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Fatty Acids
Monday, January 14, 2008
9:30 AM

1. Why does glucagon stimulation of liver cause an increase in acetyl-CoA levels in mitochondria?
   a. Drop in blood glucose leads to glucagon levels increasing, insulin levels decreasing
   b. Gluconeogenesis is stimulated
   c. FA are released from adipose
   d. Increase in FA in liver
   e. FA oxidation increases
   f. Increase in gluconeogenesis leads to decrease in overall TCA cycle
   g. Increase in Acetyl CoA concentration because production exceeds TCA cycle capacity

2. What are the two ketone bodies produced by liver? How is acetoacetyl-CoA formed in the liver? What controls the conversion of acetoacetyl-CoA to HMG-CoA?
   a. Acetoacetate + NAD --> beta-hydroxybutyrate (+NAD+)
   b. Mechanism
      i. Tholase: 2 Acetyl-CoA --> acetoacetyl-CoA
      ii. HMG CoA synthase: Acetoacetyl-CoA + H2O + Acetyl-CoA --> HMG-CoA
         1) Inhibited by succinyl-CoA
         2) Mitochondrial
      iii. HMG-CoA Lyase: HMG-CoA --> Acetoacetate + Acetyl-CoA
   c. HMG CoA Synthase is inhibited by succinyl-CoA

3. Why does an increase in the flux of the TCA cycle result in a decrease in ketone body synthesis?
   a. Increased TCA cycle --> increased succinyl-CoA --> inhibition of HMG-CoA Synthase
   b. Signal to increase gluconeogenesis --> shift away from TCA --> decrease in succinyl-CoA

4. How does an increase in an acetyl-CoA levels lead to an increase in formation of HMG-CoA?
   a. Acetyl-CoA reverses inhibition of HMG-CoA Synthase by succinyl-CoA
   b. Ketogenesis increased in fasting, prolonged exercise, high fat diet, fetal suckling
   c. Acetyl-CoA increases transcription of HMG-CoA synthase gene; insulin can reverse increase

5. How are acetoacetate and B-hydroxybutyrate metabolized in muscle and brain?
   a. Beta-hydroxybutyrate dehydrogenase: beta-hydroxybutyrate + NAD+ --> acetoacetate + NADH
   b. 3-ketoacyl-CoA transferase: Acetoacetate + Succinyl-CoA --> Acetoacetyl-CoA + Succinate
   c. Thiolase: Acetoacetyl-CoA + CoA --> 2 Acetyl-CoA

6. What enzyme is present in muscle but absent from liver?
   a. 3-ketoacyl-CoA transferase
   b. Absence of enzyme prevents futile cycle

