GLUCONEOGENESIS

1. most organs and organisms can metabolize a variety of C sources to generate needed energy

2. brain, CNS, kidney medulla, testes, erythrocytes can use only glucose

3. body has about 1 day worth of glucose
   • brain uses 120g/day; rest of body-40g
   • glycogen abt 190g; body fluids 20g

4. so need to be able to make glucose...

A. gluconeogenesis a reversal of glycolysis except for 3 rxns

• hexokinase
• PFK
• pyruvate kinase

new steps:

1. PEP formed from pyruvate via oxaloacetate

• E’s are pyruvate carboxylase (PC) and phosphoenolpyruvate carboxykinase

  * pyr carbox to oxaloacetate by PC
  * ox then decarb and phos to form PEP...USES GTP

• input of additional high energy bond makes conversion favorable:

  \[ \Delta G°^r = +0.2 \] (for reverse of PK its +7.5)

• PC containe biotin
  - can bind CO2
  - 1 end binds to lys of E, creating long arm
  - long arm swings CO2 onto pyruv to form oxalo

• PC activated by acetyl CoA
  - no CO2 bound to biotin in absence
- signals need for oxalo by TCA cycle if ATP low
- otherwise, if ATP high and acetyl CoA high, oxalo is consumed in gluconeogenesis
- PC is a mitochondrial enzyme
- oxaloacetate transported out of mitos (for gluconeo, etc) by malate-aspartate shuttle

2. F-6-P formed from F-1,6-bisP
   • E is Fructose 1,6-bisphosphatase

3. glucose is formed from glucose-6-P
   • E is glucose 6-phosphatase

B. energetics
   • gluconeogenesis:
     2 pyruvate + 4ATP + 2GTP + 2NADH + 6H₂O ➔ glucose + 4ADP + 2GDP + 6P_i + 2NAD⁺ + 2H⁺
     \( \Delta G^o = -9 \text{ kcal/mol} \)
   • reverse glycolysis:
     2 pyruvate + 2ATP + 2NADH + 2H₂O ➔ glucose + 2ADP + + 2P_i + 2NAD⁺ + 2H⁺
     \( \Delta G^o = +20 \text{ kcal/mol} \)
   • so price is 4 mol of high energy P bonds/ mol of glucose made

C. substrates for gluconeogenesis
   • lactate
   • amino acids
   • propionate
   • glycerol

*summary of pathways by which these substrates enter gluconeo

1. lactate
   • most significant, in quantitative terms
• Cori cycle
  - lactate made in muscle during intense exertion (glycogen broken down and used up)
  - enters bloodstream and goes to gluconeogenic tissues (mainly liver)
  - converted back to glucose
  - glucose enters bloodstream, goes back to muscle so glycogen stores can be replenished
  - during recovery from intense exertion, breathing rate (respiration) is elevated so lots of ATP is made, which is also used to make the glycogen
• glucose-alanine cycle:
  - when the glycogen is gone, muscle starts catabolizing protein
  - ammonia is formed (toxic)
  - to get rid of ammonia, pyruvate formed is transaminated to alanine
  - alanine then enter blood, goes to liver, converted back to pyruvate, enters gluconeogenesis

2. amino acids
• all amino acids except lys and leu generate gluconeogenic precursors ie are glucogenic
  - fasting and diabetes
    * in diabetes body can't utilize glucose normally
    * isn't taken up from the blood
    * can be tons of it there "starvation in the midst of plenty"

3. glycerol
• triacylglycerols catabolized to FA’s and glycerol
  * FA's not glucogenic w/o glyoxylate cycle, except for
  - glycerol converted to DHAP, enters gluconeogenesis

4. ethanol is not a substrate for gluconeogenesis
• can cause hypoglycemia
metabolized in liver to acetaldehyde by ADH: NADH formed
• high NADH shifts LDH rxn toward lactate formation instead of pyruvate formation
• also shifts MDH rxn toward formation of malate, not oxaloacetat
  *its not available either

REGULATION OF GLUCONEOGENESIS

• esp important for proper functioning of nervous system
• also adjusting to muscular exertion and cycles of feeding/fasting
• much of the regulation involves hormonal control:

  PEP carboxykinase

  glucose-6-phosphatase

A. glycolysis and gluconeogenesis controlled reciprocally

- otherwise get giant futile cycle
- no thermodynamic barrier to futile cycle-both pathways exergonic

• glycolysis:
- high glucose
- high cAMP (stimulates PFK; inhibits F 1,6-bisphosphatase)
- low citrate (stimulates PFK; inhibits F 1,6-bisphosphatase)

• gluconeogenesis:
- high lactate
- low cAMP (inhibits PFK; stimulates F 1,6-bisphosphatase)
- high citrate (inhibits PFK; stimulates F 1,6-bisphosphatase)
- **cAMP levels controlled by pancreatic hormone glucagon**
B. control by F 2,6-bisphosphate

• fine tuning and fast regulation
• high glucose = hormone-triggered increase in F 2,6-bisP
• stimulates PFK, inhibits F 1,6-bisPtase
• starvation = low F 2,6-bisP; gluconeogenesis stimulated

C. PK and PC also reciprocally regulated

PK:
stimulated by F 1,6-bisP; inhibited by ATP

PC:
stimulated by acetyl CoA; inhibited by ADP
PEP carboxykinase also inhibited by ADP

D. so, if energy charge is high, pyruvate is converted to PEP and gluconeogenesis is activated