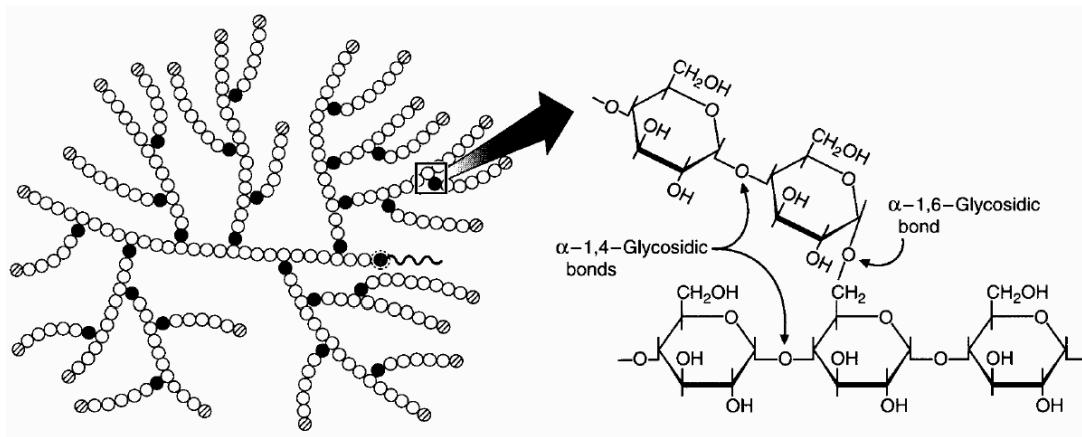


## CELLULAR GLYCOGEN



## Why Glycogen as an Energy Storage Molecule?

1. Fat cannot be as rapidly mobilized in skeletal muscle.
  2. Fat cannot be oxidized to produce energy in the absence of oxygen.
  3. Energy input required to initiate fat oxidation.
  4. The carbon atoms of fat cannot be used by any pathway of the human body in order to maintain blood glucose levels for use by other tissues such as the brain. (i.e. fat cannot be converted to glucose)

- Used when intracellular levels of glucose and ATP are low

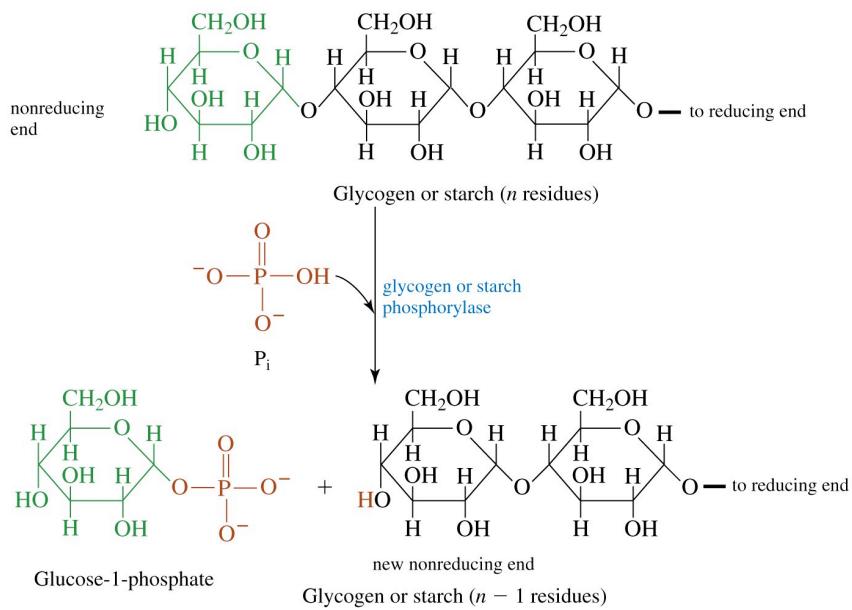
- **Glycogenolysis** - degradation of glycogen

- Muscle glycogen is fuel for muscle contraction

- Liver glycogen is mostly converted to glucose for bloodstream transport to other tissues

- NOT simple hydrolysis like dietary starch

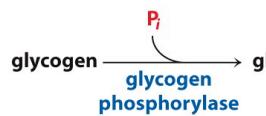
- Cleavage occurs by **phosphorolysis** – cleavage of a bond by group transfer to an oxygen atom of phosphate



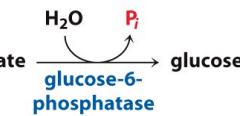
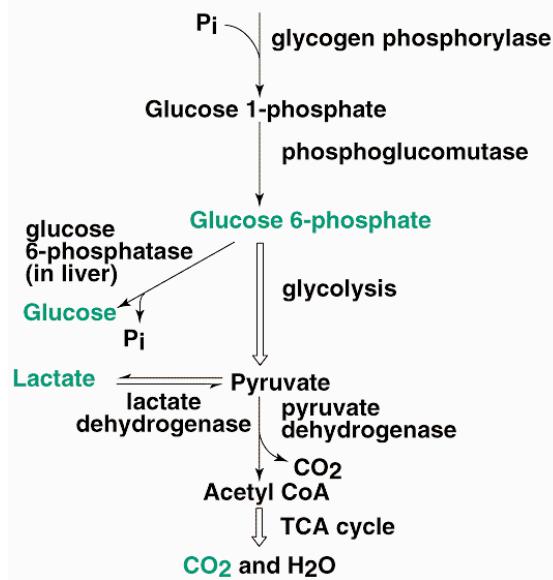
**Figure 15-5 Concepts in Biochemistry, 3/e**  
© 2006 John Wiley & Sons

## MOBILIZATION OF GLYCOGEN

- Glucose released as  $\alpha$ -D-glucose-1-phosphate
  - o Catalyzed by the enzyme **glycogen phosphorylase** in animals
  - o Enzyme removes glucose residues from the nonreducing ends of glycogen
  - o Glycogen has lots and lots of non-reducing ends
  - o Acts only on  $\alpha$ -1-4 linkages of glycogen polymer
  - o  $\alpha(1 \rightarrow 6)$  branches hydrolyzed by debranching enzymes
  - o **Glucose-1-phosphate is ISOMERIZED** readily to **glucose-6-phosphate** and enters glycolysis
  - o Note that this pathway uses LESS ATP than entry of glucose into glycolysis (bypass 1<sup>st</sup> kinase reaction)



(Glucose)<sub>n</sub>



© John Wiley & Sons, Inc. All rights reserved.

