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

Know mechanism

Stage Two – making sugar
Stage Three – remaking Ru 1,5P$_2$
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
mitochondria
Pyr carboxylase-biotin
PEPCK
FBPase
G6Pase

Glycogen Synthesis
UDP-Glc
Glycogen synthase
branching

Pentose-Phosphate Pathway
Regulation of Carbohydrate Metabolism
Anaplerotic reactions

ANABOLISM I
Carbohydrates

Carbohydrate Synthesis in Animals

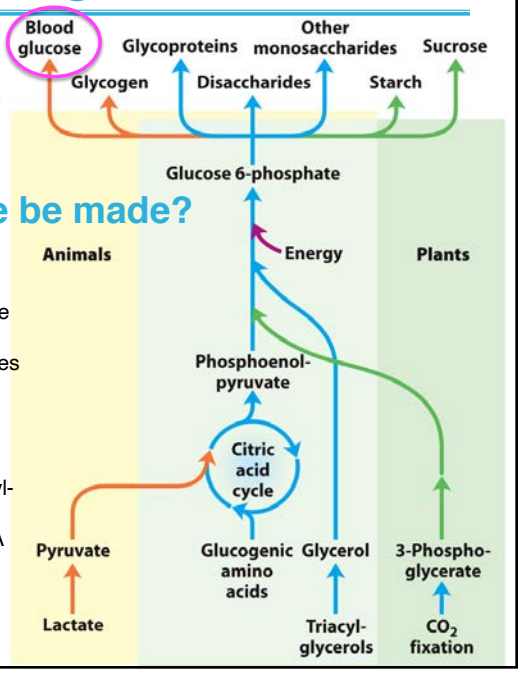
Gluconeogenesis

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

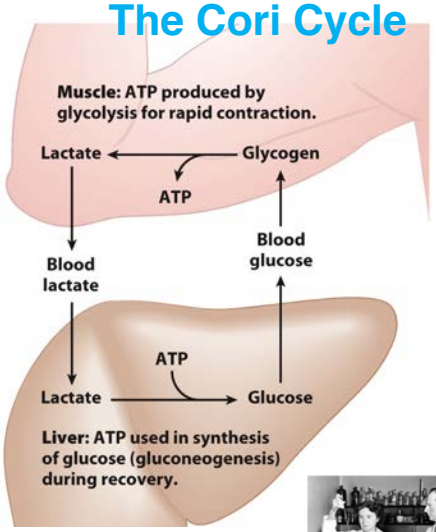
Plants, yeast, and many bacteria use the Kornberg Cycle to convert acetyl-CoA to oxaloacetate, thus producing glucose from fatty acids.



Gluconeogenesis

- 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 (Ala and Cori Cycles).

The Cori Cycle



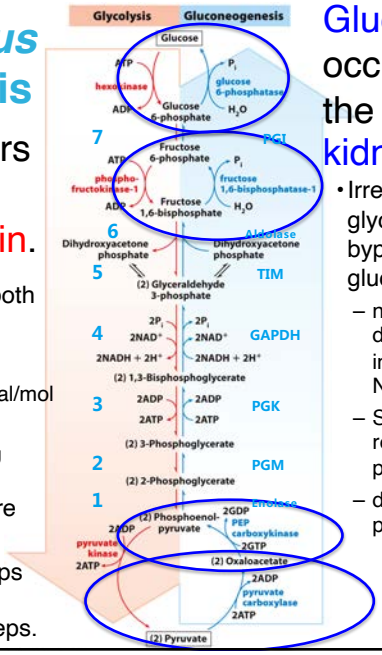
As you can see the two pathways operate in different tissues, but how is this controlled in a single cell?

Gluconeogenesis

Glycolysis *versus* Gluconeogenesis

Glycolysis occurs mainly in the muscle and brain.

- Opposing pathways that are both thermodynamically favorable:
- Glycolysis: $\Delta G^{\circ\prime}$ = –35 kcal/mol
- Gluconeogenesis: $\Delta G^{\circ\prime}$=–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.

