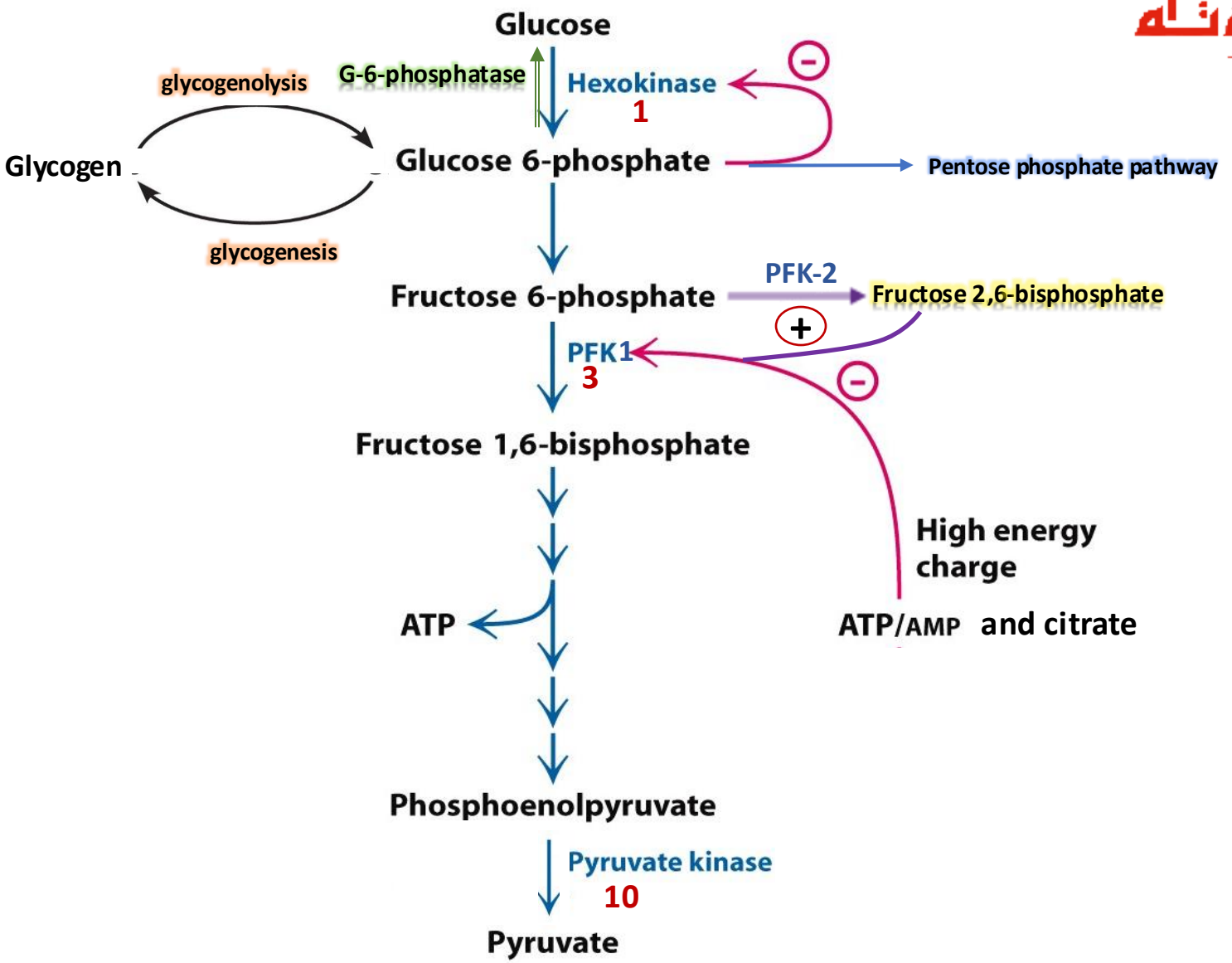
Glycolysis Regulation

- Glycolysis can be controlled at 3 points:

