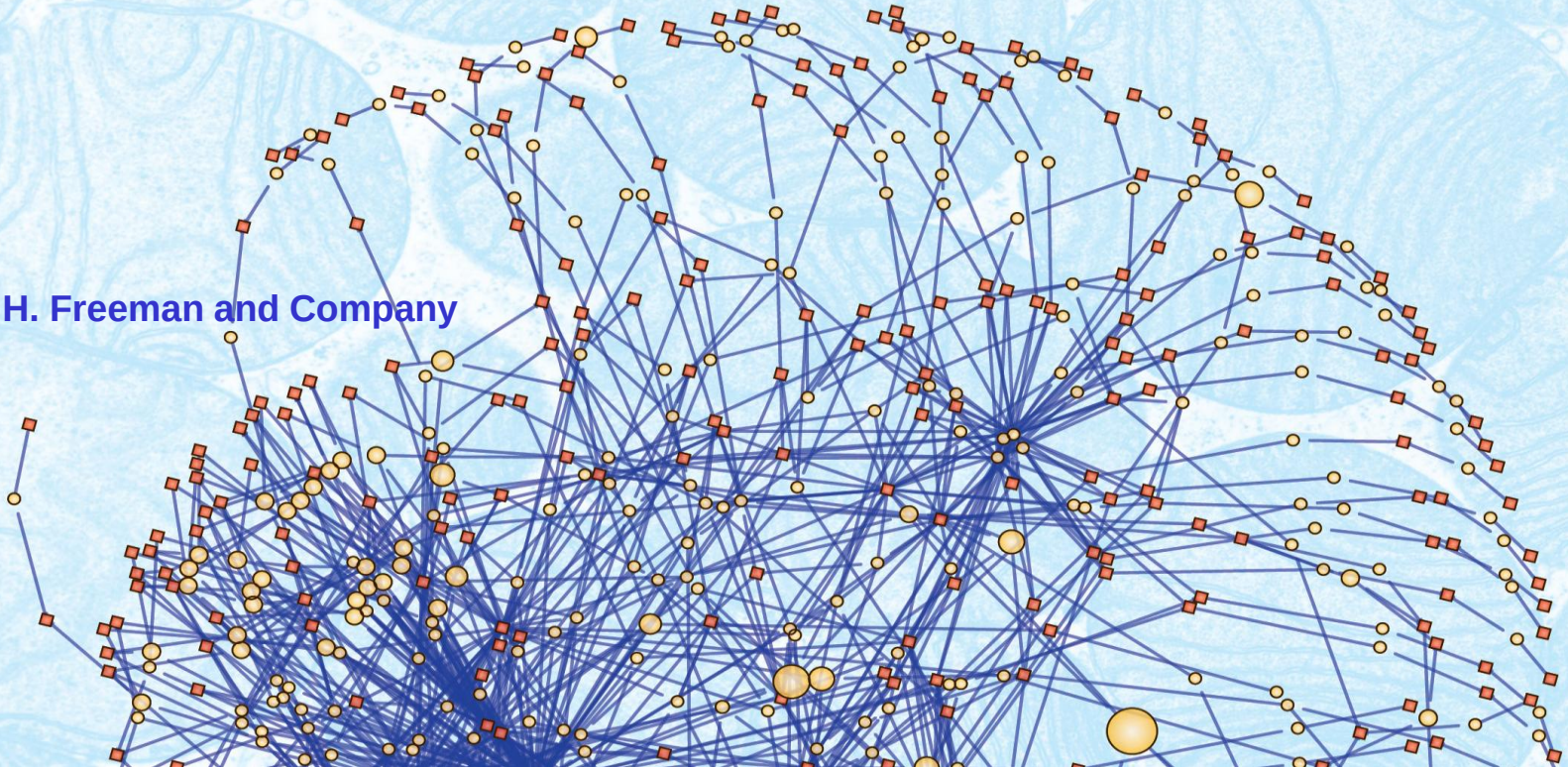
Lehninger

SIXTH EDITION

Principles of Biochemistry

David L. Nelson | Michael M. Cox

14| Glucose Utilization and Biosynthesis



Central Importance of Glucose

- Glucose is an excellent fuel
  - Yields good amount of energy upon oxidation ($\Delta G_{\text{complete oxidation}} = -2840$ kJ/mol)
  - Can be efficiently stored in the polymeric form
  - Many organisms and tissues can meet their energy needs on glucose only

- Glucose is a versatile biochemical precursor
  - Bacteria can use glucose to build the carbon skeletons of:
    - All the amino acids
    - Membrane lipids
    - Nucleotides in DNA and RNA
    - Cofactors needed for the metabolism

Four Major Pathways of Glucose Utilization

- Storage
  - Can be stored in the polymeric form (starch, glycogen)
  - When there's excess energy
- Glycolysis
  - Generates energy via oxidation of glucose
  - Short-term energy needs
- Pentose Phosphate Pathway
  - Generates NADPH via oxidation of glucose
  - For detoxification and the biosynthesis of lipids and nucleotides
- Synthesis of Structural Polysaccharides
  - For example, in cell walls of bacteria, fungi, and plants

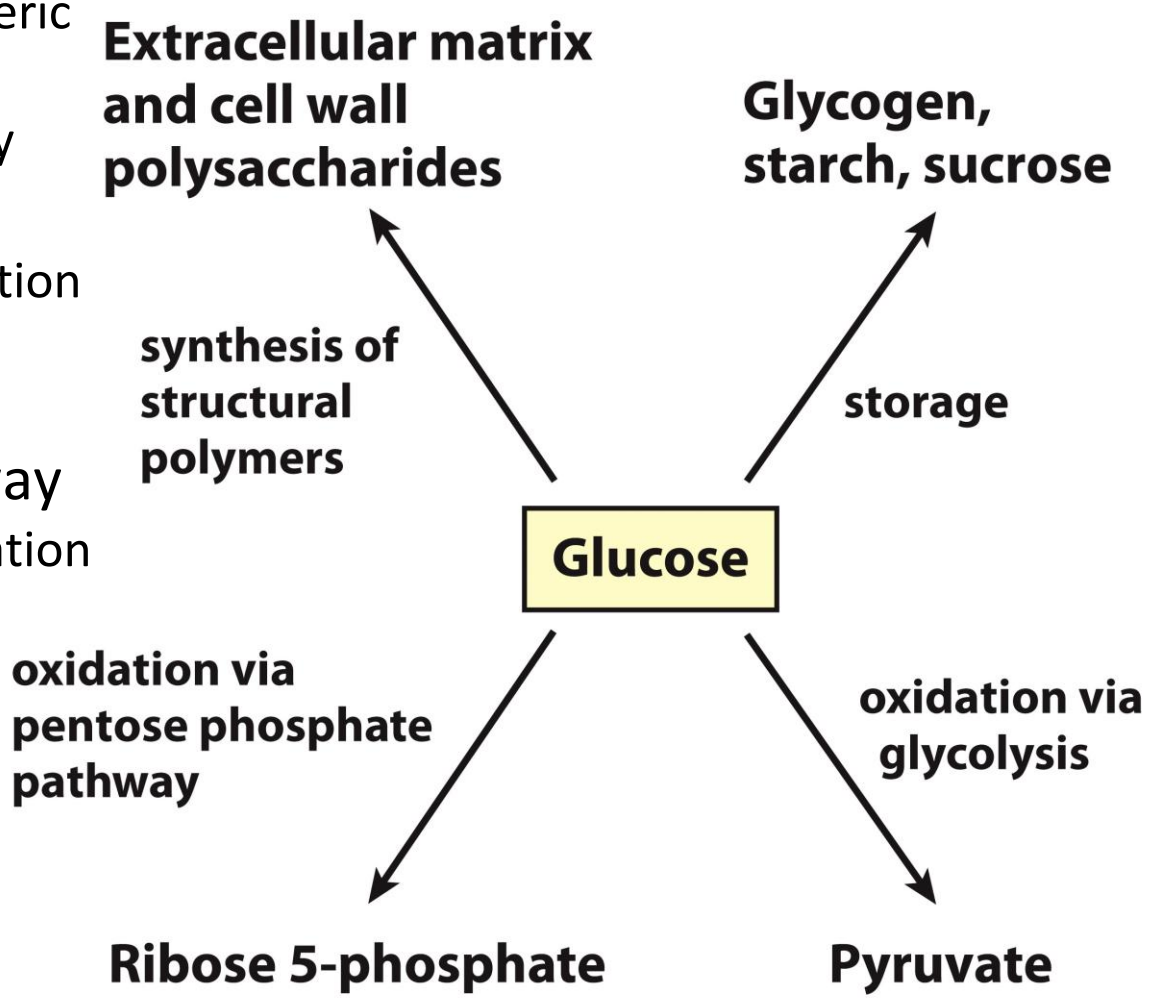


Figure 14-1
Lehninger Principles of Biochemistry, Sixth Edition

Glycolysis: Importance

- Almost universal central pathway of glucose catabolism
- Sequence of enzyme-catalyzed reactions by which glucose is converted into pyruvate
  - Pyruvate can be further aerobically oxidized
  - Pyruvate can be used as a precursor in biosynthesis

- Some of the oxidation-free energy is captured by the synthesis of ATP and NADH

- Research of glycolysis played a large role in the development of modern biochemistry
  - Understanding the role of coenzymes
  - Discovery of the pivotal role of ATP
  - Development of methods for enzyme purification
  - Inspiration for the next generations of biochemists

The 2 phases of glycolysis

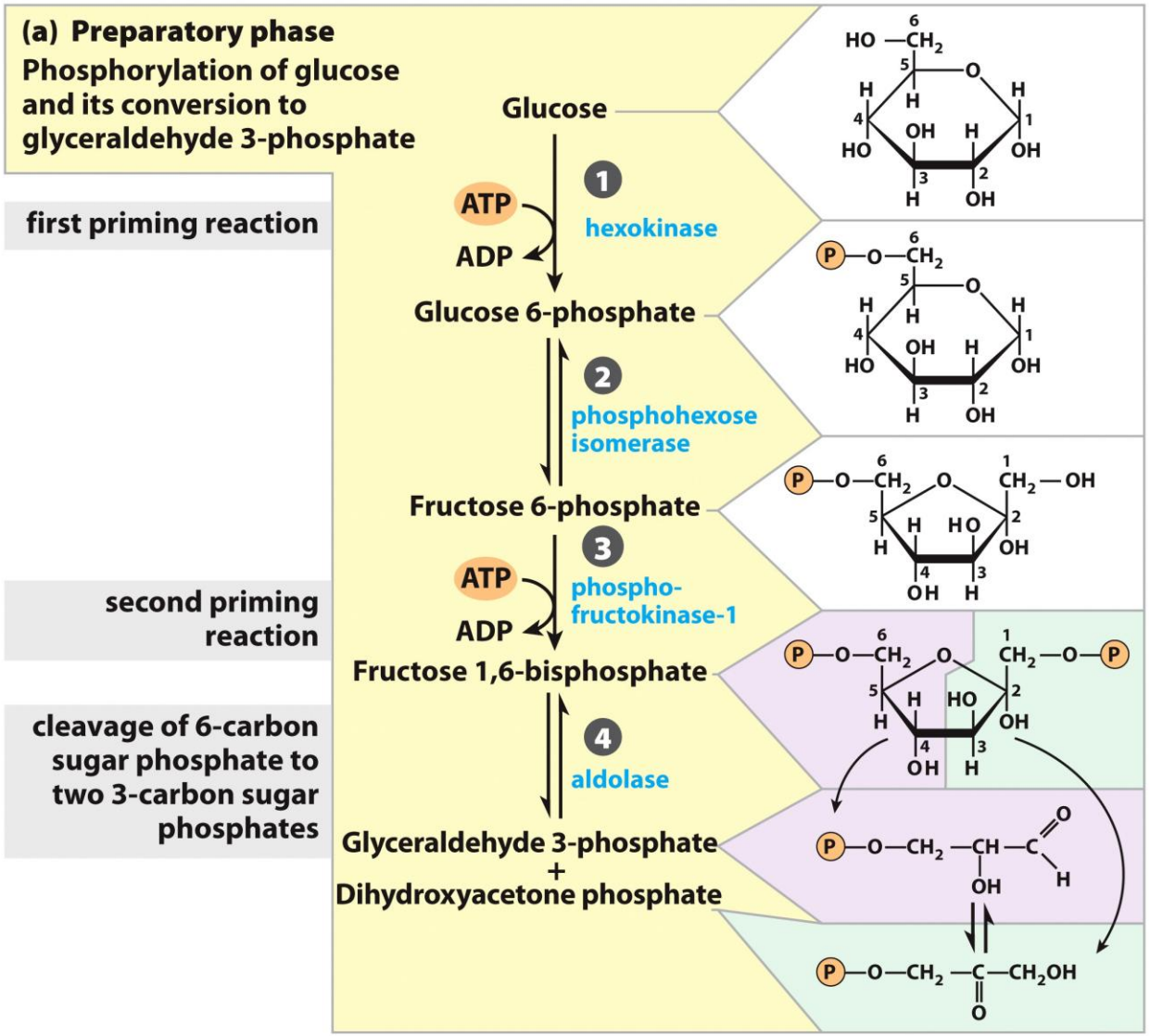
- In the evolution of life, glycolysis probably was one of the earliest energy-yielding pathways
- It developed before photosynthesis, when the atmosphere was still anaerobic

- Thus, the task upon early organisms was:
  How to extract free energy from glucose anaerobically?
- The solution:
  - First: Activate it by phosphorylation
  - Second: Collect energy from the high-energy metabolites
- Glycolysis is a sequence of 10 reactions, 5 are preparatory and 5 are energy-yielding

Glycolysis: The Preparatory Phase

2 ATP molecules are used to raise the free energy of the intermediates

*For **each molecule of glucose** that passes through the preparatory phase, **two molecules of glyceraldehyde 3-phosphate** are formed.*



