

Highlights Gluconeogenesis

1. Gluconeogenesis does not occur in all tissues of the body. The primary gluconeogenic organs of the body are the liver and part of the kidney.
2. The enzymes unique to gluconeogenesis are Pyruvate Carboxylase and PEP carboxykinase (PEPCK) instead of Pyruvate Kinase of glycolysis, Fructose 1,6 Bisphosphatase (F1,6BPase) instead of Phosphofructokinase (PFK) from glycolysis, and Glucose-6-phosphatase (G6Pase) instead of Hexokinase from glycolysis.
3. F1,6BPase and G6Pase act by similar mechanisms, clipping a phosphate from their substrates and thus avoiding synthesis of ATP, which is what would be required if the glycolysis reactions were simply reversed.
4. One reaction of gluconeogenesis occurs in the mitochondrion. It is catalyzed by pyruvate carboxylase and yields the four carbon intermediate, oxaloacetate. The carboxyl group is added in forming oxaloacetate thanks to the coenzyme biotin, which carries carbon dioxide for attachment. The remaining reactions all occur in the cytoplasm, except for the G6Pase reaction, which occurs in the lumen of the endoplasmic reticulum.
5. Anabolic and catabolic pathways occurring at the same time and place create a futile cycle. Futile cycles generate heat, but that is the only product they make. Consequently, cells usually set up controls that turn one off when the other is turned on. If the same molecule has opposite effects on catabolic and anabolic pathways, the molecule is a reciprocal regulator of the pathways. Reciprocal regulation of catabolic and anabolic pathways is a very efficient means of control.
6. The enzymes of glycolysis that are regulated have corresponding gluconeogenesis enzymes that are also regulated. PFK and F1,6BPase exhibit the most complicated regulation. Both are controlled by several mechanisms. The most important one is the allosteric regulation by fructose-2,6-bisphosphate (F2,6BP). F2,6BP activates PFK and inhibits F1,6BPase.
7. F2,6BP is made and degraded by two different portions of the same protein (I'll use PFK2 to refer to the kinase portion and FBPase -2 to refer to the phosphatase portion). The portion of the PFK2 catalyzing the synthesis of F2,6BP from F6P is PFK2. The portion of the protein catalyzing the breakdown of F2,6BP to F6P is FBPase-2. The two activities are regulated by phosphorylation of the protein by protein kinase A. When phosphorylated, the PFK2 part of the enzyme is inactive and the FBPase-2 is active. When the phosphate is removed from the protein by phosphoprotein phosphatase, the PFK2 becomes active and the FBPase-2 becomes inactive.
8. Phosphorylation of the enzyme by protein kinase A is favored by 7TM signaling whereas dephosphorylation by phosphoprotein phosphatase is activated by signaling by insulin.
9. Thus phosphorylation of the PFK2 favors the breakdown of F2,6BP and the activation of gluconeogenesis and deactivation of glycolysis. Dephosphorylation of PFK2 favors the synthesis

of F2,6BP and the activation of glycolysis and the deactivation of gluconeogenesis. This is the heart of reciprocal regulation of these pathways.

10. Pyruvate kinase, pyruvate carboxylase, and PEPCK are all regulated, as well. Pyruvate kinase is activated by feedforward activation by F1,6BP and is inhibited by ATP and alanine (a product easily made from pyruvate). Pyruvate kinase is also controlled by covalent modification as described in the previous highlights. Phosphorylation of the enzyme makes it less active, whereas dephosphorylation makes it more active.

11. Regulation of glycolysis and gluconeogenesis (besides the mechanisms noted above) occurs mostly allosterically using molecules that are indicative of the energy state of the cell. Molecules indicating high cellular energy (like ATP) favor gluconeogenesis and inhibit glycolysis, but molecules indicating low energy (like ADP or AMP) favor glycolysis and inhibit gluconeogenesis.

12. The Cori Cycle is a cycle of the body where the lactate of working muscles is dumped into the bloodstream. It travels to the liver where it is converted to pyruvate and used to make glucose in gluconeogenesis. The glucose is then dumped into the bloodstream, where it travels back to the muscles that need it.

Highlights Glycogen Metabolism I

1. The structure of glycogen consists of units of glucose linked in the alpha 1-4 configuration with branches linked in the 1-6 configuration.
2. Glycogen differs from starch in the amount of branching (much more).
3. Glycogen is a storage form of energy that can yield ATP very quickly, because glucose-1-phosphate can be released very quickly.
4. You should know the function/activities of the enzymes in glycogen breakdown - glycogen phosphorylase, phosphoglucomutase, and debranching enzyme.