BI/CH 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic

Exam-1 material

Fermentations
Pyruvate
Krebs' Cycle
Oxidative Phosphorylation
Electron transport
Chemiosmotic theory: Phosphorylation

Exam-2 material

Fat Catabolism
Fatty acid Catabolism
Mobilization from tissues (mostly adipose)
Activation of fatty acids
Transport; carnitine
Oxidation: β-oxidation, 4 steps:
Protein Catabolism
Amino-Acid Degradation
Dealing with the nitrogen; Urea Cycle
Dealing with the carbon; Seven Families
Nucleic Acid & Nucleotide Degradation

Exam-3 material

PHOTOSYNTHESIS:

Overview of Photosynthesis
Key experiments:
Light Reactions
energy in a photon
pigments
HOW
Light absorbing complexes-"red-drop experiment"
Reaction center
Photosystems (PS)
PSII - oxygen from water splitting
PSI - NADPH
Proton Motive Force - ATP
Overview of light reactions

ANABOLISM I: Carbohydrates

Carbon Assimilation - Calvin Cycle
Stage One - **Rubisco**
Carboxylase
Oxygenase
Glycolate cycle
Stage Two - making sugar
Stage Three - remaking Ru 1,5P$_2$

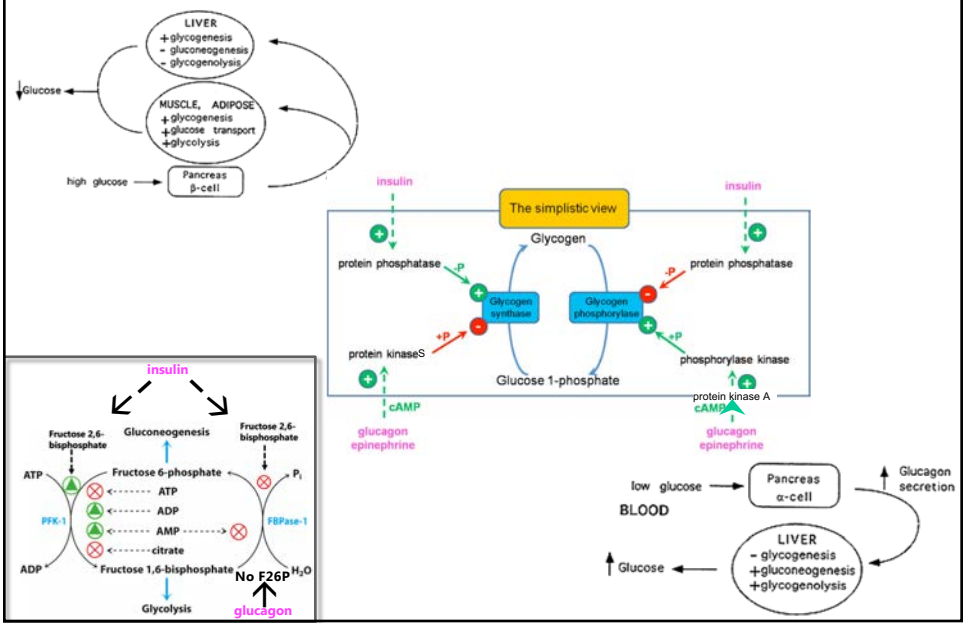
} Know mechanism

Overview and regulation
Calvin cycle connections to biosynthesis
C4 versus C3 plants
Kornberg cycle - glyoxylate

Carbohydrate Biosynthesis in Animals
precursors
Cori cycle
Gluconeogenesis
reversible steps
irreversible steps - four
energetics
2-steps to PEP in mitochondria: Pyr carboxylase-biotin & PEPCK
FBPase
G6Pase
Glycogen Synthesis
UDP-Glc
Glycogen synthase
branching
Pentose-Phosphate Pathway
oxidative-NADPH
non-oxidative-Ribose 5-P
Regulation of Carbohydrate Metabolism
Acetyl-CoA/Pyruvate
Pyruvate/PEP
F6P/FBP: Fru 2,6P$_2$
Glc/Glc6P: sequestration
Glycogen: PKA/PP1
Insulin signaling
Anaplerotic reactions