### Examples of Glycogen Storage Diseases

#### 1. von Gierke's Disease

- a. Defect in *glucose-6-phosphatase*
- b. Cannot remove the phosphate from glucose-6-phosphate so free glucose cannot be released into blood stream via transporters.
- c. Enzyme not in muscle – One reason why glycogen in muscle is not used for maintaining blood sugar levels.
- d. G6P reconverted to G1P and used for glycogen synthesis. Glycogen synthesis elevated in patients.
- e. Accumulation of glycogen enlarges liver and abdomen to protrude.
- f. Causes hypoglycemia, irritability, lethargy and in severe cases, death.
- g. Also affects gluconeogenesis.

#### 2. Cori's Disease

- a. Deficiency in debranching enzyme.
- b.  $\frac{1}{4}$  of all glycogen storage disease
- c. Affects both liver and muscle
- d. Muscle weakness and liver enlargement as a result of glycogen accumulating.

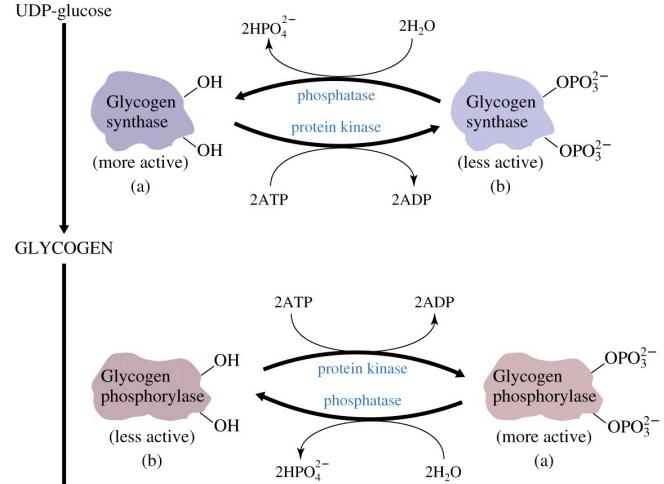


Figure 15-13 Concepts in Biochemistry, 3/e  
© 2006 John Wiley & Sons

## REGULATION OF GLYCOGEN METABOLISM

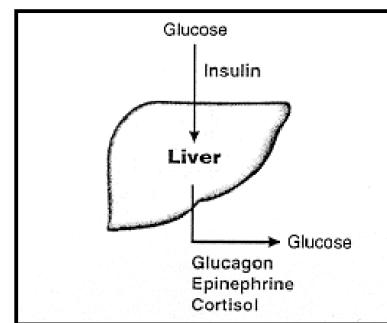
Both mobilization (Glycogen phosphorylase) and synthesis (Glycogen synthase) of glycogen are regulated by hormones

- **Insulin, glucagon, cortisol, and epinephrine regulate mammalian glycogen metabolism**

### - Insulin:

- **Insulin** - Insulin is released as a result of an increase in glucose levels, and therefore promotes the conversion of glucose into glycogen, where the excess glucose can be stored for a later date in the liver
- **Insulin** is produced by  $\beta$ -cells of the pancreas (high levels are associated with the fed state)
- Insulin stimulates the target organ/tissues to store and conserve fuel and decrease rate of fuel oxidation → An Anabolic Hormone!
- ↑ Glucose uptake of muscle and adipose tissue:
- Insulin increases rate of glucose transport into muscle, adipose tissue via GLUT 4 transporter
- Insulin stimulates glycogen synthesis in the liver

### Insulin and Insulin-Counterregulatory Hormones



**TABLE 19-1 | Summary of Insulin Action**

Target Tissue	Metabolic Effect
Muscle and other tissues	Promotes glucose transport into cells Stimulates glycogen synthesis Suppresses glycogen breakdown
Adipose tissue	Activates extracellular lipoprotein lipase Increases level of acetyl-CoA carboxylase Stimulates triacylglycerol synthesis Suppresses lipolysis
Liver	Promotes glycogen synthesis Promotes triacylglycerol synthesis Suppresses gluconeogenesis

© John Wiley & Sons, Inc. All rights reserved.

