GLYCOLYSIS AND GLUCONEOGENESIS

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Gluconeogenesis Function
Gluconeogenesis Location
Gluconeogenesis Connections
Gluconeogenesis Regulation
Gluconeogenesis ATP Costs
Gluconeogenesis Equations

(See Fig. 10-1.)
Figure 10-1

**GLYCOLYSIS** (solid lines) and **GLUCONEOGENESIS** (dotted lines) share some common enzymes, but they diverge around the control steps. Major control enzymes are boxed. Signals that turn glycolysis on turn gluconeogenesis off, and vice versa.
GLYCOLYSIS FUNCTION

Aerobic: To convert glucose to pyruvate and ATP. Pyruvate can be burned for energy (TCA) or converted to fat (fatty acid synthesis).


GLYCOLYSIS LOCATION
Cytosol of all cells.

GLYCOLYSIS CONNECTIONS
Glucose in, pyruvate or lactate out.
Glucose 6-phosphate to glycogen (reversible).
Glucose 6-phosphate to pentose phosphates (not reversible).
Pyruvate to TCA via acetyl-CoA (not reversible).
Pyruvate to fat via acetyl-CoA (not reversible).

GLYCOLYSIS REGULATION
Primary signals: Insulin turns on.
Glucagon turns off.
Epinephrine turns on in muscle, off in liver.
Phosphorylation turns off in liver, on in muscle.

Secondary signals: Glucose signals activate (fructose 2,6-bisphosphate activates phosphofructokinase).
Low-glucose signals inhibit.
High-energy signals inhibit.
Low-energy signals activate.
Arsenate (HAsO\textsuperscript{2-}/H\textsubscript{2}AsO\textsubscript{4}), an analog of phosphate, has an interesting effect on glycolysis. This makes a great exam question. Arsenate is a substrate for the enzyme glyceraldehyde-3-phosphate dehydrogenase. The enzyme, which normally uses phosphate and makes 1,3-diphosphoglycerate, is fooled by the arsenate and makes the arsenate ester instead. With the phosphate ester, the next enzyme in glycolysis makes an ATP from the 1,3-diphosphoglycerate. The arsenate analog of 1,3-disphosphoglycerate is chemically much more unstable than the phosphate ester and hydrolyzes to 3-phosphoglycerate before an ATP can be made. The product, however, is the same—3-phosphoglycerate—so glycolysis can continue as normal. But what has happened is that this step no longer makes an ATP for each three-carbon fragment. You lose 2 ATPs per glucose—all the net ATP production of glycolysis. The bottom line is that glycolysis continues (in fact it’s usually accelerated by the lack of ATP), but no ATP can be made. It is analogous to the uncoupling of oxidative phosphorylation by dinitrophenol.
The product of glycolysis is pyruvate. The pyruvate made by glycolysis can either enter the TCA cycle through pyruvate dehydrogenase or be reduced to lactate. To keep running, glycolysis requires NAD\(^+\) in the glyceraldehyde-3-phosphate dehydrogenase reaction. No NAD\(^+\), no glycolysis. NAD\(^+\) is produced by oxidation of NADH via oxidative phosphorylation, a process that requires oxygen. Under anaerobic conditions, the TCA cycle simply shuts down. The pyruvate is converted to lactate to regenerate the NAD\(^+\) and keep glycolysis going. In muscle, lactate is the usual product.

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GLUCONEOGENESIS FUNCTION
Gluconeogenesis makes glucose from pyruvate to help maintain blood glucose levels.

GLUCONEOGENESIS LOCATION
Liver and kidney—*not muscle*.

GLUCONEOGENESIS CONNECTIONS
*Pyruvate in, glucose out.*
*Lactate in, glucose out.*
*Alanine in, glucose and urea out.*

Gluconeogenesis in the liver can be fueled by molecules other than pyruvate or lactate. Alanine, a product of protein degradation, yields pyruvate by simple transamination, and this pyruvate can be converted
to glucose by the liver and kidney. Other amino acids are metabolized to pyruvate or oxaloacetate, which can also enter the gluconeogenic pathway. In addition, glycerol from the breakdown of triglycerides in adipose tissue can be used by the liver and kidney to make glucose.1

**GLUCONEOGENESIS REGULATION**

**Primary signals:**
- Insulin turns off.
- Glucagon turns on.
- Acetyl-CoA turns on.

**Secondary signals:**
- Phosphorylation turns on in liver.
- Glucose signals turn off.
- Low-glucose signals activate.
- High-energy signals activate.
- Low-energy signals inhibit.

There are two unusual aspects to the regulation of gluconeogenesis. The first step in the reaction, the formation of oxaloacetate from pyruvate, requires the presence of acetyl-CoA. This is a check to make sure that the TCA cycle is adequately fueled. If there’s not enough acetyl-CoA around, the pyruvate is needed for energy and gluconeogenesis won’t happen. However, if there’s sufficient acetyl-CoA, the pyruvate is shifted toward the synthesis of glucose.

**GLUCONEOGENESIS ATP COSTS**

\[ 2 \text{ lactate} + 6\text{ATP (equivalents)} \rightarrow 2 \text{glucose} \]

**GLUCONEOGENESIS EQUATIONS**

\[ 2 \text{ lactate} + 4\text{ATP} + 2\text{GTP} \rightarrow 2\text{glucose} + 4\text{ADP} + 2\text{GDP} + 6\text{P}_i \]

\[ 2 \text{ pyruvate} + 4\text{ATP} + 2\text{GTP} + 2\text{NADH} + 2\text{H}^+ \rightarrow 4\text{ADP} + 2\text{GDP} + 6\text{P}_i + 2\text{NAD}^+ \]

1 The glycerol produced by the action of hormone-sensitive lipase in the adipose tissue cannot be utilized by adipose tissue itself. Adipose cells lack the enzyme glycerol kinase, which is necessary to convert glycerol to glycerol phosphate.