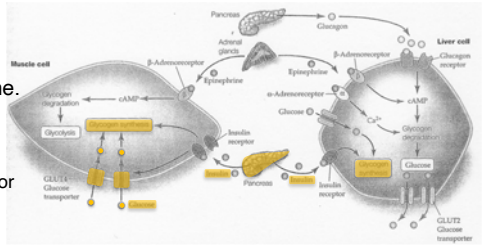
End of Exam-4 material

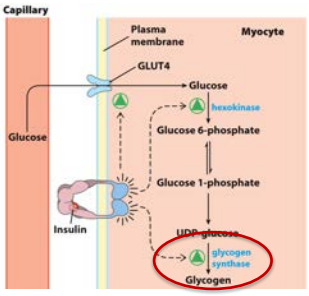
Regulation of Carbohydrate Metabolism



Regulation of Carbohydrate Metabolism

- Insulin signaling pathway activated when there is a need for energy STORAGE
  - Causes the translocation of GLUT4 from internal membranes to the plasma membrane.
    - Glucose enters muscle cells
  - Increase intracellular [Glc]
    - In liver, releases glucokinase (liver HK) from binding protein, thus it migrates to the cytosol for activity
    - In muscle, higher [S] is higher activity





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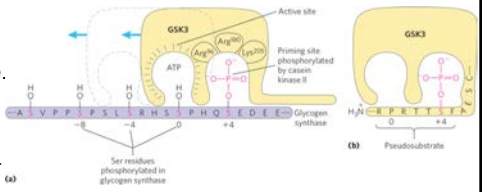
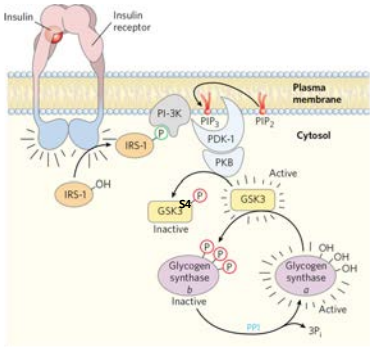
    - This inactivates GSK-3
    - Prevents the re-phosphorylation of GS so that it remains ACTIVE





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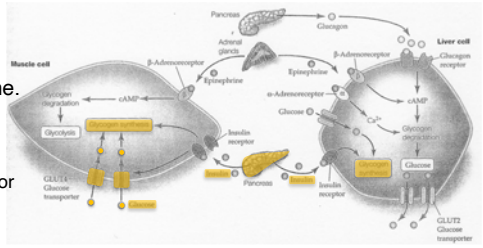
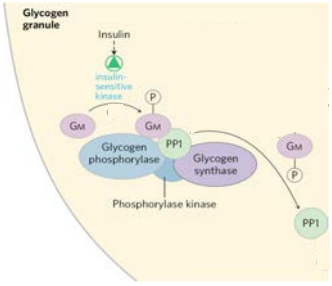
    - Example: ISK phosphorylates the glycogen-targeting proteins in muscle (G_M)
    - This dissociates it from PP-1: PP1 is more active





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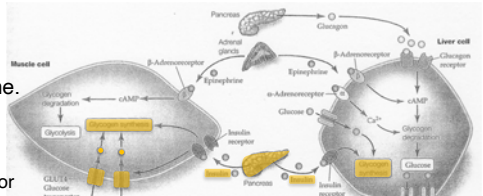
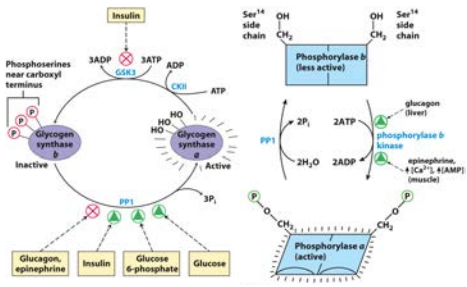
    - Example: ISK phosphorylates the glycogen-targeting proteins in muscle (G_M)
    - This dissociates it from PP-1: PP1 is more active
    - PP-1 dephosphorylates several proteins
      - Phosphorylase kinase: inhibits
      - glycogen phosphorylase: inhibits
      - Glycogen synthase (GS): activates
- GS makes glycogen for energy storage.