The "*lysis*" step of glycolysis

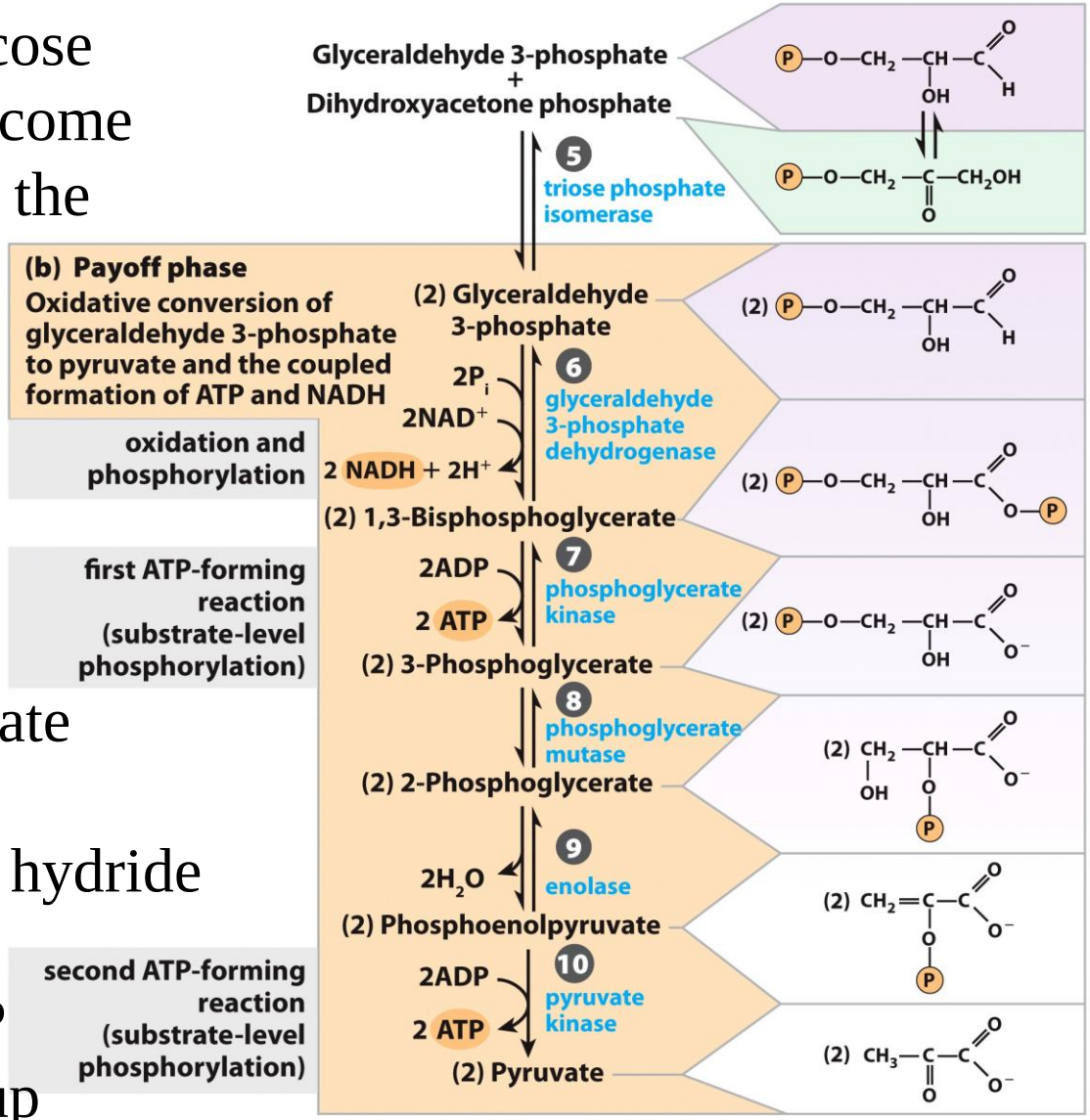
Figure 14-2 part 1
Lehninger Principles of Biochemistry, Sixth Edition

Glycolysis: The Payoff Phase

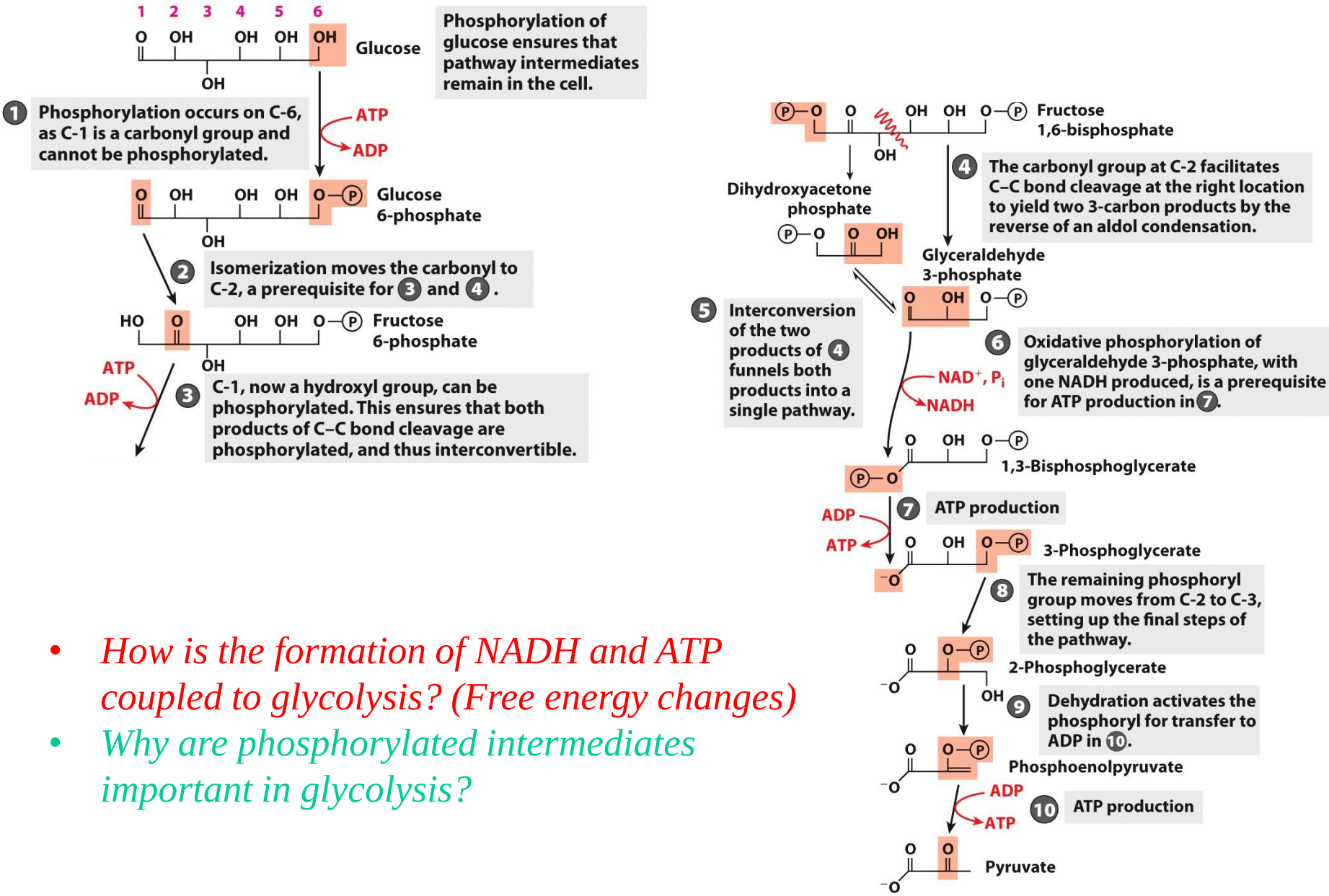
4 ATP are produced per glucose
2 ATP/glucose is the net outcome
Energy is also conserved by the formation of 2 NADH molecules

3 types of chemical transformations:

1. Breakage of glucose backbone to yield pyruvate (6C → 2x 3C)
2. Formation of NADH by hydride transfer to NAD^+
3. Phosphorylation of ADP by high phosphoryl group potential compounds to make ATP



Chemical Logic of Glycolysis



- *How is the formation of NADH and ATP coupled to glycolysis? (Free energy changes)*
- *Why are phosphorylated intermediates important in glycolysis?*

Glycolysis: Fates of Pyruvate

- In most organisms pyruvate is metabolized via one of three catabolic routes:

1. *Citric acid cycle:* pyruvate is oxidized and decarboxylated to release CO_2 (the electrons that are moving go through ETC in mito and are used to make ATP; aerobic conditions)
2. *Lactic acid fermentation:* after vigorous exercise, [O_2] in muscles is low (**hypoxia**) NADH cannot be reoxidized to NAD^+ for glycolysis to continue → pyruvate is reduced to lactate accepting electrons from NADH (regenerating NAD^+). Certain tissues (RBC and retina) ferment pyruvate into lactate even under aerobic conditions
3. *Alcohol fermentation:* some yeasts and plants can ferment pyruvate into ethanol and CO_2 (important for beverage production and baking)

- Pyruvate also some anabolic fates (can produce a.a. alanine or fatty acids)

Fates of Pyruvate

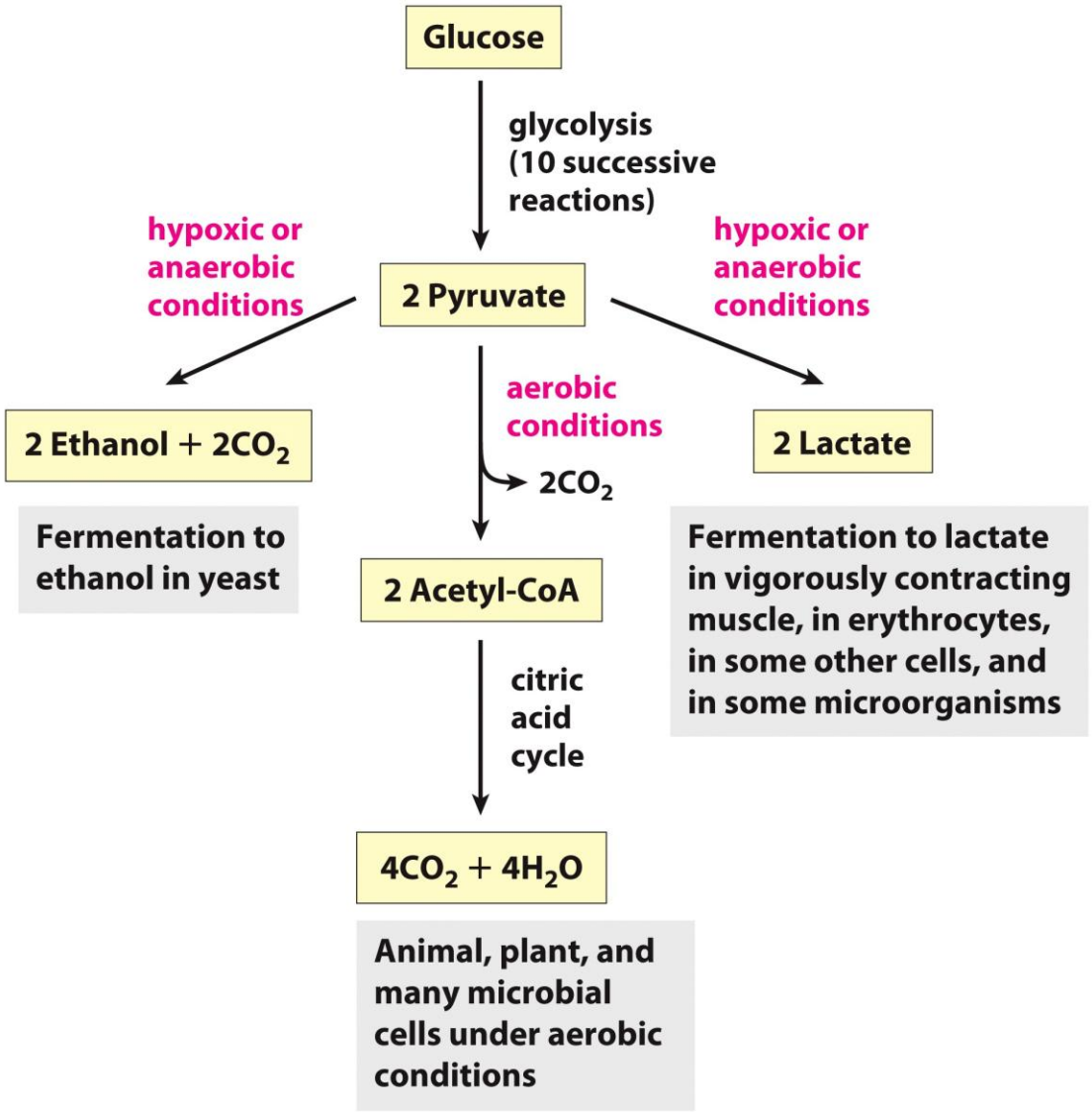
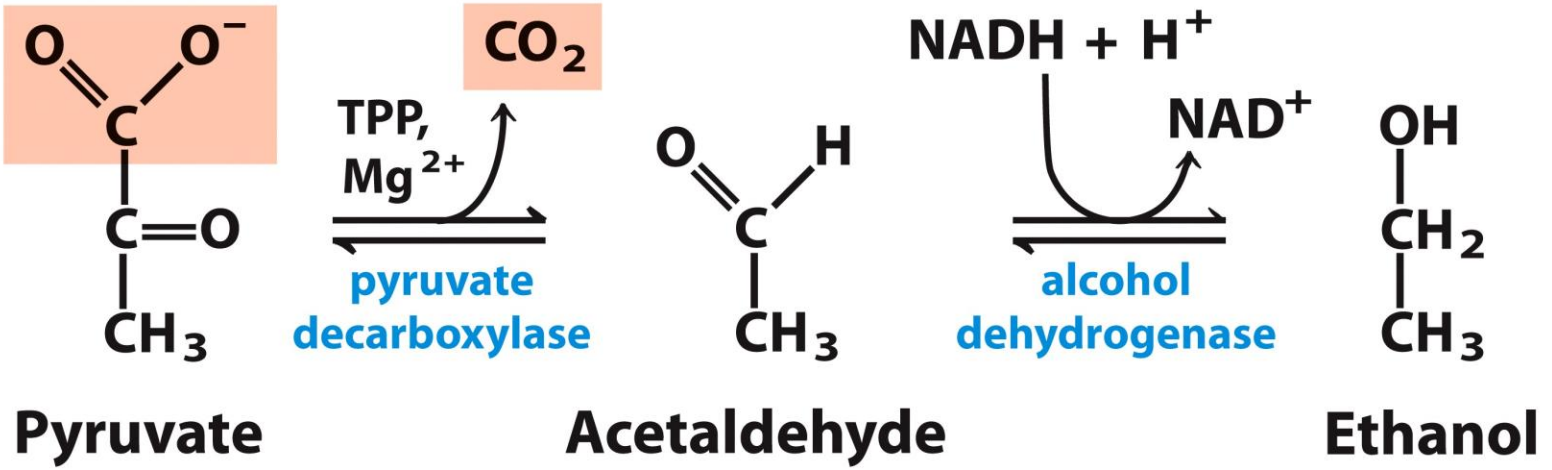


Figure 14-4
Lehninger Principles of Biochemistry, Sixth Edition

Anaerobic Glycolysis: Fermentation

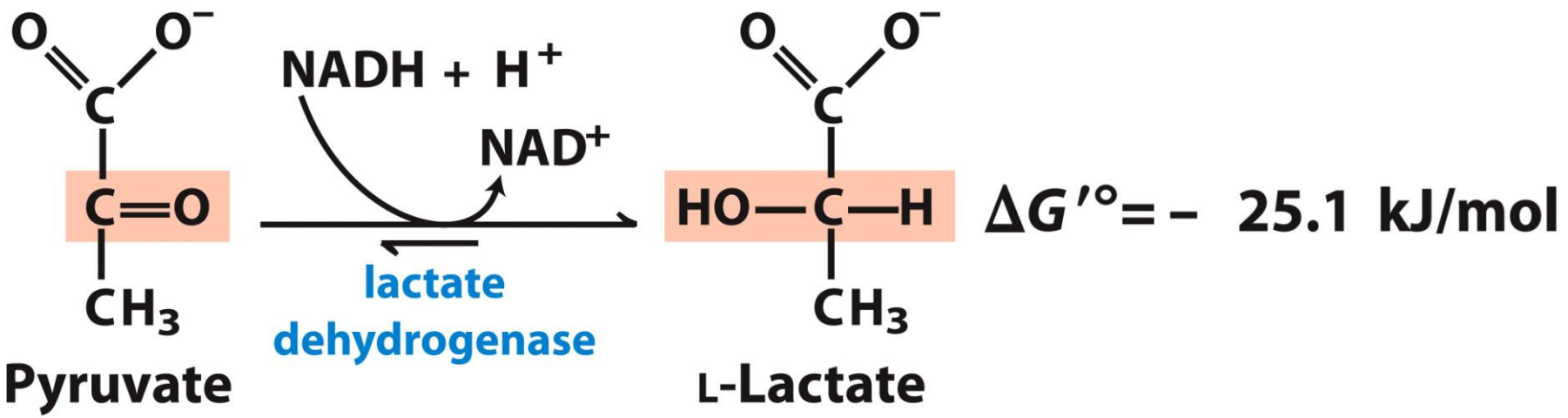
- *Generation of energy (ATP) without consuming oxygen or NAD^+*
- No net change in oxidation state of the sugars
- Reduction of pyruvate to another product
- Regenerates NAD^+ for further glycolysis under anaerobic conditions
- The process is used in the production of food from beer to yogurt to soy sauce

