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# Regulation

Wednesday, January 09, 2008  
10:00 AM

19. What are the three points in gluconeogenesis that are regulated?
  - a. Pyruvate  $\rightarrow$  PEP
    - i. PEP Carboxykinase:  $\text{OAA} + \text{GTP} \rightarrow \text{PEP} + \text{CO}_2 + \text{GDP}$
    - ii. Pyr Carboxylase:  $\text{Pyr} + \text{CO}_2 + \text{ATP} \rightarrow \text{OAA} + \text{ADP} + \text{Pi}$ 
      - 1) Activated by Acetyl CoA from FA Oxidation
      - 2) Acetyl CoA also inhibits PDH (prevents more Acetyl-CoA from being produced)
    - iii. Pyr Kinase:  $\text{PEP} + \text{ADP} \rightarrow \text{Pyr} + \text{ATP}$
  - b.  $\text{F-1,6-BP} \rightarrow \text{F6P}$
  - c.  $\text{G6P} \rightarrow \text{Glucose}$
20. What is the committed step in the synthesis of glucose via the TCA cycle? How is this enzyme regulated?
  - a. PEP Carboxykinase:  $\text{OAA} + \text{GTP} \rightarrow \text{PEP} + \text{CO}_2 + \text{GDP}$
  - b. Regulated via transcription
    - i. Increased in starvation (glucagon)  $\rightarrow$  cAMP response factor
    - ii. Increased by glucocorticoids, thyroid hormones
    - iii. Inhibited by insulin
21. How is pyruvate kinase regulated? What is the effect of glucagons? What is the mechanism for this action and why is the control important? How does insulin modulate the activity and what is the significance?
  - a. Inhibited by ATP and Ala, stimulated by F-1,6-BP
  - b. In liver, also regulated by phosphorylation
  - c. Transcriptional regulation
    - i. High carb  $\rightarrow$  insulin increase  $\rightarrow$  increased transcription
  - d. Must turn off in conditions that require gluconeogenesis
    - i. Prevents recycling from PEP to pyruvate
    - ii. Glucagon is hormonal message to initiate gluconeogenesis
      - 1) PKA phosphorylates Pyr Kinase to inactivate it
      - 2) Insulin activates PPP to activate pyr kinase
22. How is the fructose-6-P/fructose-1,6-bisP reaction regulated? What controls the synthesis of fructose-2,6-bisP? What is the mechanism for the regulation by glucagons and insulin? How does the regulation in liver, cardiac muscle and skeletal muscle differ?
  - a.  $\text{F6P} + \text{ATP} \rightarrow \text{F-1,6-BP} + \text{ADP}$ 
    - i. 6-PF-1-K
    - ii. Stimulated by AMP, inhibited by ATP
    - iii. Inhibited by citrate
    - iv. Stimulated by F-2,6-BP
  - b.  $\text{F-1,6-BP} \rightarrow \text{F6P} + \text{Pi}$ 
    - i. F-1,6-Bpase
    - ii. Inhibited by AMP
    - iii. Inhibited by F-2,6-BP
  - c. F-2,6-BP levels
    - i. F6P-2Kinase:  $\text{F6P} \rightarrow \text{F-2,6-BP}$ 
      - 1) Active in dephosphorylated form
      - 2) Phosphorylated by PKA
    - ii. F-2,6-PTase:  $\text{F-2,6-BP} \rightarrow \text{F6P}$ 
      - 1) Active in phosphorylated form by PKA
    - iii. Glucagon therefore activates PKA by cAMP; net result of glucagon is decrease in F-2,6-BP and therefore increase in gluconeogenesis
    - iv. In reality, the two enzymes are a single complex with one phosphorylation
      - 1) The phosphorylation results in the PTase being exposed and kinase hidden

- 2) So really, only one ATP is used in the process of phosphorylation
- v. Insulin increases PPP therefore, dephosphorylating the complex and increasing glycolysis by increasing F-2,6-BP
- d. Regulation differences in organs
  - i. Liver: active PKA --> phosphorylation of PFK-2/F-2,6-Ptase --> inactivation of kinase and activation of phosphatase --> decrease in F-2,6-BP --> decreased glycolysis and increased gluconeogenesis
  - ii. Cardiac: active PKA via EPI --> phosphorylation of PFK-2 --> activation --> increased F-2,6-BP --> increased glycolysis
  - iii. Skeletal: PFK-2 activated by F6P --> increased F-2,6-BP --> increased glycolysis
- 23. How is glucose produced from glucose-6P? Where does the reaction take place in the hepatocyte?
  - a. G6P brought into ER Lumen via translocase
  - b. G6PTase on luminal membrane dephosphorylates G6P --> Glucose
  - c. Regulation
    - i. Insulin
      - 1) Increases glucokinase transcription
      - 2) Represses transcription of G6PTase
      - 3) Result is increase in Glucose --> G6P
    - ii. Glucagon
      - 1) Decreases transcription of glucokinase
      - 2) Increased transcription of G6PTase
      - 3) Result is increase in G6P-->Glucose
- 24. How is glycerol converted to glucose?
  - a. FA breakdown --> Glycerol
  - b. Glycerol + ATP --> Glycerol-3-P + ADP
  - c. Oxidation converts Glycerol-3-P to DHAP (Glycerol-3-P + NAD+ --> DHAP + NADH)
  - d. Moves through rest of gluconeogenesis