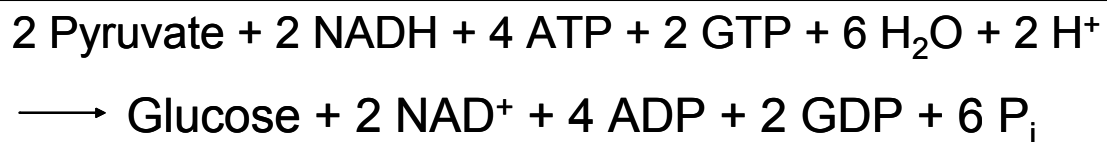


GLUCONEOGENESIS

- Gluconeogenesis is the **re-synthesis** of **glucose**
- Provides the source of blood glucose other than glycogen to **prevent hypoglycemia**
- Major **users** of **glucose**: **brain and muscles**

Top Priority glucose supply for Brain, because the brain:

1. Need relative large amount of Energy:
 2. Does not have significant energy store
 3. Dependent on blood glucose as energy source
 4. Not sensitive to hormone regulation
 5. Can adapt to use ketone body (fatty acids) but only after prolonged fasting
- Major **producers** of glucose: **Liver (90%) and kidney (10%)**
 - o Pyruvate and lactate produced returned to liver and kidney
 - Under fasting conditions, gluconeogenesis supplies almost all of the body's glucose
 - Gluconeogenesis is the process by which glucose is **MADE** from **small, non-carbohydrates**
 - Major gluconeogenic precursors in mammals:
 - (1) **Lactate and pyruvate**
 - (2) Most **amino acids** (especially alanine)
(Muscle proteins break down and aa transported to liver)
 - (3) **Glycerol** (from triacylglycerol hydrolysis)
 - Any metabolite that can be converted to **pyruvate** or **oxaloacetate** can be a glucose precursor

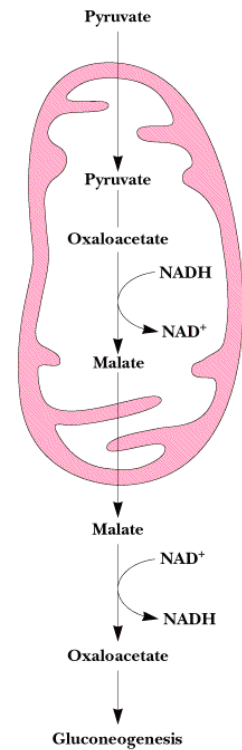
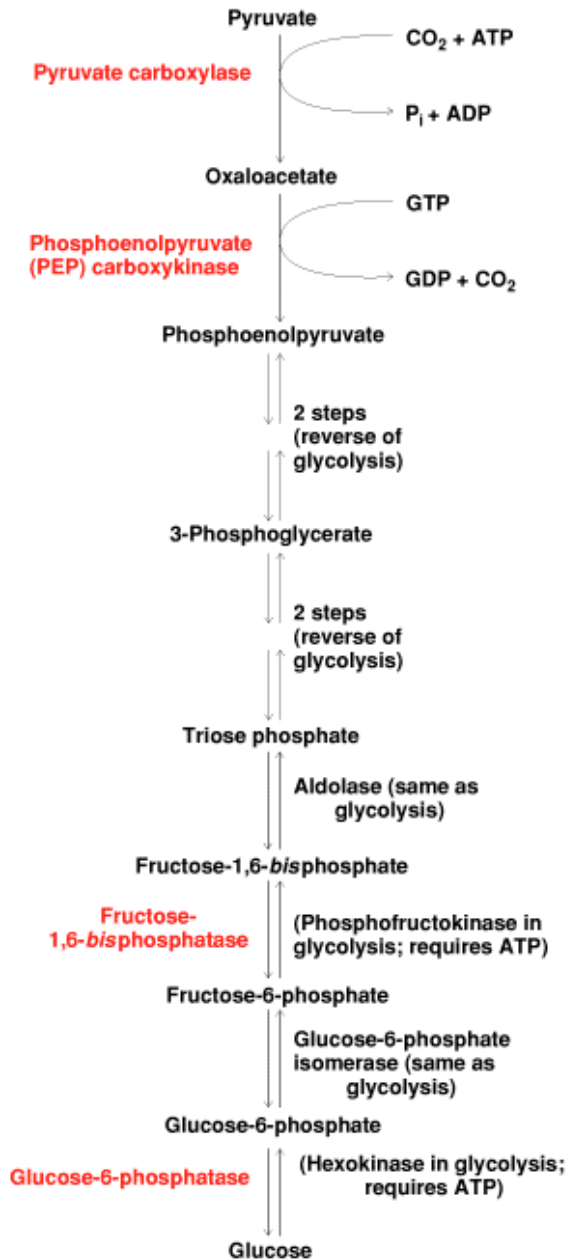


