CARBOHYDRATE METABOLISM

Clinical importance of Glucose

Glucose-preferred source of energy for most tissues.

Brain cells derive energy mainly from glucose.

Normal fasting glucose levels---70-110mg/dL

GLYCOLYSIS

Glucose is converted to

Pyruvate—aerobic conditions.

OR

Lactate----anaerobic conditions.

Site of reactions----Cytoplasm

Significance of Glycolysis

- Only pathway –in all the cells of the body.
- Only source of energy for erythrocytes.
- Anaerobic glycolysis---major source of energy for muscles.
- Provides carbon skeleton for synthesis of non-essential amino acids as well as glycerol for fat.

Gibbs Free Energy Changes

Rxn#	Enzyme	ΔG°'(kJ/mol)	ΔG(kJ/mol)
1	Hexokinase	-16.7	-33.5
2	Phosphogluco-isomerase	+1.7	-2.5
3	Phosphofructokinase	-14.2	-22.2
4	Aldolase	+23.9	-1.3
5	Triose phos. Isomerase	+7.6	+2.5
6	G-3-PDH	+12.6	-3.4
7	Phosphoglycerate kinase	-37.6	+2.6
8	Phosphoglycerate mutas	+8.8	+1.6
9	Enolase	+3.4	-6.6
10	Pyruvate kinase	-62.8	-33.4

Identify:

