SYSTEMS BIOMEDICINE Molecules, Cells and Networks
Diabetes Module

Human metabolism: Principles as seen through the lens of Diabetes
Metabolism-1, September 15-16 2009
Terry Krulwich

***Required**

***"Journal Club" for hour-3 September 16 (Lunch will be provided on that day):** Please work on the following paper. Everyone should be prepared to talk about the Introduction and Discussion. The specific student pairs indicated below should meet and plan a presentation (try to make it within 10 minutes) of the indicated part of the paper. Powerpoint is permitted but not required; we'll all have copies.

Mussmann, R., Geese, M., Harder, F., Kegel, S., Andag. U., Lomow, A., Burk, U., Onichtchouk, D., Dohrmann, C. and Austen, M. (2007) Inhibition of GSK3 Promotes Replication and Survival of Pancreatic Beta Cells. *J. Biol. Chem.* 282, 12030-12037.

Introduction and Discussion: all students be prepared to present/discuss.

Presenters: Group 1 - Figure 1 and methods/text of results relating to it.

Presenters: Group 2 - Figure 2 and Table 1 and related text/methods.

Presenters: Group 3 – Figure 3 and methods/text of results related to it.

Presenters: Group 4 – Figure 4 and methods/text of results related to it.

For contrast: Take a look at a review by Zhang, Zhhou and Li, pages 407-409, that makes a case for small molecule AMPK activators as potential type 2 diabetes therapeutics and note the discussion of concerns and challenges on pages 412-414.

General reading and references for the two sessions:

*1. Review as needed: in the text of your choice, review intermediary metabolism that you have encountered before ---- glycolysis, glycogen metabolism and breakdown, PDH/Krebs cycle; gluconeogenesis; fatty acid synthesis and breakdown; and oxidative phosphorylation; keep in mind that the Pentose Phosphate pathway is a major source of NADPH as well as pentoses. In Lippincott, 4th edition these topics are in chapters 6-11,16.

*2. Work through the discussion and questions on the following friendly Insulin-Glucagon web-site:
http://cal.man.ac.uk/student_projects/2000/mnby7lc2/default.htm

*3. Reminder of some key facts about different tissues:

What two tissues must have glucose? Brain---because blood-brain barrier prevents major parts of the brain from accessing other nutrients so glucose is always essential (even under conditions in which ketone bodies can replace part of the glucose need) and RBCs --- because they lack mitochondria and must use fermentative metabolism to meet their energy supply

What tissues are insulin-dependent? Muscle (cardiac and skeletal; and adipose tissue).

Isn't the liver insulin-dependent? No. The liver responds to insulin signaling but it is not dependent upon insulin.

What is the basis for the property called insulin-dependence? The insulin dependent tissues, muscle and adipose, are those that use GLUT4 transporter (GLUT type transporters support "facilitated diffusion" --- not active transport) for a major part of their glucose acquisition from the blood.

What tissues make glucose from scratch, i.e. gluconeogenesis from glycogenic amino acids or lactate? Liver and kidney (only liver gluconeogenesis responds to low blood glucose via glucagon (or to elevated glucagon even when blood glucose is already high).

What tissues store glycogen? Muscle and liver, but for different purposes and with different end products of glycogen breakdown.

Which tissues are lipogenic (synthesize fatty acids)? Adipose, liver and mammary gland.

*Questions for you:

What accounts for the elevated hepatic glucose production (HGP) by both gluconeogenesis and glycogenolysis (glycogen breakdown) during diabetes?

About Hepatic Glucose Production:

How does partial fatty acid oxidation support the energy needs of HGP?

Why is fatty acid oxidation by the "gluconeogenic liver cell" only partial? Why isn't it complete?

What good does it do the liver to make ketone bodies under these circumstances when the liver does not use ketone bodies?

What accounts for the failure of the liver to use ketone bodies and the contrasting ability of muscle and brain to use ketone bodies when adapted to do so?

What enzyme is involved in that adaptation?