1.Step 1 which is catalyzed by hexokinase enzyme (allosteric enzyme). Hexokinase isoforms (except glucokinase) are allosterically inhibited by excess G6P

- When the glycolysis pathway is switched off, the accumulated G6P either enters the PPP or glycogenesis according to the cellular need.
- Once needed, glycogen is broken into G6P and according to cell type is either dephosphorylated by **glucose 6-phosphatase** (but not in brain or muscle cells) or continue downstream the glycolysis to generate energy so G6P is an important intermediate and can follow different fates
- Our cells are smart and can follow the right road map to reach their required need or demand

Glycolysis Regulation



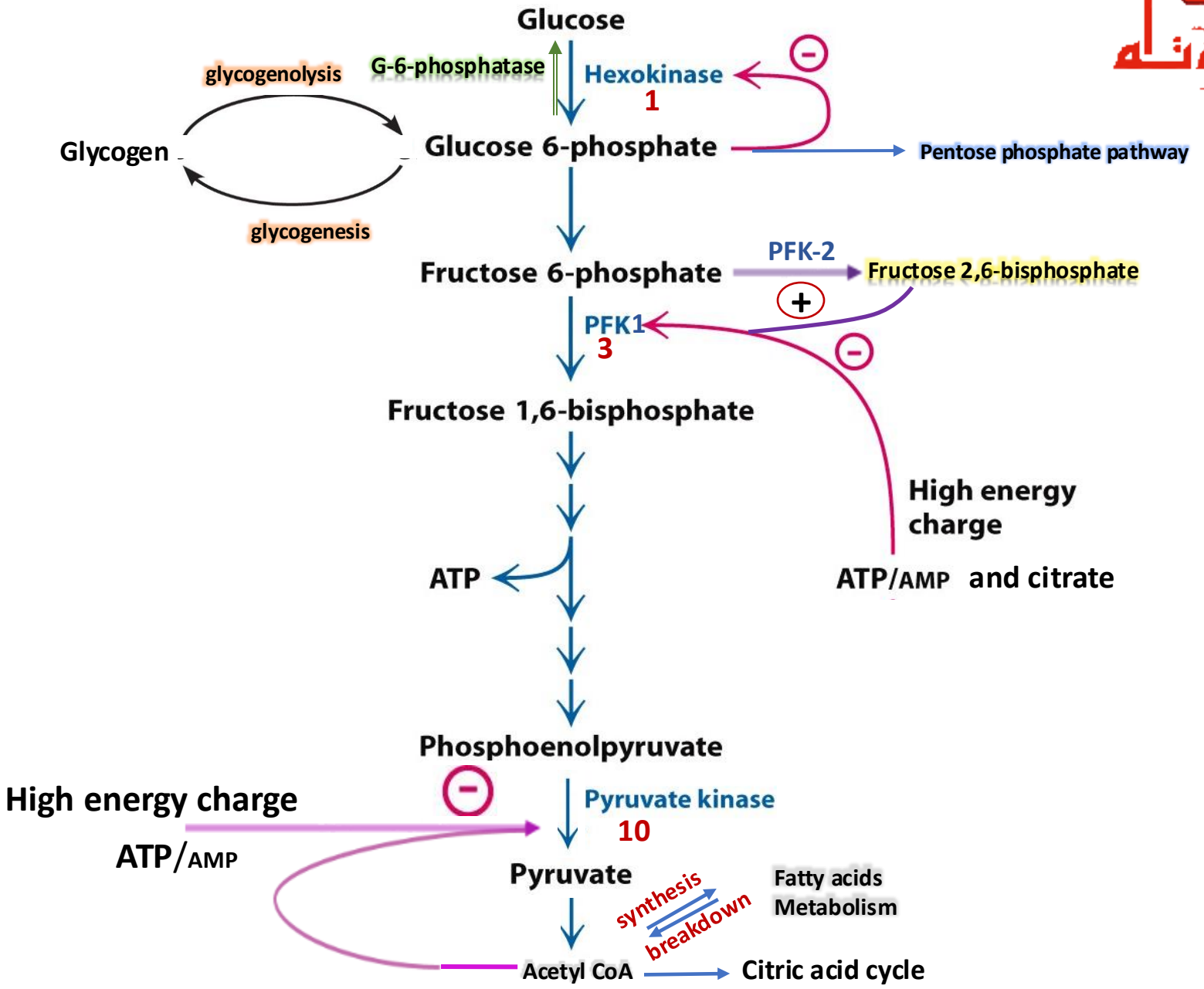
Glycolysis Regulation

- Glycolysis can be controlled at 3 points:

2. Step 3 which is catalyzed by phosphofructokinase-1 enzyme. It is an allosteric enzyme. Two inhibitors are citrate and ATP whereas AMP and recently fructose 2,6-biphosphate (in liver) are activators. Actually this is the most important control point and it is considered as the main **rate-limiting step** in glycolysis

- Citrate is an indirect indicator of cell high energy state as its presence in the cytosol indicates that Krebs cycle in mitochondrial matrix is blocked so it can cross the mitochondrial double membranes to cytosol and switching off the glycolysis

Glycolysis Regulation



Glycolysis Regulation

- Glycolysis can be controlled at 3 points:

3. Step 10 which is catalyzed by pyruvate kinase enzyme. It is controlled by the level of ATP and Acetyl CoA (both are allosteric inhibitors).

- Acetyl CoA is synthesized in the matrix and can not cross to cytosol due to absence of its specific transporter in mitochondrial membranes. It is indirectly transported to cytosol in the form of citrate which is then cleaved into Acetyl CoA and oxaloacetate
- **Accumulated Acetyl CoA in the cytosol** is an indicator that the energy is now available from fat breakdown so no need to proceed in glycolysis