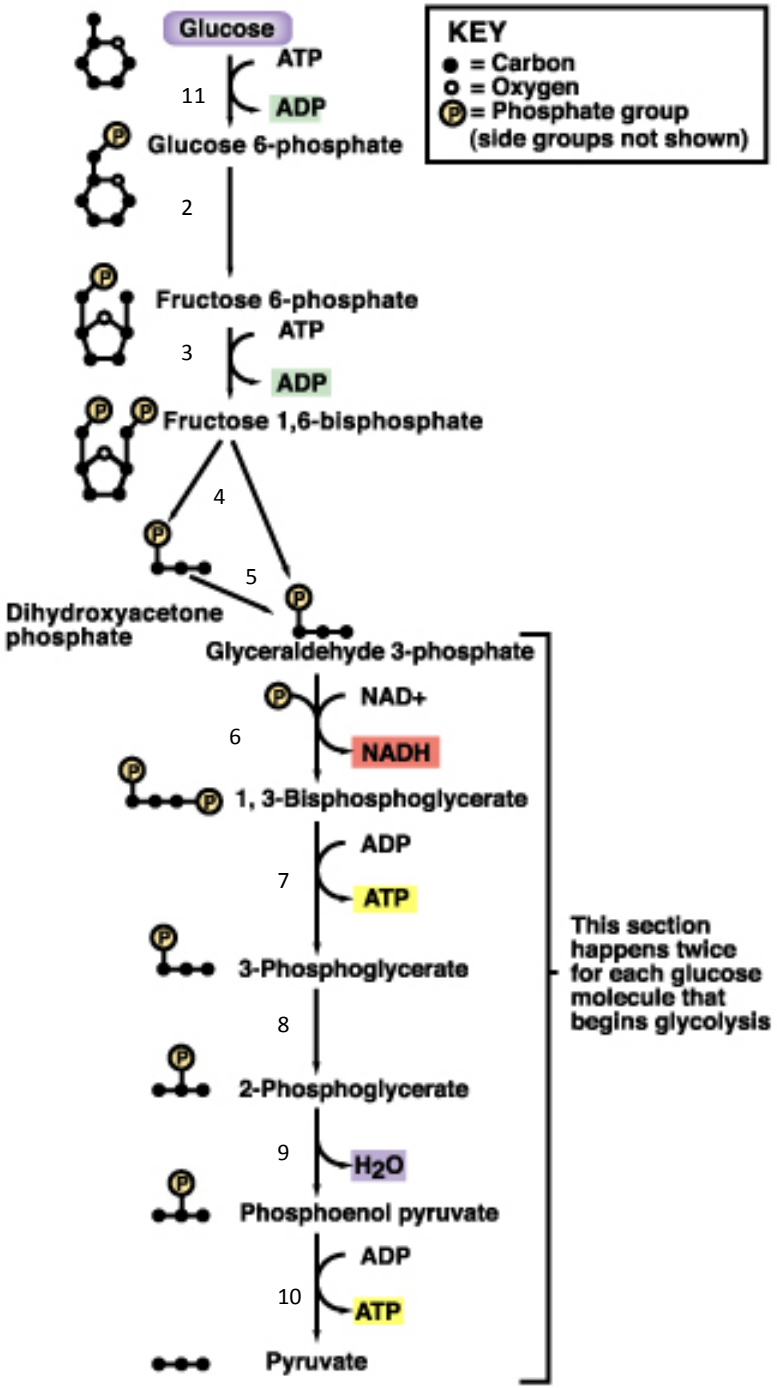
endergonic rxns

exergonic rxns

coupled reactions

oxidation/reduction rxns

transfer reactions



Steps of Glycolytic Pathway

Step 1

- Glucose-----G-6-P
- Enzyme-----HK/GK
- Reaction –irreversible
- Commited step

Step-2 of Glycolysis

- G-6-p → F-6-P (Isomerisation)
- Enzyme-----isomerase
- Reversible.
- **Step-3 of Glycolysis**
- F-6-p → F-1,6-BP
- Irreversible.
- Enzyme-----PFK-1
- Steps 1,2 and 3 are energy investment phase.

Step-4- of Glycolysis

- F-1,6-BP →Glyceraldehyde-3-P and DHAP.
- Enzyme—Aldolase.
- Splitting Reaction.
- Reversible.
- Step-4A- of Glycolysis
- Glyceraldehyde-3-P ↔ DHAP.
- Enzyme—Triose phosphate isomerase.

Step-5- of Glycolysis

- Glyceraldehyde-3-P →1,3 BPG
- Enzyme--- Glyceraldehyde-3-P dehydrogenase.
- Dehydrogenation and phosphorylation.
- Reversible reaction.
- $NAD^+ \rightarrow$ NADH
- **Step-6- of Glycolysis**
- 1,3 BPG →3PG
- ATP is released.

- Substrate level phosphorylation.

- **Step-7- of Glycolysis**
- **3PG** →2PG
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- Enzyme---Phosphoglycerate mutase.
- Reversible reaction.
- **Step-8- of Glycolysis**

