Diabetes Module: Problem Set 1

1. A number of studies have shown that patients with pre-diabetes often go on to develop Type 2 diabetes. Many of the studies have shown that life-style (diet and exercise) as well as certain drugs such as acarbose, metformin and thiazolidinediones (drugs used for treating established Type 2 diabetes) are effective at preventing diabetes.

Can you hypothesize how these agents and life-style change can prevent or delay the onset of diabetes, remembering that Type 2 diabetes needs beta cell dysfunction and insulin resistance to be present? [See Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. Perreault L, Kahn SE, Christophi CA, Knowler WC, Hamman RF; Diabetes Prevention Program Research Group. Diabetes Care. 2009 Sep;32(9):1583-8. Epub 2009 Jul 8. PMID: 19587364]

2 A. Assume that the steady state kinetics of GK and HK can be approximated as following Michaelis-Menton kinetics, i.e, the fractional activity θ of GK or HK at a given sugar concentration $[S]$ is given by:

$$\theta = \frac{V}{V_{\max}} = \frac{[S]}{K_{0.5} + [S]}$$

where $V, V_{\max}, K_{0.5}$ are the GK activity, maximal GK activity, and sugar concentration at the half-maximal activity. When the $K_{0.5}$ for GK and HK are measured in biochemical assays, they are found to be 7.9 mM and 0.061 mM. Plot the θ vs $[S]$ for $[S]$ varying from 0 to 50 mM and compare the curves using both a linear and log scale for the X axis.

How is the activity of GK and HK changed if blood sugar is elevated?

The liver is a major location for storage of glucose as glycogen. Why do you think it expresses GK?

The activation of GK in the pancreatic cell serves as a sensor of glucose and stimulates insulin production which reduces blood sugar. Why do you think the pancreas uses GK for this instead of HK?

2.B. Recent clinical analysis[1] of diabetic patients reveals that wild-type patients have $V_{\max} = 55.5$ and $K_{0.5} = 7.9mM$. A variety of GK mutations have been identified to cause MODY2. Two mutants are an insertion mutant (inserN161) which has a $V_{\max} = 0.29$ and $K_{0.5} = 155mM$, and a missense mutant which substitutes a tryptophan for an arginine (R308W) and has a $V_{\max} = 22.3$ and $K_{0.5} = 10.7mM$.

(i) What do you think are the differences in the glucose sensing and uptake capabilities between the patients with these mutations and the wild-type? (Hint: Plot the V vs $[S]$ for varying $[S]$ and compare the curves.)

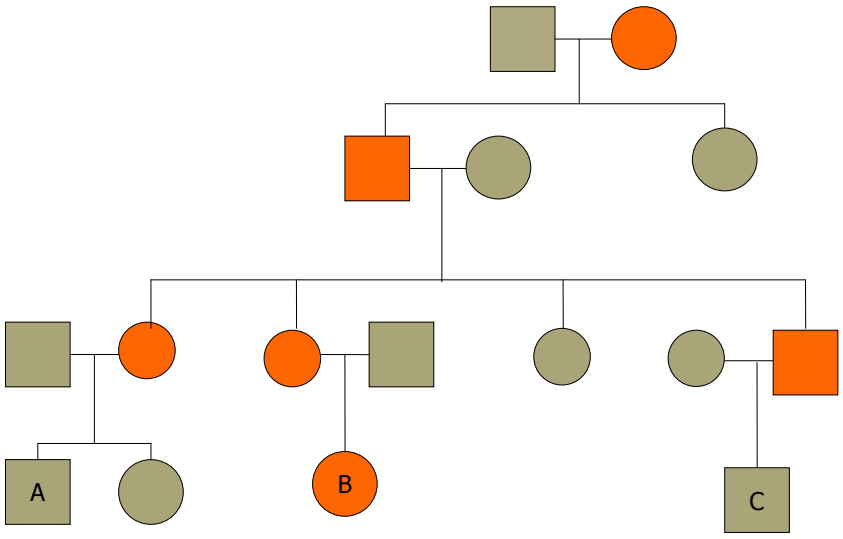
(ii) What do you think are the differences in the glucose sensing and uptake capabilities between the patients with these mutations and the wild-type?

(iii) What do you think should be the clinical phenotype caused by these mutations in each case.

2.C. Take a look at Box 3 on page 412 of Matschinsky, FM (2009) Assessing the potential of glucokinase activators in diabetes therapy. Nature Reviews Drug Discovery 8:399-416. What is the rationale for trying to develop small molecule glucokinase activators as diabetes? Do you think the results are promising? What are the concerns? [see Assessing the potential of glucokinase activators in diabetes therapy. Matschinsky FM. Nat Rev Drug Discov. 2009 May;8(5):399-416. Epub 2009 Apr 17. PMID: 19373249]

3 A) List 3 key factors you would look for when assessing the evidence that a gene is associated with diabetes – give reasons why they are important.

3 B) The following is a family tree for MODY1



Key: Green = unaffected, Orange = affected
Squares = male, Circle = female

i) What can you say about the mode of inheritance?

ii) What are the chances of MODY being inherited by any children of subjects A, B or C?

4. Glucose stimulates biphasic insulin secretion (first and second phases), which involves the KATP channel-dependent and KATP channel-independent pathways. How do you experimentally separate two pathways (you may get some idea from the attached review)? Refer to: [Glucose-stimulated signaling pathways in biphasic insulin secretion. Straub SG, Sharp GW. Diabetes Metab Res Rev. 2002 Nov-Dec;18(6):451-63. PMID: 12469359]