- Not a simple reversal of glycolysis, but employs many of the same enzymes of glycolysis
- Employs 4 new steps to avoid “irreversible steps” of glycolysis
 - Irreversible and regulated steps of glycolysis
 - **Hexokinase**
 - **Phosphofructokinase**
 - **Pyruvate kinase**
- Gluconeogenesis occurs when pyruvate kinase, PFK and hexokinase are relatively inactive
- These steps must be bypassed to prevent futile cycles
- Making glucose is **expensive**
 - Synthesis of 1 mole of glucose from 2 moles of pyruvate needs 6 moles of ATP

Subcellular Locations of Gluconeogenic Enzymes

- Gluconeogenesis enzymes are **cytosolic** except:
 - (1) Glucose 6-phosphatase (endoplasmic reticulum)
 - (2) Pyruvate carboxylase (mitochondria)

GLUCONEOGENESIS



Compartmentalization

Table 15.4

The reactions of gluconeogenesis beginning with pyruvate

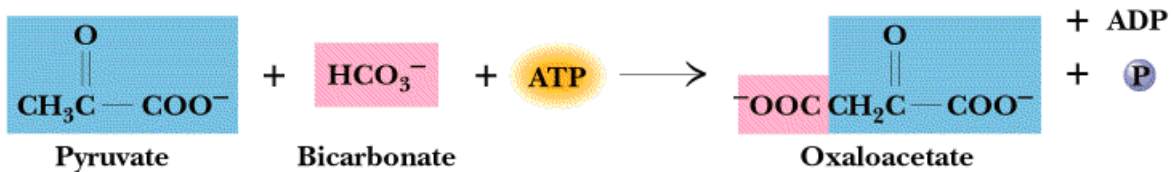
Number	Reaction
1	Pyruvate + CO ₂ + ATP → oxaloacetate + ADP + P _i
2	Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO ₂ + GDP
3	Phosphoenolpyruvate + H ₂ O ⇌ 2-phosphoglycerate
4	2-Phosphoglycerate ⇌ 3-phosphoglycerate
5	3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP
6	1,3-Bisphosphoglycerate + NADH + H ⁺ ⇌ glyceraldehyde-3-phosphate + NAD ⁺ + P _i
7	Glyceraldehyde-3-phosphate ⇌ dihydroxyacetone phosphate
8	Glyceraldehyde-3-phosphate + dihydroxyacetone phosphate ⇌ fructose-1,6-bisphosphate
9	Fructose-1,6-bisphosphate + H ₂ O → fructose-6-phosphate + P _i
10	Fructose-6-phosphate ⇌ glucose-6-phosphate
11	Glucose-6-phosphate + H ₂ O ⇌ glucose + P _i

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STEPS 1 and 2 by-pass **pyruvate kinase** step of glycolysis; cleavage of 2 phosphoanhydride bonds necessary; goes through an oxaloacetate intermediate