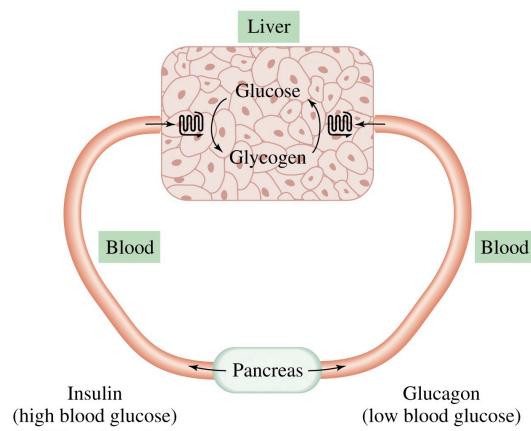


Figure 20-7 Concepts in Biochemistry, 3/e

© 2006 John Wiley & Sons

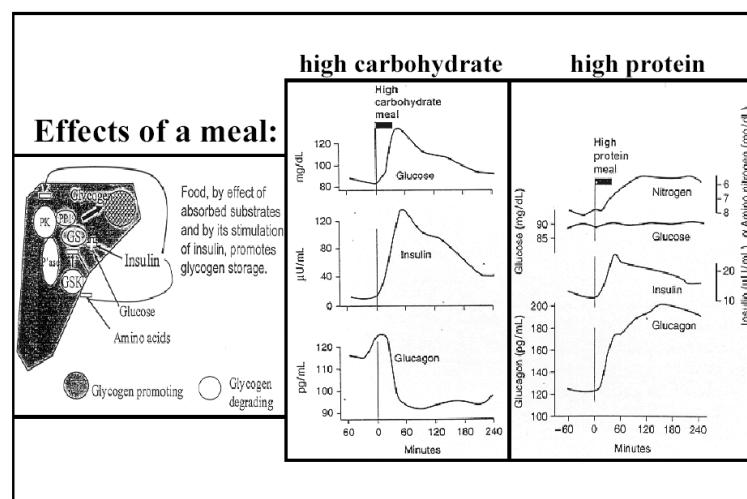
### EXAMPLE:

#### Fasting (rest)

Blood: Insulin ↓  
Glucose transport ↓  
Glycogen synthesis ↓

#### Carbohydrate meal (rest)

Blood: Insulin ↑  
Glucose transport ↑  
Glycogen synthesis ↑



**TABLE 19-3 | Source of Metabolic Fuels Under Different Conditions**

	Carbohydrates (%)	Fatty Acids (%)	Amino Acids (%)
Immediately after a meal	50	33	17
After an overnight fast	12	70	18
After a 40-day fast	0	95 <sup>a</sup>	5

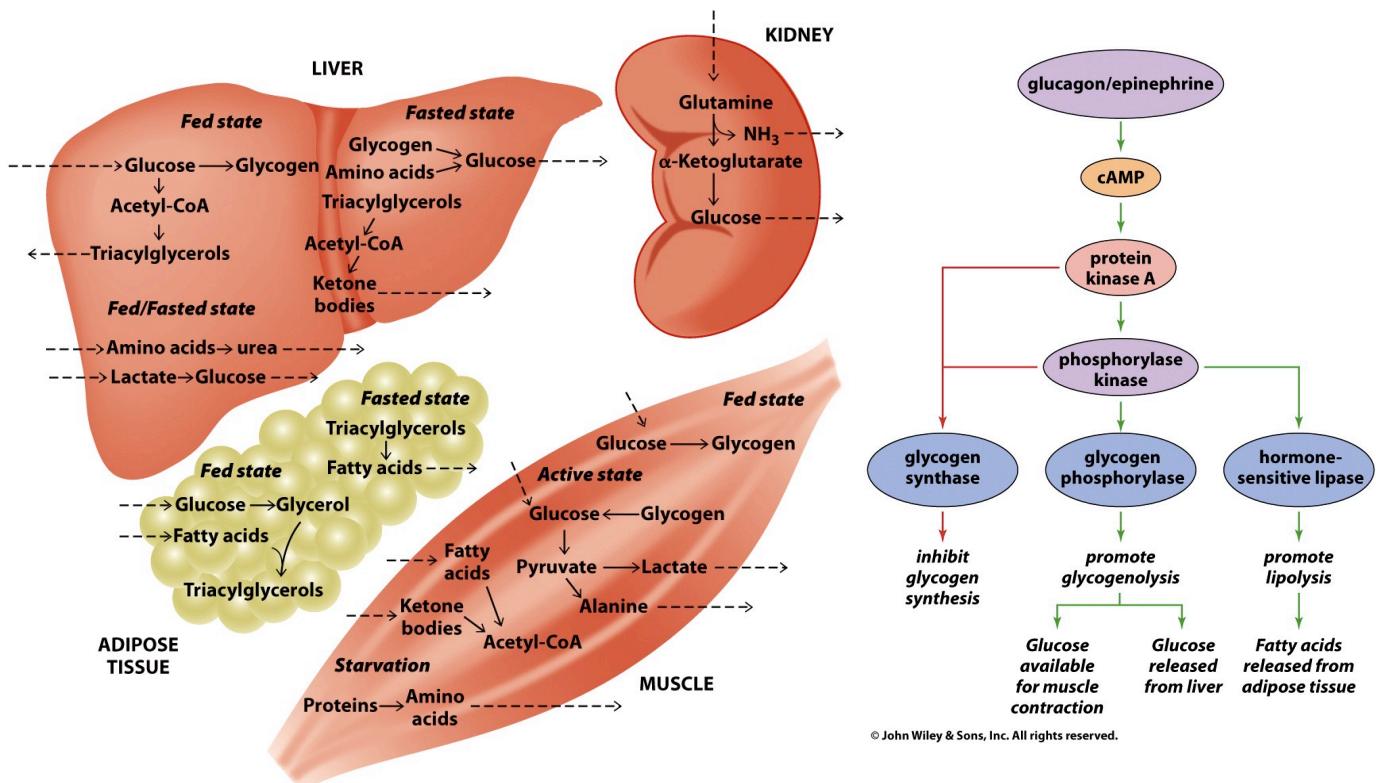
<sup>a</sup>This value reflects a high concentration of fatty acid-derived ketone bodies.

© John Wiley & Sons, Inc. All rights reserved.

