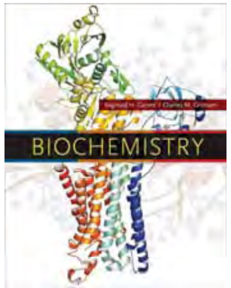
Chapter 22



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Gluconeogenesis, Glycogen metabolism, and the Pentose Phosphate Pathway

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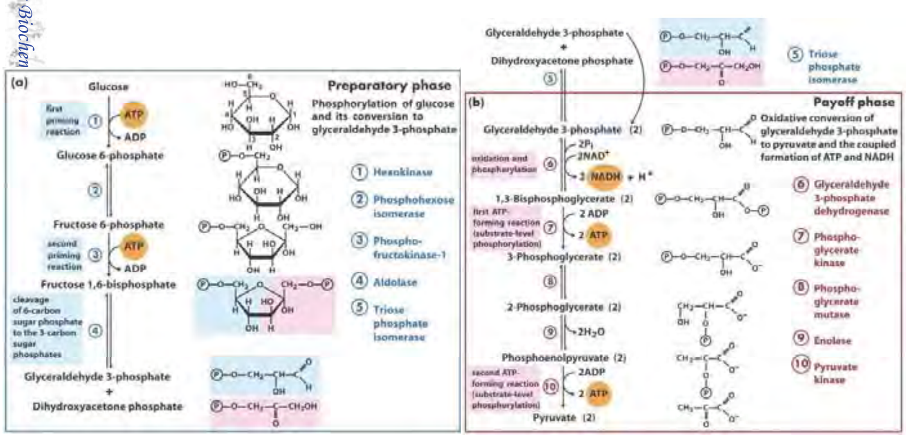
Before the class

- Can you tell the ten steps of glycolysis?
- Do you know how glucoses are synthesized?
- Do you know how glycogen is synthesized?
- Do you know how riboses are synthesized?

Outline

- Part 1
  - Review of the Glycolysis
  - Glyconeogenesis
- Part 2
  - Glycogen metabolism
  - Pentose phosphate pathway

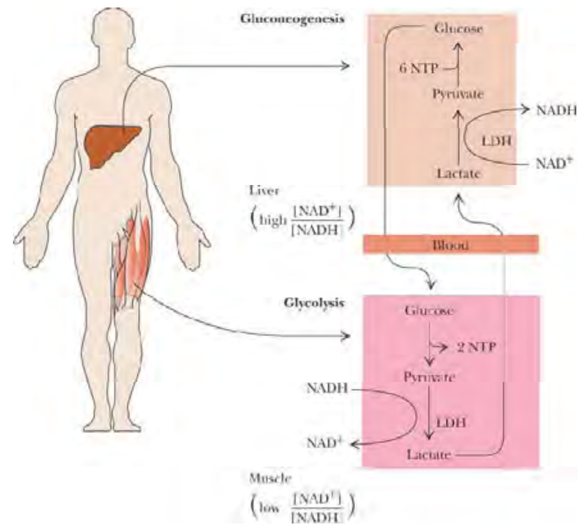
10 Steps of glycolysis



Gluconeogenesis occurs in..

- Mainly in liver and kidney
- Organs consuming the most glucose carry out very little glucose synthesis (brain, muscle)
- Pyruvate or lactate transfers to liver and kidney to produce glucose

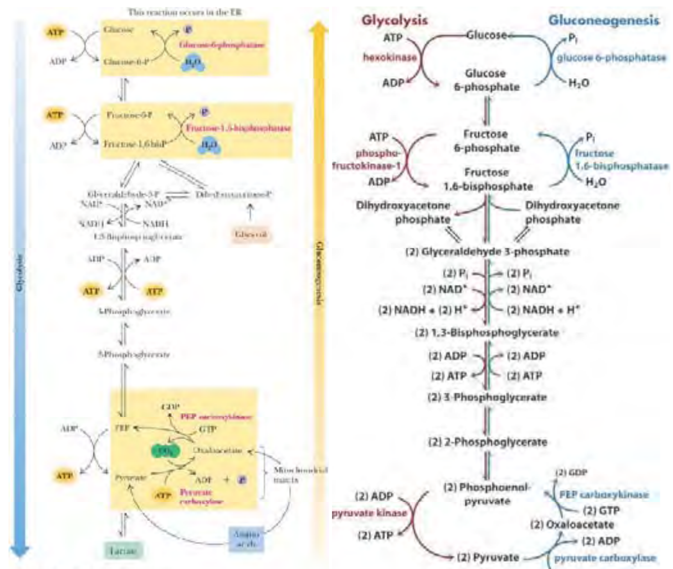
Cori cycle



Glycolysis and Gluconeogenesis

- Not just reverse reaction…
  - Reversed glycolysis would be endergonic..
    - Glycolysis has a ΔG = -74 kJ/mol
  - Their regulation must be a reciprocal fashion..