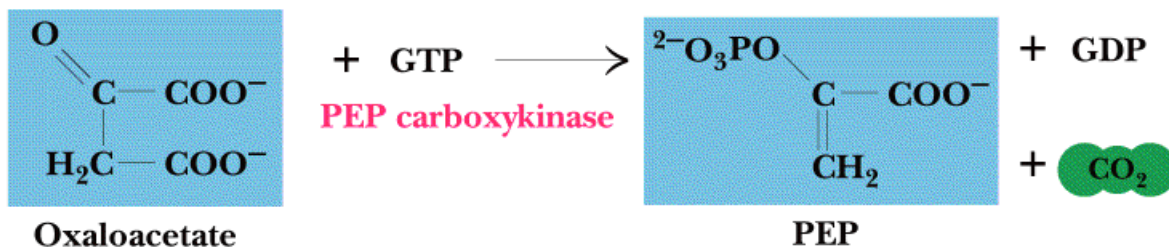
Step 1: Pyruvate Carboxylase

- Mitochondrial localization
- Pyruvate enters the mitochondria via a transporter
- pyruvate + ATP + CO₂ + H₂O → oxaloacetate + ADP + Pi + 2H⁺
- Catalyzes a metabolically irreversible carboxylation reaction
- Reaction type: Synthesis of a carbon-carbon bond using energy of ATP hydrolysis
- Activated by acetyl CoA (allosteric activation)
- Accumulation of **acetyl CoA** from fatty acid oxidation signals **abundant energy**, and directs **pyruvate to oxaloacetate for gluconeogenesis**



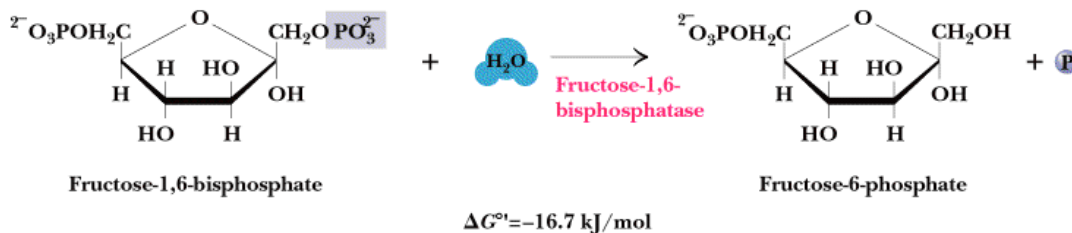
Step 2: Phosphoenolpyruvate carboxykinase

- Cytosolic localization
- Oxaloacetate gets reduced to malate in mitochondria which can diffuse out of the mitochondria to the cytosol; Malate then gets reoxidized to oxaloacetate
- Oxaloacetate too polar to diffuse out of mitochondria and there are no transporters
- oxaloacetate + GTP \leftrightarrow phosphoenolpyruvate + GDP + CO₂
- A **decarboxylation** reaction in which **GTP donates a phosphoryl group**



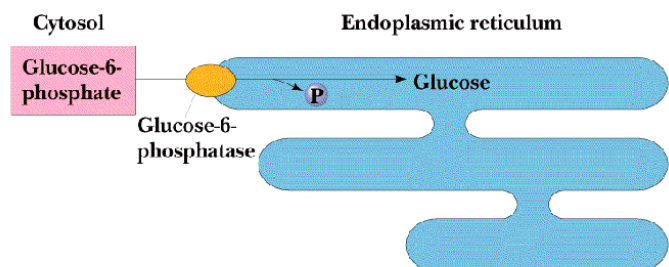
Step 3: Fructose-1,6-bisphosphatase

- fructose-1,6-bisphosphate + H₂O \rightarrow fructose-6-phosphate + Pi
 – reverses Phosphofructokinase (PFK)
- A metabolically **irreversible** reaction ($\Delta G^{\circ} = -16.7 \text{ kJ mol}^{-1}$)
- Simple **hydrolysis** reaction



Step 4: Glucose-6-phosphatase

- Endoplasmic reticulum membrane localization
- GLUT7 transporter transports G6P from cytosol to enzyme on the endoplasmic reticulum membrane (liver, kidney, pancreas, small intestine)
- Glucose-6-phosphate + H₂O \rightarrow glucose + Pi
 – Reverses hexokinase



- A metabolically irreversible hydrolysis reaction ($\Delta G^{\circ} = -13.8 \text{ kJ mol}^{-1}$)
- Simple **hydrolysis** reaction
- Glucose is exported from the ER to bloodstream

