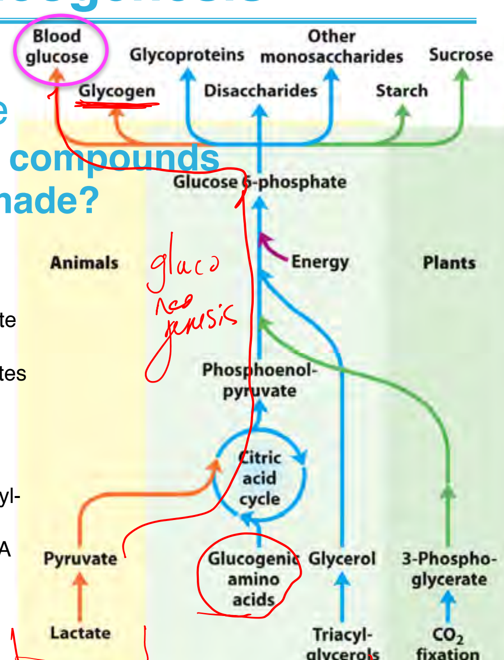
ANABOLISM I
Carbohydrates

Carbohydrate Synthesis in Animals

Gluconeogenesis

Gluconeogenesis: Making "New" Glucose

Precursors: From what compounds can glucose be made?



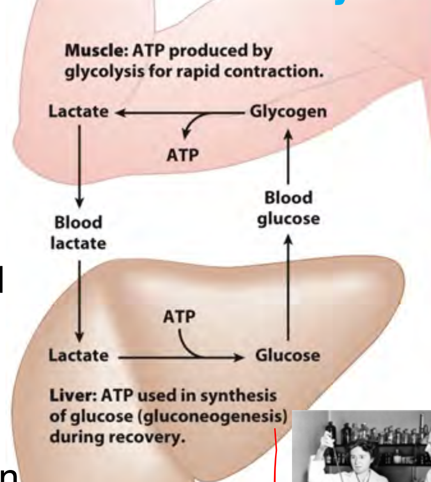
- Animals can produce glucose from sugars or proteins.
  - sugars: pyruvate, lactate, or oxaloacetate
  - protein: from amino acids that can be converted to citric acid cycle intermediates (or glucogenic amino acids)
- Animals cannot produce glucose from fatty acids.
  - product of fatty acid degradation is acetyl-CoA
  - There is no net conversion of acetyl-CoA to oxaloacetate in Kreb's Cycle

Plants, yeast, and many bacteria use the Kornberg Cycle to convert acetyl-CoA to oxaloacetate, thus producing glucose from fatty acids.

Gluconeogenesis

The Cori Cycle

- Blood glucose is largely made in the liver, although other organs can reverse glycolysis, but not deliver free glucose into the blood
- Synthesis of glucose from simpler compounds: **called gluconeogenesis**
- Operates only if ATP and NADH are plentiful
- Other tissues deliver carbon to liver from "waste" products.



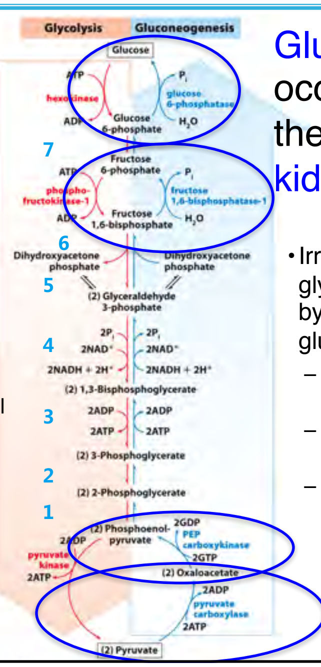
As you can see the two pathways operate in different tissues, but how is this controlled in a single cell?

Gluconeogenesis

Glycolysis *versus* Gluconeogenesis

Glycolysis occurs mainly in the muscle and brain.

- Opposing pathways that are both thermodynamically favorable:
- Glycolysis: $\Delta G^{o\prime} = -35$ kcal/mol
- Gluconeogenesis: $\Delta G^{o\prime} = -9$ kcal/mol
  - operate in opposite direction
    - end product of one is the starting compound of the other
- Seven Reversible reactions are used by both pathways.
- Three "glycolysis-specific" steps are reversed with Four "gluconeogenesis-specific" steps.



Gluconeogenesis occurs mainly in the liver and kidney cortex.

