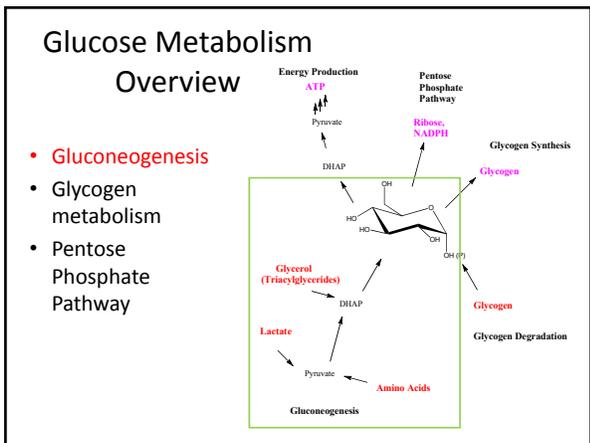


Gluconeogenesis

Chapter 17 Stryer Short Course



Precursors for Gluconeogenesis

- Names of compounds?
- Type of reaction?
- Type of enzyme?
- Cofactor(s)?
- More on lactate processing later...

C(C(O)O)O

\rightleftharpoons

C(C(=O)O)OP(=O)([O-])[O-]

C(C(=O)[O-])N

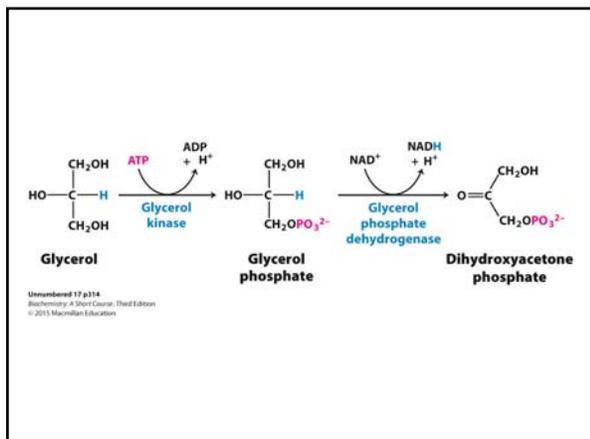
\rightarrow

C(C(=O)[O-])C(=O)C(=O)[O-]

C(C(=O)[O-])O

\rightarrow

C(C(=O)[O-])C(=O)C(=O)[O-]

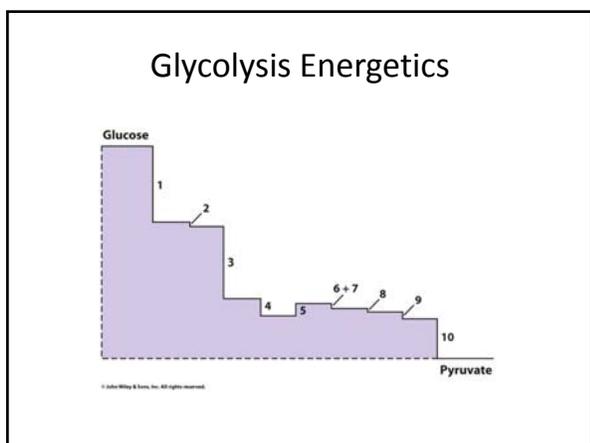


Chemistry of Gluconeogenesis

$$2 \text{ Pyruvate} + 2 \text{ NADH} + 4 \text{ ATP} + 2 \text{ GTP} + 6 \text{ H}_2\text{O} + 2 \text{ H}^{\oplus} \longrightarrow \text{Glucose} + 2 \text{ NAD}^{\oplus} + 4 \text{ ADP} + 2 \text{ GDP} + 6 \text{ P}_i$$

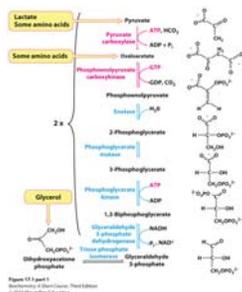
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- Chemically opposite of glycolysis (mainly)
- Energetically costly—no perpetual motion machine!
- Points of regulation



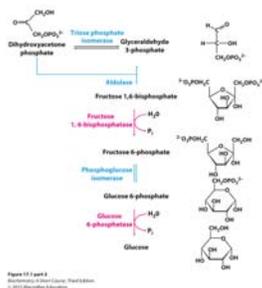
Gluconeogenesis

- Two steps to overcome last step of glycolysis
- Reverse flux through near equilibrium steps
- Net expenditure of 3 ATP equivalents per pyruvate

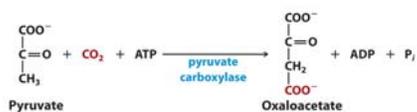


Glycolysis

- No ATP expenditure
- But also no recoup of ATP
- Points of regulation



Step 1a

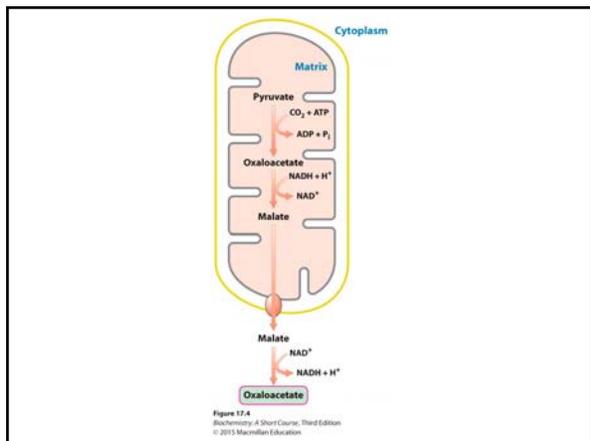


- Pyruvate Carboxylase
 - Biotin
 - Costs ATP to make driving force for next reaction
 - First step in biosynthesis of glucose and many other molecules
 - Related to which amino acid?