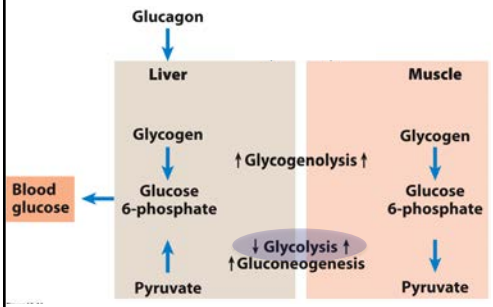
Regulation of Carbohydrate Metabolism

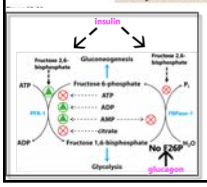
In the Liver:

Remember:

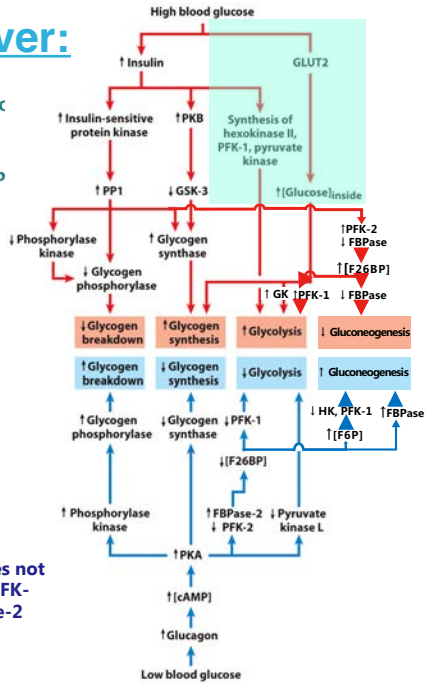
- Insulin is fed state-gc through PP
- Glucagon is hungry state-goes through P

Liver versus the Muscle





? Muscle does not express PFK-2/FBPase-2



Regulation of Carbohydrate Metabolism

The Amount of Many Metabolic Enzymes Is Controlled by Transcription

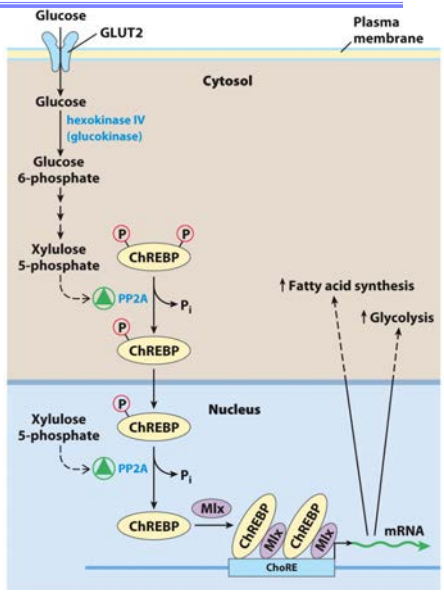
TABLE 15-5 Some of the Many Genes Regulated by Insulin