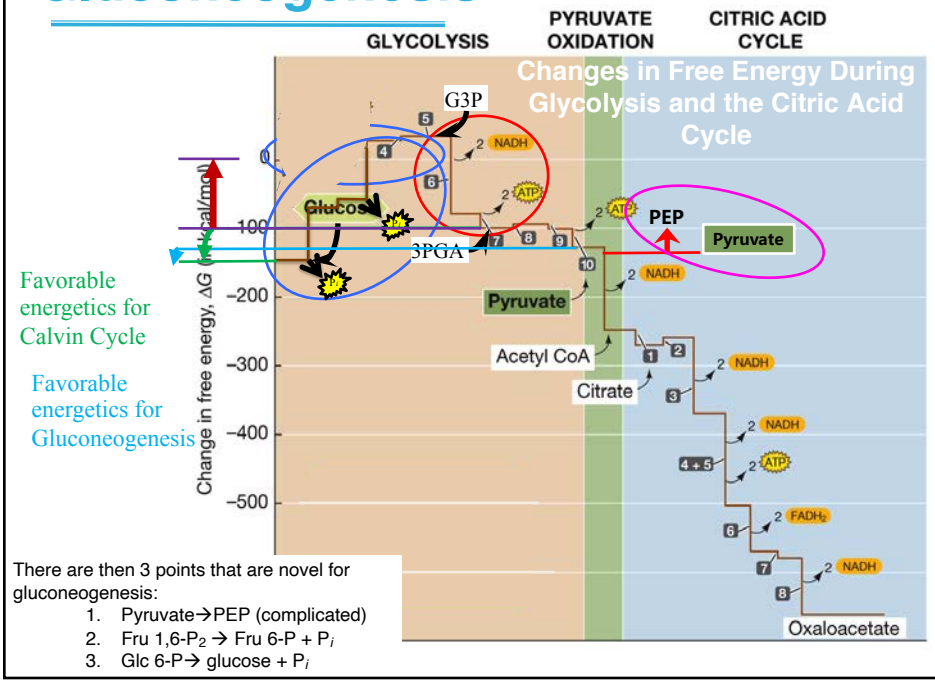


Gluconeogenesis occurs mainly in the liver and kidney cortex.

- Irreversible reactions of glycolysis must be bypassed in gluconeogenesis.
  - no ATP generated during gluconeogenesis; instead 6 ATPs and 2 NADH needed per Glc.
  - Some different enzymes results in the different pathways
  - differentially regulated to prevent a futile cycle

Lets look at the energetics of making glucose…..

Gluconeogenesis



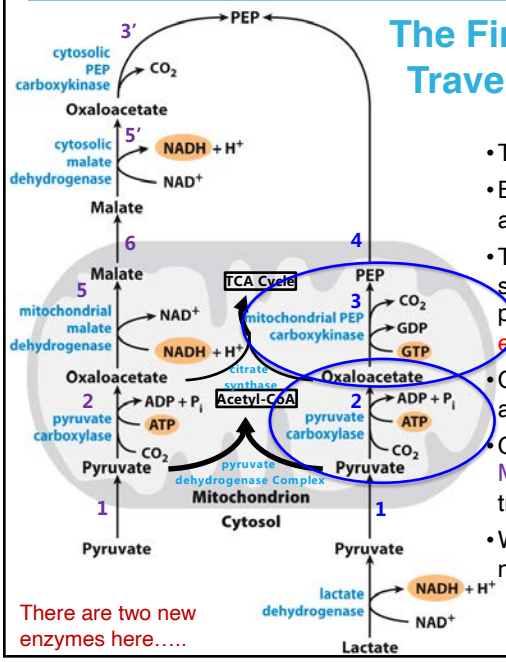
Favorable energetics for Calvin Cycle

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 + P_i
3. Glc 6-P→ glucose + P_i