Mechanism

- Mixed anhydride
- Coupled through biotin coenzyme

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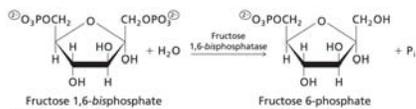
Step 1b

- PEP carboxykinase
 - ATP cost to restore PEP
 - CO₂ loss drives rxn

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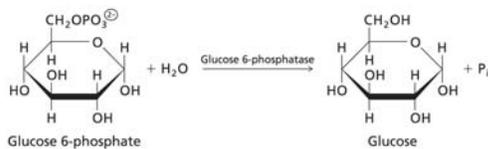
Step 8

- Fructose-1,6-bisphosphatase
- No additional energy input
- Phosphate ester hydrolysis is spontaneous



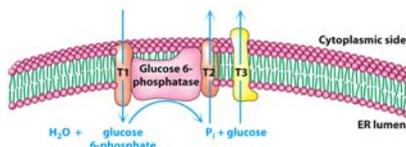
Step 10

- Glucose 6-phosphatase
 - Liver (and others)
 - Not in muscle



Release of Glucose

- Liver and Kidney
- Compartmental regulation



Problem 34

- A liver biopsy of a four-year old boy indicated that the F-1,6-Bpase enzyme activity was 20% normal. The patient's blood glucose levels were normal at the beginning of a fast, but then decreased suddenly. Pyruvate and alanine concentrations were also elevated, as was the glyceraldehyde/DHAP ratio. Explain the reason for these symptoms.

Regulation

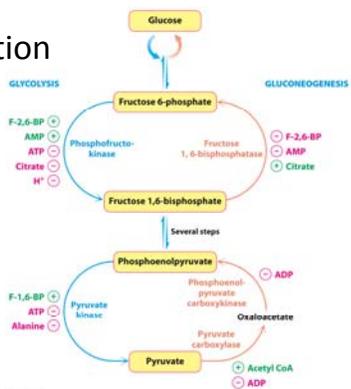


Figure 17.6
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Keys of Regulation

- At the committed step in glucogenic cells
- Principle of Reciprocal regulation
- Local regulation vs Hormone regulation

Local Regulation

- Energy charge
 - ATP downregulates glycolysis
 - AMP, ADP downregulate GNG
- Building blocks
 - Citrate, alanine, acetyl CoA
 - Upregulate GNG (storage)
 - Downregulate glycolysis (Don't produce pyruvate!)

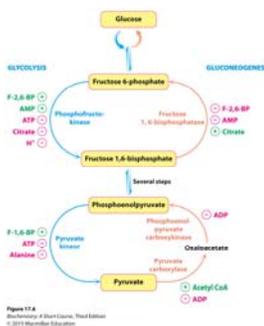
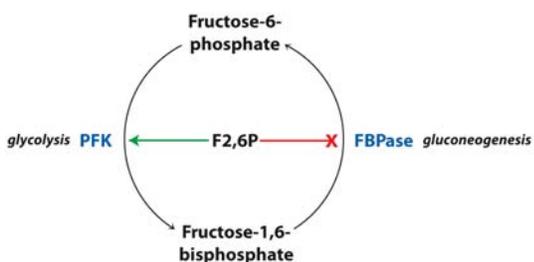


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Hormone Level Regulation



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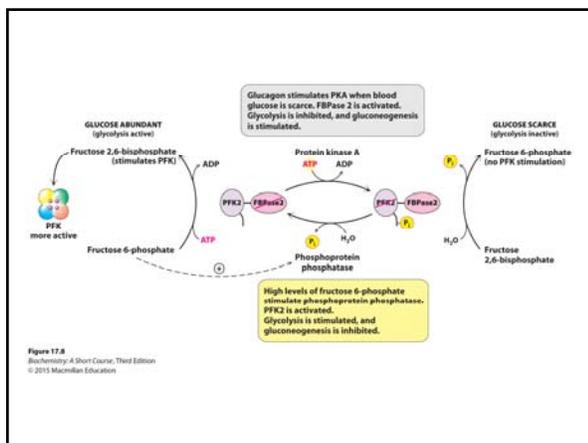


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Problem

- Brazilin, a compound found in aqueous extracts of sappan wood, has been used to treat diabetics in Korea. It increases the activity of the enzyme that products F-2,6-BP and stimulates the activity of pyruvate kinase. What is the effect of adding brazilin to liver cells in culture? Why would brazilin be an effective treatment for diabetes?

Fuels for Gluconeogenesis

- Come from other tissues
- Pyruvate from red blood cells
- Lactate from muscle

