Diabetes Module: Integration Problems

1.

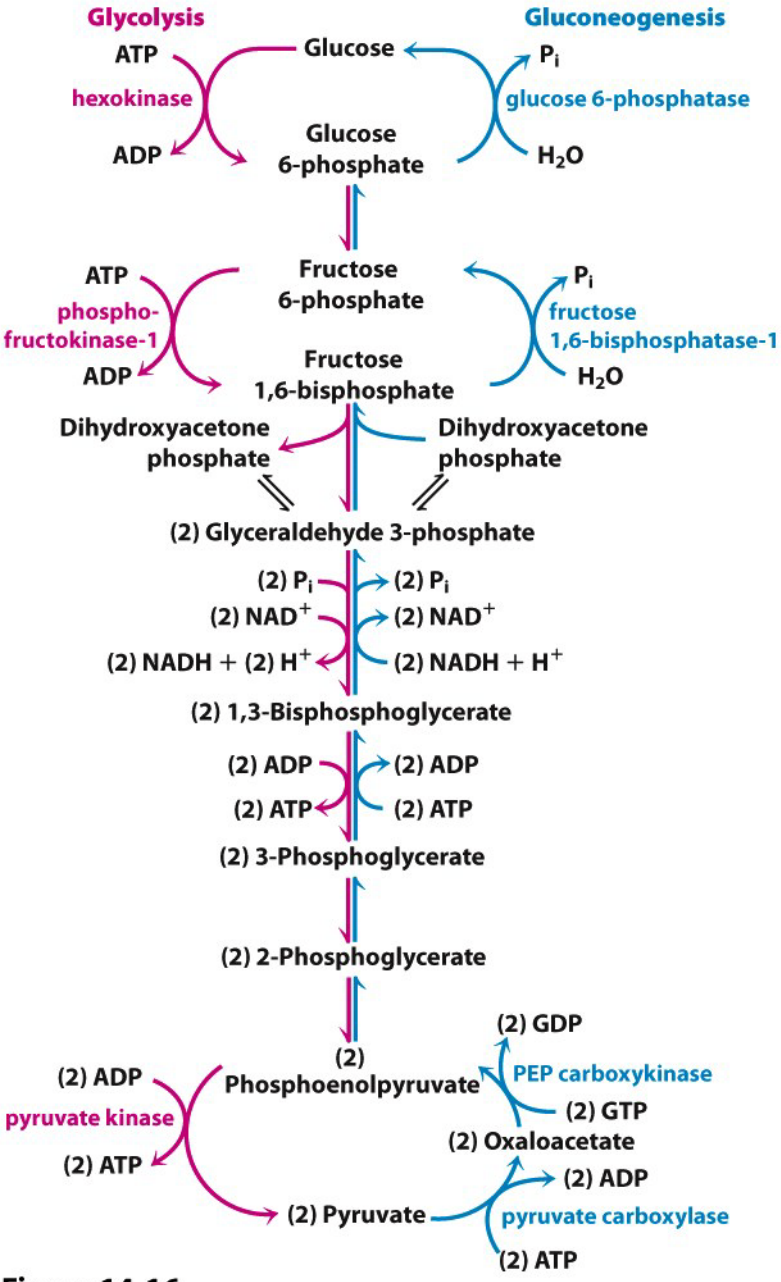

Figure 14-16
Lehninger Principles of Biochemistry, Fifth Edition

The diagram above shows the pathway of glycolysis (glucose breakdown to pyruvate) on the left, top to bottom. It also shows the pathway of gluconeogenesis (*de novo* glucose synthesis from pyruvate or oxaloacetate [OAA] --- actually from lactate or "glycogenic amino acids" that are converted to either pyruvate or OAA --- on the right, bottom to top. Note the 3 irreversible steps of glycolysis and the 4 irreversible steps of gluconeogenesis. Phosphofructokinase-1

(PFK-1) is the major site of regulation for glycolysis and PEP (phosphoenolpyruvate) carboxykinase (PEPCK) is the major site of regulation for gluconeogensis. Both of these pathways are active in the liver, but under different conditions:

Answer briefly:

A. What would happen if glycolysis and gluconeogenesis were active at the same time?

B. What would happen if liver glycolysis was negatively regulated by glucagon-mediated signaling at the glyceraldehyde-3-phosphate dehydrogenase step instead of at the PFK-1 step?

C. What would happen if liver glycolysis was negatively regulated at glyceraldehydes-3-phosphate dehydrogenase step instead of at the PFK-1 step by "metabolite signals", i.e., inhibited by a high [ATP]/[ADP] ratio (high energy signal) and high [citrate] signal (a signal of abundant carbon skeletons for syntheses)?

D. Why would it be problematic if all the steps of the pathway were reversible instead of having multiple irreversible steps on each pathway?

E. At the Glucose + ATP → Glucose-6-phosphate + ADP step, liver has both the low K_m hexokinase enzyme but also has a high K_m (and more glucose-specific) enzyme called glucokinase; the high K_m refers to the K_m for glucose. The liver also has a glucose transporter of the GLUT transporter family, GLUT2, that is always present in the membrane and, like glucokinase, has a high K_m for glucose. The insulin-secreting beta-cells of the pancreas are the other cells that have the same glucokinase/GLUT2. Can you suggest how possession of this pair of high K_m glucose-transporting and phosphorylating protein enables the liver and pancreas to be the first tissues to acquire glucose when blood glucose levels rise after glucose ingestion?

2.

In lecture you discussed the concept of physiological homeostasis. Here you will illustrate some of these concepts using a mathematical model of weight gain and loss.

The paper linked below describes an extremely simple model for how input (food), output (exercise) and metabolism affect changes in a person's weight with time. Your assignment is to perform some analysis of this model.

http://www.ams.jhu.edu/~castello/400/Handouts/DietingModel.pdf

The model represents the temporal evolution of a person's weight with a single differential equation:

Where W is the individual's weight, λ represents the difference between the number of calories consumed each day and the number of calories burned through exercise, and β is a constant parameter that reflects a person's metabolism. If an individual attempts to lose weight or gain weight, he or she does so by changing the parameter λ, i.e. the balance between food intake and exercise.

a. According to the model, is a person more likely to be successful losing weight by changing his/her diet, or by exercising more?

b. Compared with the contestants on "The Biggest Loser," do the models currently walking down the runway in Bryant Park have a large value or a small value of β?