Gluconeogenesis



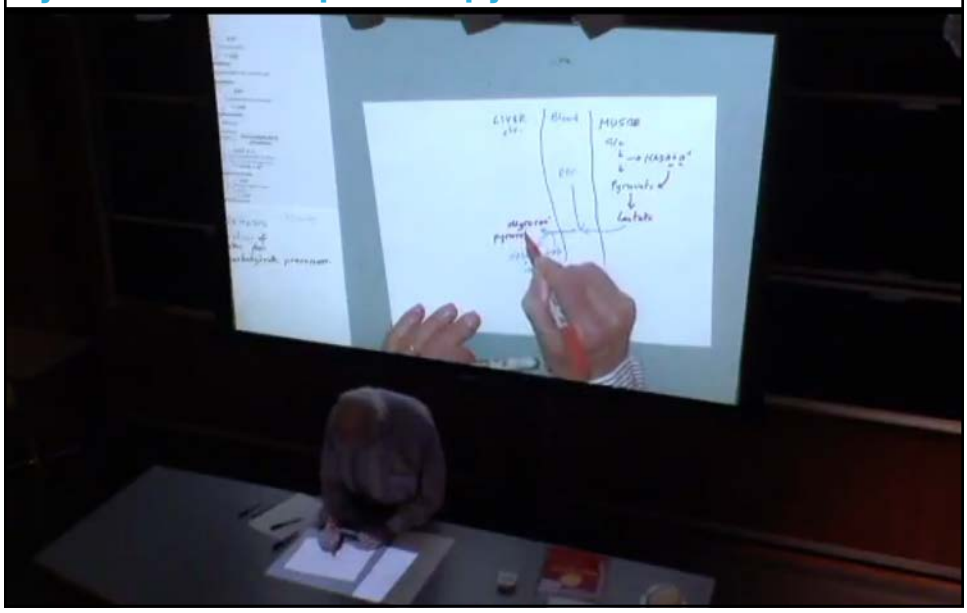
There are two new enzymes here…..

The First Gluconeogenic Steps Travel Through Mitochondria

- There are **two** ways from pyruvate to PEP.
- 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, while oxaloacetate cannot escape.
- Oxaloacetate can be utilized in the citric acid cycle (Kreb's cycle) if needed.
- Oxaloacetate can be converted to PEP or Malate in the mitochondria, then transported to cytosol for gluconeogenesis.
- Will discuss the decision that pyruvate must make later…..

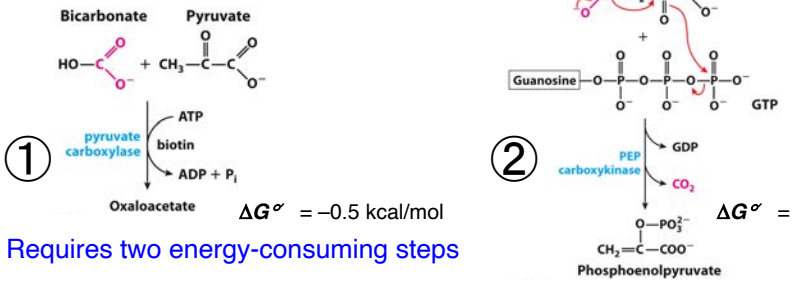
Gluconeogenesis

Pyruvate to Phosphoenolpyruvate



Gluconeogenesis

Pyruvate to Phosphoenolpyruvate

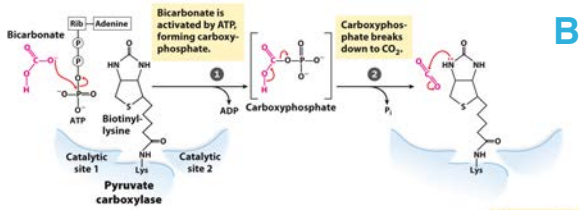


- Requires two energy-consuming steps
- The first step, pyruvate carboxylase (PC) converts pyruvate to oxaloacetate.
  - carboxylation using a biotin cofactor
  - This enzyme is only in the mitochondria; requires transport of pyruvate
- The second step, phosphoenolpyruvate carboxykinase (PEPCK) converts oxaloacetate to PEP.
  - phosphorylation from GTP and decarboxylation
  - occurs in mitochondria or cytosol depending on the organism
- During this 2-step conversion, the same carbon from CO_2 is added and immediately removed from the structure.

Lets look at the PC mechanism more closely…..