Glycolysis Regulation

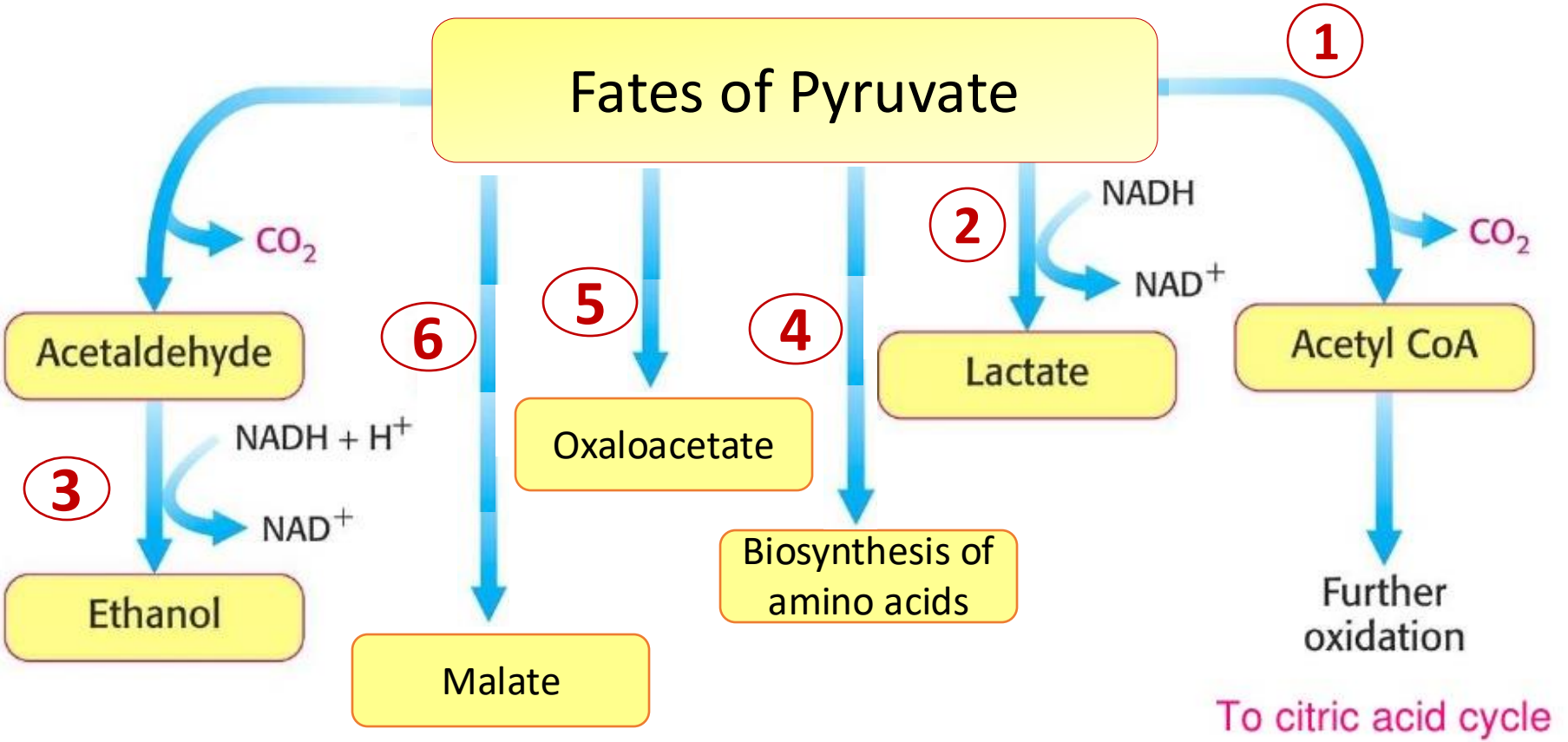
- Two links between carbohydrate and fat metabolism:

1. **DHAP:** excess DHAP can be converted to glycerol 3-phosphate (found in the backbone of triglyceride)

2. **Acetyl CoA:** it can be produced from pyruvate irreversibly (CHO