- Diabetes Mellitus is a common form of diabetes where the sufferer does **not** have the ability to produce sufficient insulin or are resistant to the effects of insulin, meaning that glucose cannot be converted into glycogen. Usually has to take injections of insulin after meals and snacks to maintain their storage of glucose needed in emergencies.

## Physical Actions of Insulin and Insulin Counterregulatory Hormones

Hormone	Function	Major Metabolic Pathways Affected
Insulin	<ul style="list-style-type: none"> <li>Promotes fuel storage after a meal</li> <li>Promotes growth</li> </ul>	<ul style="list-style-type: none"> <li>Stimulates glucose storage as glycogen (muscle and liver)</li> <li>Stimulates fatty acid synthesis and storage after a high carbohydrate meal</li> <li>Stimulates amino acid uptake and protein synthesis</li> </ul>
Glucagon	<ul style="list-style-type: none"> <li>Mobilizes fuels</li> <li>Maintains blood glucose levels during fasting</li> </ul>	<ul style="list-style-type: none"> <li>Activates gluconeogenesis and glycogenolysis (liver) during fasting</li> <li>Activates fatty acid release from adipose tissue</li> </ul>
Epinephrine	<ul style="list-style-type: none"> <li>Mobilizes fuels during acute stress</li> </ul>	<ul style="list-style-type: none"> <li>Stimulates glucose production from glycogen (muscle and liver)</li> <li>Stimulates fatty acid release from adipose tissue</li> </ul>
Cortisol	<ul style="list-style-type: none"> <li>Provides for changing requirements over the long-term</li> </ul>	<ul style="list-style-type: none"> <li>Stimulates amino acid mobilization from muscle protein</li> <li>Stimulates gluconeogenesis</li> <li>Stimulates fatty acid release from adipose tissue</li> </ul>



© John Wiley & Sons, Inc. All rights reserved.

© John Wiley & Sons, Inc. All rights reserved.

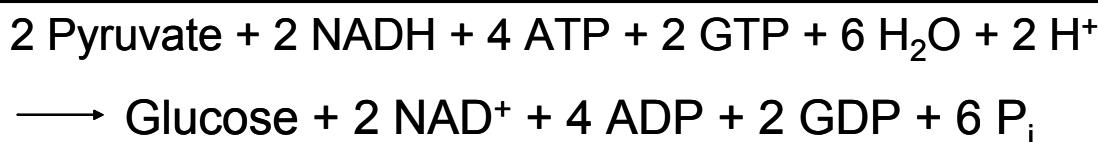
## GLUCONEOGENESIS

- Gluconeogenesis is the **re-synthesis of glucose**
- Provides the source of blood glucose other than glycogen to **prevent hypoglycemia**
- Major **users of glucose: brain and muscles**

**Top Priority glucose supply for Brain, because the brain:**

1. Need relative large amount of Energy:
2. Does not have significant energy store
3. Dependent on blood glucose as energy source
4. Not sensitive to hormone regulation
5. Can adapt to use ketone body (fatty acids) but only after prolonged fasting

- Major **producers** of glucose: **Liver (90%) and kidney (10%)**
  - o Pyruvate and lactate produced returned to liver and kidney
- Under fasting conditions, gluconeogenesis supplies almost all of the body's glucose
- Gluconeogenesis is the process by which glucose is **MADE** from **small, non-carbohydrates**
  - Major gluconeogenic precursors in mammals:
    - (1) **Lactate and pyruvate**
    - (2) Most **amino acids** (especially alanine)
      - (Muscle proteins break down and aa transported to liver)
    - (3) **Glycerol** (from triacylglycerol hydrolysis)
  - Any metabolite that can be converted to **pyruvate** or **oxaloacetate** can be a glucose precursor

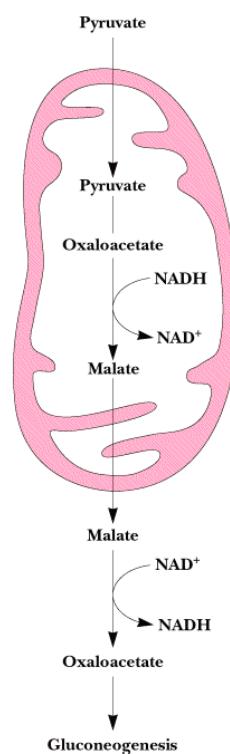
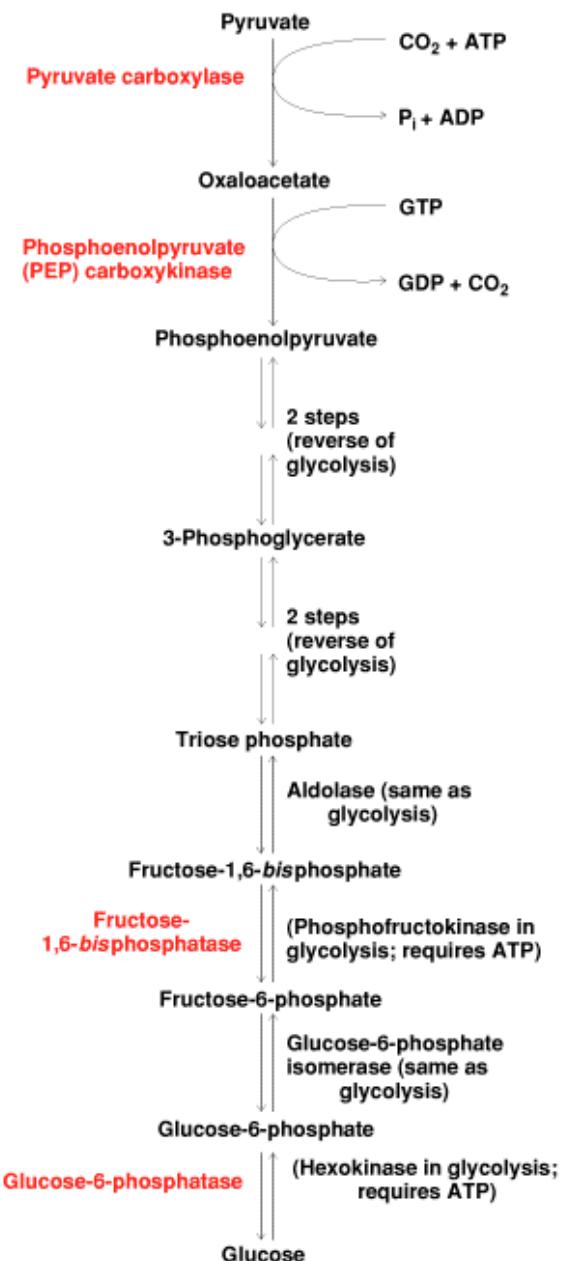