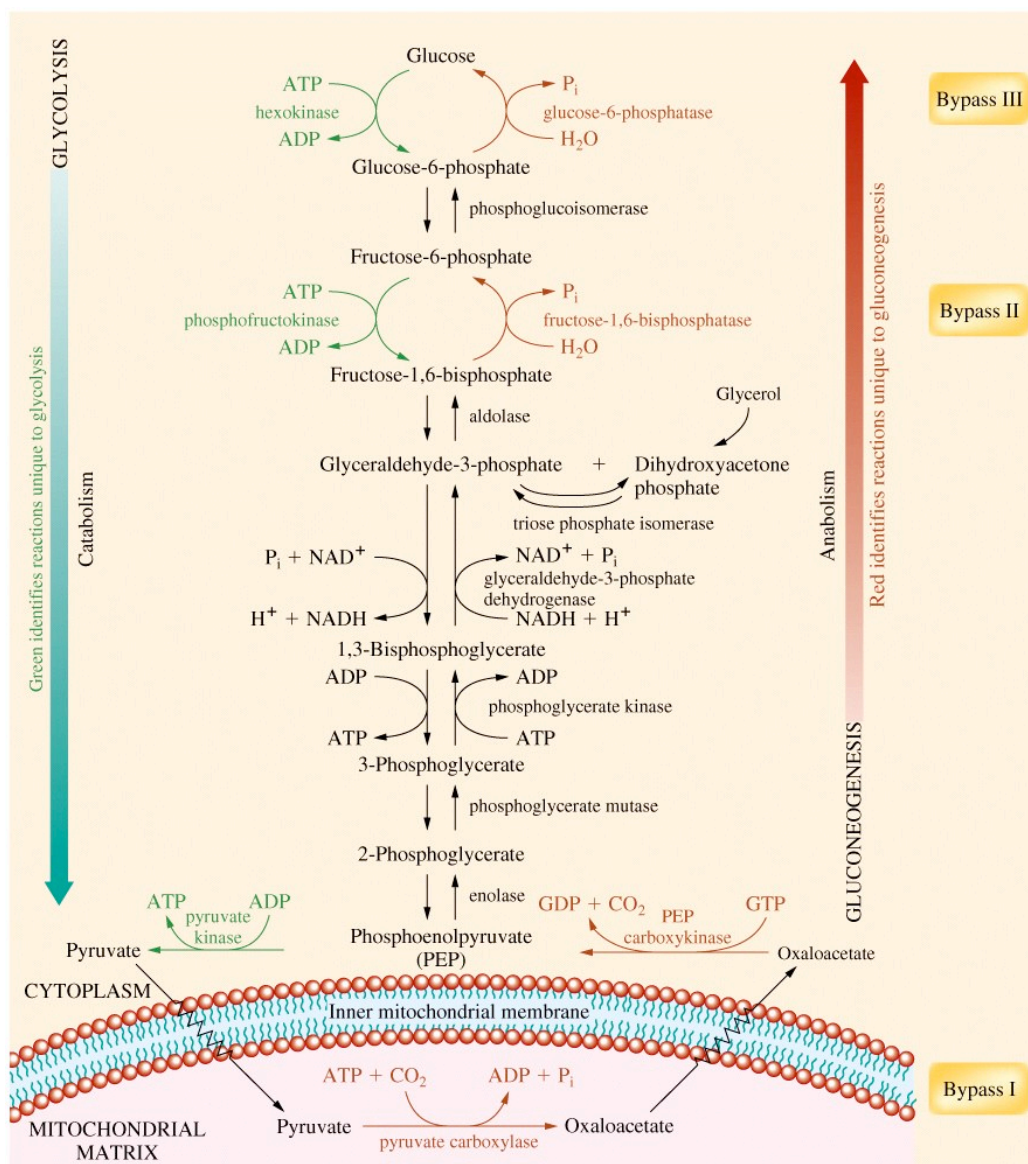
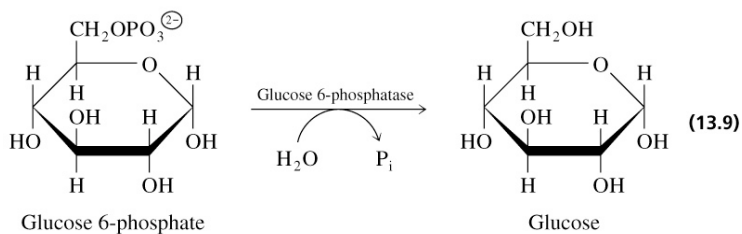


