Problem Based Exercise- Kinetics, glucose metabolism and diabetes

Group Members

Only write the names of the students who are present. The grade for this exercise is based on participation and the reported answers.

1. Glucose transport into muscle is regulated by the number of glucose transporters at the cell surface (the Glut4 transporters). However, apart from the number of transporters, glucose uptake into muscle is proportional to the rate of glucose metabolism. Since muscle does not have glucose 6-phosphatase, glucose is effectively trapped as soon as it is phosphorylated. The fasting blood glucose levels are in the range of 4.5 mM, the Km of hexokinase is 0.2 mM and the Km of glucokinase is 10 mM. As a group answer questions in part one. Your instructor will assign groups to each particular question. As a class we will report the answers. After reviewing answers go back to answer the rest of the questions. No answers are turned in during class. See notes at end of this document.

a) How many different types of Glut transporters are there and what do they do? Where are they expressed? What are the different functions of the glucose transporters?
b) What thermodynamic principle drives these transporters? Does Glucose 6-phosphate impact the transport of glucose? IF, after glucose is transported into a cell, then does the metabolism of glucose into glucose-6 phosphate impact glucose transport? How?
c) What is glucokinase and hexokinase and where are these enzymes expressed?
d) Which enzyme is more sensitive to the changing concentration of glucose? Describe the impact of each isoform of the enzyme on changing both intracellular glucose levels and the transport of glucose into the cell.
e) How do the Glut transporter kinetics and hexokinase kinetics align in liver, muscle, pancreas, and other tissues like brain? Is there a pattern?

2. Like the liver, ß-cells of the pancreas have the high capacity Glut2 glucose transporter and expresses glucokinase rather than hexokinase. The ß-cells secrete insulin when they "sense" an increase in blood glucose. Insulin then stimulates glucose clearance. Most of that clearance occurs in muscle cells. The ability of ß-cells to sense glucose requires glucose to be metabolized (i.e. glucose uptake alone is not sufficient to trigger insulin secretion). *Part two will be conducted both in and out of class as a group. No reporting out.*

a) What is Insulin, what are its general effects on blood glucose and what hormone antagonizes its actions?
b) The statement "elevated blood glucose stimulates insulin secretion" is not very accurate. How does the increase in blood glucose lead to increased ß-cell glucose levels? Is the simple increase in glucose really responsible for insulin secretion? If no (hint it is no) what is?
c) There are mutations in people that decrease the abundance of glucokinase in the pancreatic ß-cells. **What are these mutations and what would be the effect of these mutations of blood glucose?**
d) Which would be better to have in the ß-cells hexokinase or glucokinase in beta islet cells? Explain why with a detailed mechanism. Include issues of Vmax, Km and Glut transport in your answer.

FOR ALL: Big picture question – Look at the integration of metabolism section of your book. Brain should get a steady supply of glucose while liver reduces its use of blood glucose in low sugar conditions and muscle increases its metabolism after high blood glucose and during fight or flight. How does the combination of glucose transporters and glucokinase/hexokinase ensure brain, muscle and liver integrate glucose entry into the cell and the start of glycolysis?

Explain your answers (no credit given without explanation). **Each group should be prepared to present your answer and reasoning to the class. Each group is required to submit a detailed typed answer for the BOLDED questions from part 1 and 2**