Yeast undergo Ethanol Fermentation



- Two-step reduction of pyruvate to ethanol, irreversible
- Humans do not have *pyruvate decarboxylase*
- Humans do express *alcohol dehydrogenase* for ethanol metabolism
- CO_2 produced in the first step is responsible for:
  - carbonation in beer
  - dough rising when baking bread
- Both steps require cofactors
  - Pyruvate decarboxylase: Mg^{2+} and thiamine pyrophosphate (TPP)
  - Alcohol dehydrogenase: Zn^{2+} and NADH

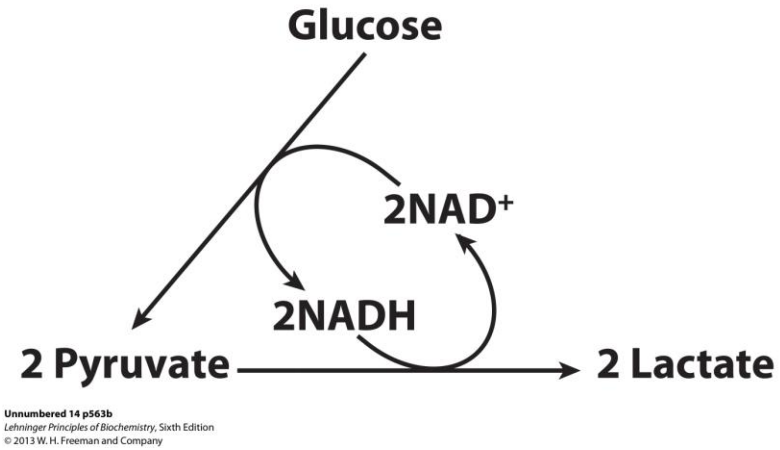
Animals undergo lactic acid fermentation



- Reduction of pyruvate to lactate, reversible
- Equilibrium favors lactate formation
- During strenuous exercise, lactate builds up in the muscle
  - Generally less than 1 minute (even most toned athletes cannot sprint at highest speeds for more than a minute!)
- The acidification of muscle prevents its continuous strenuous work

Lactic Acid Fermentation

- *No net change in NAD^+ or NADH levels*



Unnumbered 14 p563b
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

- Lactate can be transported to the liver to be converted to glucose (the Cori cycle)
- Requires a recovery time
  - High amount of oxygen consumption to fuel gluconeogenesis
  - Restores muscle glycogen stores
  - Heavy breathing is required to replenish oxygen to repay the "oxygen debt"

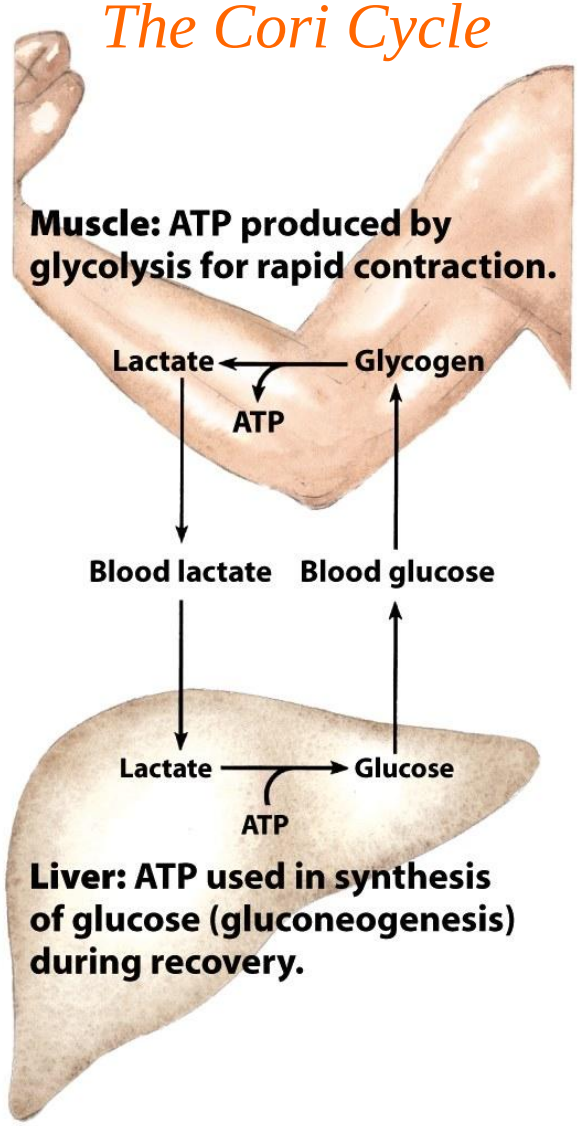
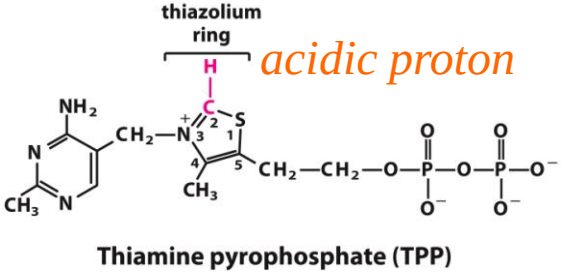


Figure 23-20
Lehninger Principles of Biochemistry, Fifth Edition
© 2008 W. H. Freeman and Company

TPP is a common acetaldehyde carrier



- Coenzyme derived from vitamin B_1 (thiamine)
- Lack of B_1 → *beriberi* (swelling, pain, paralysis and death)
- Cleavage of bonds adjacent to carbonyl groups
- Thiazolium ring of TPP stabilizes carbanion intermediates by providing an electrophilic structure into which the carbanion electrons can be delocalized by resonance "electron sinks"

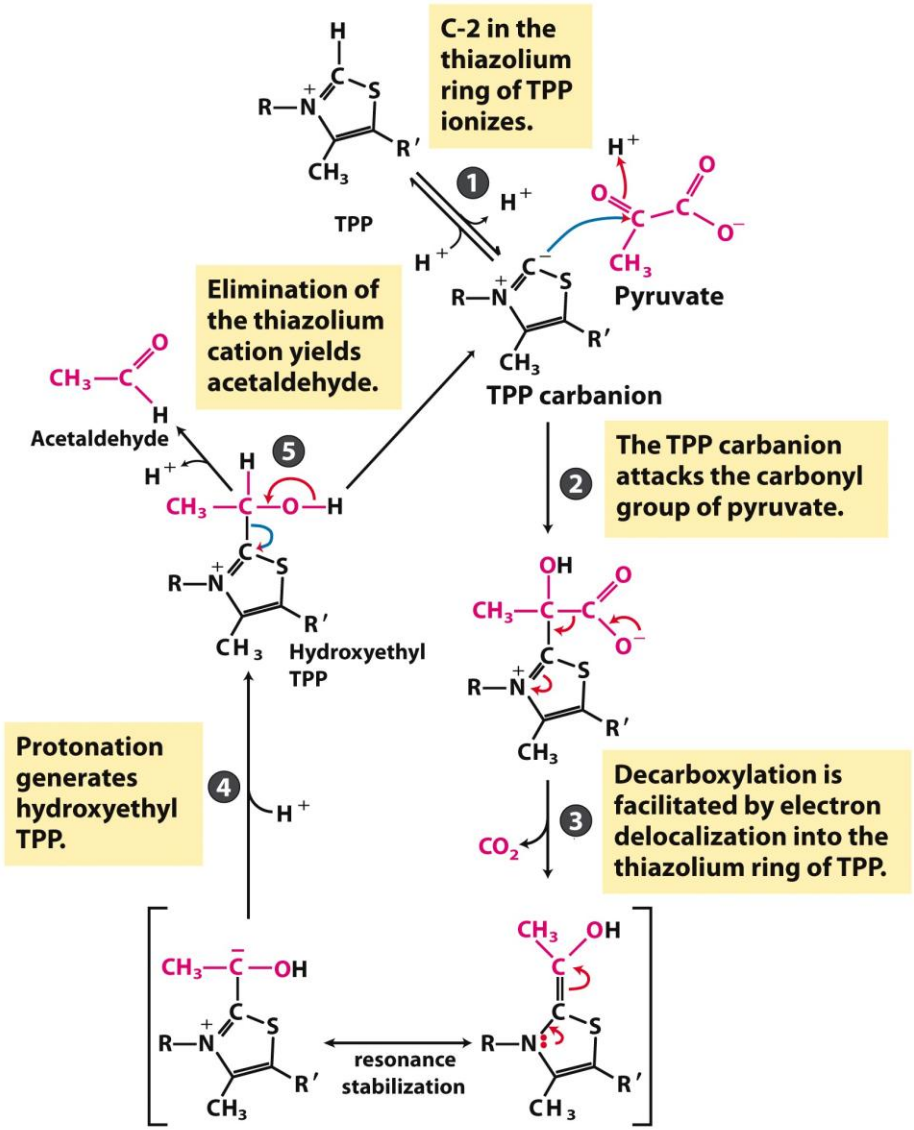
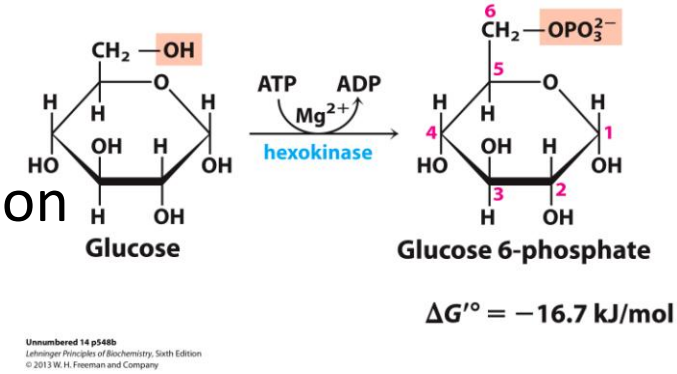


Figure 14-15c
Lehninger Principles of Biochemistry, Sixth Edition

The Preparatory Phase

Step 1: Phosphorylation of Glucose

- Rationale
  - Traps glucose inside the cell
  - Lowers intracellular glucose concentration to allow further uptake

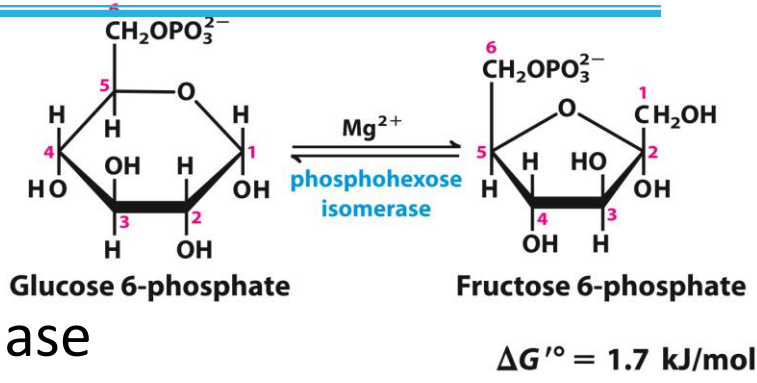


- This process uses the energy of ATP
- The first "priming" reaction
- Hexokinase in eukaryotes, and glucokinase in prokaryotes and liver (**isozymes**: 2 or more enzymes encoded in different genes but catalyze the same reaction)
- Soluble cytosolic enzyme (like all other glycolytic enzymes)
- Nucleophilic oxygen at C6 of glucose attacks the last (γ) phosphate of ATP
- ATP-bound Mg^{2+} facilitates this process by shielding the negative charges on ATP

- Highly thermodynamically favorable/irreversible
  - Regulated mainly by substrate inhibition

Step 2: Phosphohexose Isomerization

- Rationale
  - C1 of fructose is easier to phospho-rylate by PFK
  - Allows for symmetrical cleave by aldolase



- An aldose (glucose) can isomerize into a ketose (fructose) via an *enediol* intermediate
- The isomerization is catalyzed by the active-site glutamate, via general acid/base catalysis

- Slightly thermodynamically unfavorable/reversible
  - Very small positive $\Delta G'^{o}$ indicates that the reaction can proceed readily in either direction
  - Product concentration kept low to drive forward

Mechanism of Phosphohexose Isomerase

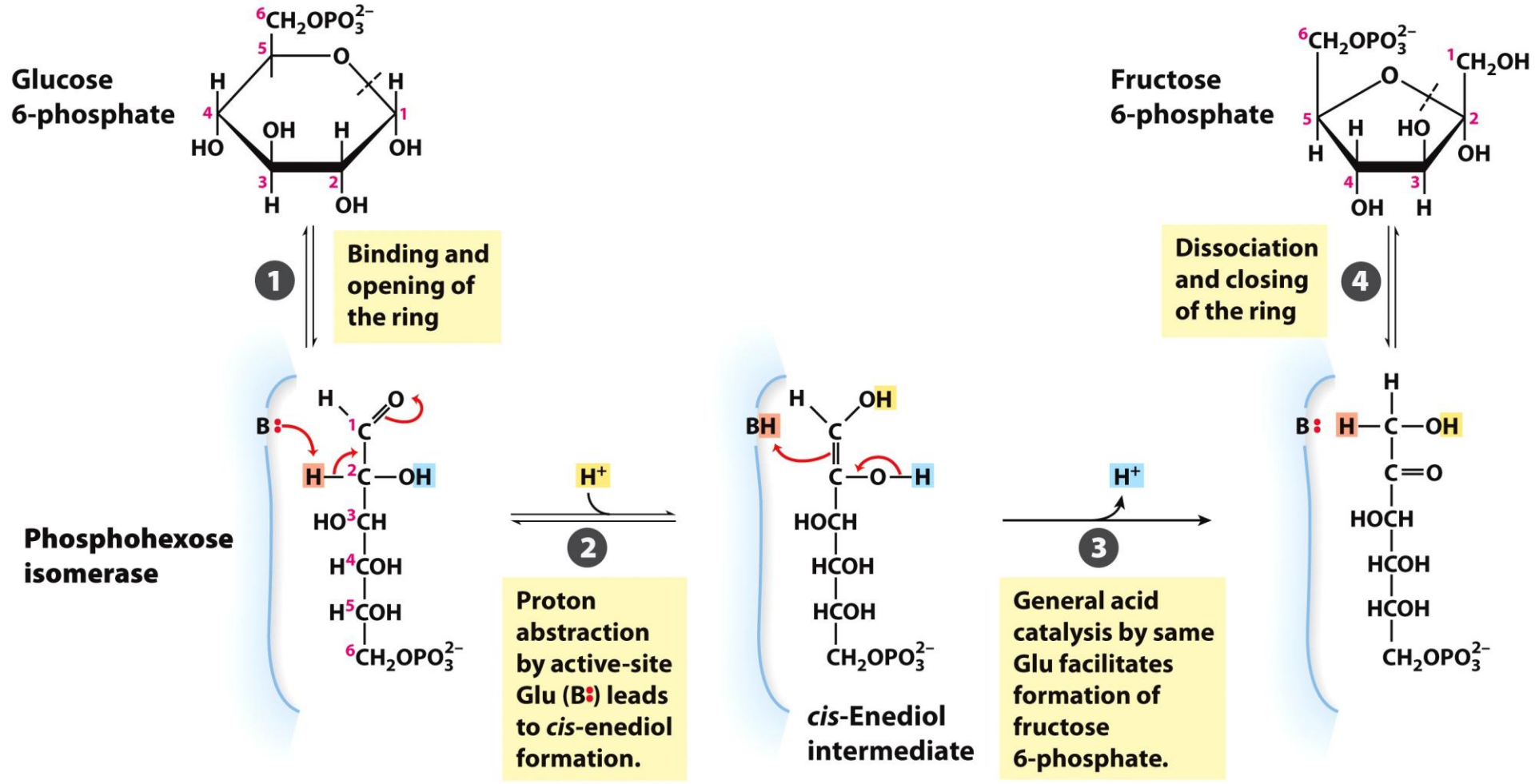
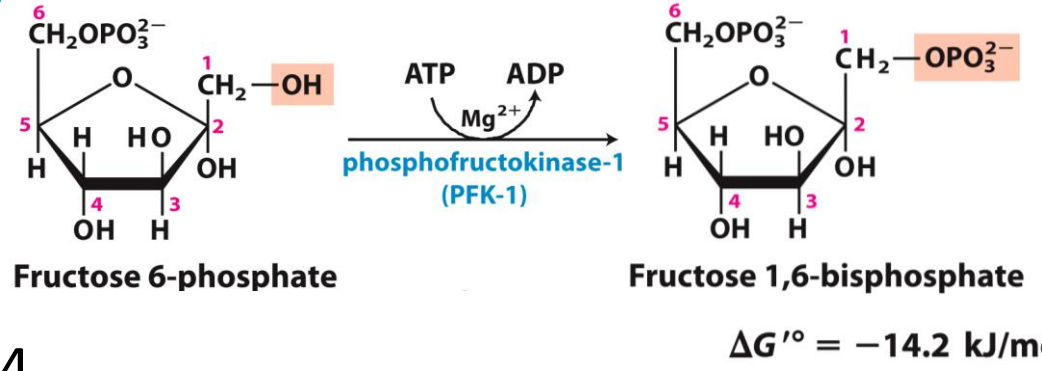