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Regulation of Gluconeogenesis

- **Substrate cycle** - two opposing enzymes:
 - (1) Phosphofructokinase-1 (glycolysis)
 - (2) Fructose 1,6-*bis*phosphatase (gluconeogenesis)
- Modulating one enzyme in a **substrate cycle** will alter the flux through the opposing pathways
- **Energy level** (ATP vs AMP level) of cell dictates which pathway is ON: This insures that when cellular ATP is high (AMP would then be low), glucose is not degraded to make ATP. It is more useful to the cell under such conditions to store glucose as glycogen.
- **Phosphofructokinase** (Glycolysis) is inhibited by ATP and stimulated by AMP.
 - Inhibiting Phosphofructokinase **stimulates** gluconeogenesis
- **Fructose-1,6-bisphosphatase** (Gluconeogenesis) is inhibited by AMP and fructose 2,6-*bis*phosphate (F2,6BP)
 - Inhibiting Fructose 1,6-*bis*phosphatase stimulates glycolysis

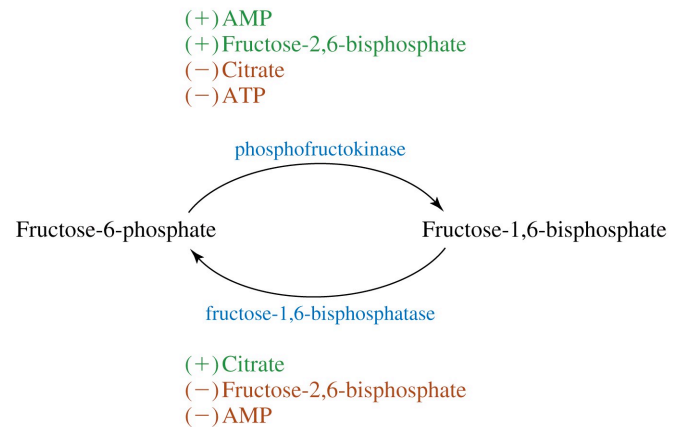
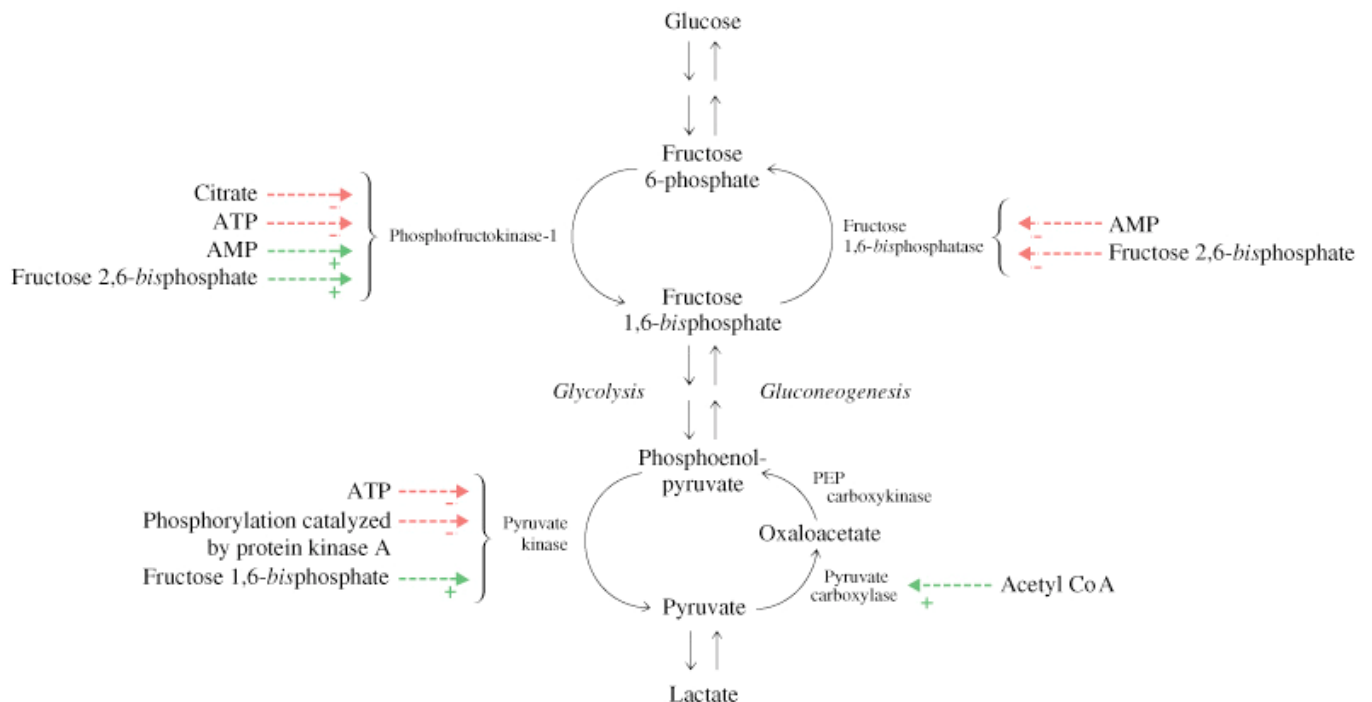