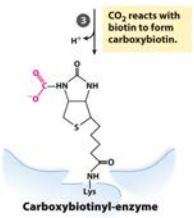
Gluconeogenesis

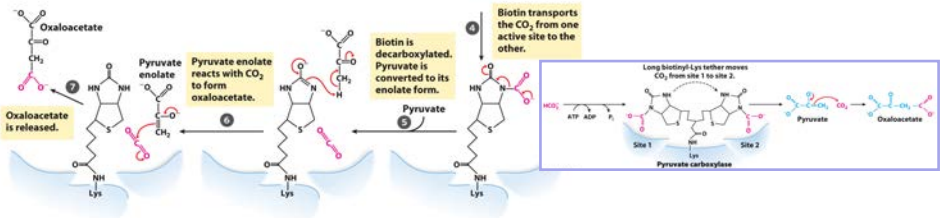
Biotin is a CO_2 Carrier



Pyruvate Carboxylase

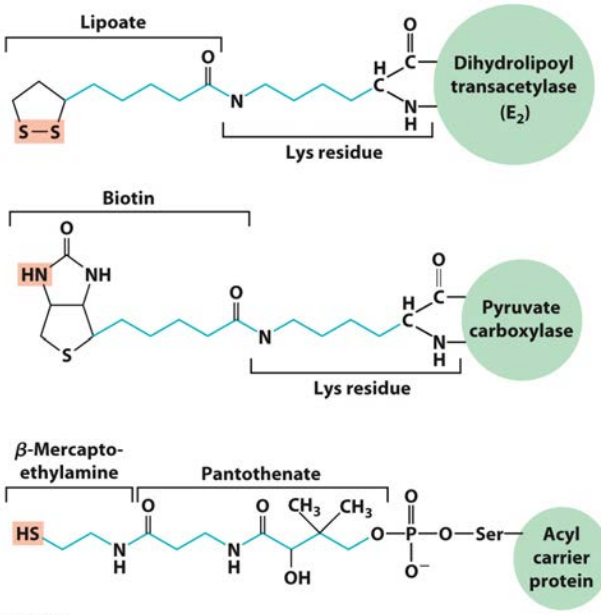
Mechanism





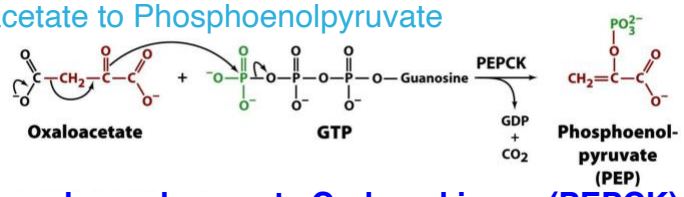
Gluconeogenesis

Biological Tethers Allow Flexibility



Gluconeogenesis

Oxaloacetate to Phosphoenolpyruvate

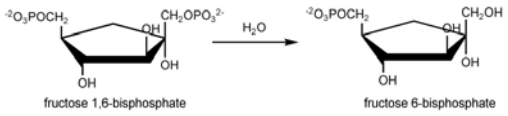


Phosphoenolpyruvate Carboxykinase (PEPCK)

Phosphoenolpyruvate to Fru 6-P

[PEP →(−3) 2PGA →(−0.5) 3PGA →(−1) 1,3BPGA →(0) GA3P →(−2) DHAP →(+5) Fru 1,6P_2] (−1.3)

Fructose 1,6-bisphosphatase



$\Delta G^{\circ\prime}$ = –4 kcal/mol

- Catalyze reverse reaction of PFK in glycolysis
- Fructose 1,6-bisphosphate → fructose 6-phosphate
  - by fructose 1,6-bisphosphatase-1
  - coordinately/oppositely regulated with PFK
  - cleaves phosphate with water
  - DOES NOT generate ATP

Glucose 6-phosphatase

$\Delta G^{\circ\prime}$ = –3.3 kcal/mol

Glucose 6-phosphate → glucose

- Water hydrolyzes the His-P_i
- DOES NOT generate ATP

Gluconeogenesis

Why do we need glucose?

RECALL:

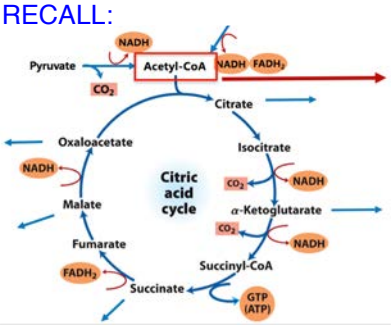


TABLE 14-4 Glucogenic Amino Acids, Grouped by Site of Entry

Pyruvate	**Succinyl-CoA**
Alanine	Isoleucine[a]
Cysteine	Methionine
Glycine	Threonine
Serine	Valine
Threonine	**Fumarate**
Tryptophan[a]	Phenylalanine[a]
α-Ketoglutarate	Tyrosine[a]
Arginine	**Oxaloacetate**
Glutamate	Asparagine
Glutamine	Aspartate
Histidine	
Proline	

Note: All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis.
[a]These amino acids are also ketogenic (see Fig. 18-15).