Figure 14-5
Lehninger Principles of Biochemistry, Sixth Edition

Step 3: 2nd Priming Phosphorylation

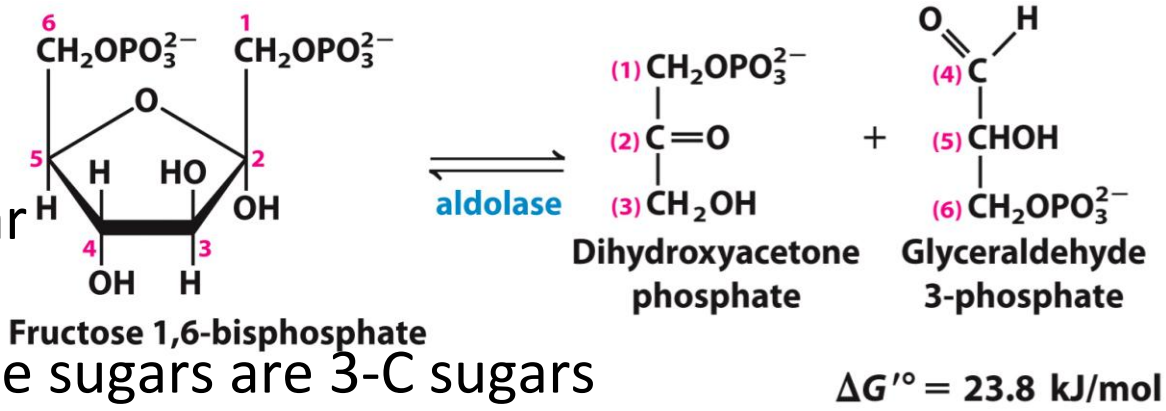


- Rationale
  - Further activation of glc
  - Allows for 1 phosphate/ 3-carbon sugar after step 4
- First Committed Step of Glycolysis
  - fructose 1,6-bisphosphate is committed to become pyruvate and yield energy whereas g-6-p and f-6-p have other possible fates
- This process uses the energy of ATP

- Highly thermodynamically favorable/irreversible
- Phosphofructokinase-1 is highly regulated
  - By ATP, ADP, AMP, fructose-2,6-bisphosphate, and other metabolites (detailed next chapter)
  - Do not burn glucose if there is plenty of ATP

Step 4: Aldol Cleavage of F-1,6-bP

- Rationale
  - Cleavage of a 6-C sugar into two 3-C sugars
  - High-energy phosphate sugars are 3-C sugars

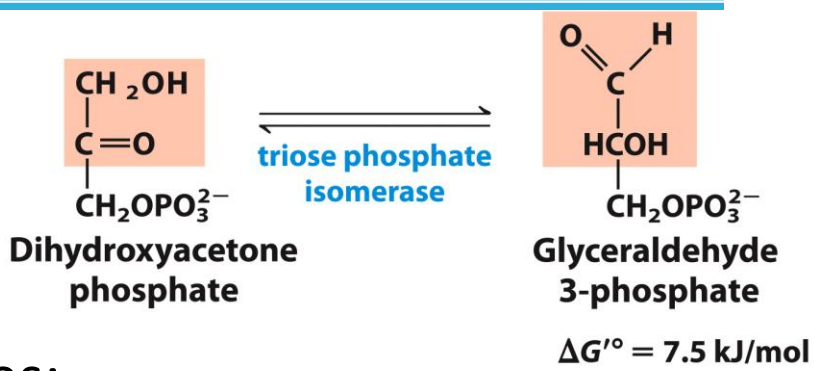


- The reverse process is the familiar aldol condensation
- Animal and plant aldolases employ covalent catalysis
- Fungal and bacterial aldolases employ metal ion catalysis

- Thermodynamically unfavorable/reversible
  - The actual free energy change is small and therefore the reaction is readily reversible. It is small because the concentration of the reactant is kept low
  - GAP concentration kept low to pull reaction forward
- *What is the mechanism of aldolase (class I)?*

Step 5: Triose Phosphate Interconversion

- Rationale:
  - Allows glycolysis to proceed by one pathway



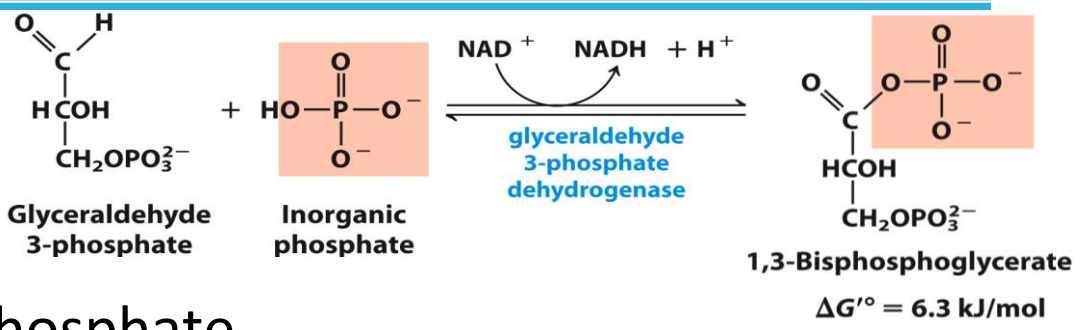
- Aldolase creates two triose phosphates:
  - Dihydroxyacetone Phosphate (DHAP)
  - Glyceraldehyde-3-Phosphate (GAP)
- Only GAP is the substrate for the next enzyme
- DHAP must be converted to GAP

- Similar mechanism as phosphohexose isomerase
- Completes preparatory phase

- Thermodynamically unfavorable/reversible
  - GAP concentration kept low to pull reaction forward

The Payoff Phase

Step 6: Oxidation of GAP



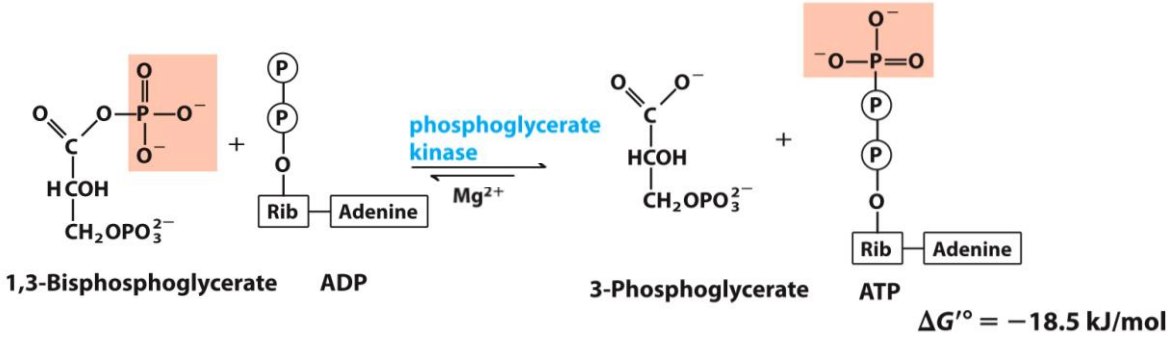
- Rationale:
  - Generation of a high-energy phosphate cpd
  - Incorporates inorganic phosphate
  - **Which allows for net production of ATP via glycolysis!**

- First energy-yielding step in glycolysis
- Oxidation of aldehyde with NAD^+ gives NADH and an **acyl phosphate** (very high $\Delta G'^{o} = -49.3$ kJ/mol)
- Active site cysteine
  - Forms high-energy thioester intermediate
  - Subject to inactivation by oxidative stress

- Thermodynamically unfavorable/reversible
  - Coupled to next reaction to pull forward
- *GAPDH mechanism (self study)*

Step 7: 1st Production of ATP

- Rationale:
  - Substrate-level phosphorylation to make ATP



- 1,3-bisphosphoglycerate is a high-energy compound
  - can donate the phosphate group to ADP to make ATP
- The enzyme is named after the reverse reaction
- **Substrate-level phosphorylation**: the fprmation of ATP by group transfer from a substrate

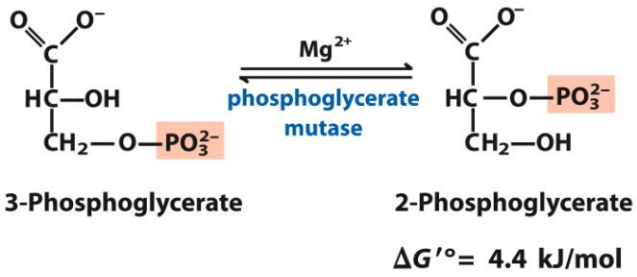
- Highly thermodynamically favorable/reversible
  - Is reversible because of coupling to GAPDH reaction
  - Steps 6 and 7 are strongly coupled·

Glyceraldehyde 3-P + ADP + P_i + NAD^+ $\rightleftharpoons$ 3-phosphoglycerate + ATP + NADH + H^+

$\Delta G'^{o} = -12.2$ kJ/mol

Step 8: Migration of the Phosphate

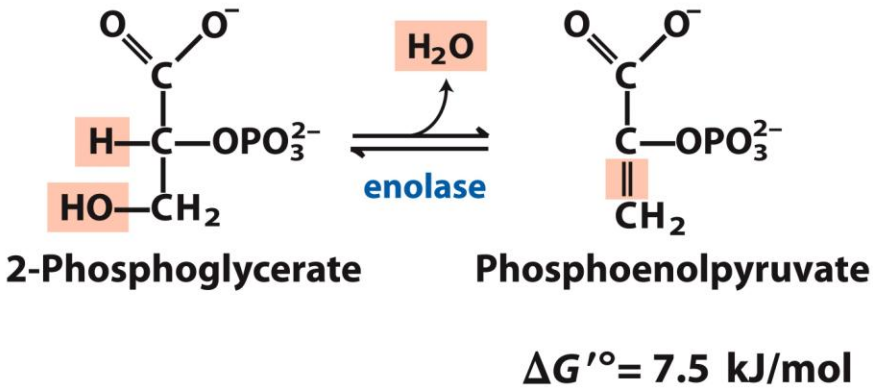
- Rationale:
  - Be able to form high-energy phosphate compound



- Mutases catalyze the (apparent) migration of functional groups
- One of the active site histidines is post-translationally modified to phosphohistidine
- Phosphohistidine donates its phosphate to O at C2 before retrieving another phosphate from O at C3
  - 2,3-bisphosphoglycerate intermediate
  - Note that the phosphate from the substrate ends up bound to the enzyme at the end of the reaction
- Thermodynamically unfavorable/reversible
  - Reactant concentration kept high by PGK to push forward

Step 9: Dehydration of 2-PG to PEP

- Rationale
  - Generate a high-energy phosphate compound

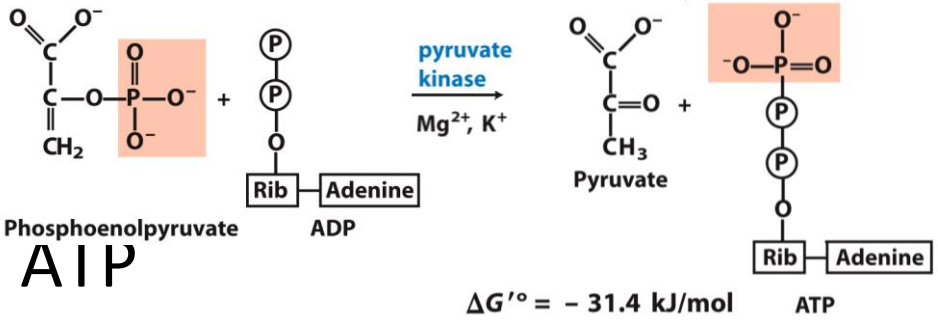


- 2-Phosphoglycerate is not a good enough phosphate donor ($\Delta G'^{o} = -17.6$ kJ/mol; $\Delta G'^{o}_{PEP} = -61.9$ kJ/mol)

- Slightly thermodynamically unfavorable/reversible
  - Product concentration kept low to pull forward

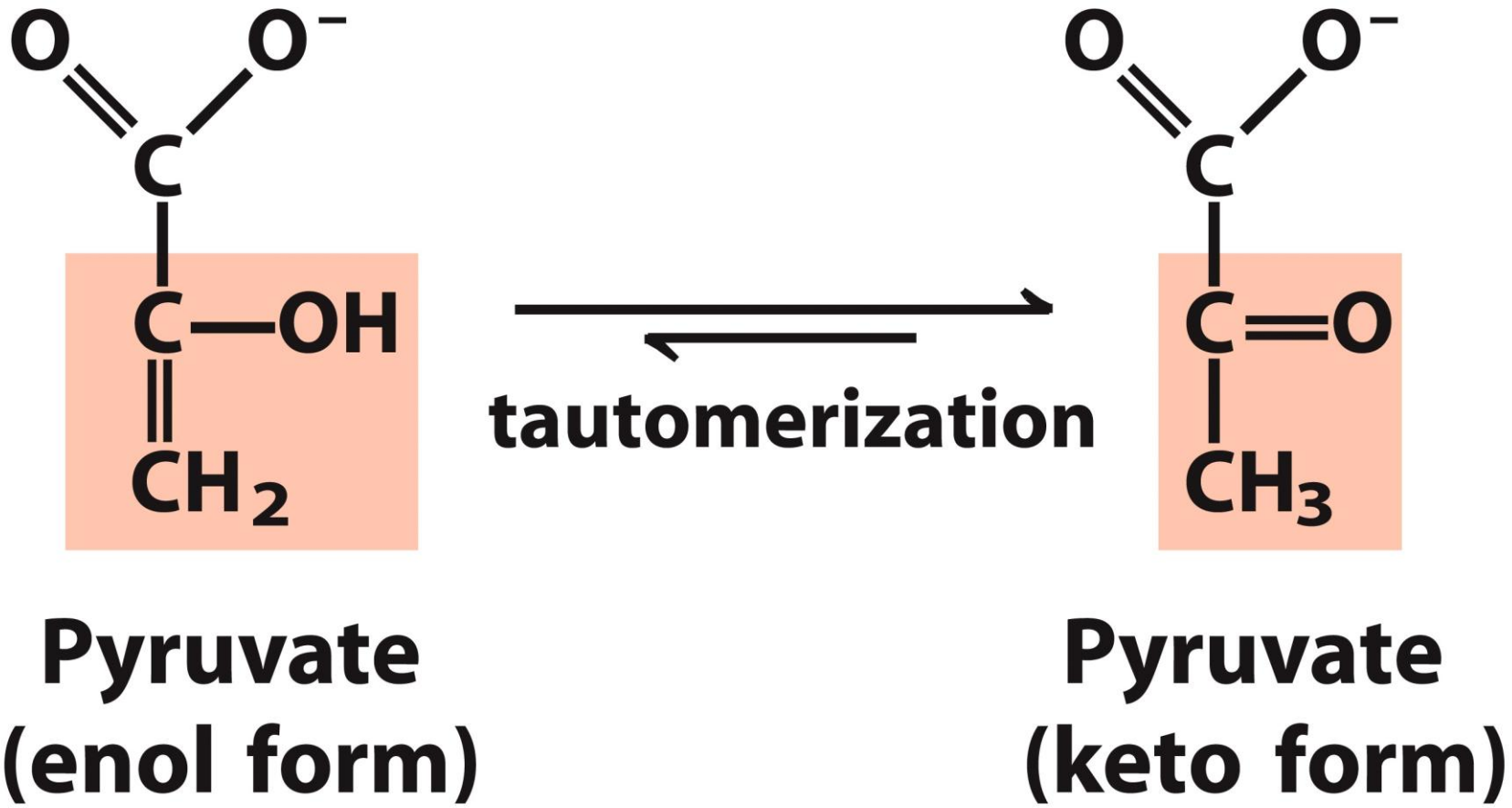
Step 10: 2nd Production of ATP

- Rationale
  - Substrate-level phosphorylation to make ATP
  - Net production of 2 ATP/glucose