- Not a simple reversal of glycolysis, but employs many of the same enzymes of glycolysis
- Employs 4 new steps to avoid “irreversible steps” of glycolysis
  - Irreversible and regulated steps of glycolysis
    - **Hexokinase**
    - **Phosphofructokinase**
    - **Pyruvate kinase**
- Gluconeogenesis occurs when pyruvate kinase, PFK and hexokinase are relatively inactive
- These steps must be bypassed to prevent futile cycles
- Making glucose is **expensive**
  - Synthesis of 1 mole of glucose from 2 moles of pyruvate needs 6 moles of ATP

## Subcellular Locations of Gluconeogenic Enzymes

- Gluconeogenesis enzymes are **cytosolic** except:
  - (1) Glucose 6-phosphatase (endoplasmic reticulum)
  - (2) Pyruvate carboxylase (mitochondria)

## GLUCONEOGENESIS



## Compartmentalization

**Table 15.4****The reactions of gluconeogenesis beginning with pyruvate**

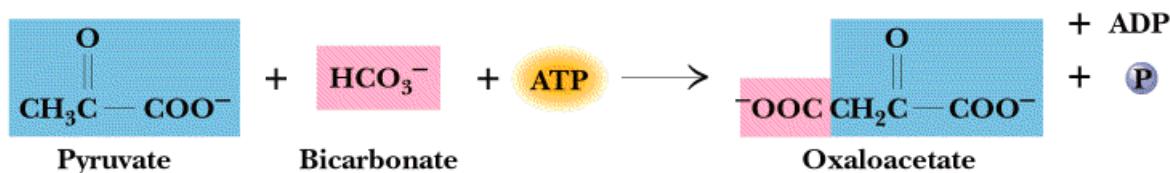
Number	Reaction
1	Pyruvate + CO <sub>2</sub> + ATP → oxaloacetate + ADP + P <sub>i</sub>
2	Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO <sub>2</sub> + GDP
3	Phosphoenolpyruvate + H <sub>2</sub> O ⇌ 2-phosphoglycerate
4	2-Phosphoglycerate ⇌ 3-phosphoglycerate
5	3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP
6	1,3-Bisphosphoglycerate + NADH + H <sup>+</sup> ⇌ glyceraldehyde-3-phosphate + NAD <sup>+</sup> + P <sub>i</sub>
7	Glyceraldehyde-3-phosphate ⇌ dihydroxyacetone phosphate
8	Glyceraldehyde-3-phosphate + dihydroxyacetone phosphate ⇌ fructose-1,6-bisphosphate
9	Fructose-1,6-bisphosphate + H <sub>2</sub> O → fructose-6-phosphate + P <sub>i</sub>
10	Fructose-6-phosphate ⇌ glucose-6-phosphate
11	Glucose-6-phosphate + H <sub>2</sub> O ⇌ glucose + P <sub>i</sub>

Table 15-4 Concepts in Biochemistry, 3/e  
© 2006 John Wiley & Sons

**STEPS 1 and 2** by-pass **pyruvate kinase** step of glycolysis; cleavage of 2 phosphoanhydride bonds necessary; goes through an oxaloacetate intermediate

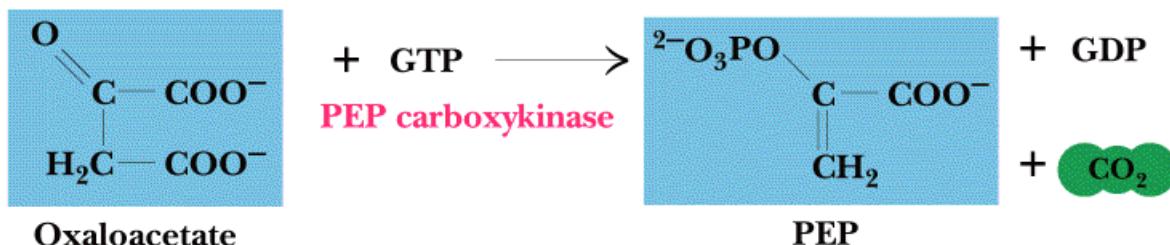
### Step 1: Pyruvate Carboxylase

- Mitochondrial localization
- Pyruvate enters the mitochondria via a transporter
- pyruvate + ATP + CO<sub>2</sub> + H<sub>2</sub>O → oxaloacetate + ADP + Pi + 2H<sup>+</sup>
- Catalyzes a metabolically irreversible carboxylation reaction
- Reaction type: Synthesis of a carbon-carbon bond using energy of ATP hydrolysis
- Activated by acetyl CoA (allosteric activation)
- Accumulation of **acetyl CoA** from fatty acid oxidation signals **abundant energy**, and directs **pyruvate to oxaloacetate for gluconeogenesis**



