Problem Set 3
MCDB 108B

1. Answer True or False to the following statements, and briefly explain the physiological rationale. In response to increased glucagon:

a) ____ Increased F-2,6-BP is generated in liver.
b) ____ Phosphofructokinase is inhibited in liver.
c) ____ Phosphofructokinase is activated in muscle.

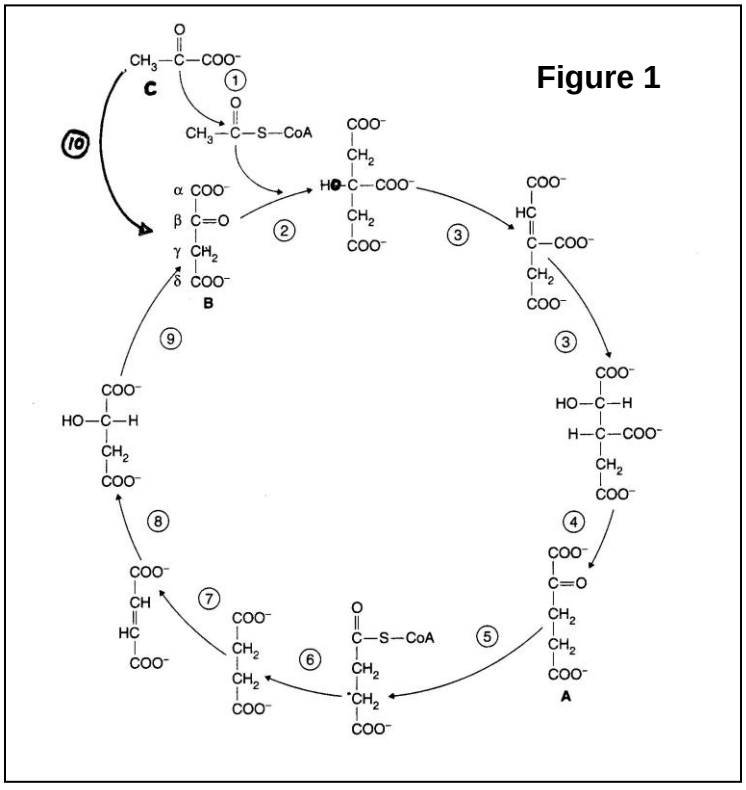
2. a) Decarboxylation of pyruvate is catalyzed by pyruvate dehydrogenase, which requires thiamine, lipoic acid, and FAD. Look up the structure of pyruvate in a text book, and draw the product(s) of this reaction. Has net oxidation/reduction occurred in this reaction? Demonstrate by indicating the oxidation state of all carbons in both pyruvate and the reaction products.

b) Decarboxylation of pyruvate can also be catalyzed by pyruvate decarboxylase in yeast. Draw the product of this reaction. Has net oxidation/reduction occurred? Demonstrate by indicating the oxidation state of all carbons in pyruvate and the reaction products. In general, why are lipoic acid and FAD not needed?

3. a) In figure 1, if the methyl carbon of compound C is labeled with ^{14}C, which carbon atoms in compound B will be labeled after one turn of the TCA cycle? Answer by showing all the carbon atoms that become labeled in all intermediates. Explain any unintuitive patterns.

b) Control of the TCA cycle is governed largely by the levels of NADH. Explain the role of NAD^+, the effects of high NADH, and the principle mechanism of regulation by NADH. Which steps in Fig 1 are under regulation by NADH?

4. Under conditions of high mitochondrial NADH, gluconeogenesis is stimulated. Which carbons in compound B (Figure 1) will be labeled under these conditions? Explain why the labeling is the same or different compared to the situation in question 3a.



5. The following are true for which reactions in Figure 1 (1-10, or none)?

1) CO_2 is liberated
2) FAD is required
3) H_2O is incorporated
4) inhibited by NADH
5) activated by Ca^{2+}
6) require biotin
7) require lipoic acid
8) inhibited by phosphorylation

6. Show the chemical basis for the requirement of thiamine in metabolism by drawing a typical chemical reaction scheme that involves thiamine pyrophosphate (TPP). (Choose an appropriate structure from Figure 1 as the reactant). Show the reaction between TPP and reactant, and explain why TPP is particularly reactive. Show the electron movements that are consistent with the overall reaction.

7. Answer True or False to the following. If true, provide a brief explanation of the rationale and explain the mechanism. If false explain why:

a) Gluconeogenesis is activated in muscle during exercise and starvation to produce glucose for fuel .
b) Gluconeogenesis is activated in liver during exercise and starvation to produce glucose for fuel.
c) When acetyl-CoA is abundant, reaction 10 in Figure 1 is turned on (2).
d) Glycolysis and glucogeogenesis are reciprocally regulated by energy charge and biosynthetic precursors (4).

8. (5) The active site of a metabolic enzyme faces the *lumen* of the endoplasmic reticulum, but its substrate is produced, and its product used, by other enzymes in the *cytosol*. Defects associated with this enzyme's *activity* result in human disease. However, defects at the molecular level do not necessarily reside in the enzyme itself. Explain. How could you distinguish between defects in the actual enzyme as opposed to elsewhere, experimentally?

9. (6) Answer True or False to the following statements, and explain how your answer makes sense physiologically. Gluconeogenesis is active in:

a) ___ muscle during exercise
b) ___ liver during exercise or fasting
c) ___ brain during fasting

10. In muscle, lactate dehydogenase produces lactate from pyruvate, whereas in the heart it preferentially synthesizes pyruvate from lactate. Explain how this is possible. Explain the physiological rationale.