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CYTOPLASM

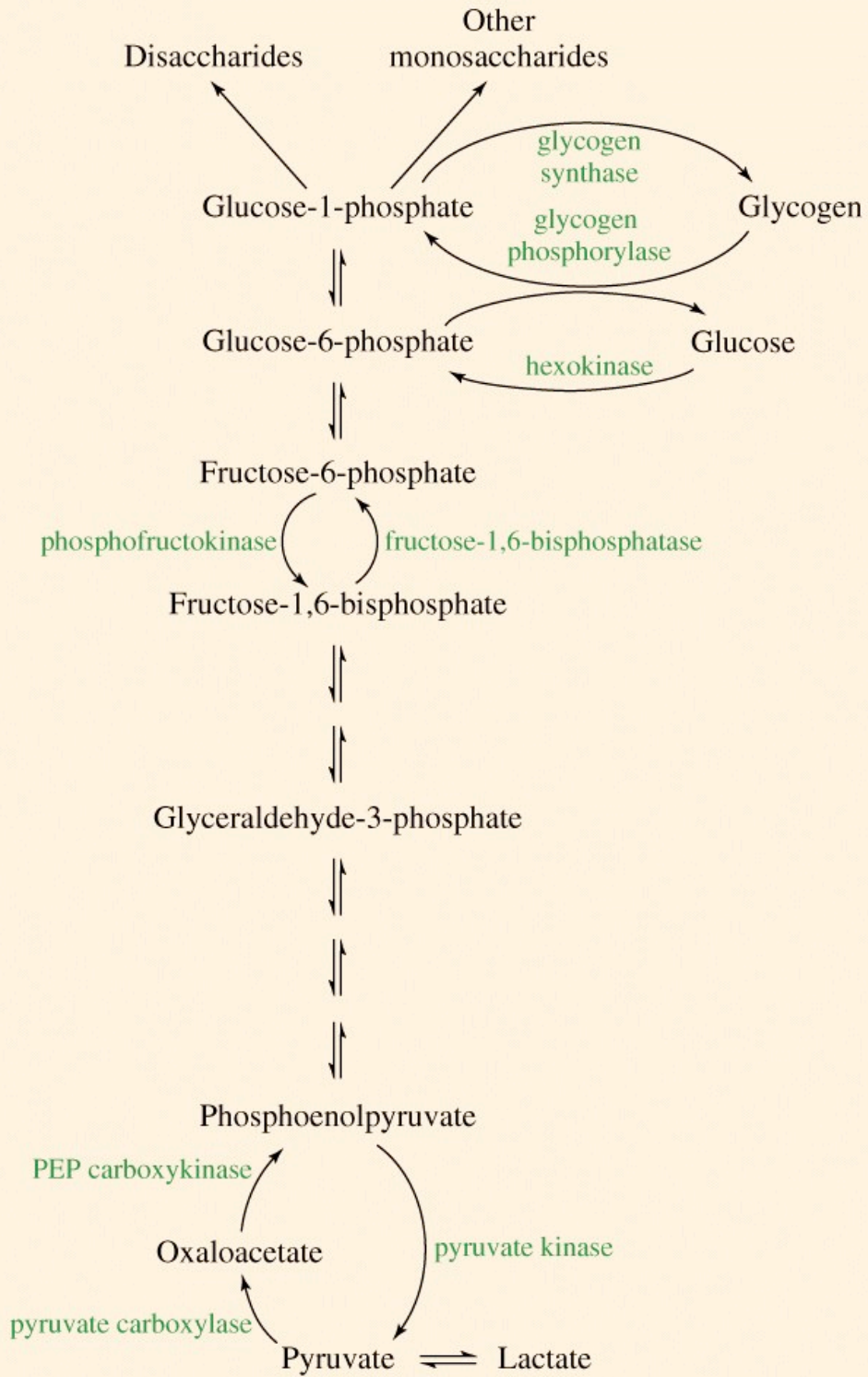
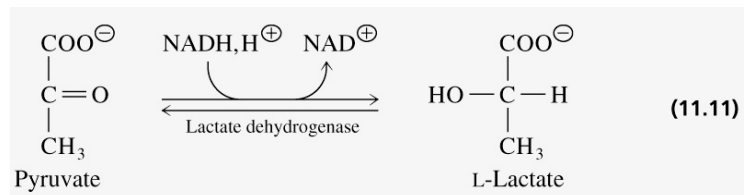
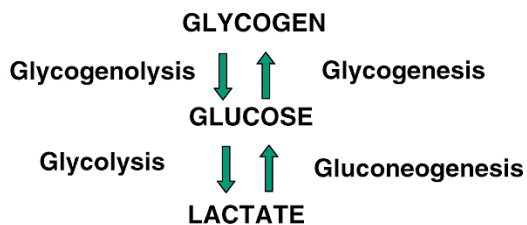