7. Why do ketone bodies increase in an uncontrolled diabetic? What is the relationship between liver and adipose tissue?
   a. Lack of insulin --> glucagon secretion -->
      i. High blood glucose
      ii. Increase in glucose synthesis
      iii. Increase in FA release from adipose
   b. Liver
      i. Fatty acids --> acetyl-CoA --> ketone bodies
      ii. Acetyl-CoA + OAA --> citrate is decreased
      iii. Leads to even more glucose production
   c. Muscle
      i. Metabolism of ketone bodies decreased
      ii. Lack of insulin decreases GLUT4 transport --> no source of OAA to combine w/ Acetyl-CoA
         for use in TCA cycle
   d. Starvation
      i. Increase in gluconeogenesis, release of FA from adipose, ketone body production
      ii. Depletion of TCA intermediates in muscle
iii. Reduces capacity of muscle to use acetyl CoA  
iv. Ketone bodies increase in blood  
v. Ketoacidosis  
   1) Not as severe as in diabetics b/c there is still some insulin to FA release from adipose  
      is moderated  
   2) Glucose can still enter muscle to some extent allowing greater operation of TCA  
      cycle and better use of Acetyl CoA  
8. What tissues are most active in the synthesis of fatty acids?  
   a. Liver and adipose tissue  
   b. All tissues synthesize FA  
9. How is acetyl-CoA transported out of mitochondria for fatty acid synthesis?  
   a. Citrate synthase: Acetyl-CoA + OAA -> citrate  
   b. Carried through citrate transporter on inner mito membrane  
   c. Citrate lyase: citrate + CoA + ATP -> Acetyl-CoA + OAA +ADP  
   d. Malate dehydrogenase: OAA + NADH + H+ --> Malate + NAD+  
   e. Malic Enzyme: Malate + NADP+ --> Pyruvate + NADPH + H+ + CO2  
   f. Pyruvate is exported back into mitochondria via pyruvate transporter  
   g. Pyruvate + CO2 + ATP --> OAA + ADP + Pi  
10. How is NADPH generated for use in fatty acid biosynthesis?  
   a. Generated in conversion of malate to pyruvate  
   b. Used in reduction step of FA synthesis  
11. What is the sequence of reaction carried out by the fatty acid synthase complex? How is malonyl-CoA used? When does acetyl-CoA enter the sequence? What is required for the reduction processes? Is CO2 incorporated into fatty acids?  
   a. Acetyl CoA Carboxylase: Acetyl-CoA + ATP + HCO3- --> Malonyl-CoA + ADP + Pi + H+  
      i. Biotin cofactor carries CO2 from HCO3- and attaches it to acetyl CoA  
      ii. Regulated (see question 12)  
   b. FA Synthase complex carries out steps of synthesis ketoacyl-ACP synthase  
      i. Acetyl-CoA binds to cysteine -SH on ketoacyl-ACP synthase  
      ii. Malonyl-CoA binds to phosphopantetheine on ACP  
      iii. Condensation reaction between malonyl and acetyl, releases CO2  
      iv. Reduction using NADPH  
      v. Dehydration  
      vi. Reduction using NADPH  
      vii. Saturated acyl lengthened by two carbons  
   c. Requires pantothenic acid, NADPH, biotin  
   d. CO2 is not incorporated into FA  
   e. Once at palmitic acid, chain is released by thioesterase  
12. How is acetyl-CoA carboxylase regulated? What are the effects of citrate and palmitoyl-CoA? What is the role of phosphorylation and how is it regulated?  
   a. Begins as protomer (several subunits)  
   b. Citrate causes polymerization of subunits into long chain, malonyl-CoA and palmitoyl-CoA inhibit polymerization  
   c. Phosphorylation inactivates polymer  
      i. Palmitoyl CoA --> AMP Kinase --> inactive carboxylase  
         1) AMPK activated via phosphorylation  
         2) AMP and Acyl-CoA activate AMPK Kinase  
         3) Dephosphorylated/inactivated by PPP  
      ii. Glucagon --> PKA --> inactive Acetyl CoA Carboxylase  
      iii. Dephosphorylated by PPP  
   d. Transcriptional regulation  
      i. High carb diet --> increased transcription of gene --> increased FA synthesis  
      ii. High fat diet --> reduced transcription of gene, b/c fat in diet is same as what we
13. How are fatty acid oxidation and fatty acid synthesis coordinately regulated?

a. Glucose-6-P → Gluconeogenesis → Pyruvate → Oxaloacetate → Malate → Citrate → Carnitine acyl transferase → Cytosol → Acetyl CoA → Citrate → Mitochondria → Fatty Acyl CoA → Malonyl CoA → Fatty Acyl CoA → Ketone Bodies

b. Glucagon → increase gluconeogenesis → decrease in citrate → decreased malonyl CoA → increase in carnitine acyl transferase → increase in FA ox → increase in ketone bodies

Glucagon → increase in cAMP → increase in PKA → inactivated ACC → decrease in malonyl CoA

c. Increase in FA → decrease in malonyl CoA → increase in FA transport → increase in FA Ox

d. Insulin → increase in ACC → increase in malonyl CoA → inhibition of FA transport → decrease FA Ox → increase FA synthesis

e. Increase in AMP → increase in AMPK → inactive ACC → decrease in malonyl-CoA and FA synthesis → increase in FA transport and FA Ox