Something borrowed, something new



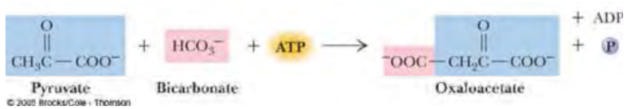
Control points of glycolysis

- Rx 1. The first priming reaction
- Rx 3: Phosphofructokinase
- Rx 10: Pyruvate Kinase
- Three exergonic reactions…..
  Replaced by three different pathways
  (4 reactions) in gluconeogenesis.

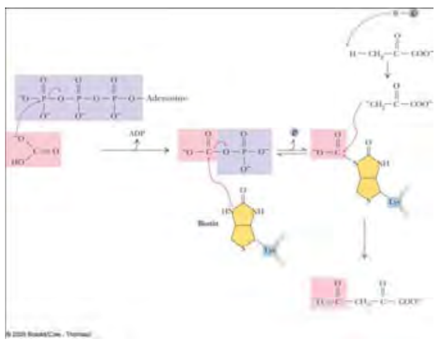
Start point of Gluconeogenesis

- Pyruvate to PEP
- Two reactions involved
  - Pyruvate to oxaloacetate (by pyruvate carboxylase)
  - Oxaloacetate to PEP (by PEP carboxykinase)
- ΔG close to zero

Unique reaction 1



- Pyruvate carboxylase is a biotin-dependent enzyme.

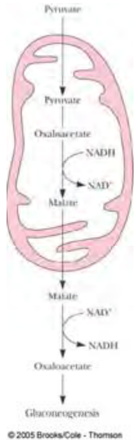


Regulation of pyruvate carboxylase

- Allosteric control
  - Acyl-CoA derivatives are activators in the carboxylation of biotin reaction part.
  - Reason:
    - Acetyl-CoA abundant: activate pyruvate carboxylase for Gluconeogenesis or anaplerotic reaction for OAA.
    - Acetyl-CoA deficient: inactivate pyruvate carboxylase; pyruvate enters TCA cycle

Regulation of pyruvate carboxylase

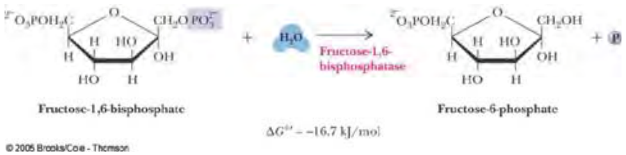
- Compartmentation
- Pyrovate carboxylase only found in matrix
- PEP carboxykinase appeared in cytosol or mitochondria, however, OAA cannot pass the membrane of mitochondria.
- In human liver, PEP carboxykinase appeared both in cytosol or mitochondria
- In tissues expressing PEP carboxykinase only in the cytosol, OAA must convert into malate first.



Unique reaction II

- PEP is a high-energy metabolite.
- The energy for synthesis of PEP comes from:
  - Decarboxylation
  - High-energy phosphate consumption

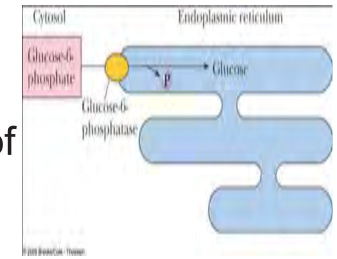
Unique reaction III

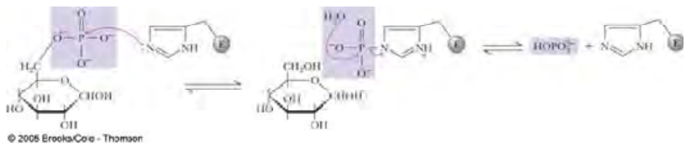


- Thermodynamic favorable reaction
- Allosteric control point
  - Inhibitors: fructose-2,6-bisphosphate; AMP

Unique reaction IV

- Glucose-6-phosphatase: convert G-6-P to glucose
- Present in the membrane of ER
- Phosphohistidine involved