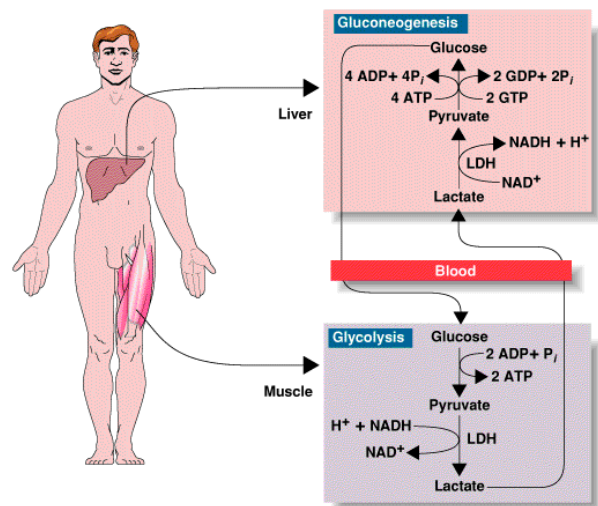
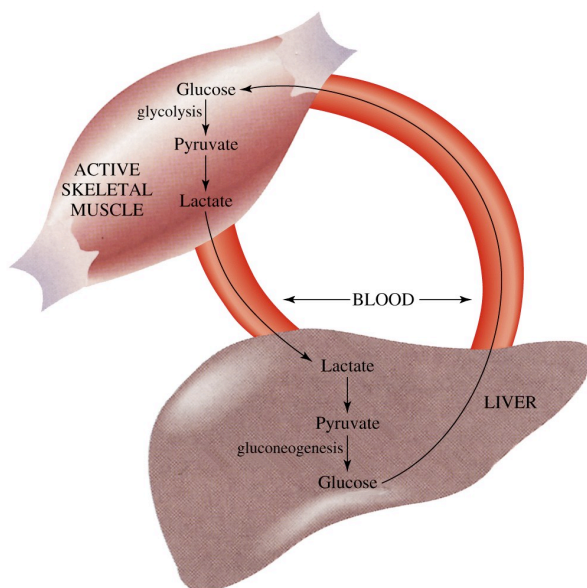
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Interaction of glycolysis and gluconeogenesis: The Cori Cycle