- Irreversible reaction of glycolysis must be bypassed in gluconeogenesis.
  - no ATP generated during gluconeogenesis
  - different enzymes in the different pathways
  - differentially regulated to prevent a futile cycle

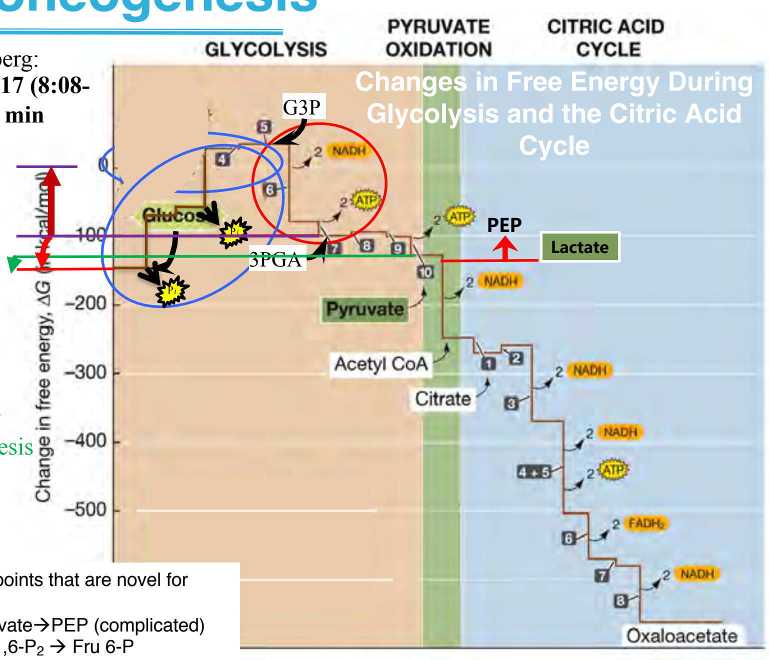
Lets look at the energetics of making glucose.....

Gluconeogenesis

Dr. Kornberg:
Lecture 03.22.17 (8:08-11:36) 3.5 min

Favorable energetics for Calvin Cycle

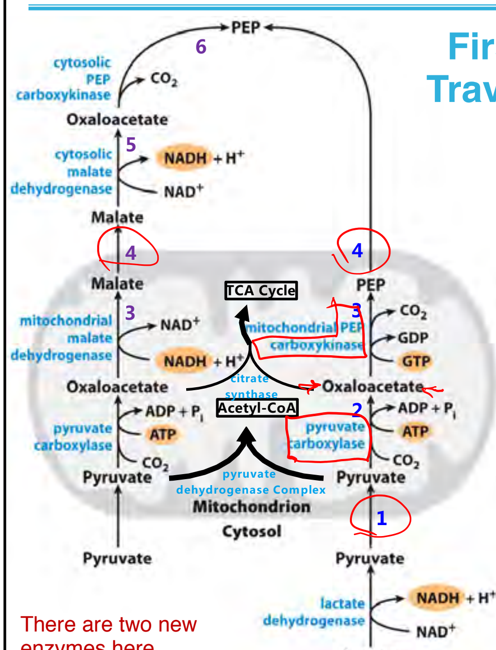
Favorable energetics for Gluconeogenesis



There are then 3 points that are novel for gluconeogenesis:

1. Pyruvate→PEP (complicated)
2. Fru 1,6-P_2 → Fru 6-P
3. Glc 6-P→ glucose

Gluconeogenesis



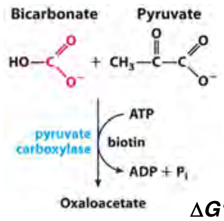
There are two new enzymes here…..

First Gluconeogenic Steps Travel Through Mitochondria

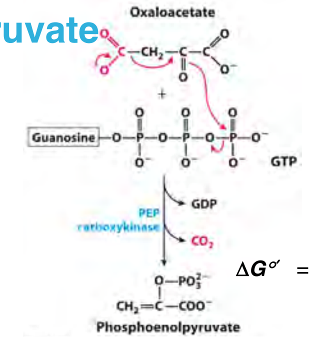
- Best place to assess whether there is ample ATP and NADH is the mitochondria.
- The inner mitochondrial membrane is selectively permeable: Malate, PEP, and pyruvate are permeable, while oxaloacetate cannot escape.
- Oxaloacetate can be utilized in the citric acid cycle (Kreb's cycle) if needed.
- There are two ways from pyruvate to PEP.
- Oxaloacetate can be converted to PEP or malate to allow transport to cytosol for gluconeogenesis.
- Will discuss the decision that pyruvate must make later…..

Gluconeogenesis

Pyruvate to Phosphoenolpyruvate



$\Delta G^{\circ\prime}$ = –0.5 kcal/mol



$\Delta G^{\circ\prime}$ = +0.7 kcal/mol

- Requires two energy-consuming steps
- The first step, pyruvate carboxylase (PC) converts pyruvate to oxaloacetate.
  - carboxylation using a biotin cofactor
  - This enzyme is only in the mitochondria; requires transport of pyruvate
- The second step, phosphoenolpyruvate carboxykinase converts oxaloacetate to PEP.
  - phosphorylation from GTP and decarboxylation
  - occurs in mitochondria or cytosol depending on the organism

During this conversion, the same carbon from CO_2 is added and immediately removed from the structure.

Lets look at the PC mechanism more closely…..