Sugar Metabolism Regulation

1. 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.

2. PFK and F1,6BPase (also called FBPase or FBPase1) 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. It is the most sensitive allosteric regulator.

3. PFK is also regulated by AMP (on), ATP (off). F1,6BPase is also regulated by citrate (on) and AMP (off). Thus, the reciprocal regulation extends to energy indicators. The high energy indicator, ATP, turns off PFK and turns on F1,6BPase. The low energy indicator, AMP, has the opposite effect. Citrate is also an indicator of high energy.

4. 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. Phosphorylation of the enzyme makes it less active, whereas dephosphorylation make it more active.

5. Pyruvate carboxylase is inhibited by ADP (low energy indicator) and activated by acetyl-CoA (high energy indicator)

6. PEPCK is mostly regulated by whether or not the enzyme is synthesized, but ADP (low energy indicator) can inhibit the enzyme.

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 PFK2/FBPase-2 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/FBPase-2 enzyme favors the breakdown of F2,6BP and the activation of gluconeogenesis and deactivation of glycolysis. Dephosphorylation of PFK2/FBPase-2 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. Overall, 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 molecular indicating low energy (like ADP or AMP) favor glycolysis and inhibit gluconeogenesis.

11. The Cori Cycle is a cycle of the body where the liver supplies glucose to muscles when needed. This occurs, for example, during heavy exercise when muscles are using oxygen faster than it can be delivered. When this happens, muscles start to make lactate and export it into the blood stream. Lactate travels to the liver where it is converted to pyruvate and then to glucose. The glucose is exported to the book and is taken up the by muscles.