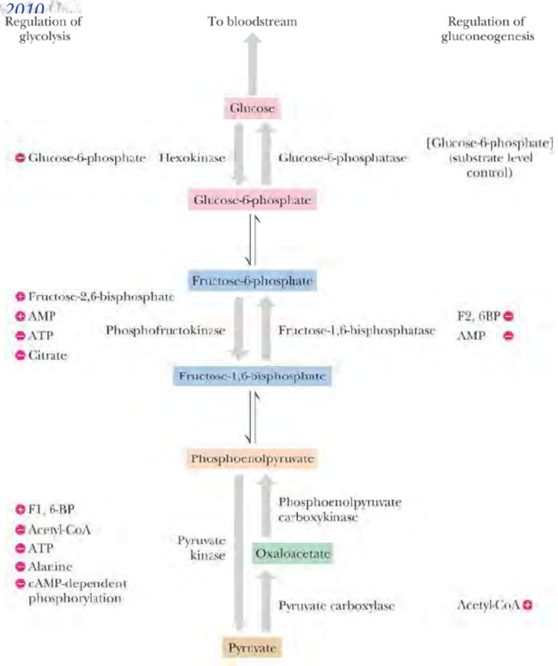


Coupling reactions drive gluconeogenesis

- 2 pyruvate + 4 ATP + 2 GTP +2 NADPH +2 H^+ + 6H_2O → glucose + 4ADP + 2 GDP +6 Pi +2 NAD^+
- ΔGo' -37.7 kJ/mol (reversed glycolysis will be +74 kJ/mol)

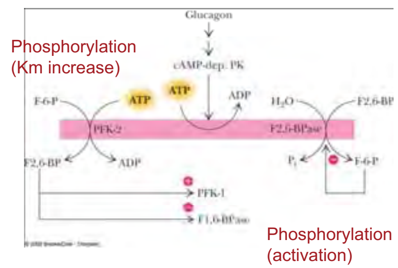
Regulation of Gluconeogenesis

- Reciprocal control, depend on energy status
- Substrate level control: ex. Glucose-6-phosphatase (high Km)
- Allosteric control:
  - Acetyl-coA: inhibit pyruvate kinase, pyruvate dehydrogenase; activate pyruvate carboxylase.
  - F-1,6-bisphosphatase: inhibited by AMP and activated by citrate. Opposite effect on phosphofructokinase.



Fructose-2,6-bisphosphate

- Synergistic with AMP
- F-2,6-BP level is controlled by a bifunction protein: phosphofructokinase-2 (PFK-2)/fructose-2,6-bisphosphatase (F-2,6-BPase)



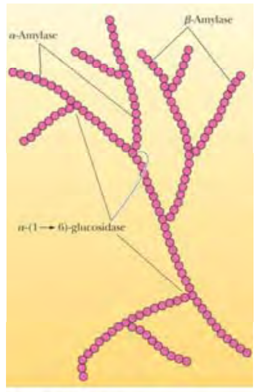
End of Part 1

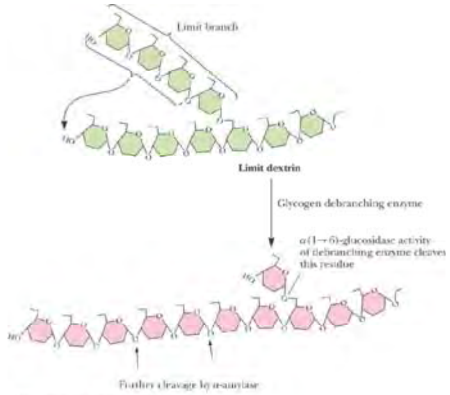
- Ask yourself…
  - Where does gluconeogenesis take place?
  - What is Cori cycle?
  - What are the 4 unique steps in gluconeogenesis?
  - What is the relationship between TCA cycle and gluconeogenesis?
  - What are the control points of gluconeogenesis?

21

Digestion of Glycogen/Starch

- α-amylase
- α (1→6) glucosidase debranching enzyme



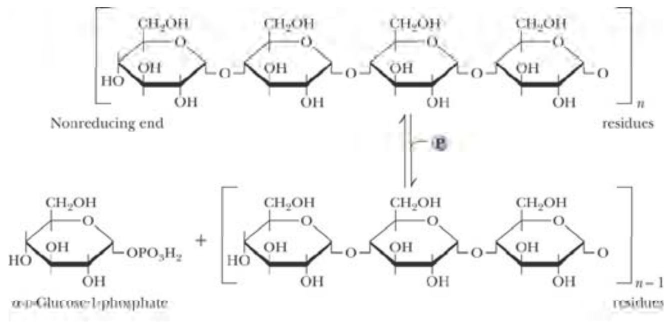


Metabolism of Tissue Glycogen

- Digest breakdown is not regulated.
- Tissue Glycogen is tightly regulated.
- Glycogen granule consists of glycogen, enzymes for synthesizing and catabolyzing, and enzymes for glycolysis