metabolism) or from β-oxidation of fatty acid occurring in mitochondrial matrix (lipid metabolism) in reversible pathway with fatty acid synthesis occurring in cytosol

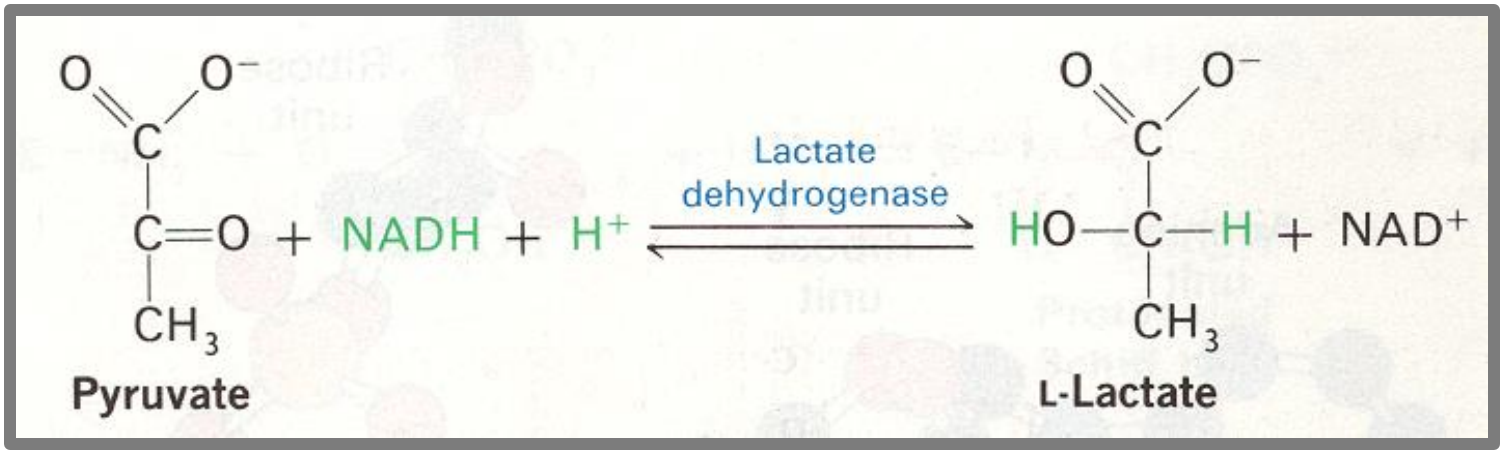
Note: excess CHO will be converted to fat but excess fat cannot be converted to carbohydrate