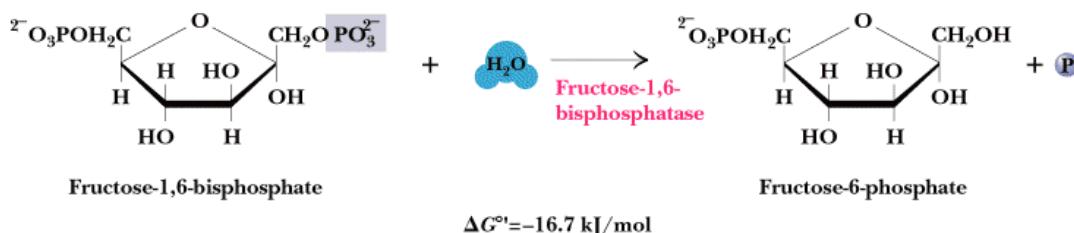
## Step 2: Phosphoenolpyruvate carboxykinase

- Cytosolic localization
- Oxaloacetate gets reduced to malate in mitochondria which can diffuse out of the mitochondria to the cytosol; Malate then gets reoxidized to oxaloacetate
- Oxaloacetate too polar to diffuse out of mitochondria and there are no transporters
- oxaloacetate + GTP  $\leftrightarrow$  phosphoenolpyruvate + GDP + CO<sub>2</sub>
- A **decarboxylation** reaction in which **GTP donates a phosphoryl group**



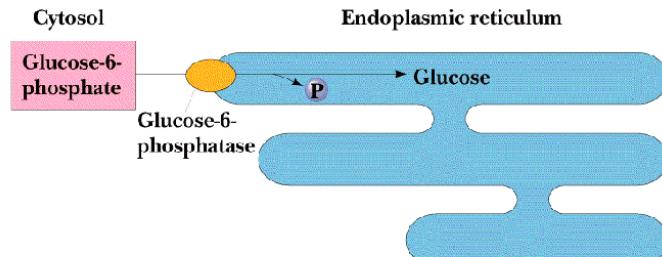
## Step 3: Fructose-1,6-bisphosphatase

- fructose-1,6-bisphosphate + H<sub>2</sub>O → fructose-6-phosphate + Pi
  - reverses Phosphofructokinase (PFK)
- A metabolically **irreversible** reaction ( $\Delta G^\circ = -16.7 \text{ kJ mol}^{-1}$ )
- Simple **hydrolysis** reaction



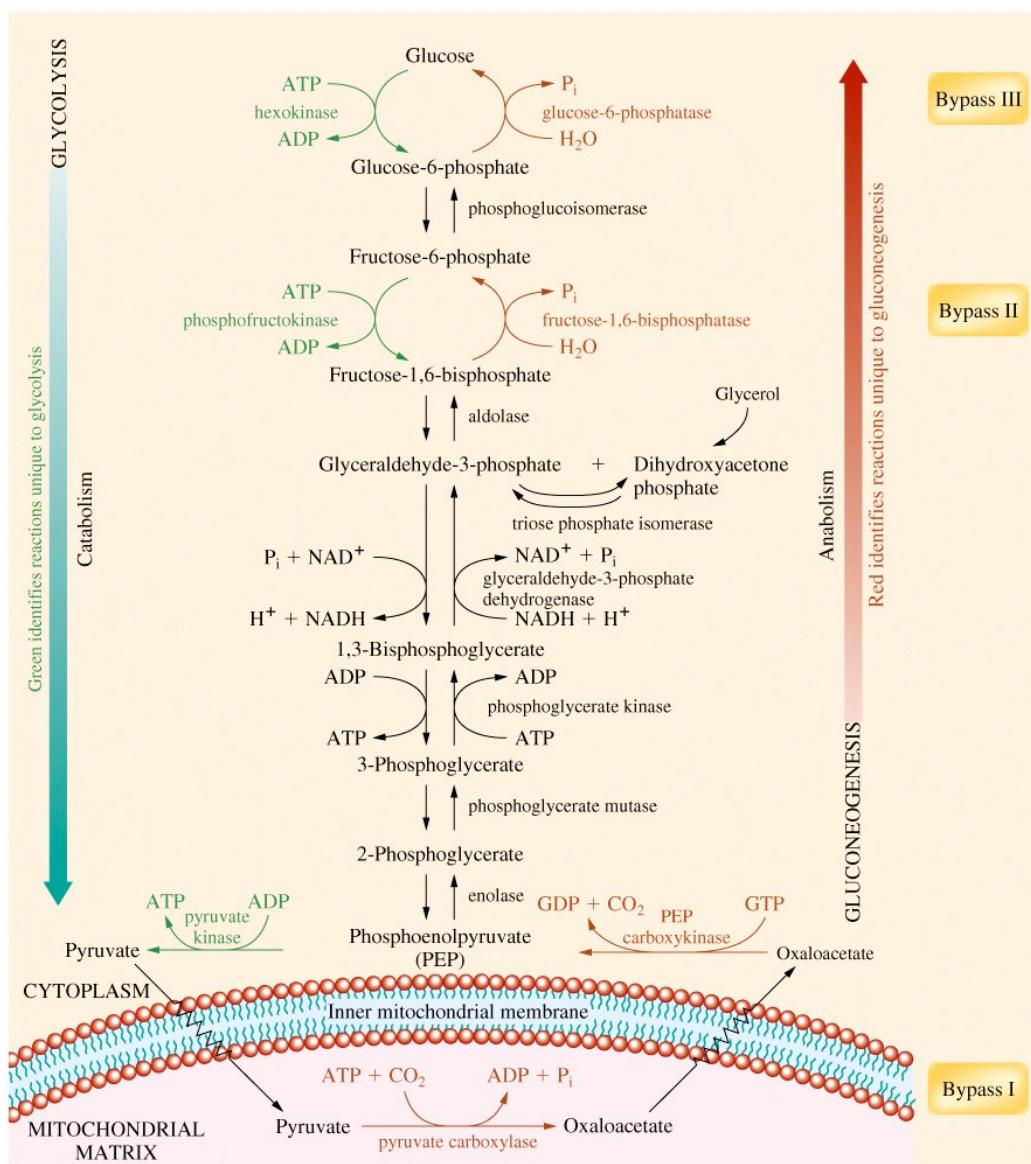
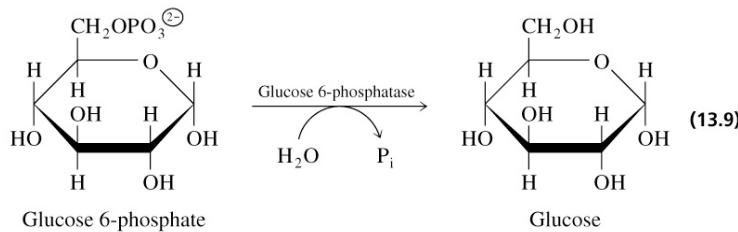
## Step 4: Glucose-6-phosphatase