Phosphorolysis of glycogen

- Glycogen phosphorylase



Glycogen synthesis

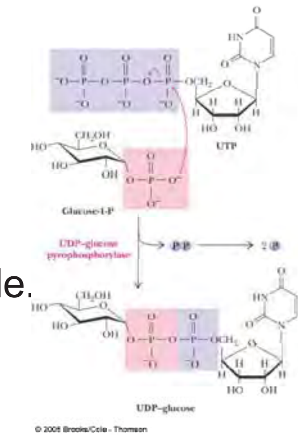
- Glucose units are transferred to glycogen chains.
- Transferred unit must be "activated"
  - Activated acetate: acetyl-CoA
  - Activated phosphate: ATP
  - Activated sugar: sugar nucleotide (UDP-glucose)

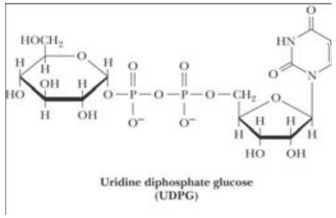
Synthesis of UDP-glucose

- UDP-glucose pyrophosphorylase

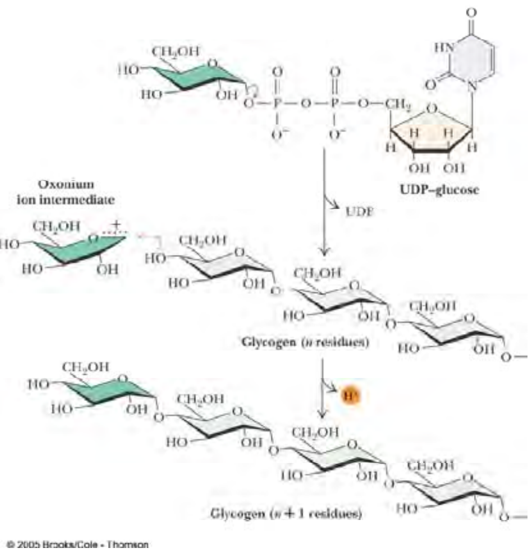
G-1-P + UTP → UDP-glucose + PPi

- Pyrophosphate hydrolysis makes the reaction irreversible.



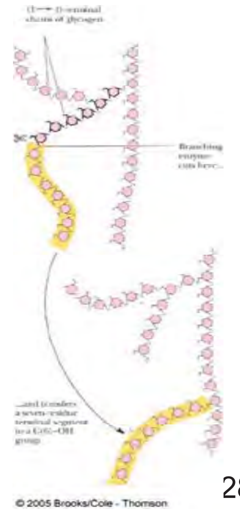


Elongation by glycogen synthase



Starting and branching of glycogen

- Glycogenin: first glucose join to the enzyme through the tyrosine –OH.
- Branching enzyme: amylo-(1,4→1,6)-transglycosylase (transfer 6-, 7- residues)



Glycogen metabolism is highly regulated

- Why?
  - Glucose conc. in circulating blood must be maintained at about 5 mM.
- Allosteric control
- Covalent modification (phosphorylation) by the action of hormone

Phosphorylation of Glycogen synthase

- Two forms of glycogen synthase:

Glycogen synthase I	dephosphorylation	G-6-P independent	active
Glycogen synthase II	phosphorylation	G-6-P dependent	Less active

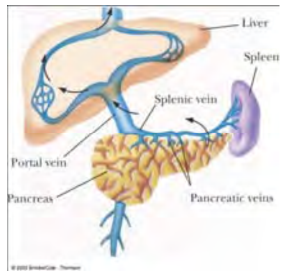
- Dephosphorylation by Phosphoprotein phosphatase-1: inactivates glycogen phosphorylase; activates glycogen synthase