- Physiologically necessary: Brain, nervous system, and red blood cells generate ATP ONLY from glucose.
- When we can't get it from pyruvate, amino acids are utilized, which allows generation of glucose when glycogen stores are depleted:
  - during starvation
  - during vigorous exercise
  - can generate glucose from amino acids, but not fatty acids
- Costs 4 ATP, 2 GTP, and 2 NADH. Net reaction:

$\Delta G^{\circ\prime}$ = –9 kcal/mol

2 Pyruvate + 4 ATP + 2 GTP + 2 NADH + 2 H^+ + 4 H_2O →

Glucose + 4 ADP + 2 GDP + 6 P_i + 2 NAD^+

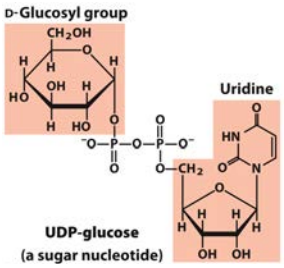
Glycogen Synthesis

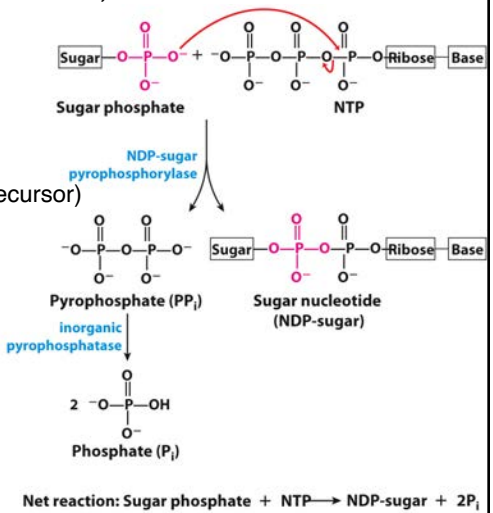
Storing a ready-reserve of carbohydrate

Glycogen Synthesis

- Synthesis of glycogen requires two enzymes, whereas glycogen degradation, only used phosphorylase. Both pathways use α-phosphoglucomutase; the start and end junction is Glc 1-P.

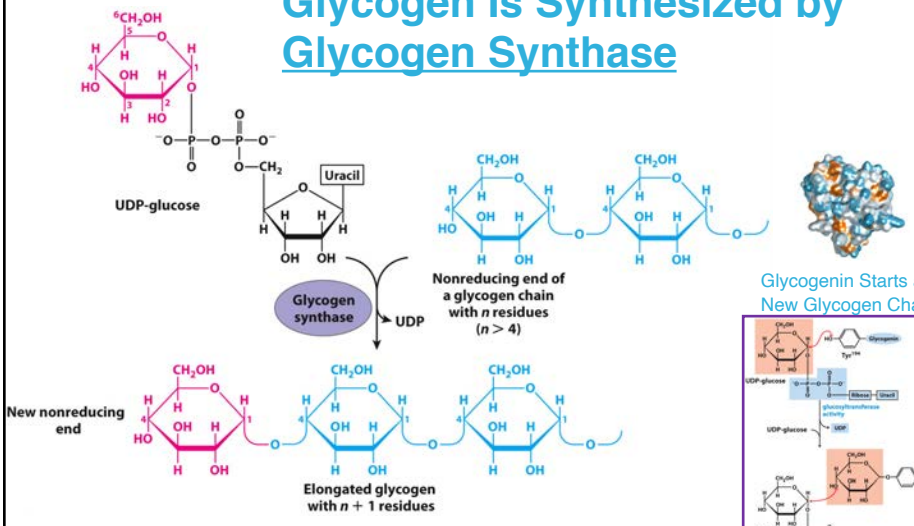
- Blood glucose must be:
  - Phosphorylated: Glc → Glc-6-P
  - Then converted: Glc 6-P → Glc 1-P
  - Activated with UDP (UDP-Glc is the precursor)
  - Added to glycogen