- Endoplasmic reticulum membrane localization
- GLUT7 transporter transports G6P from cytosol to enzyme on the endoplasmic reticulum membrane (liver, kidney, pancreas, small intestine)



- Glucose-6-phosphate + H<sub>2</sub>O → glucose + Pi
  - Reverses hexokinase

- A metabolically irreversible hydrolysis reaction ( $\Delta G^\circ = -13.8 \text{ kJ mol}^{-1}$ )
  - Simple **hydrolysis** reaction
  - Glucose is exported from the ER to bloodstream



**Figure 15-9 Concepts in Biochemistry, 3/e**  
© 2006 John Wiley & Sons

## Regulation of Gluconeogenesis

- Substrate cycle - two opposing enzymes:
  - (1) Phosphofructokinase-1 (glycolysis)
  - (2) Fructose 1,6-bisphosphatase (gluconeogenesis)
- Modulating one enzyme in a **substrate cycle** will alter the flux through the opposing pathways
- Energy level (ATP vs AMP level) of cell dictates which pathway is ON: This insures that when cellular ATP is high (AMP would then be low), glucose is not degraded to make ATP. It is more useful to the cell under such conditions to store glucose as glycogen.
- **Phosphofructokinase** (Glycolysis) is inhibited by ATP and stimulated by AMP.
  - Inhibiting Phosphofructokinase **stimulates** gluconeogenesis
- **Fructose 1,6-bisphosphatase** (Gluconeogenesis) is inhibited by AMP and fructose 2,6-bisphosphate (F2,6BP)
  - Inhibiting Fructose 1,6-bisphosphatase stimulates glycolysis