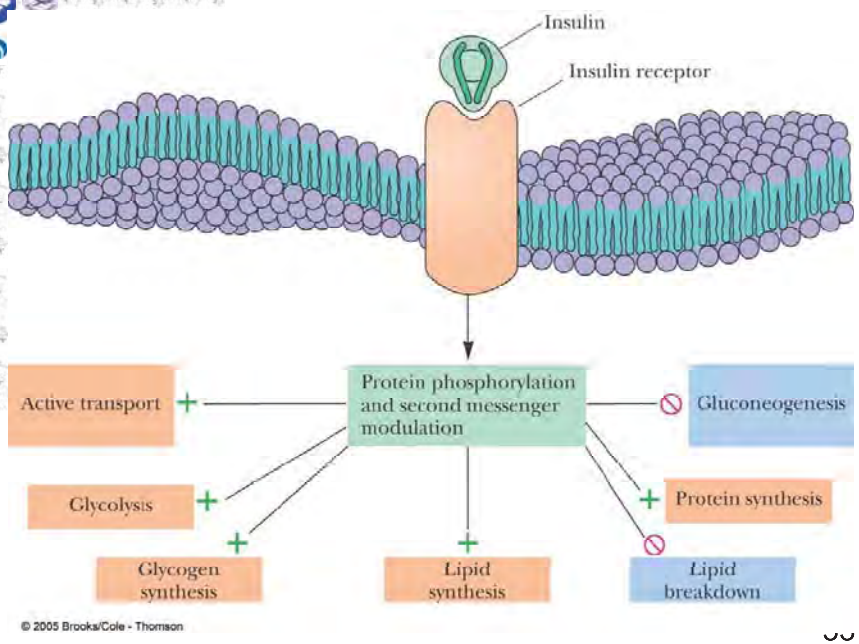
Hormones regulate glycogen synthesis and degradation

- Stimulating synthesis by insulin and glucocorticoid (醣皮質素)
- Stimulating degradation by glucagon (昇醣素) and epinephrine (腎上腺素)

Insulin

- Peptide hormone, secreted by beta cells in islets of Langerhans.
- Rapid lower blood glucose
  - Stimulates glycogen synthase and inhibit breakdown
  - Stimulates the active transport of glucose in muscle and adipose tissue
  - Increase cellular utilization of glucose (induce enzyme expression: glucokinase, phosphofructokinase, pyruvate kinase….)





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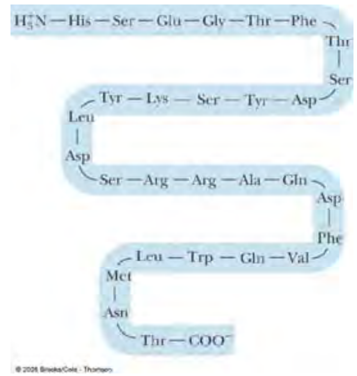
Lin's Biochemistry Lecture

Glucagon

- Peptide hormone, secreted by alpha cells in islets of Langerhans
- target on liver and adipose tissue
- Receptor on the cell surface and transfer the signal into glycogen metabolism enzymes



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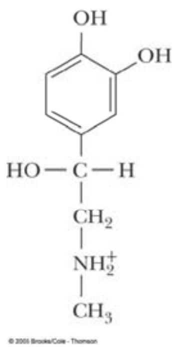
Epiphrine

- Signal from central nervous system
- Secreted from adrenal gland
- Acs on liver and muscles.



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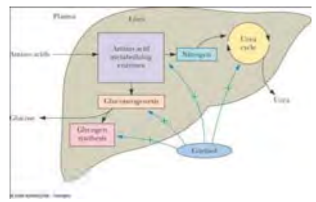
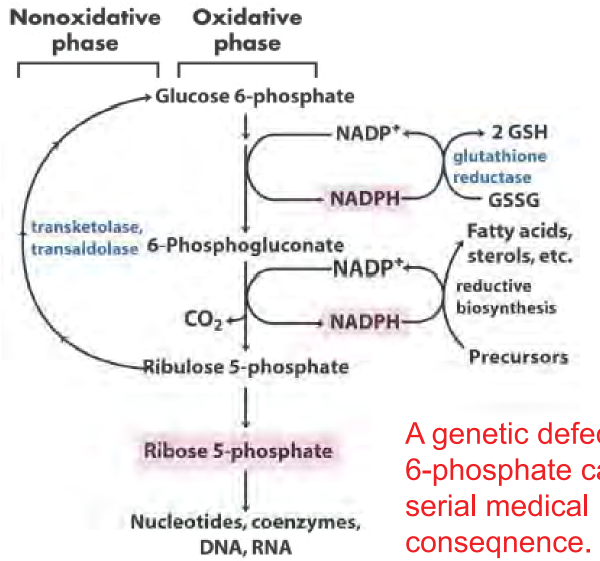
Cortisol and glucocorticoid

- Steroid hormones
- effects on liver:
  - stimulated gluconeogenesis and glycogen synthesis (gluconeogensis from amino acid at here)
- On skeletal muscle and adipose tissue:
  - Promote protein breakdown and decrease protein synthase



Pentose phosphate pathway (PPP) of glucose oxidation

- PPP is active in
  - Rapidly dividing cells, such as those of bone marrow, skin, and intestinal mucosa → use the pentose to make RNA, DNA, coenzymes
  - Cells extensive synthesis cells of fatty acid, cholesterol and steroid hormone, such as liver, adipose, lactating mammary, adrenal, and gonad → requires the NADPH provided by PPP.
  - Maintaining a reducing atmosphere (a high ratio of NADPH to $NADP^+$ and reduced to oxidized glutathione), erythrocytes and the cells of the lens and cornea can prevent or undo oxidative damage of free radicals to proteins, lipids and other sensitive molecules.



