BB 422/622

OUTLINE:

Introduction and review
Transport
Glycogenolysis
Glycolysis
Other sugars
Pasteur: Anaerobic vs Aerobic
Fermentations — Exam-1 material

Pyruvate — Exam-2 material
Krebs' Cycle
Oxidative Phosphorylation
- Electron transport
- Chemiosmotic theory: Phosphorylation

Fat Catabolism — Exam-3 material
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

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) } Know mechanism
  - Glycolate cycle
- Stage Two – making sugar
- Stage Three – remaking Ru 1,5P$_2$

Overview and regulation
Calvin cycle connections to biosynthesis — Know pathway
C4 versus C3 plants
Kornberg cycle – glyoxylate

Carbohydrate Biosynthesis in Animals

precursors
Cori cycle
Gluconeogenesis — Know pathway
- 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 — Know 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

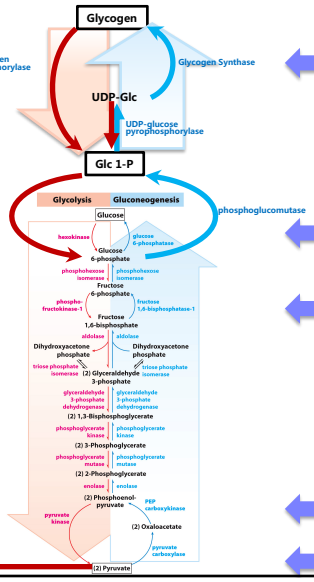
Anaplerotic reactions
Biosynthesis of Lipids

Regulation of Carbohydrate Metabolism

Gene controlled

Glycogenolysis *versus* **Glycogen Synthesis**

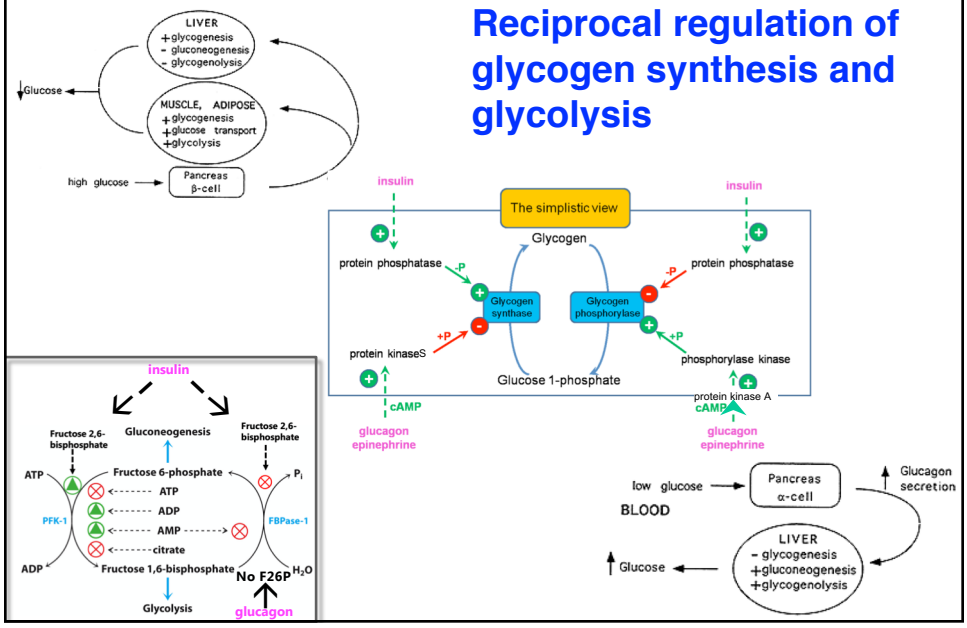
Glycolysis *versus* **Gluconeogenesis**



- Regulated enzymes often correspond to points in the pathways that have the same substrate and product, but a different enzyme.
- Can you name those enzymes?

	Catabolism	Anabolism
Glycogen Synthase / Glycogen Phosphorylase	Phosphorylase ✓	Glycogen Synthase ✓
Hexokinase / Glucose 6-phosphatase	Hexokinase ✓	Glucose 6-phosphatase
Phosphofructokinase-1 / Fructose 1,6-bisphosphatase	Phosphofructo-kinase-1 ✓	Fructose 1,6-bisphosphatase ✓
Pyruvate Kinase / PEPCK – Pyruvate carboxylase	Pyruvate Kinase ✓	PEPCK – Pyruvate carboxylase ✓
Pyruvate Dehydrogenase Complex	Pyruvate Dehydrogenase Complex ✓	