Metabolic Fates of Pyruvate



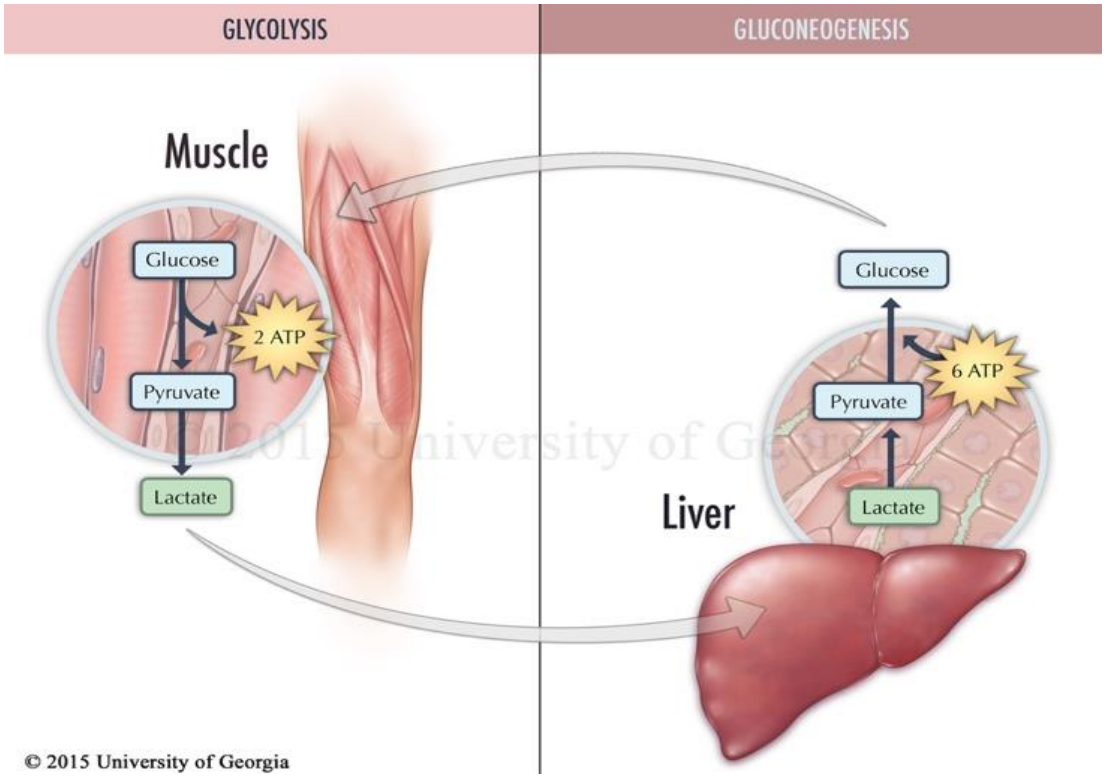
Metabolic Fates of Pyruvate

2. Lactic Acid Fermentation: **bacteria, RBCs and O_2-starved muscle cells**

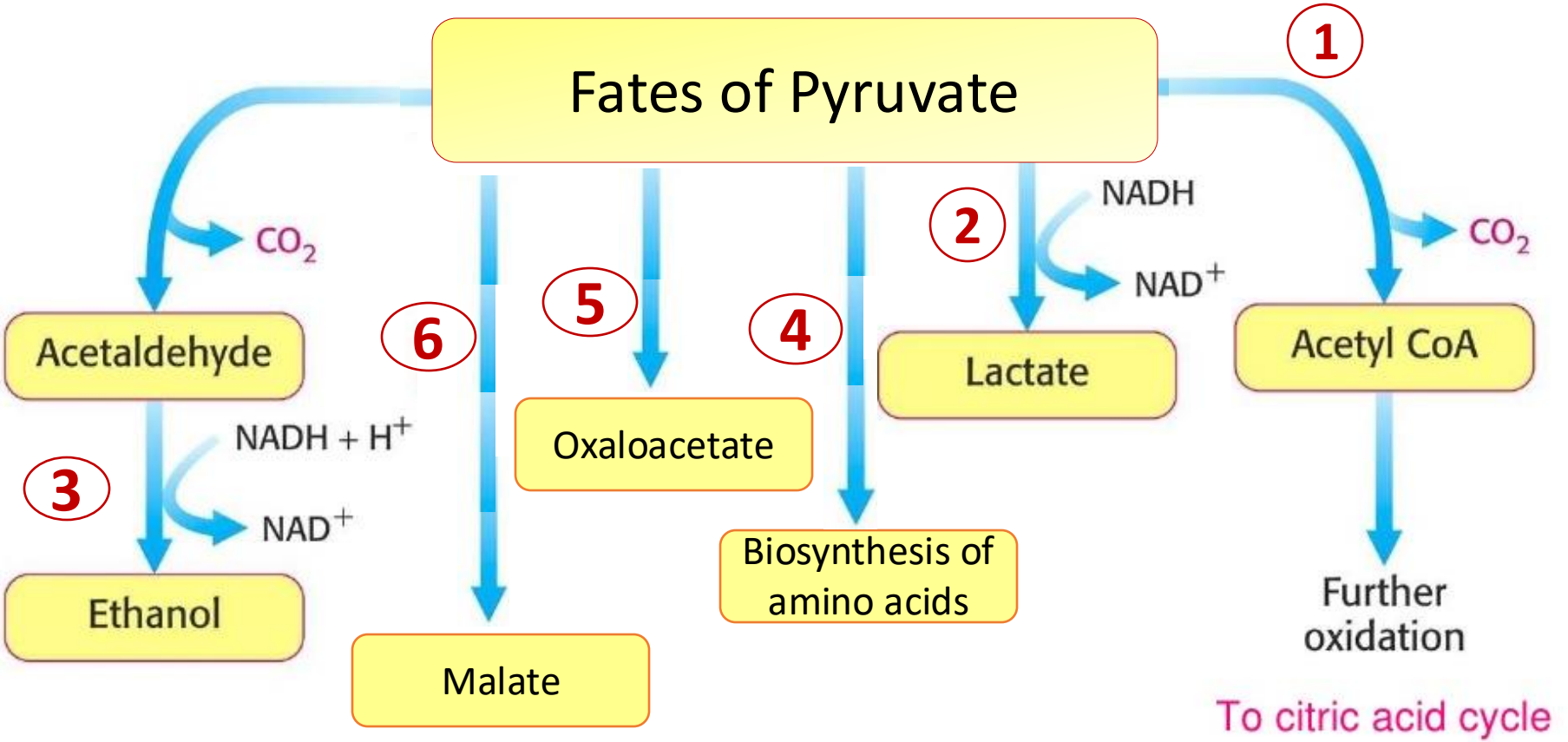


Cori Cycle

- Cori cycle "lactic acid cycle" is the metabolic pathway in which lactic acid produced in muscles during the time of oxygen depletion is converted back to glucose in the liver by gluconeogenesis process (a metabolic process of synthesizing glucose from non-carbohydrate sources like lactate occurs primarily in liver)