A genetic defect in glucose 6-phosphate can have a serial medical conseqnence.

Two phases of Pentose phosphate pathway

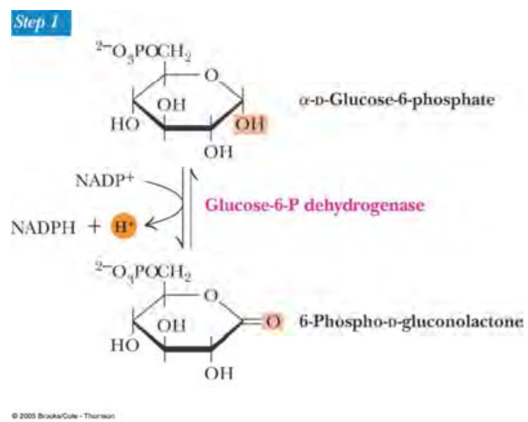
- First phase: the oxidative phase
- End produces: pentose 6-phosphate and NADPH.
- Overall reaction:

$$\text{Glucose 6-phosphate} + 2NADP^+ + H_2O \rightarrow \text{Ribose 5-phosphate} + CO_2 + 2NADPH + H^+$$

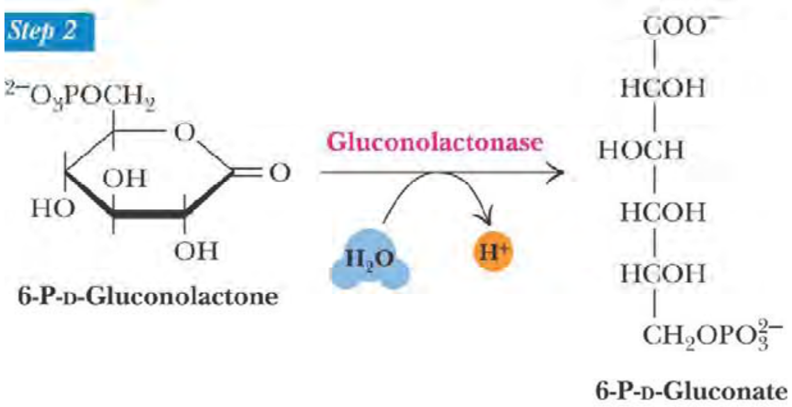
- , and in PPP.

Oxidative phase step 1: Glucose 6-phosphate dehydrogenase

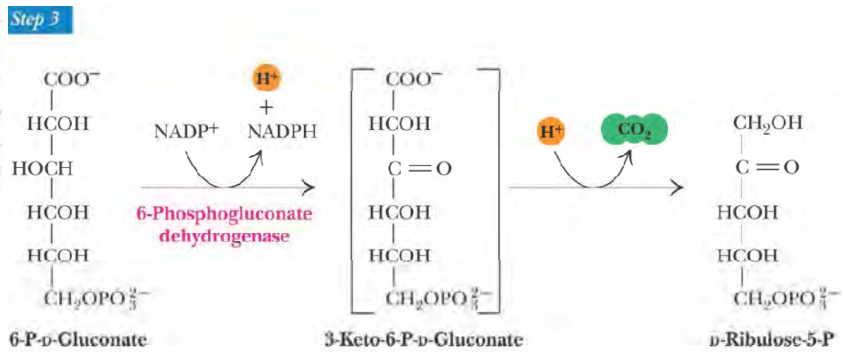
- Inhibited by NAPDH and acyl-CoA



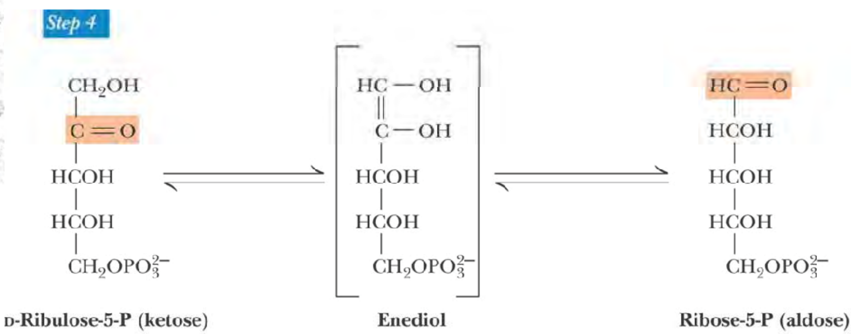
Oxidative phase step 2: gluconolactonase



