Biochemistry 673 **Your Name:** _____

Regulation of Metabolism **Assoc. Prof. Jason Kahn**

Final Exam (150 points total) **December 19, 2007**

You have 120 minutes for this exam.

Explanations should be concise and clear.

You do not need a calculator for this exam, and no other study aids or materials are permitted.

Generous partial credit will be given, *i.e.*, if you don't know, guess.

Honor Pledge: At the of the exam time, please write out the following sentence and sign it, or talk to me about it:

"I pledge on my honor that I have not given or received any unauthorized assistance on this examination."

1. Energy Metabolism and Diabetes (40 pts):

(a; 24 pts) Give the primary function that we discussed for each of the following pathways. Indicate whether it consumes or produces NADH and ATP, and the primary carbon inputs and outputs.

Example: Pentose phosphate pathway: Oxidizes glucose (via glucose-6-phosphate) to provide ribose and reducing equivalents for biosynthesis, especially of fat. Produces NADPH, no direct effect on ATP. Input is G6P, output is CO_2 and ribose.

Glycolysis under anaerobic conditions:

TCA cycle:

Gluconeogenesis:

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(b; 6 pts) List three ways in which insulin causes blood glucose to decrease.

(c; 6 pts) In terms of pathways (not purposes) briefly explain why protein can be converted to sugar but fat cannot. Why do starving mammals avoid digesting too much protein to make sugar, even though it would seem metabolically simpler than the alternatives?

(d; 4 pts) Why is the production of ketone bodies elevated in starving people and some diabetics?

Score for page:_____

2. Insulin Signal transduction (50 pts):

(a; 20 pts) Sketch the pathway leading from insulin binding to the phosphorylation of glycogen synthase kinase 3β (GSK3β). Identify the catalytic activity of each protein that has one.

Score for page:_____

(b; 8 pts) We have emphasized that turning signals off is just as important as turning them on. For each of the following signal transduction proteins, identify how the activity of the protein itself is down-regulated and also how its downstream signal is turned off.

Example: Protein kinase A (PKA): Decrease in [cAMP] leads to reassociation of inhibitory R subunit. Phosphorylation of target proteins like phosphorylase kinase is reversed by protein phosphatase I.

(i) PI3K:

(ii) GPCRs that signal to Adenylyl Cyclase:

(c; 8 pts) How can the elevated free fatty acids and/or continual insulin signalling found in some obese people eventually lead to insulin resistance and Type II diabetes?

Score for page:_____

(d; 8 pts) We read a paper on genome-wide association studies used to identify genes linked to Type II diabetes. In general, how are such screens done? Perhaps surprisingly, none of the proteins we covered up to this point of this exam was identified in the screens. Why not? What might explain the existence in the population of some alleles that predispose their owners to diabetes?

(e; 6 pts) Very briefly discuss an ethical issue surrounding the substantial research investment in Type II diabetes on the part of the pharmaceutical industry.

Score for page:_____

3. G-Proteins and G-protein Coupled Receptors (25 pts):

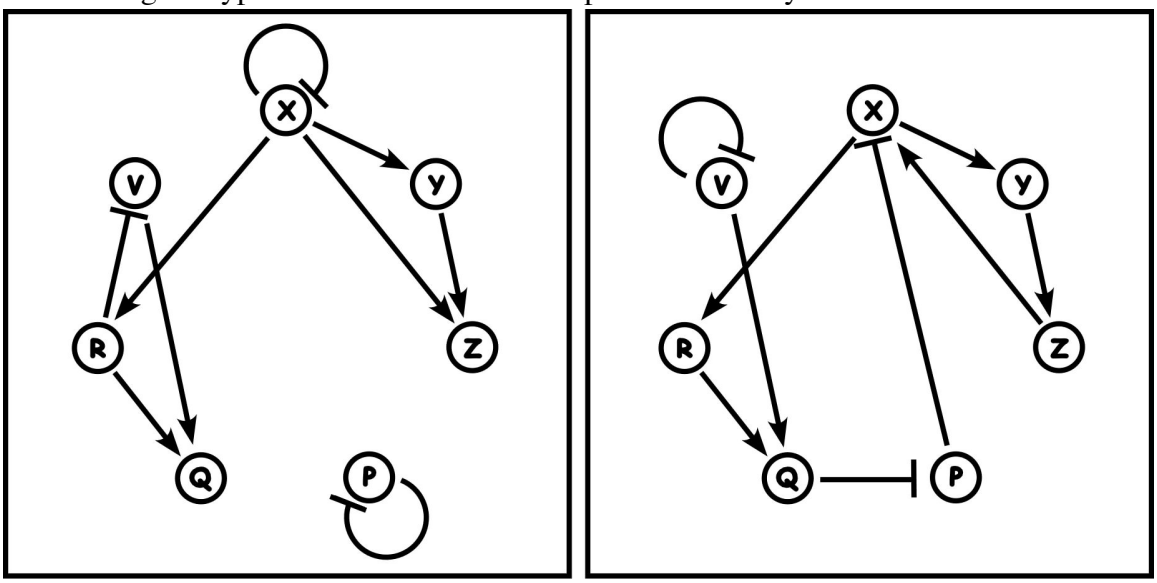
(a; 10 pts) Define GPCR agonists, inverse agonists, and antagonists. Why is it often difficult to tell the difference experimentally between an inverse agonist and an antagonist?

(b; 15 pts) Give three reasons that GPCR structures have been so difficult to obtain. What experimental trick enabled the recent structures, and why did the advance, ironically, make the resulting structures less interesting?

Score for page:_____

4. Systems Biology (35 pts):

(a; 12 pts) The sketch below shows one transcriptional regulation network that might be a real one and one randomized network with the same number and type of nodes and edges. Which is which? Identify a negative autoregulatory loop, a coherent feed-forward loop, and an incoherent feed-forward loop in the diagrams. How are randomized networks like the one below useful in determining the types of networks that are important in real systems?



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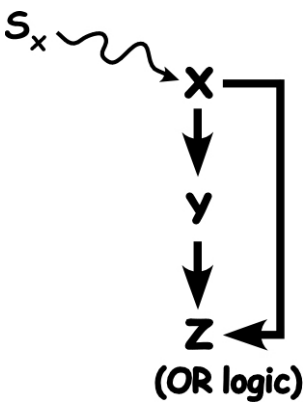
(b; 15 pts) We have discussed the idea that a coherent feedback loop with "OR" logic at the promoter serves as a circuit with a rapid "ON" but a delayed "OFF" response to a decrease in signal S_x. Explain how this works. It also acts as a filter that rejects (i.e. prevents response to) either (i) transient increases or (ii) transient decreases in S_x activity. Which is it (i or ii), and why?



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(c; 8 pts) Give an everyday example of a bistable switch. What is necessary for its state to change? Why might a system that is poised to go back and forth quickly often be undesirable in biology?

Page	**Score**
1	_____/24
2	_____/16
3	_____/20
4	_____/16
5	_____/14
6	_____/25
7	_____/12
8	_____/15
9	_____/8
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