Metabolic Fates of Pyruvate



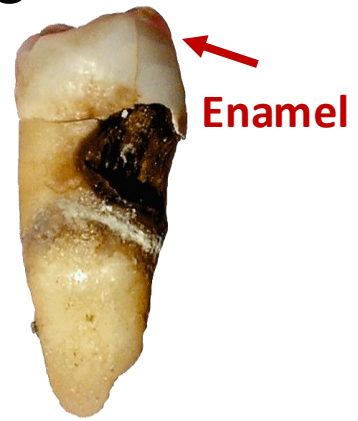
Metabolic Fates of Pyruvate

1. In aerobic conditions, pyruvate is converted to acetyl CoA which enters the citric acid cycle for further oxidation to CO_2 followed by oxidative phosphorylation
2. In anaerobic conditions like in lactic acid bacteria and some human cells (e.g. RBCs and O_2-starved muscle cells), pyruvate is reduced to lactic acid with the concomitant oxidation of NADH to NAD^+ (lactic acid fermentation)
3. In anaerobic conditions like in some M.O's (e.g. yeast), pyruvate is converted to ethanol with release of CO_2
4. Amino acid biosynthesis: pyruvate is a precursor of some amino acids like alanine

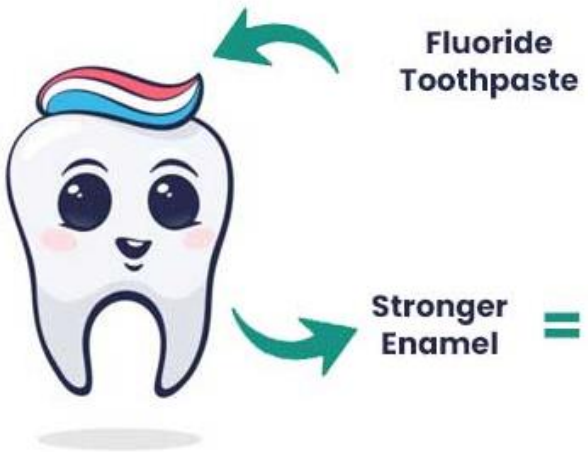
5. & 6. Pyruvate can be used for synthesis of oxaloacetate or malate (both are TCA cycle intermediates)

Fluoride as Inhibitor of Enolase

- Oral bacteria depends on the food debris or dietary sugars found on the tooth surface as a primary source of energy. Acids are produced through fermentation process (harmful)
- Fluoride is a competitive inhibitor of enolase enzyme catalyzing Step 9



- Drinking fluoridated water or using a toothpaste containing fluoride inhibits the oral bacteria enolase activity. This will disrupt the bacteria glycolytic pathway and prevents formation of dental caries



Fluoride as Inhibitor of Enolase

- Sodium fluoride is known to have antiglycolytic effect that inhibits glycolysis by erythrocytes
- NaF tubes (gray top) are widely used for blood collection for glucose measurement
- Fluoride-containing tubes are suitable for blood collection if there is a long delay in blood separation following collection (false negative result)

Glycolysis as Anabolic Pathway

- Glycolysis acts as catabolic as well as anabolic pathway. Therefore, glycolysis is very important central metabolic pathway
- Glycolysis intermediates with biosynthetic roles:

1. Nucleotides biosynthesis: G6P is an initial substrate in pentose phosphate pathway (metabolic pathway which generates pentoses)
2. Glycogenesis via G6P
3. Lipids biosynthesis: DHAP is converted to glycerol-3-P
4. Amino acids biosynthesis: pyruvate as precursor of alanine

Glycolysis as Anabolic Pathway