Oxidative phase step 3: 6-phosphogluconate dehydrogenase



Oxidative phase step 4: phosphopentose isomerase

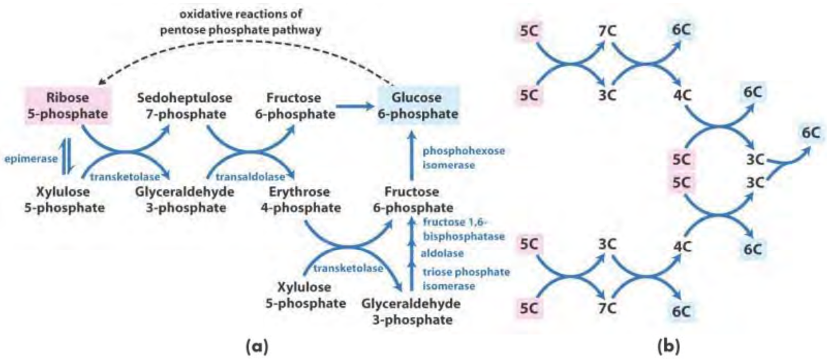


The nonoxidative phase recycles pentose phosphate to glucose 6-phosphate

- In tissues that requires primarily NADPH, the pentose phosphates produced in oxidative phase of PPP are recycled into glucose 6-phosphate.
- Nonoxidative reaction of the PPP: six pentose to five hexose.
- Continued recycling leads ultimately to the conversion of glucose 6-phosphate to six CO2

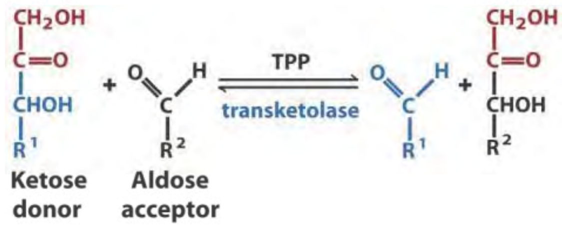
Second phase of PPP

- Nonoxidative phase



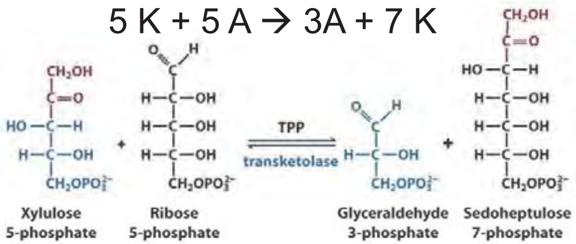
Transketolase

- Transketolase catalyzed the transfer of a two-carbon fragment from a ketose donor to an aldose acceptor
- Use TPP as coenzyme!

