READING GUIDE

GLUCONEOGENESIS

Objectives

1. Diagram and describe gluconeogenesis, including the rate-determining enzymes and the conversion of glycerol, lactate, and certain amino acids into glucose
2. Diagram and describe how the Cori cycle operates and its significance

GLUCONEOGENIC PRECURSORS

Big picture

Gluconeogenesis is the synthesis of glucose from suitable precursor molecules. Most of the process is simply glycolysis running in reverse. But the three highly energetically favorable reactions in glycolysis need to be bypassed with alternative reactions in gluconeogenesis. These three reactions and their regulation is where most of our attention will be focused.

What are the three precursor molecules that are used in gluconeogenesis?

What is the Cori cycle and why is it important? (Fig. 10.2)

KEY REACTIONS IN GLUCONEOGENESIS

Conversion of pyruvate to phosphoenolpyruvate (Fig. 10.3)

The 1-step conversion of phosphoenolpyruvate (PEP) to pyruvate is reversed in 4 synthetic steps. What are they?

What is the role of biotin in pyruvate carboxylase? (remember this role, it will come in handy when we discuss lipid metabolism)

What is the metabolic difference to the cell when PEP carboxykinase in the mitochondria converts oxaloacetate to PEP, with subsequent transport of PEP to the cytosol, versus transporting malate and having PEPCK act in the cytosol to produce PEP? (think redox balance between mitochondria and cytosol)

What molecule serves as a positive allosteric effector of pyruvate carboxylase?

Conversion of fructose 1,6-bisphosphate to fructose 6-phosphate

(Fig. 10.4,4,5)

What enzyme catalyzes this reaction?

How does the energy state of the cell regulate this step of gluconeogenesis?

What prevents the activities of phosphofructokinase-1 and fructose bisphosphatase-1 from setting up a futile cycle of converting fructose back and forth between the 6-phosphate form and the 1,6-bisphosphate form?

How is glucagon involved in the regulation of this important step of gluconeogenesis?

Conversion of glucose 6-phosphate to glucose (Fig. 10.6)

Glucose 6-phosphatase is expressed specifically in the liver and kidney. Why would that be?

Where within the cell is glucose 6-phosphatase located?

REGULATION OF GLUCONEOGENESIS

Role of glucagon (Fig. 10.5,8,9)

What are the three ways, mentioned in Harvey's, that glucagon regulates stimulates gluconeogenesis?

What trans-acting factor would you predict would be involved with the glucagon-induced transcription of the PEPCK gene? (think back . . .)

Cortisol also up-regulates the PEPCK gene. What transcription factor (hint: ligand activated) would you predict to be involved in this pathway?

What is the role of amino acids in gluconeogenesis? (more on this later . . .)

What is the source of acetyl-CoA that is necessary to stimulate gluconeogenesis in the liver?

How does acetyl-CoA influence gluconeogenesis?

How does AMP influence gluconeogenesis?

SUMMARY (Fig. 10.9)