- The Cori Cycle operates during exercise, when aerobic metabolism in muscle cannot keep up with energy needs.
- Glucose synthesized in liver and transported to muscle and blood.
- A highly exercising muscle generates a lot of NADH from glycolysis but without oxygen there is no way to regenerate NAD⁺ from the NADH (need NAD⁺!)
- Lactic acidosis can and would result from insufficient oxygen (an increase in lactic acid and decrease in blood pH)
- So, the NADH is reoxidized by reduction of **pyruvate to lactate** by enzyme **lactate dehydrogenase**; Results in replenishment of NAD⁺ for glycolysis



- Then the lactate formed in skeletal muscles during exercise is transported to liver where it is used for **gluconeogenesis**
 - o Lactate is transported through the bloodstream to the liver
 - o Lactate is oxidized to pyruvate in the liver
 - o Liver lactate dehydrogenase reconverts lactate to pyruvate since has high NAD⁺/NADH ratio
 - o Pyruvate is used to remake glucose by gluconeogenesis
- Glucose is transported back to the muscles via the bloodstream



CORI CYCLE

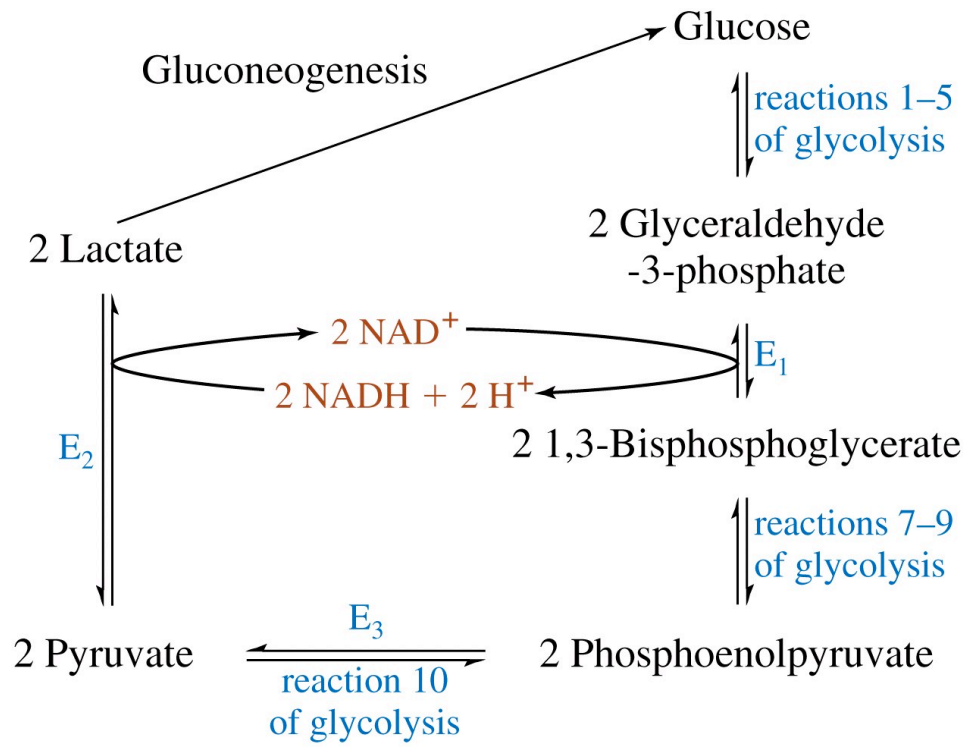


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