- Loss of phosphate from PEP yields an enol that tautomerizes into ketone
- Tautomerization
  - effectively lowers the concentration of the reaction product
  - drives the reaction toward ATP formation
- Pyruvate kinase requires divalent metals (Mg^{2+} or Mn^{2+}) for activity
- Highly thermodynamically favorable/irreversible
  - Regulated by ATP, divalent metals, and other metabolites

Pyruvate Tautomerization Drives ATP Production



Unnumbered 14 p555a

Lehninger Principles of Biochemistry, Sixth Edition

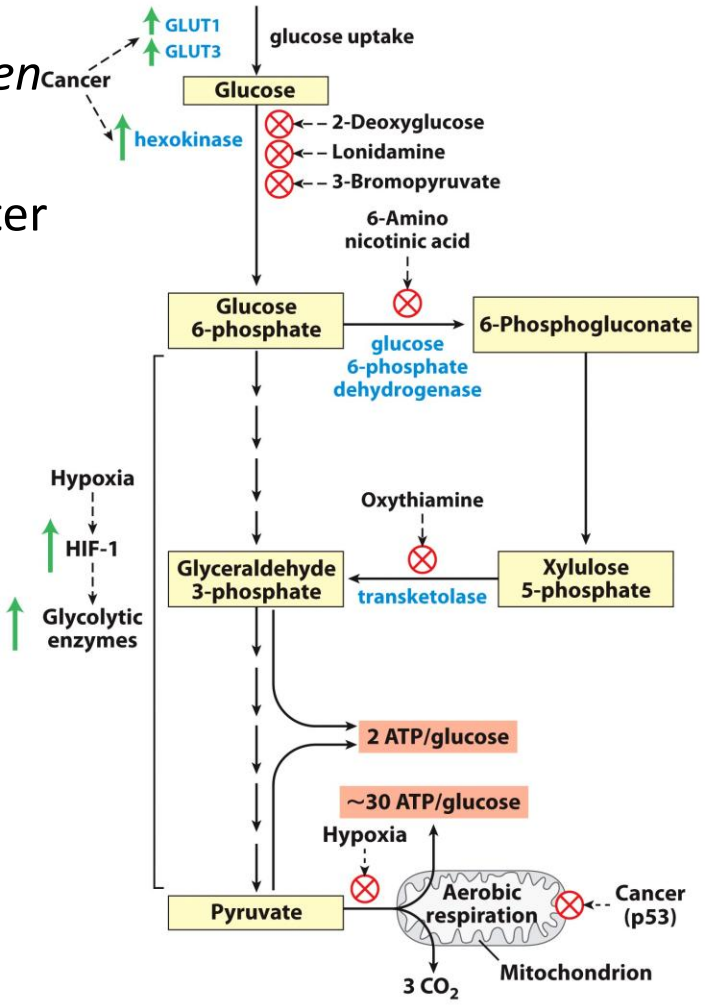
Summary of Glycolysis

$$Glucose + 2\ NAD^+ + 2\ ADP + 2\ P_i \rightarrow 2\ Pyruvate + 2\ NADH + 2\ H^+ + 2\ H_2O + \mathbf{2\ ATP}$$

- Used:
  - 1 glucose; 2 ATP; 2 NAD^+
- Made:
  - 2 pyruvate
    - Various different fates
  - 4 ATP
    - Used for energy-requiring processes within the cell
  - 2 NADH
    - Must be reoxidized to NAD^+ in order for glycolysis to continue
- Glycolysis is heavily regulated
  - Ensure proper use of nutrients
  - Ensure production of ATP only when needed
  - Under anaerobic conditions, both the rate and the total amount of glucose consumption are many times greater than with oxygen present, **why???**

Glycolysis occurs at elevated rates in tumor cells

- ***Warburg effect:*** tumor cells carry out glycolysis at a much higher rate than normal cells *even when oxygen is available (~10x)*
- In general, the more aggressive the tumor, the greater is its rate of glycolysis
- HIF-1 (hypoxia-inducible transcription factor) stimulates the production of at least 8 glycolytic enzymes and glucose transporters when the oxygen supply is limited
- HIF-1 also stimulates the production of VEGF (which stimulates angiogenesis)
- Overreliance of tumors on glycolysis suggests a possibility for anticancer therapy: deplete ATP from cancer cells by blocking glycolysis
- PET scans take advantage of the high uptake of glucose by tumor cells. Used to pinpoint cancers



Box 14-1 figure 1
Lehninger Principles of Biochemistry, Sixth Edition

Glucose uptake is deficient in type 1 Diabetes Mellitus

- Glucose uptake into cells is mediated by GLUT family
- GLUT1 & GLUT2 (hepatocytes) and GLUT3 (brain neurons) are always present in the plasma membrane of these cells
- GLUT4 (skeletal and cardiac muscles and adipose) only move to the plasma membrane in response to an insulin signal
- Patients with type 1 DM have too few β cells in the pancreas (cannot synthesize enough insulin) → heart, muscles and fat tissues cannot uptake glucose → hyperglycemia (after carb-rich meals)
- Fat cells turn to fat metabolism to provide alternative energy → formation of ketone bodies
- In untreated type 1 DM ketoacidosis is common and is life-threatening
- Reversed by insulin injection

Feeder Pathways for Glycolysis

Many carbs are metabolized by glycolysis

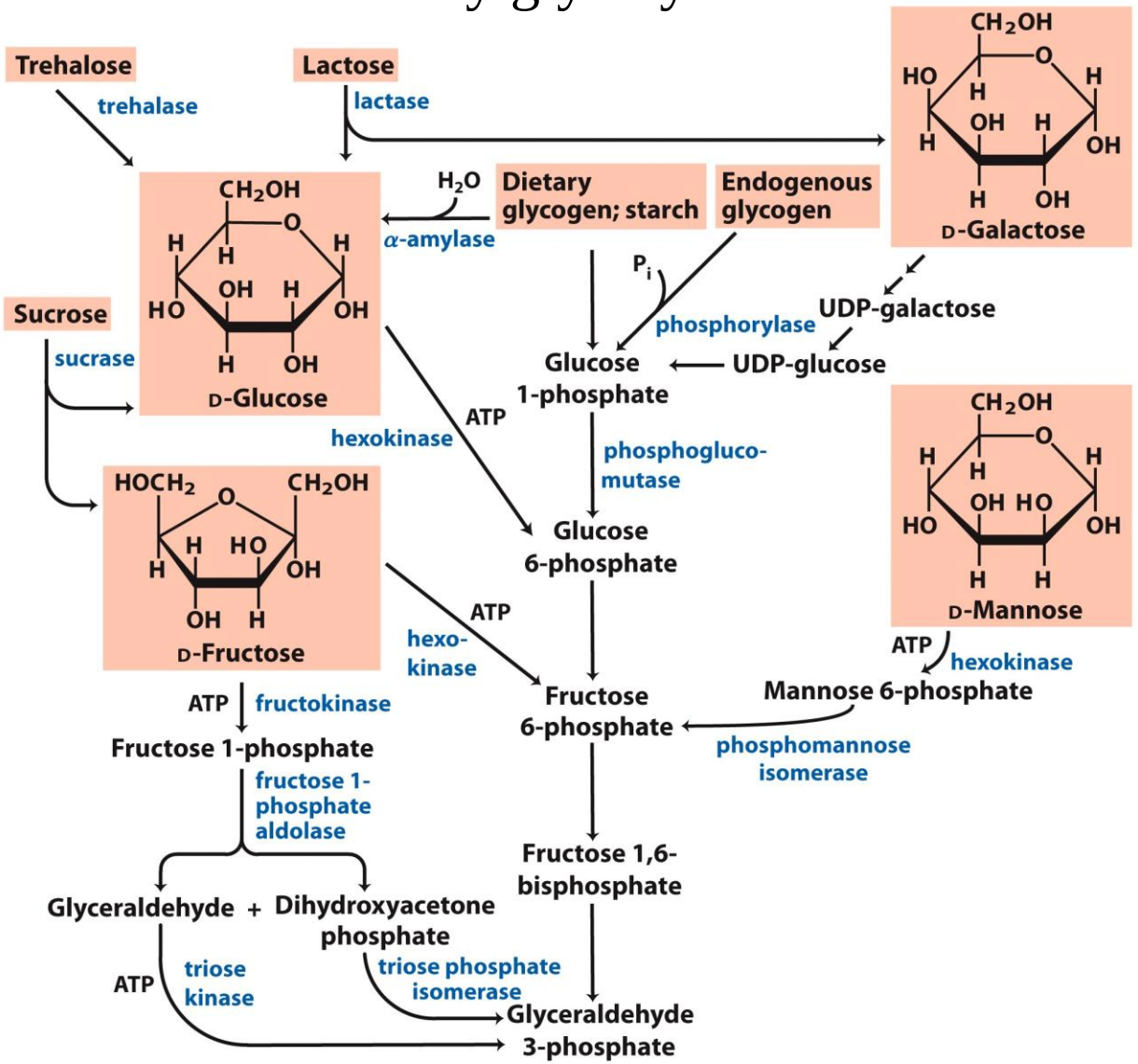


Figure 14-11
Lehninger Principles of Biochemistry, Sixth Edition

Feeder Pathways for Glycolysis

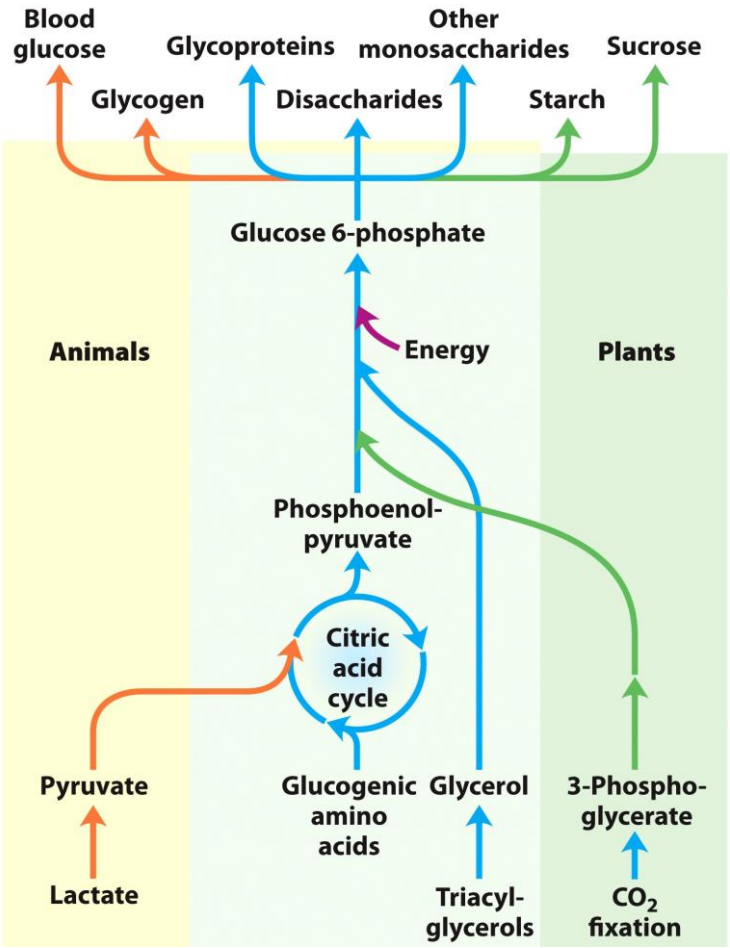
- Glucose molecules are cleaved from endogenous glycogen by glycogen phosphorylase (*phosphorolysis*)
  - Yielding glucose-1-phosphate
- Dietary starch and glycogen are cleaved by α-amylase to produce oligosaccharides and subsequently maltose and maltotriose in the small intestine, by pancreatic α-amylase (*hydrolysis*)
- Disaccharides are hydrolyzed
  - Lactose: glucose and galactose *(lactose intolerance?)*
  - Sucrose: glucose and fructose
  - Fructose, galactose, and mannose enter glycolysis at different points

Gluconeogenesis: Precursor for Carbohydrates

- Brain and nerve cells, RBC, renal medulla, testes an embryonic tissue use only glucose as the energy source
  - 120 g of glucose daily (brain)

- Synthesizing glucose from noncarbohydrate precursors – ***gluconeogenesis***

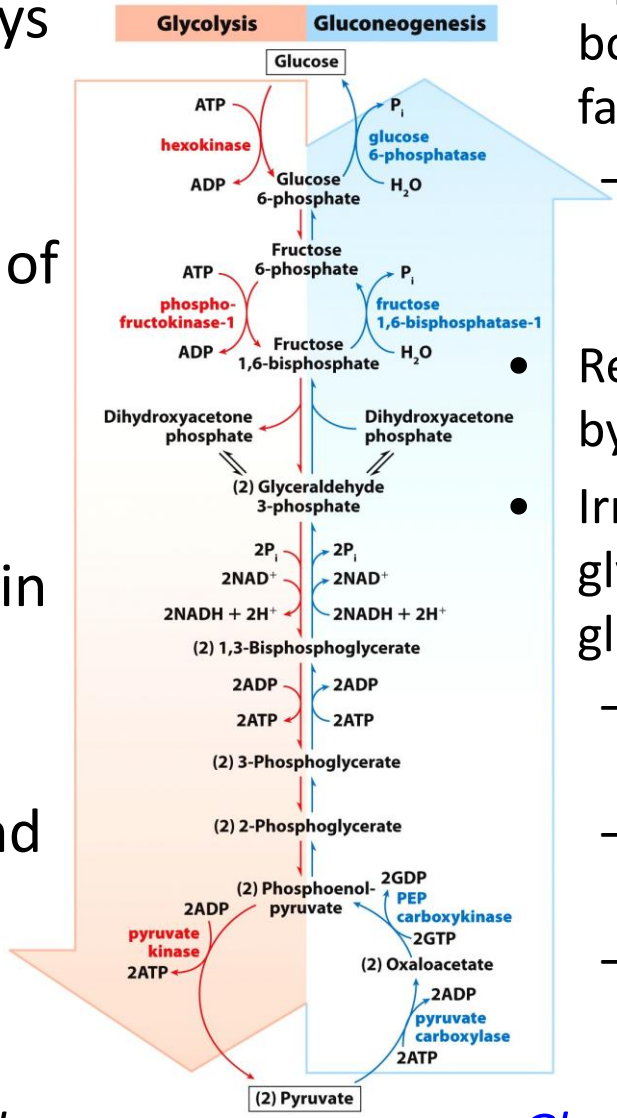
- In mammals, occurs in the liver (mainly) and in renal cortex



Notice that mammals cannot convert fatty acids to sugars.