Regulation of Carbohydrate Metabolism

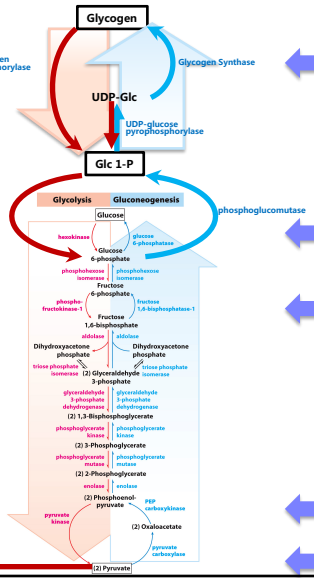


Regulation of Carbohydrate Metabolism

Gene controlled

Glycogenolysis *versus* **Glycogen Synthesis**

Glycolysis *versus* **Gluconeogenesis**



	Catabolism	Anabolism
	Phosphorylase ✓	Glycogen Synthase ✓
	Hexokinase ✓	Glucose 6-phosphatase
	Phosphofructo-kinase-1 ✓	Fructose 1,6-bisphosphatase ✓
	Pyruvate Kinase ✓	– PEPCK – Pyruvate carboxylase ✓
	Pyruvate Dehydrogenase Complex ✓	

- Regulated enzymes often correspond to points in the pathways that have the same substrate and product, but a different enzyme.
- Can you name those enzymes?

Regulation of Carbohydrate Metabolism

The Amount of Many Metabolic Enzymes Is Controlled by Transcription

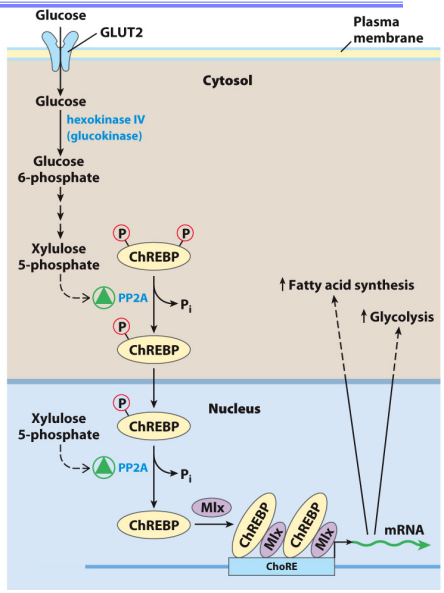
TABLE 15-5 Some of the Many Genes Regulated by Insulin

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

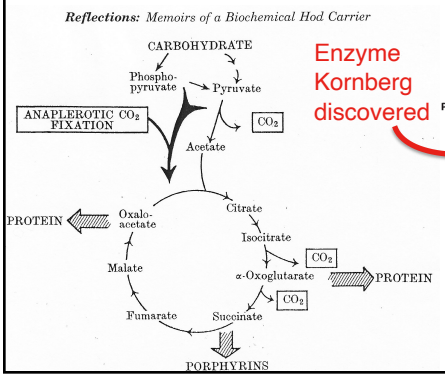
The Carbohydrate Response Element Binding Protein (ChREBP) Activates Transcription in Response to Glucose

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

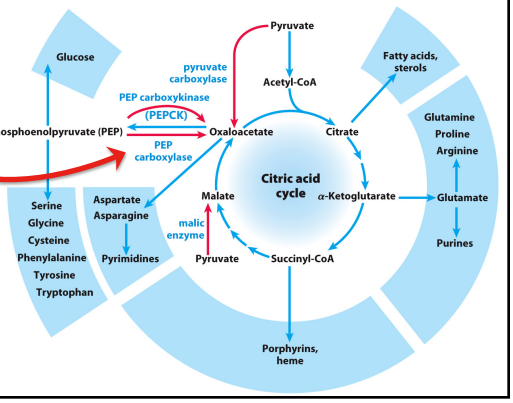


Anaplerotic Reactions

- 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



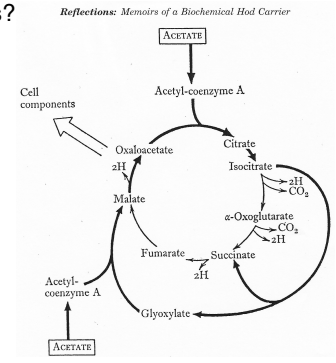
Enzyme Kornberg discovered

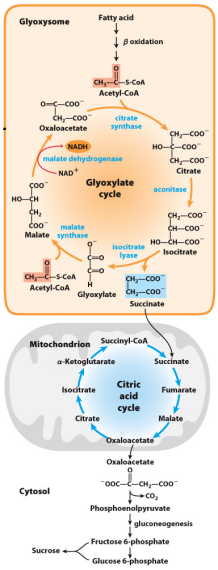


Anaplerotic Reactions

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

- 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 $\xrightleftharpoons{\text{AMP deaminase, adenylosuccinate synthetase, adenylosuccinate lyase}}$ 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/inactivating key enzymes in the pathway by phosphorylation/de phosphorylation
- 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…….