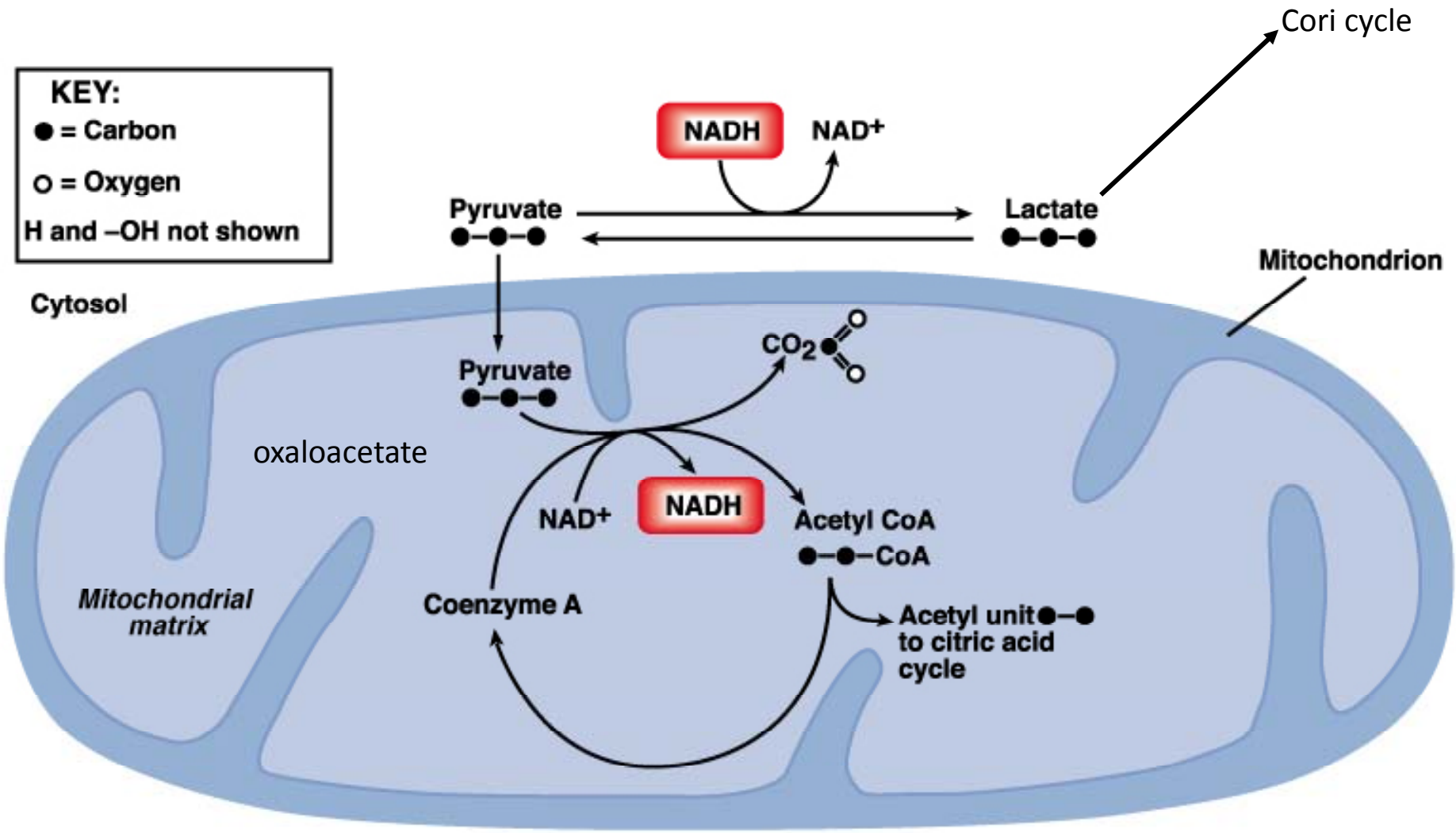
- **2PG converted to phosphoenolpyruvate (PEP).**
- **Enzyme---Enolase.**
- **Fluoride irreversibly inhibits the enzyme.**

- **Step-9- of Glycolysis**

- **PEP dephosphorylated to pyruvate.**

- Enzyme ---Pyruvate kinase.
- Irreversible reaction.
- **Step-10- of Glycolysis**

- During anaerobic conditions Pyruvate is converted to Lactate which enters Cori's cycle.


Cori cycle
KEY:
● = Carbon
○ = Oxygen
H and –OH not shown
NADH
NAD+
Pyruvate
Lactate
Mitochondrion
Cytosol
Pyruvate
CO2
oxaloacetate
NAD+
NADH
Acetyl CoA
CoA
Mitochondrial matrix
Coenzyme A
Acetyl unit to citric acid cycle

Regulation of glycolysis

• Glycolytic flux is controlled by need for ATP and/or for intermediates formed by the pathway (e.g., for fatty acid synthesis).