Glycogen Synthesis

Glycogen Is Synthesized by Glycogen Synthase

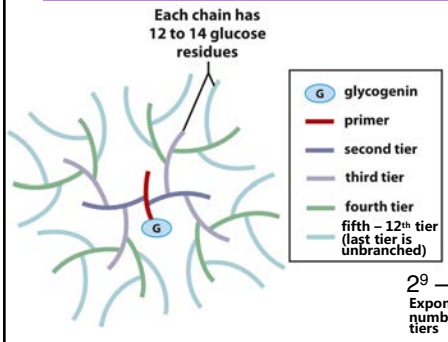


Glycogenin Starts a New Glycogen Chain

Takes 2 "ATPs" to put Glc into polymer (Glc1P & UDP-Glc), but get 33 ATP of potential energy.

Glycogen Synthesis

General Structure of a Glycogen Particle



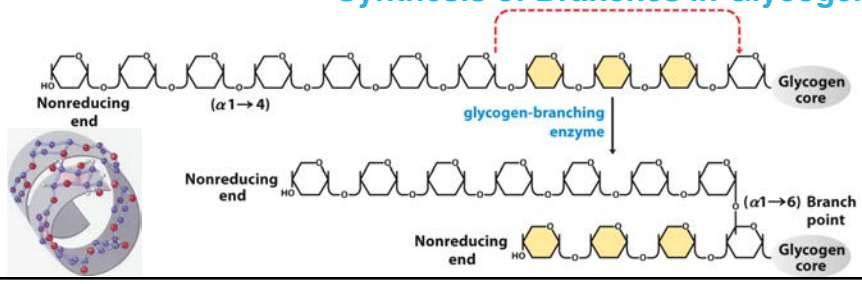
Calculate the number of Glc residues in a glycogen molecule:

$2^9 - 2^{12}$ x 12-14 = 6,000–57,000 Glc per glycogen

Exponent= number of tiers

(MW = $10^6 - 10^7$)

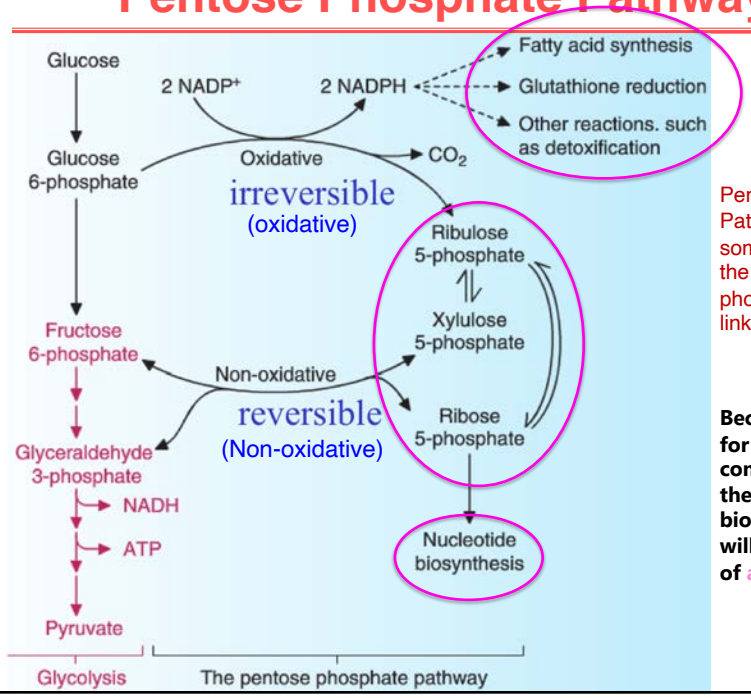
Synthesis of Branches in Glycogen



Pentose Phosphate Pathway

Providing reduced electrons and ribose

Pentose Phosphate Pathway



Pentose Phosphate Pathway, sometimes called the pentose-phosphate shunt, is linked to Glycolysis

Because it provides for essential components of these biomolecules, we will consider it part of anabolism.

Pentose Phosphate Pathway