Glycolysis vs. Gluconeogenesis

- Not identical pathways running in opposite directions
- 7 of the 10 reactions of gluconeogenesis are the reverse of glycolysis
- Both are irreversible in cells
- Both occur in the cytosol (reciprocal and coordinated regulation)



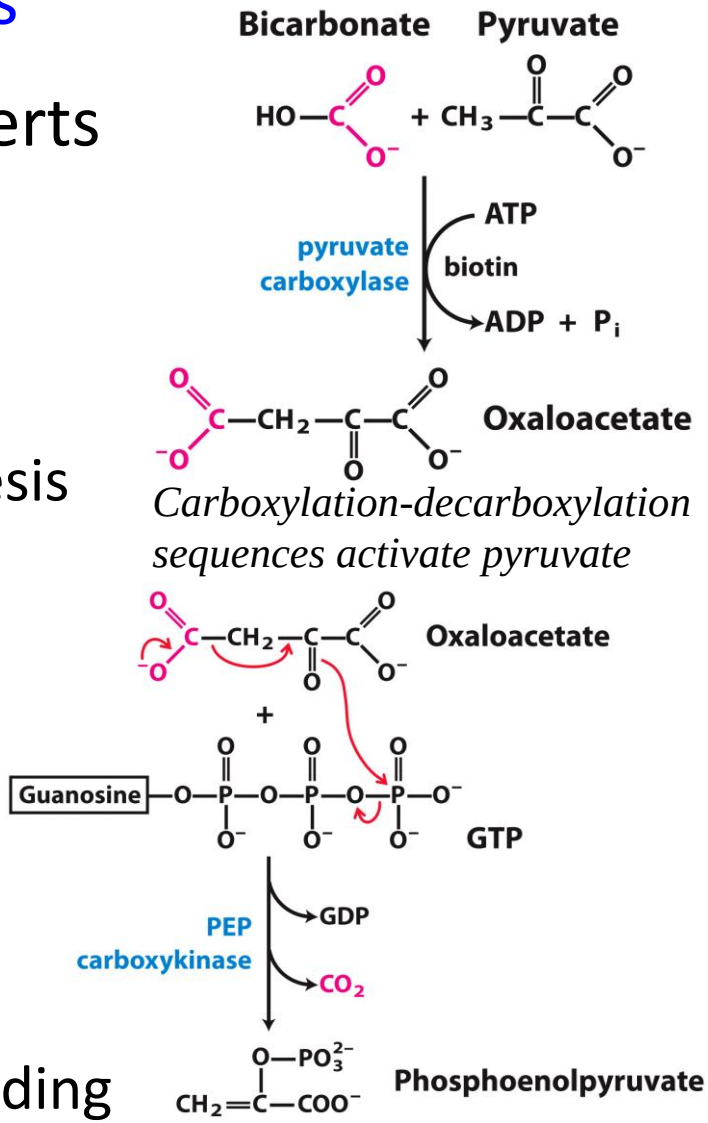
- Opposing pathways that are both thermodynamically favorable
  - Operate in opposite direction
    - end product of one is the starting cpd of the other
- Reversible reactions are used by both pathways
- Irreversible reaction of glycolysis must be bypassed in gluconeogenesis
  - Highly thermodynamically favorable, and regulated
  - Different enzymes in the different pathways
  - Differentially regulated to prevent a futile cycle

Glycolysis occurs mainly in the muscle and brain.

Gluconeogenesis occurs mainly in the liver.

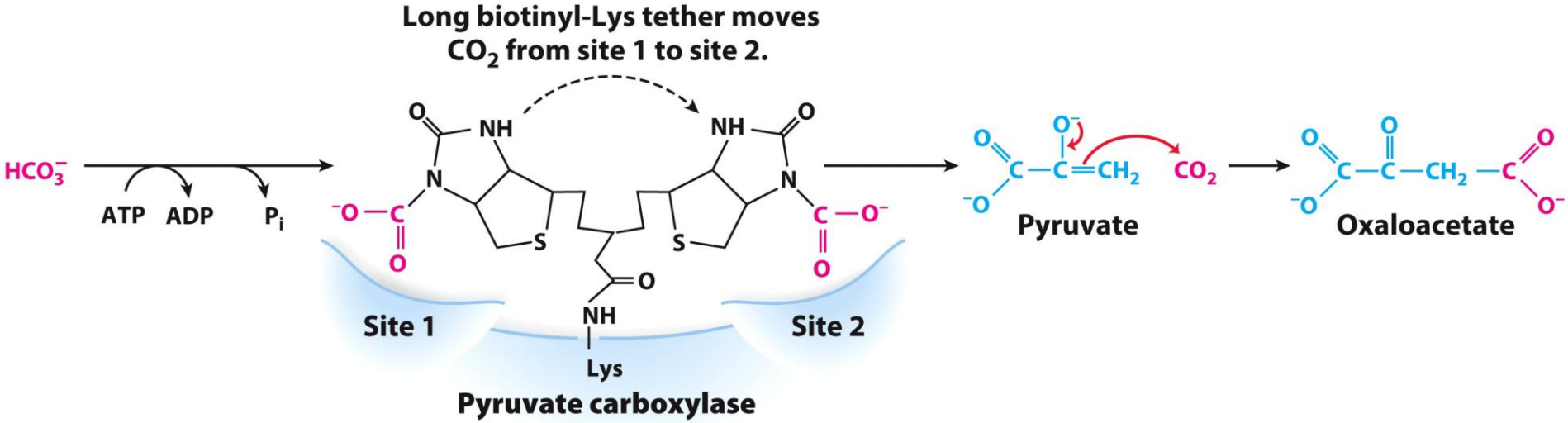
Pyruvate to Phosphoenolpyruvate

- Requires two energy-consuming steps
- First step, pyruvate carboxylase converts pyruvate to oxaloacetate
  - Carboxylation using a biotin cofactor
  - Requires transport into mitochondria
  - First regulatory enzyme in gluconeogenesis (acetyl CoA is +ve effector)
- Second step, phosphoenolpyruvate carboxykinase converts oxaloacetate to PEP
  - Phosphorylation from GTP and decarboxylation
  - Occurs in mitochondria or cytosol depending on the organism



Carboxylation-decarboxylation sequences activate pyruvate

Biotin is a CO_2 Carrier



- Biotin is covalently attached to the enzyme through an amide linkage to the ε-amino group of a Lys residue
- The reaction occurs in two phases (at two different sites):
- At catalytic site 1, bicarbonate ion is converted to CO_2 at the expense of ATP. CO_2 reacts with biotin, forming carboxybiotinyl-enzyme
- The long arm carries the CO_2 of carboxybiotinylenzyme to catalytic site 2 on the enzyme surface, where CO_2 is released and reacts with the pyruvate, forming oxaloacetate
- The general role of flexible arms in carrying reaction intermediates between enzyme active sites

Malate dehydrogenase

- No transporter of oxaloacetate in mitochondria
- OA must be reduced to malate by mitochondrial malate dehydrogenase using NADH

$$OA + NADH + H^+ \leftrightarrow \text{L-malate} + NAD^+$$

- Very low [OA] makes the $\Delta G \sim 0$ despite the high $\Delta G'^o$
- In cytosol, L-malate is reoxidized producing NADH

$$\text{L-malate} + NAD^+ \rightarrow OA + NADH + H^+$$

- $[NADH]/[NAD^+]_{mito} > [NADH]/[NAD^+]_{cyto}$ 10^5x
  cytosolic NADH is consumed in gluconeogenesis, glucose production cannot continue unless NADH is available. Moving malate from mito to cytosol moves also NADH equivalents to allow the process to occur

Overall bypass reaction

- OA + GTP ←→ PEP + CO_2 + GDP (PEP carboxykinase)
- Reversible under cellular conditions: formation of one high energy phosphate is balanced by the hydrolysis of another
- Pyruvate + ATP + GTP + HCO_3^- ←→ PEP + CO_2 + ADP + GDP + P_i $\Delta G'^o$ = 0.9 kJ/mol
- ΔG for the reaction ~ –25 kJ/mol because the actual cellular [PEP] is very low ➔ the reaction is irreversible in vivo

Additional bypasses

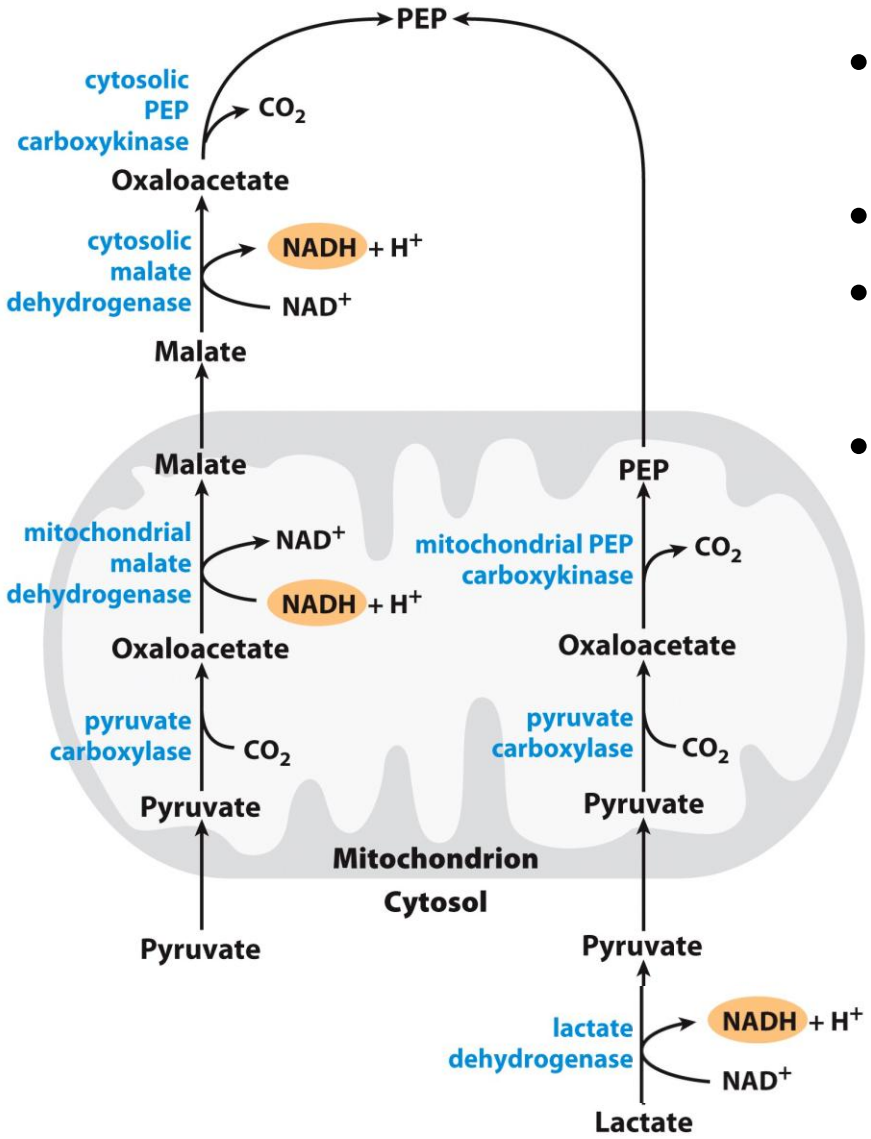


Figure 14-20
Lehninger Principles of Biochemistry, Sixth Edition

- RBC and anaerobic muscle cells, lactate predominates
- Converted to pyruvate by LDH
- Produces NADH in the cytosol, no need for malate conversion
- OA is decarboxylated by mito PEP carboxykinase and PEP is exported from mito

Additional Bypasses

- Catalyze reverse reaction of opposing step in glycolysis
- Are irreversible themselves

- Fructose 1,6-bisphosphate → Fructose 6-Phosphate
  - By fructose bisphosphatase-1 (FBPase-1)
  - Coordinately/oppositely regulated with PFK
  - A hydrolysis reaction with $\Delta G'^{o} = -16.3$ kJ/mol

- Glucose 6-phosphate → Glucose
  - By glucose 6-phosphatase
  - A hydrolysis reaction with $\Delta G'^{o} = -13.8$ kJ/mol
  - Enzyme found in hepatocytes, renal medulla and intestinal epithelial cells, NOT anywhere else (*if it were found everywhere, … what do you expect would happen?*)

Gluconeogenesis is expensive

2 Pyruvate + 4 ATP + 2 GTP + 2 NADH + 2 H^+ + 4 H_2O →
Glucose + 4 ADP + 2 GDP + 6 P_i + 2 NAD^+

- Costs 4 ATP, 2 GTP, and 2 NADH
- Not the reversal of the conversion of pyr to glc
- But physiologically necessary to ensure irreversibility
- Also, there's a need to keep pyruvate inside the cell instead of secreting it outside. Pyruvate has the potential to make more than 10 ATP per full oxidation of pyruvate

- Brain, nervous system, and red blood cells generate ATP ONLY from glucose

Precursors for Gluconeogenesis

- Glucose can be produced from all intermediates of the CAC (citrate, isocitrate, α-KG, succinyl-CoA , succinate, fumarate and malate) since all of them can undergo oxidation to OA

- Also, most a.a. can undergo transformations to pyruvate or CAC intermediate, and therefore has the potential to make glucose: i.e. ***glucogenic***
  - Only Leu and Lys are non-glucogenic
  - Ala and Gln are particularly important glucogenic a.a. in mammals

Precursors for Gluconeogenesis

- Animals can produce glucose from sugars or proteins and parts of fat (triacylglycerol)
  - Sugars: pyruvate, lactate, or oxaloacetate
  - Protein: from glucogenic a.a.
  - Glycerol: the breakdown product of fats can be used after a two step reaction. *Glycerol kinase* phosphorylates it and the oxidation of the central C yields dihydroxyacetone phosphate (an intermediate in gluconeogenesis)

- Animals cannot produce glucose from fatty acids
  - Product of fatty acid degradation is acetyl-CoA
  - Cannot have a net conversion of acetyl-CoA to oxaloacetate (2 C that enter the CAC are removed as $2CO_2$)
    - Plants, yeast, and many bacteria can do this (the glyoxylate cycle), thus producing glucose from fatty acids

Pentose Phosphate Pathway

- Glc 6-P has another catabolic fate which leads to specialized products needed by cells
- The main products are NADPH and ribose 5-phosphate
- NADPH is an electron donor
  - Reductive biosynthesis of fatty acids and steroids (liver, adipose, gonads, etc.)
  - Repair of oxidative damage esp. in cells directly exposed to O_2 (RBC, cornea)

- Ribose-5-phosphate is a biosynthetic precursor of nucleotides
  - Used in DNA and RNA synthesis esp. in rapidly dividing cells (skin, bone marrow, tumors, etc.)
  - Or synthesis of some coenzymes (ATP, NADH, $FADH_2$)