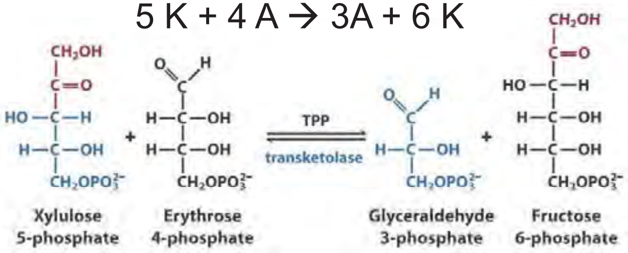


Two transketolase reactions

5 K + 5 A → 3A + 7 K



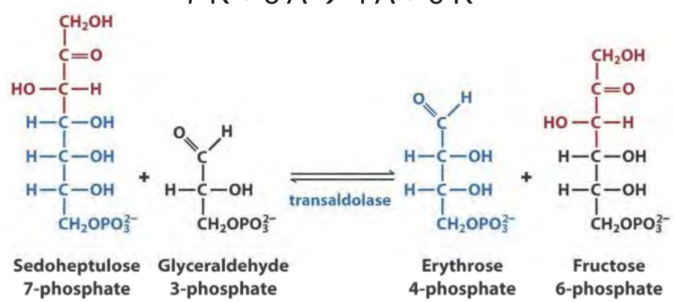
5 K + 4 A → 3A + 6 K



Transaldolase

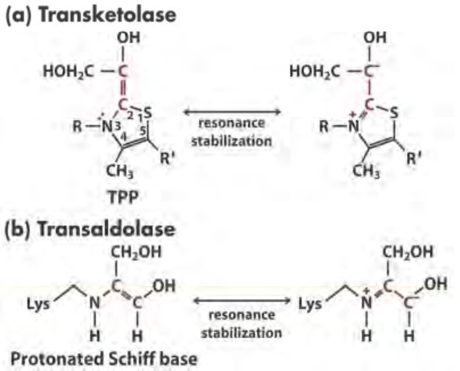
- Transaldolase catalyzes the transfer of a three-carbon fragment from a ketose to an aldose acceptor.

7 K + 3 A → 4 A + 6 K



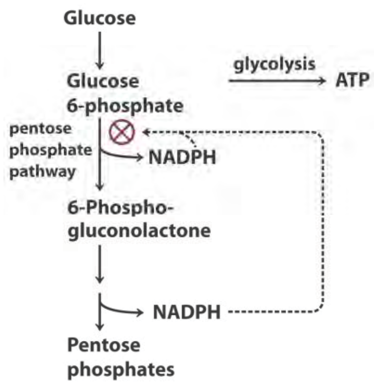
Transketolase *vs*. transaldolase

enzyme	Active center	Transferred group	reactions
Transketolase	TPP	2 C	5 K + 5 A 5 K + 4 A
transaldolase	Lys residue Schiff base	3C	7 K + 3 A



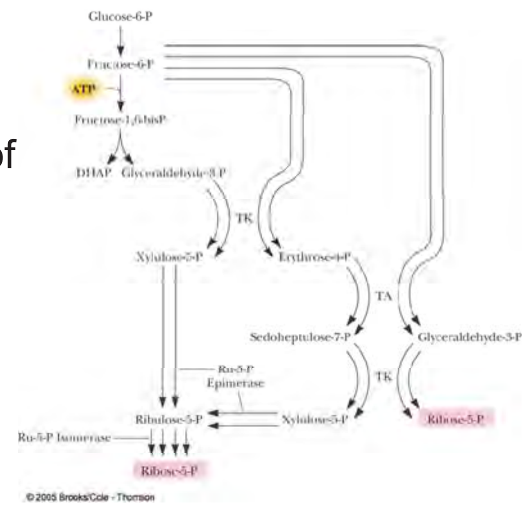
Overview of PPP

- The first two steps in the oxidation phase are oxidation with large, negative ΔG'°, and are essentially irreversible.
- The nonoxidation part of PPP are readily reversible and thus also provide a means of converting hexose phosphate to pentose phosphate.
- All the enzymes in PPP, glycolysis and gluconeogenesis are located in cytosol. These three pathways are connected through several shared intermediates and enzymes.
- **Glucose 6-phosphate is partitioned between glycolysis and PPP by the role of NADPH.**



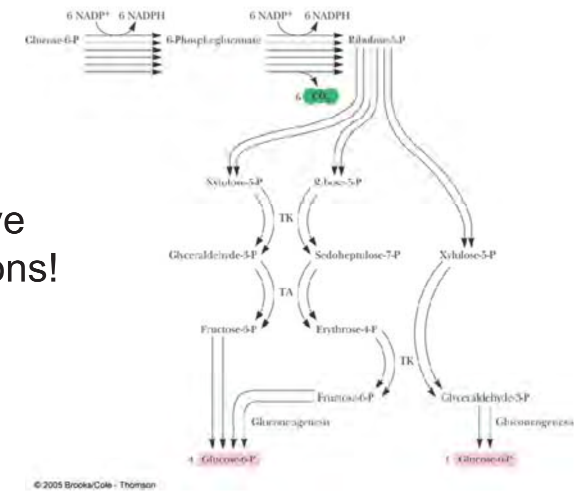
When cell needs ribose-5-P More

- No oxidative phase!
- Dark reaction of photosynthesis



When cell needs NADPH More

- More oxidative phase reactions!



End of Part 2

- Ask yourself…
  - How glycogen is metabolized inside the cell?
  - What are the hormones which could regulate glycogen metabolism?
  - What is the overall reaction of PPP?
  - What are the two phases of PPP?
  - What kinds of tissue are PPP actived?

End of the class

- You should have learned..
  - The 4 unique reaction of gluconeogenesis!
  - The regulation of gluconeogenesis!
  - The metabolism of glycogen metabolism!
  - The regulation of glycogen metabolism!
  - What is PPP?
  - The physiological meanings of PPP!