

Diabetes Module: Problem Set 2

1. Acetyl CoA carboxylase-1 (ACC1) is the rate-limiting cytoplasmic enzyme on the pathway of fatty acid biosynthesis that makes malonylCoA, a substrate for the fatty acid synthase reaction. ACC1 is found at its highest levels in lipogenic tissues. Null mutants of mice in ACC1, *Acc1*^{-/-} die in early embryonic stages. By contrast a distinct acetyl CoA carboxylase-2 (ACC2) is associated with the outer mitochondrial surface where the malonyl CoA it produces inhibits the carnitine shuttle enzyme CPT1). ACC2 levels are higher in non-lipogenic tissues, such as skeletal muscle, than in liver. Both ACC1 and ACC2 are thought to be inhibited by phosphorylation, e.g. by AMPK kinase (or by glucagon signaling in liver). Wakil and colleagues suggest that inhibitors of acetylCoA carboxylase-2 (ACC-2) would be of potential use for diabetes and obesity.

1A. What is the rationale for ACC2 inhibition as a therapeutic strategy for obesity or diabetes?

1B. Randle proposed that if fatty acid oxidation is favored, glucose oxidation would decrease. If that happened upon ACC2 inhibition, would it prevent a positive effect of the inhibition on post-prandial glucose homeostasis?

1C. What do the findings of Wakil's group on *Acc2*^{-/-} mice (as shown by Oh et al, 2005, or Choi et al 2007 if you prefer) indicate about the concern that ACC2 inhibitors might fail to increase glucose utilization even if they reduced fatty acid storage?

2. Insulin action requires activation of the insulin receptor and down-stream intracellular pathways. To block this effect there are physiological mechanisms within the cell, and these mechanisms may also be involved when pathological conditions obtain and insulin resistance occurs. Understanding these mechanisms that cause insulin resistance by affecting down-stream pathways may aid in considering therapeutic options. Describe some of these processes and elaborate on one that may be useful. Consider designing a “new” drug to combat or prevent insulin resistance.

3. Molecular chaperones promote protein folding in the endoplasmic reticulum. When the load of unfolded protein exceeds the capacity of the chaperone machinery to promote folding, then unfolded proteins are exported to the cytosol for degradation (ER associated degradation). What would happen if ERAD was blocked? What would be the fate of the unfolded proteins - and would this affect the ER stress response?

4. IRS proteins are important signaling molecules in tyrosine kinase signaling. A brain specific KO (gene knock out) of IRS2 results in obesity. Explain.

5. Discuss why DPP4 inhibitors are weight neutral while exendin often leads to significant weight loss.