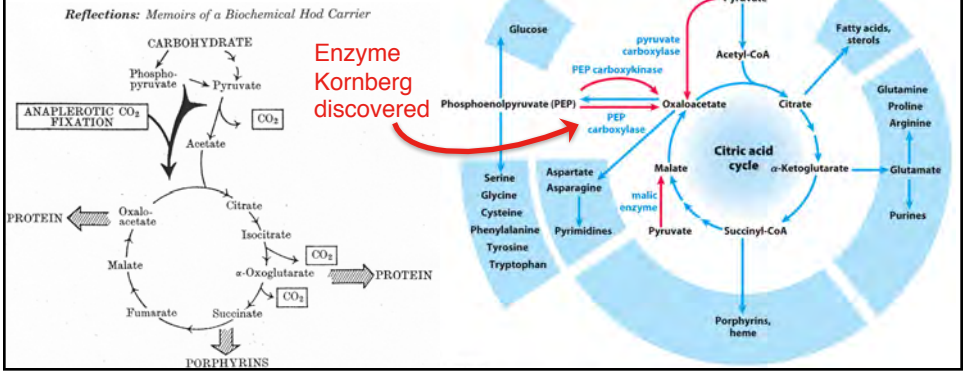
Anaplerotic Reactions

- 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

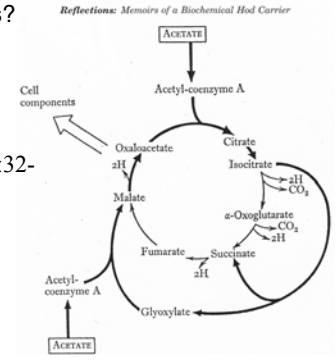


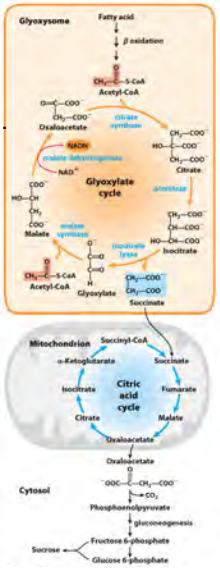
Anaplerotic Reactions

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?

Dr. Kornberg:
Lecture 03.29.17 (31:32-35:09) 3.5 min

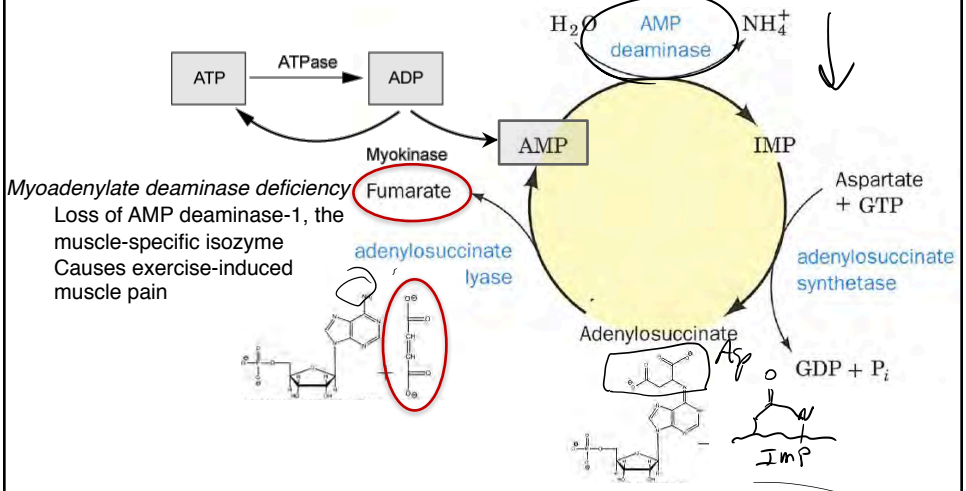




2 Acetyl-CoA + NAD⁺ ⇌ Succinate + 2 CoASH + NADH

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 $\xrightleftharpoons{\text{AMP deaminase, adenylosuccinate synthetase, adenylosuccinate lyase}}$ 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 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…….