Pentose Phosphate Pathway

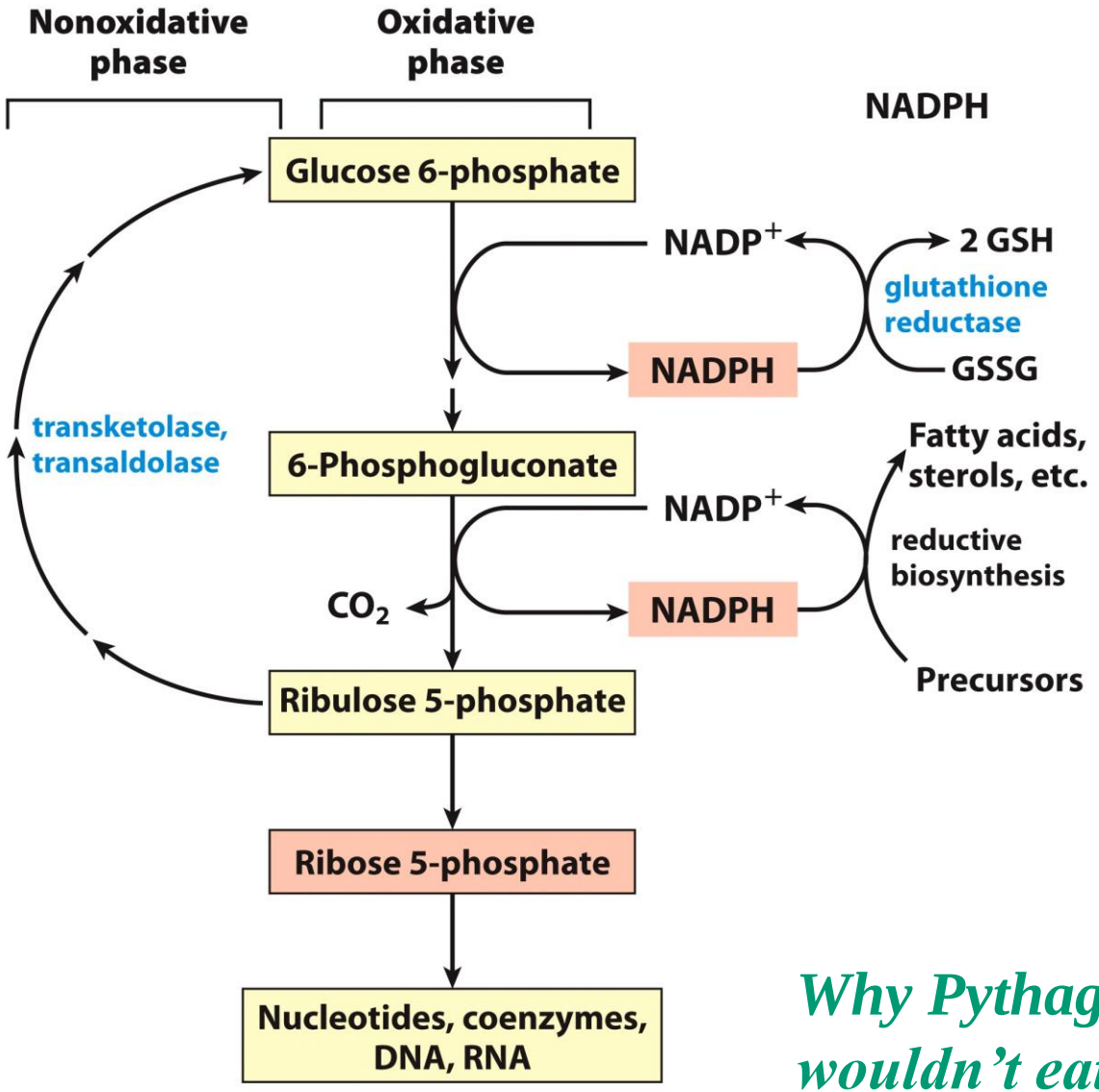


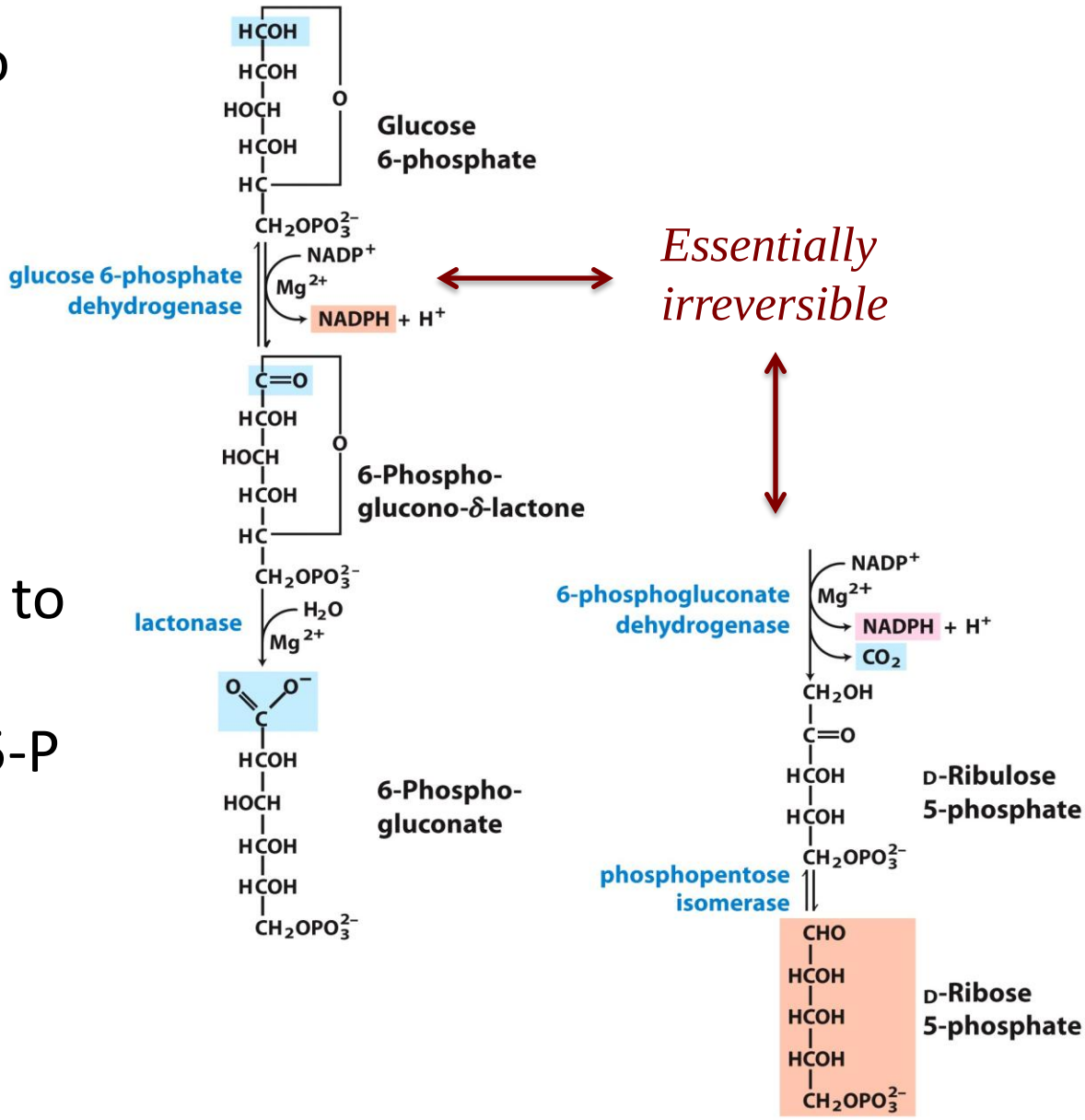
Figure 14-21
Lehninger Principles of Biochemistry, Sixth Edition

Why Pythagoras wouldn't eat falafel???
Box 14-4: self check

Oxidative phase generates NADPH and R-5-P

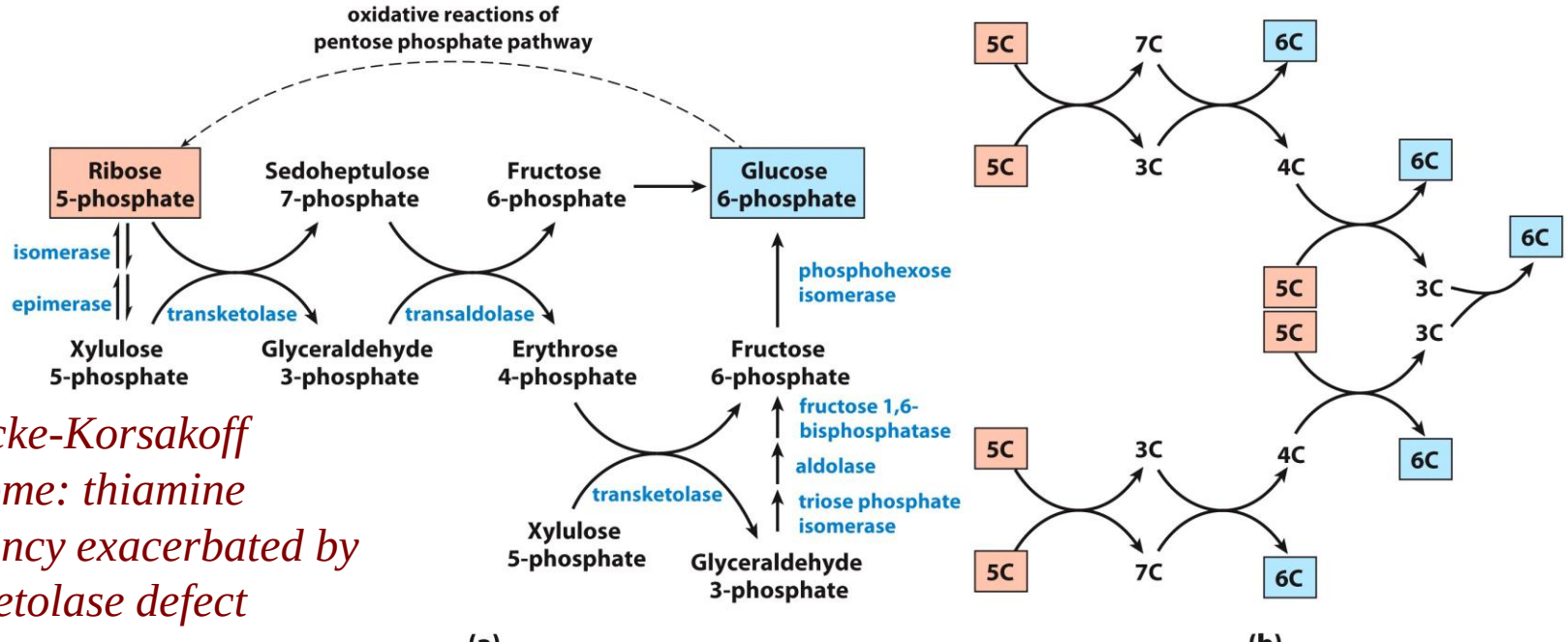
1. Oxidation of G-6-P to δ-lactone by ***G6PD***, reduction of $NADP^+$
2. Lactone hydrolysis by ***lactonase***
3. Oxidation and decarboxylation by ***6-PG dehydrogenase*** to produce ribulose 5-P
4. Formation of ribose 5-P by ***phosphopentose isomerase***

- Pentose pathway ends here in some tissues



Non-oxidative phase regenerates G-6-P from R-5-P

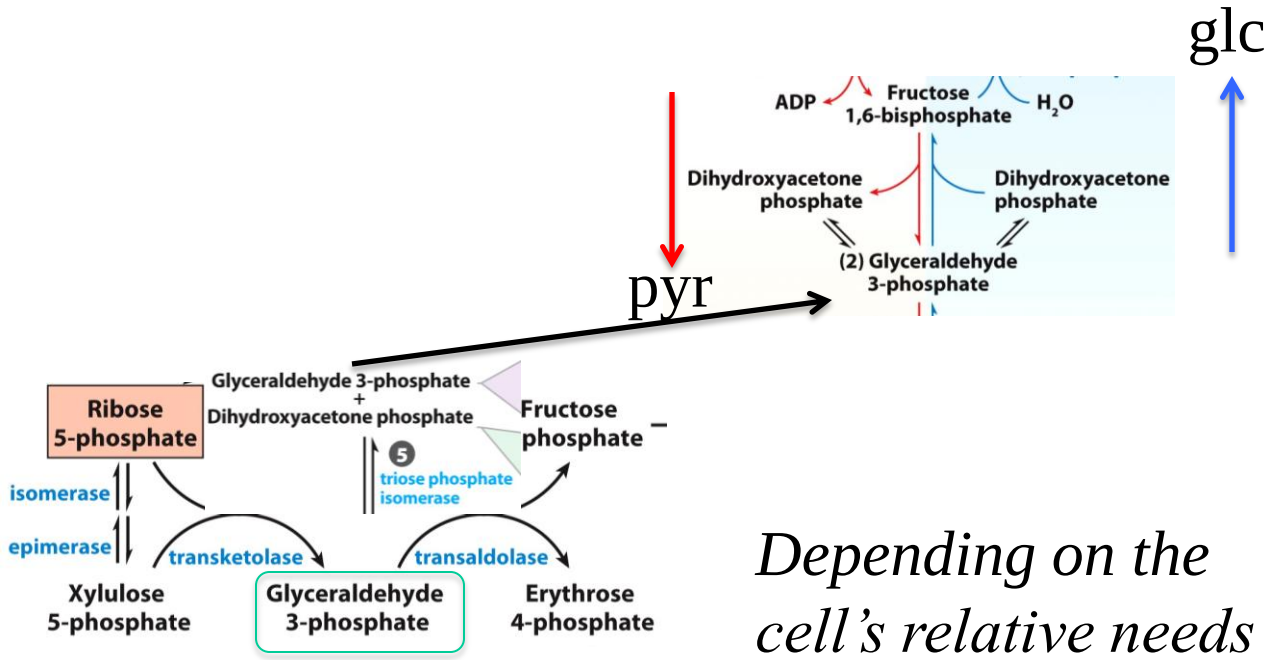
- Used in tissues requiring more NADPH than R-5-P (e.g. liver and adipose)
- Six 5-C sugar phosphates are converted into five 6-C ones, allowing continued G6P oxidation and NADPH production
- Details are not important, but remember the two key enzymes unique in this pathway: **transketolase** and **transaldolase**



Wernicke-Korsakoff syndrome: thiamine deficiency exacerbated by transketolase defect

Glycolysis, gluconeogenesis and pentose phosphate pathway

- All enzymes of PP are in the cytosol
- Glycolysis, gluconeogenesis and PP are connected through several shared intermediates and enzymes:



Depending on the cell's relative needs for NADPH, ATP and pentose phosphates

NADPH regulates partitioning into glycolysis vs. pentose phosphate pathway

G6P can enter glycolysis or PP depending on the current needs to the cell and the concentration of $NADP^+$ and NADPH