Change in gene expression	Role in glucose metabolism
Increased expression Hexokinase II Hexokinase IV Phosphofructokinase-1 (PFK-1) PFK-2/FBPase-2 Pyruvate kinase	Essential for glycolysis, which consumes glucose for energy
Glucose 6-phosphate dehydrogenase 6-Phosphogluconate dehydrogenase Malic enzyme	Produce NADPH, which is essential for conversion of glucose to lipids
ATP-citrate lyase Pyruvate dehydrogenase	Produce acetyl-CoA, which is essential for conversion of glucose to lipids
Acetyl-CoA carboxylase Fatty acid synthase complex Stearoyl-CoA dehydrogenase Acyl-CoA–glycerol transferases	Essential for conversion of glucose to lipids
Decreased expression PEP carboxykinase Glucose 6-phosphatase (catalytic subunit)	Essential for glucose production by gluconeogenesis

Regulation of Carbohydrate Metabolism

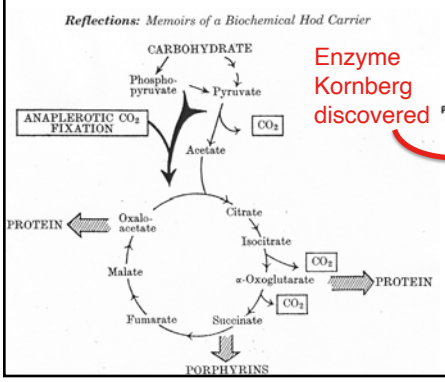
The Carbohydrate Response Element Binding Protein (ChREBP) Activates Transcription in Response to Glucose

Mice with KO of the ChREBP have interesting phenotype. They are intolerant to fructose

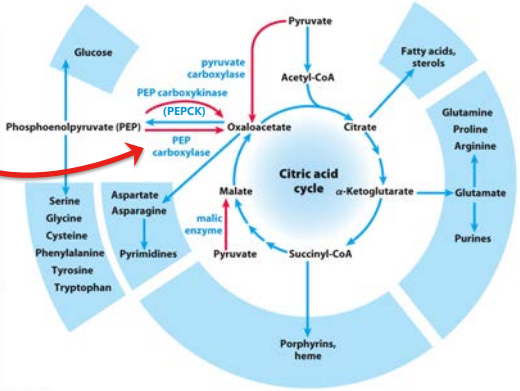


Anaplerotic Reactions

- We introduced the citric acid cycle as a key **catabolic** pathway.
- It has an equal, if not more important, role in **anabolism**.
  - The biosynthesis of biological precursors has to begin with elementary materials
  - Many, if not most, of these starting points come from the several intermediates in the Kreb's cycle.
  - This was first appreciated by Hans Kornberg: how to organisms grow on carbohydrates only?
    - The term comes from the Greek, to "fill up" or replenish
    - Recall that without this replenishment, the TCA cycle would grind to a halt
    - Anaplerotic reactions are critical



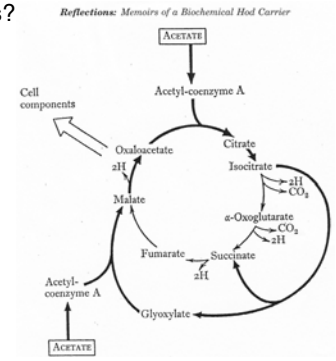
Enzyme Kornberg discovered

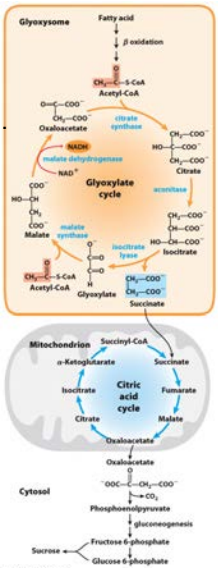


Anaplerotic Reactions

Kornberg Cycle = Glyoxylate Cycle

- Was intrigued by the fact that bacteria could grow very effectively on a little ammonium and phosphate salts with acetate (2C)
- From these they can synthesize all the components of the cell; DNA, DNA, proteins, membrane lipids, cytochromes, everything…..
- How do you build all this from a 2-carbon compound knowing how the Kreb's cycle works?