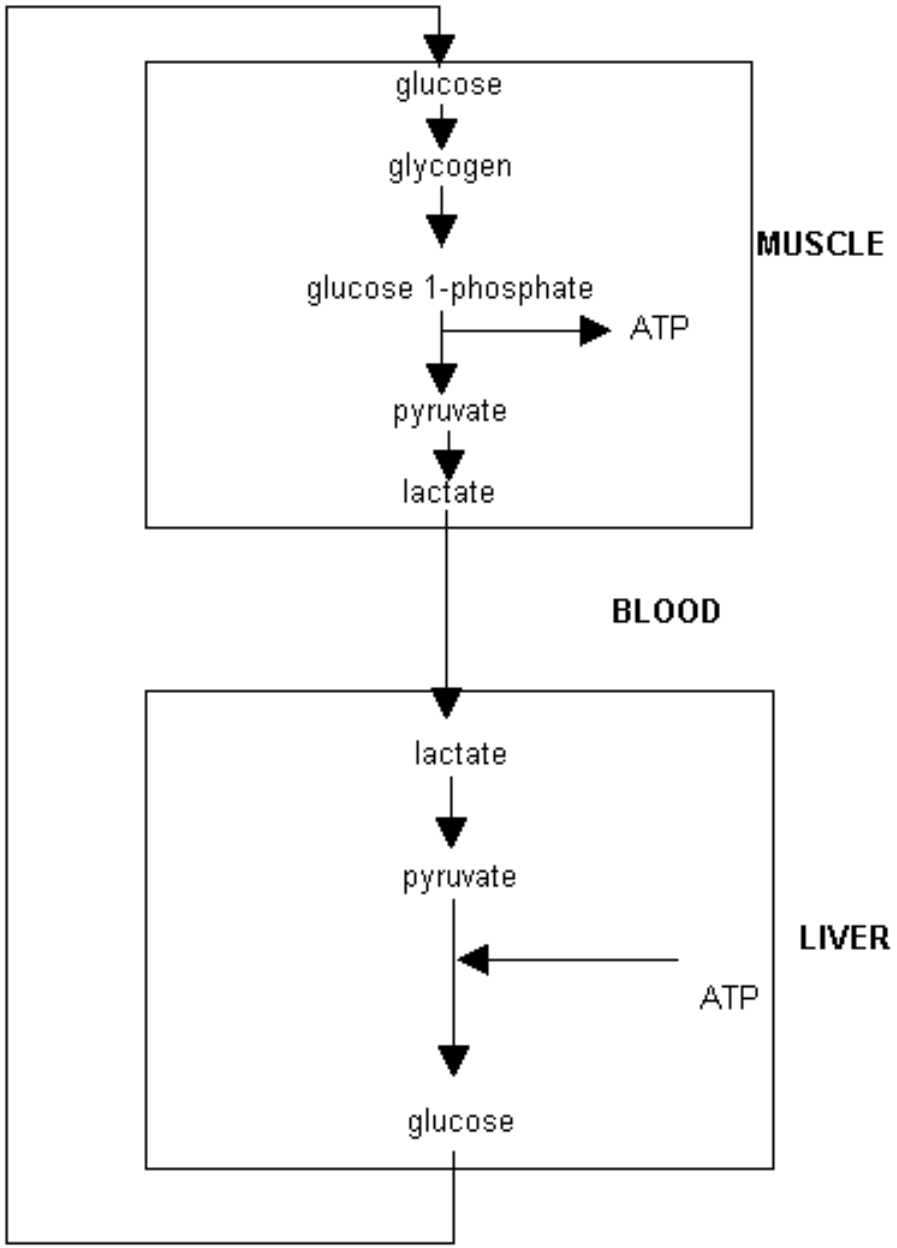
• Control occurs at sites of irreversible reactions

- **Hexokinase or glucokinase**
- **Phosphofructokinase- major control point; first enzyme "unique" to glycolysis**
- **Pyruvate kinase**

•**Phosphofructokinase responds to changes in**:

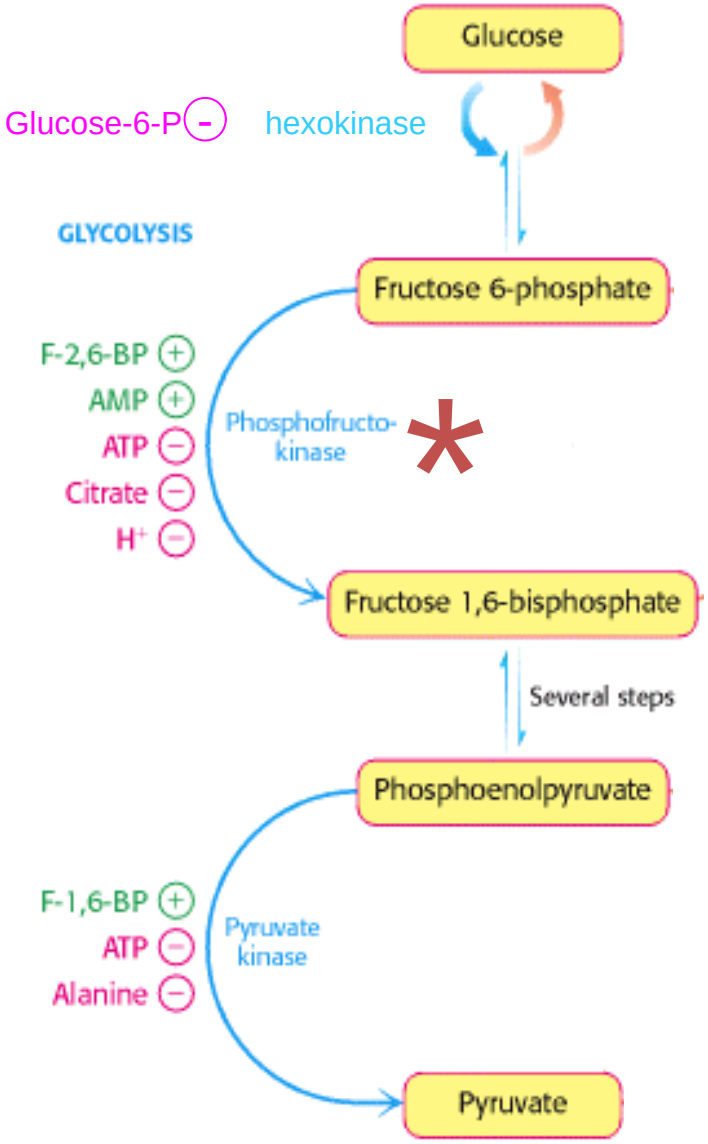
- Energy state of the cell (high ATP levels inhibit)
- H+ concentration (high lactate levels inhibit)
- Availability of alternate fuels such as fatty acids, ketone bodies (high citrate levels inhibit)
- Insulin/glucagon ratio in blood (high fructose 2,6-bisphosphate levels activate)

Cori Cycle



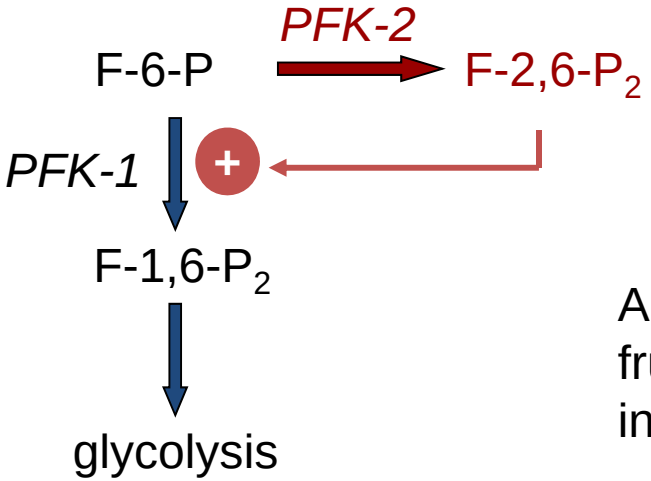
GLYCOLYSIS & GLUCONEOGENESIS

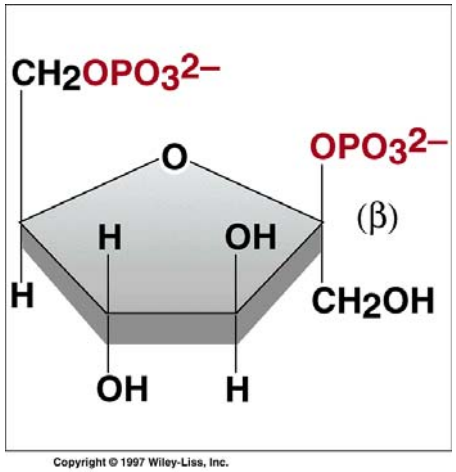
Control points in glycolysis



Phosphofructokinase (PFK-1) as a regulator of glycolysis

PFK-1 activated by:
Fructose-2,6-bisphosphate (F-2,6-P_2)





F-2,6-P_2

Activates PFK-1 by increasing its affinity for fructose-6-phosphate and diminishing the inhibitory effect of ATP.

Phosphofructokinase-2 (PFK-2) is also a phosphatase (bifunctional enzyme)

Bifunctional enzyme has two activities:

- **6-phosphofructo-2-kinase activity, decreased by phosphorylation**
- **Fructose-2,6-bisphosphatase activity, increased by phosphorylation**