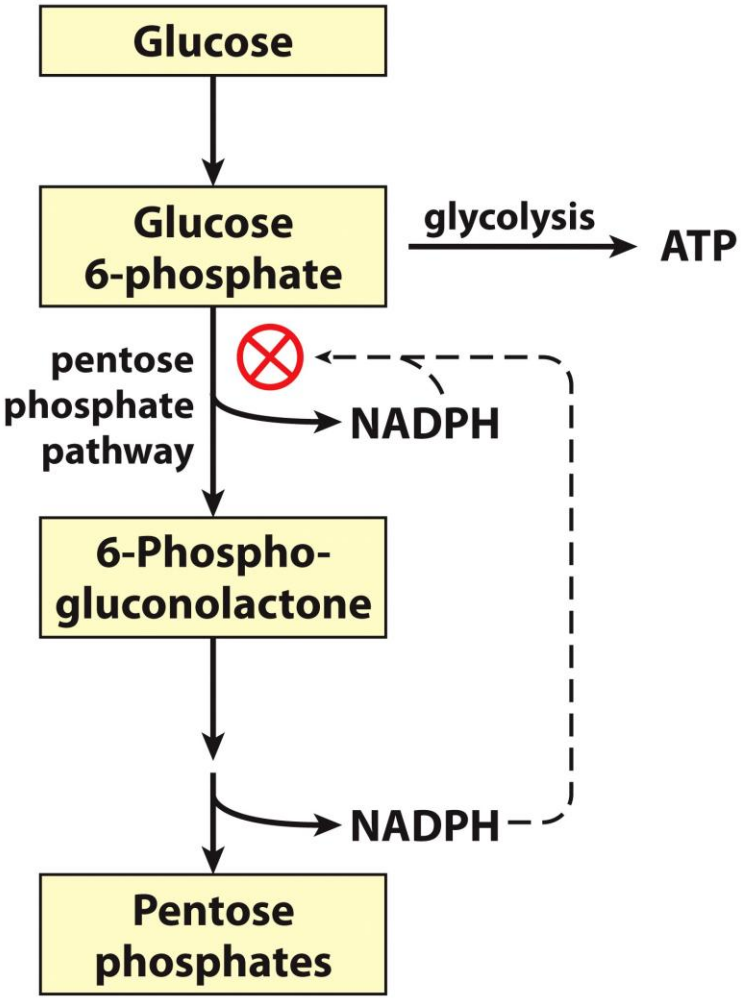


Figure 14-28
Lehninger Principles of Biochemistry, Sixth Edition

Diabetes

- Chronic disease
- Characterized by excessive urine excretion, **polyuria**
- Greek word for “passing through” i.e. urine

- Two main forms:

Diabetes Insipidus

Diabetes Mellitus

Diabetes Insipidus

- Insipidus means “tasteless”. Diabetes insipidus = tasteless urine
- Due to a deficiency of antidiuretic hormone (ADH, aka arginine vasopressin, AVP)
- AVP increases water resorption in kidneys
- Deficiency of AVP can be
  - **Neurogenic:** decrease in AVP release (e.g. due to alcohol intoxication or tumor)
  - **Nephrogenic:** decreased renal sensitivity to AVP (e.g. by mutations of receptors or aquaporins)
- Either neurogenic or nephrogenic → little water retention → excessive output of dilute urine → **diabetes insipidus**, **hypernatremia** (elevated $[Na^+]_{blood}$), **polyuria** (excess urine production), and **polydipsia** (thirst)
- *Has nothing to do with carbohydrate metabolism*

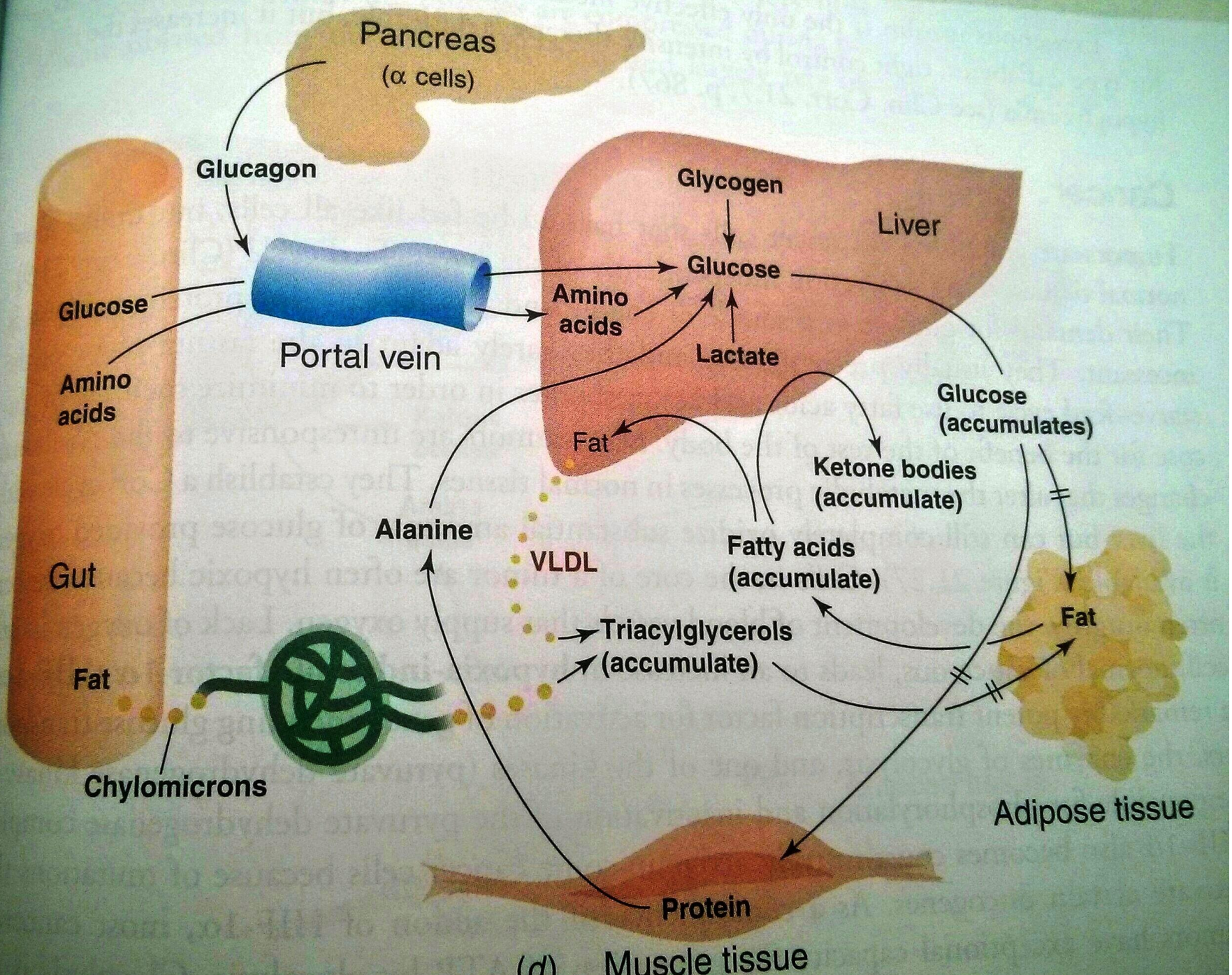
Diabetes Mellitus

- Mellitus means “honey”. Diabetes mellitus = honey urine
- Due to defects in CHO, fats, and/or protein metabolism
- Elevated glucose in the plasma and urine
- Excessive urine excretion is due to ***osmotic diuresis*** (high blood sugar leaking into the urine and taking excess water along with it)
- Two major types:

TYPE 1 and TYPE 2

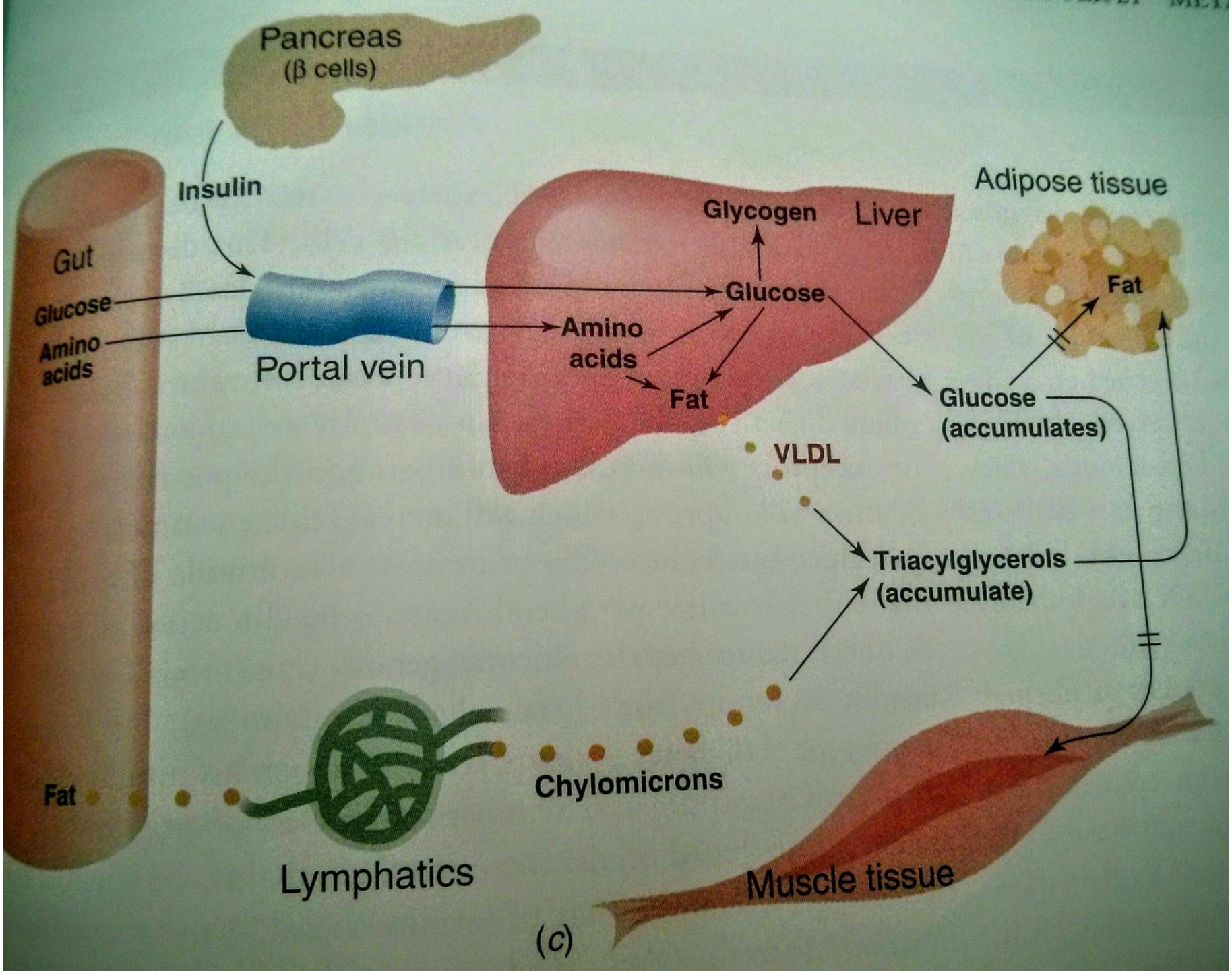
Type 1 Diabetes Mellitus

- Usually appears in childhood
- Complete absence of insulin production from pancreas due to defective beta cell function (autoimmune)
- Inability of tissues to uptake glucose and continuous gluconeogenesis in liver ➔ **high $[glc]_{blood}$**
- Increased lipolysis in adipose and increased beta oxidation in liver ➔ **ketoacidosis**
- Absence of insulin (TF) will induce lower lipoprotein lipase activity ➔ **hyperchylomicronemia**
- **Body is always in a starved state**
- Exogenous insulin is the only effective medication which doesn't cure it but alleviates clinical symptoms. Must keep changing the dose to match nutritional states


Pancreas
(α cells)
Glucagon
Glycogen
Liver
Glucose
Amino acids
Portal vein
Glucose
Amino acids
Lactate
Glucose (accumulates)
Fat
Ketone bodies (accumulate)
Alanine
VLDL
Fatty acids (accumulate)
Gut
Fat
Triacylglycerols (accumulate)
Fat
Chylomicrons
Adipose tissue
Protein
(d) Muscle tissue

Type 2 Diabetes Mellitus

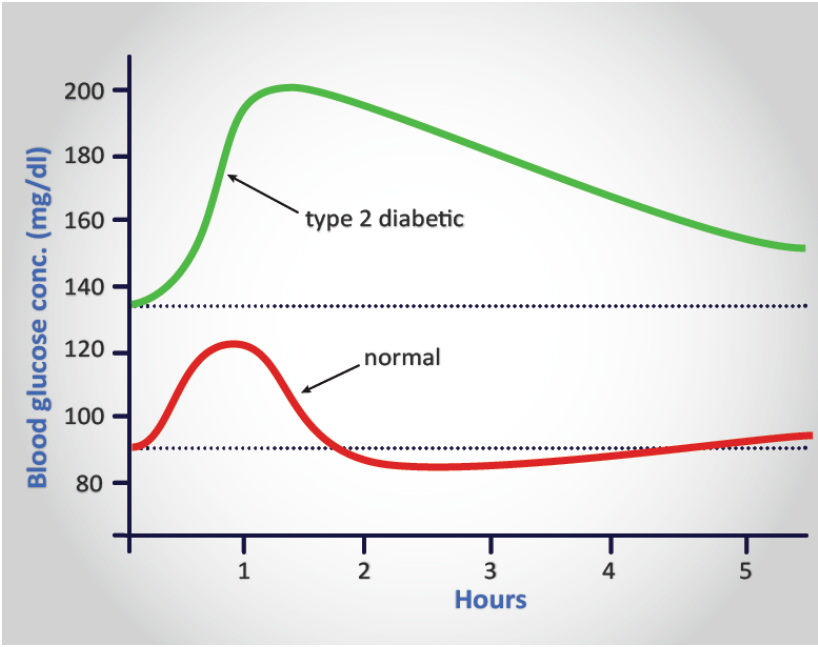
- β cell failure and insulin resistance in obese diabetic patients
- Insufficient production of insulin to promote glucose uptake into tissues or to block gluconeogenesis in liver ➔ **hyperglycemia**
- **Ketoacidosis** ***rarely*** develops of (enough insulin is present to prevent uncontrolled release of fatty acids from adipocytes)
- **Hypertriacylglycerolemia** occurs (increase in VLDL without hyperchylomicronemia because fatty acids are combined in the liver to form TAGs and VLDL)
- Note that concurrent lipogenesis and gluconeogenesis should never occur, yet they occur in type 2 DM because of the ***state of mixed insulin resistance*** and its effects on different pathways (more on that in later chapters)
- To treat: (1) diet and exercise (2) **metformin** (inhibitor of gluconeogenesis) and (3) **insulin injections** (most effective despite insulin resistance)


Pancreas
(β cells)
Insulin
Gut
Glucose
Amino acids
Portal vein
Glycogen
Liver
Glucose
Amino acids
Fat
Adipose tissue
Fat
Glucose (accumulates)
VLDL
Triacylglycerols (accumulate)
Fat
Chylomicrons
Lymphatics
Muscle tissue

(c)

Type 2 Diabetes Mellitus diagnosis

- OGTT for diagnosis (measuring $[glc]_{blood}$ every 30-60 min for 2-4 h after ingesting 100 g carbohydrate)
- Normal individuals → $[glc]_{blood}$ returns to normal in 2 h
- Diabetics → $[glc]_{blood}$ starts high and remains high for longer periods
- An abnormal OGTT does not mean diabetes in all cases
- Common cold can contribute to abnormal reading
- Fasting blood sugar of more than 126 mg/dL is a better indication of the occurrence of diabetes



Question 1
Due: NEXT WEEK (jstiban@birzeit.edu)

- **Please solve questions:**

1. **14 (Arsenate poisoning)**
2. **16 (Niacin)**
3. **18 (Clinical symptoms of enzyme deficiency)**
4. **25 (Ethanol affects blood glucose)**
5. **28 (Phloridzin)**

For written answers, I prefer to have them typed in Word. I can accept the assignment in one file sent to my email. For answers that require solving mathematically, you can either type them or write them down and scan them.