2 Acetyl-CoA + NAD^+ ⇌ Succinate + 2 CoASH + NADH

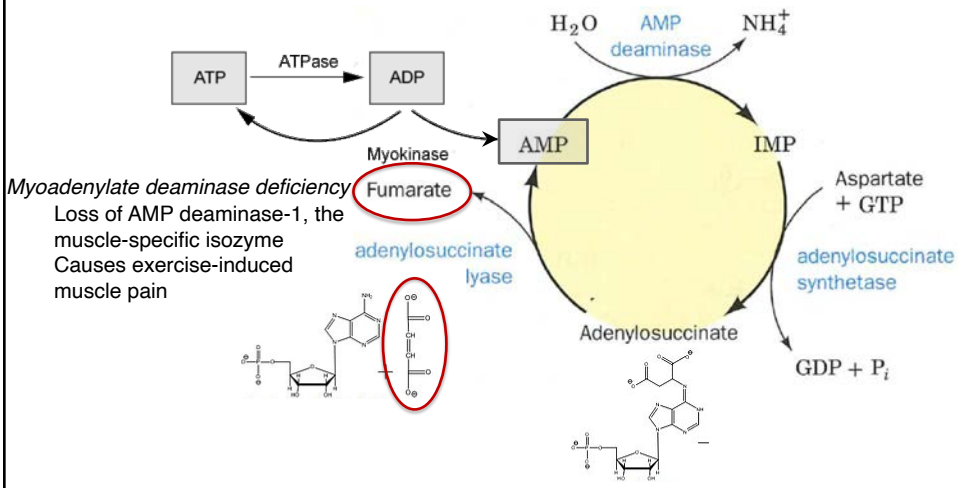
Anaplerotic Reactions

Kornberg Cycle = Glyoxylate Cycle

Dr. Kornberg Discovers the Glyoxylate Cycle

Anaplerotic Reactions

- Purine Nucleotide Cycle
  - was first thought be be part of nucleotide degradation or synthesis
  - In muscle, its now realized as an important anaplerotic pathway



Myoadenylate deaminase deficiency
Loss of AMP deaminase-1, the muscle-specific isozyme
Causes exercise-induced muscle pain

H_2O + Aspartate + GTP ⇌ NH_4^+ + GDP + P_i + Fumarate

Anaplerotic Reactions

- Intermediates in the citric acid cycle can be used in biosynthetic pathways.
- Must replenish the intermediates in order for the cycle and central metabolic pathway to continue.
- In animals, these 4-carbon intermediates are formed by carboxylation of 3-carbon precursors.

Pyruvate carboxylase deficiency
- an inherited metabolic disorder where anaplerosis is greatly reduced.
- What is the problem?
- How to treat this disorder?
- Other anaplerotic substrates such as the odd-carbon-containing triglyceride triheptanoin are used

Enzyme Kornberg discovered

TABLE 16-2 Anaplerotic Reactions

Reaction	Tissue(s)/organism(s)
Pyruvate + HCO_3^- + ATP $\xrightleftharpoons{\text{pyruvate carboxylase}}$ oxaloacetate + ADP + P_i	Liver, kidney
Phosphoenolpyruvate + CO_2 + GDP $\xrightleftharpoons{\text{PEP carboxykinase}}$ oxaloacetate + GTP	Heart, skeletal muscle
Phosphoenolpyruvate + HCO_3^- $\xrightleftharpoons{\text{PEP carboxylase}}$ oxaloacetate + P_i	Higher plants, yeast, bacteria
Pyruvate + HCO_3^- + NAD(P)H $\xrightleftharpoons{\text{malic enzyme}}$ malate + NAD(P)$^+$	Widely distributed in eukaryotes and bacteria
Aspartate + GTP $\xrightleftharpoons[\text{synthetase, adenylosuccinate lyase}]{\text{AMP deaminase, adenylosuccinate}}$ NH_4^+ + GDP + P_i + Fumarate	Muscle

ANABOLISM I: Summary

What we learned:

- Gluconeogenesis, a process by which cells can use a variety of metabolites for the synthesis of glucose
- The differences between glycolysis and gluconeogenesis
  - how they are both made thermodynamically favorable
  - how they are differentially regulated to avoid a futile cycle
- The pentose phosphate pathway, a process by which cells can generate pentose phosphates and NADPH. The pentose phosphates can be regenerated into glucose 6-phosphate, for which NO ATP is required.
- living organisms regulate the flux of metabolites through metabolic pathways by:
  - increasing or decreasing enzyme concentrations
  - activating or inactivating key enzymes in the pathway
- the activity of key enzymes in glycolysis and gluconeogenesis is tightly and coordinately regulated via various activating and inhibiting metabolites (Fru **2**,6P_2)
- glycogen synthesis and degradation is regulated by hormones insulin, epinephrine, and glucagon that report on the levels of glucose in the body
- the citric acid cycle plays important anabolic roles in the cell: Anaplerosis
- organisms have multiple ways to replenish intermediates that are used in other pathways: Lipid and Nitrogen biosynthesis…….

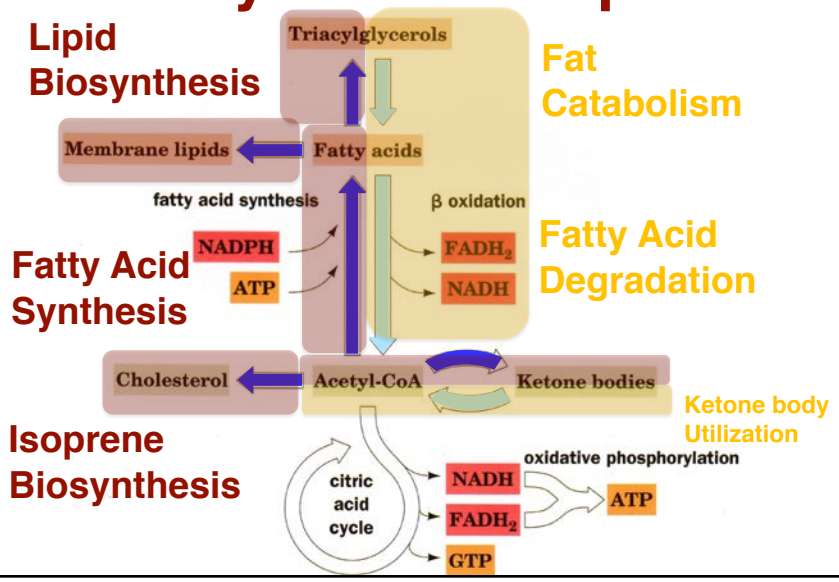
End of Material for Exam 4

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids

1. Biosynthesis of fatty acids
2. Regulation of fatty acid degradation and synthesis
3. Assembly of fatty acids into triacylglycerol and phospholipids
4. Metabolism of isoprenes
   a. Ketone bodies and Isoprene biosynthesis
   b. Isoprene polymerization
      i. Cholesterol
      ii. Steroids & other molecules
      iii. Regulation
      iv. Role of cholesterol in human disease

ANABOLISM II: Biosynthesis of Fatty Acids & Lipids



Fatty Acid Biosynthesis

Catabolism
Anabolism

- Contrast with Sugars
  - Lipids have hydro-carbons not carbo-hydrates
  - more reduced=more energy
  - Long-term storage vs short-term storage
  - Lipids are essential for structure in ALL organisms: membrane phospholipids
- **Catabolism** of fatty acids
  - *produces* acetyl-CoA
  - *produces* reducing power (NADH, $FADH_2$)
  - takes place in the *mitochondria*
- **Anabolism** of fatty acids
  - *requires* acetyl-CoA and sufficient carbohydrates
  - *requires* reducing power from NADPH
  - takes place in *cytosol* in animals, *chloroplast* in plants

Anabolism of fat will occur only when there is excess, carbon, electrons, and ΔG

Acetyl-CoA & carbohydrates → NADPH → ATP

How is this monitored in the cell?