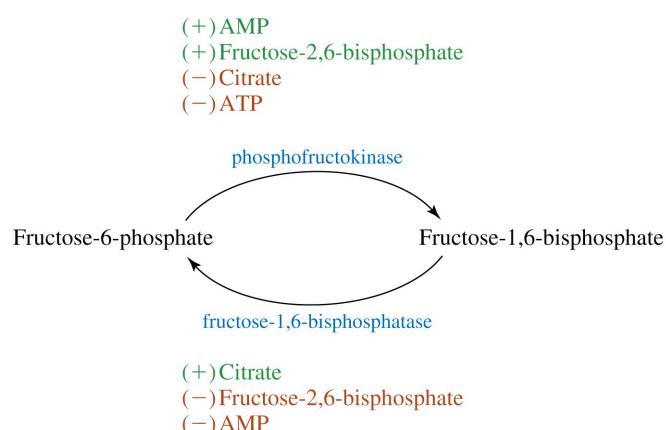
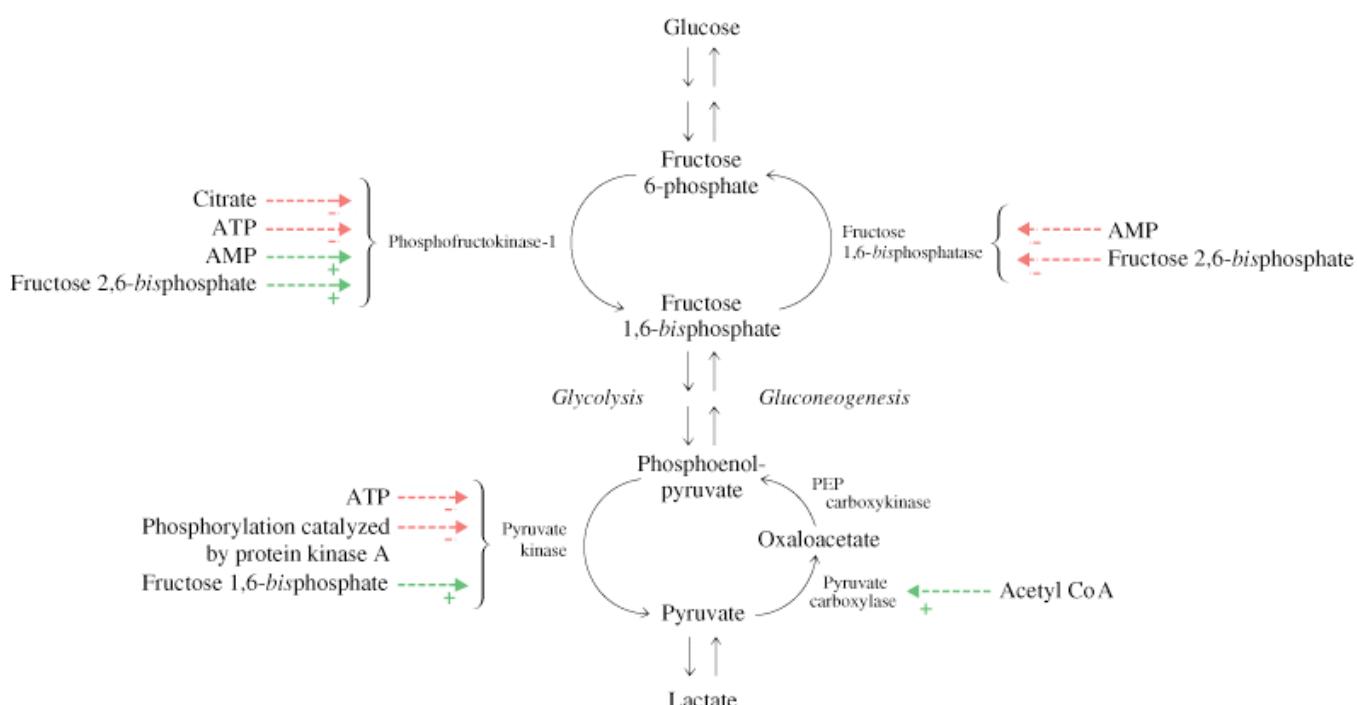
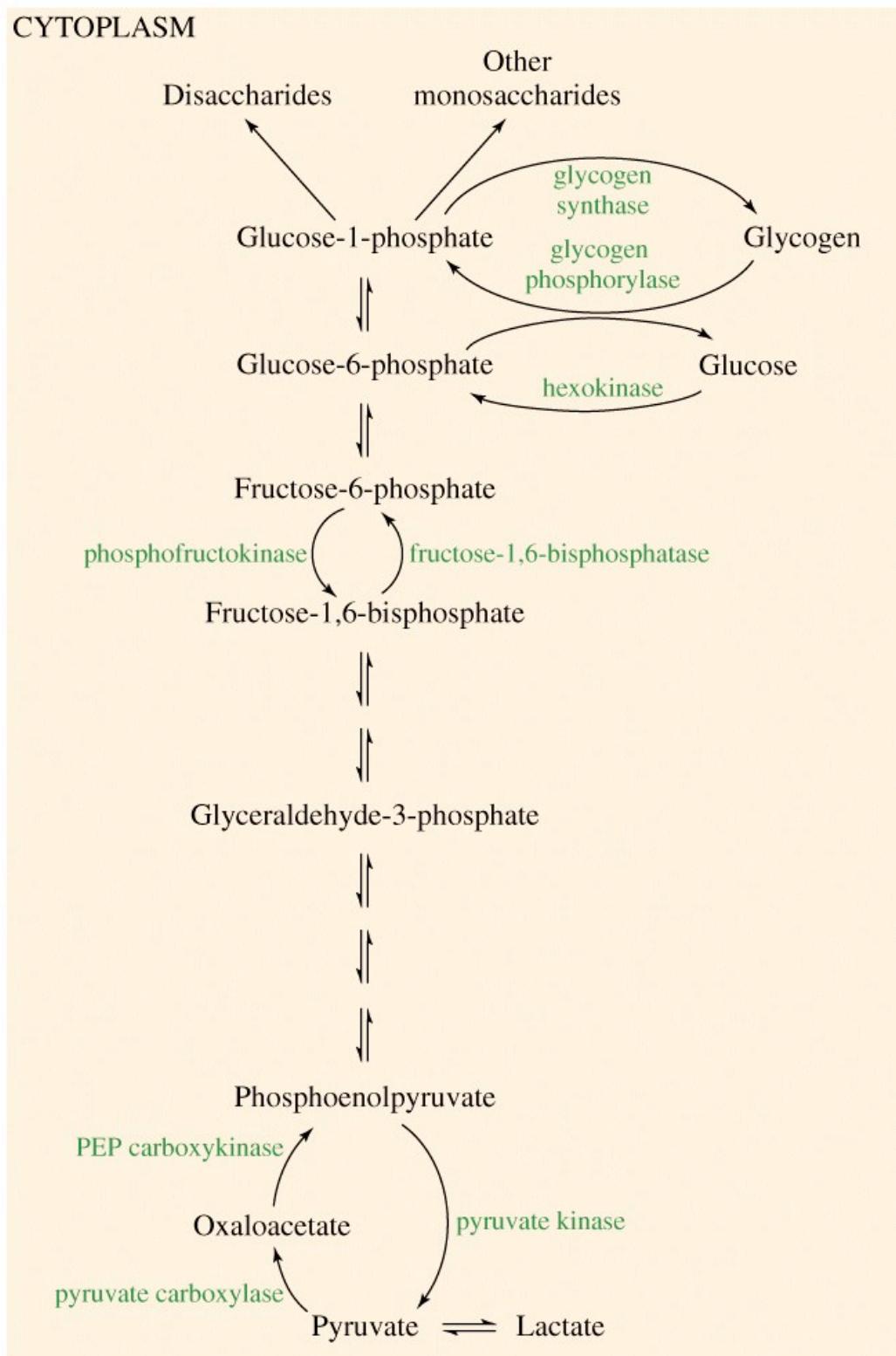


Figure 15-15 Concepts in Biochemistry, 3/e  
© 2006 John Wiley & Sons

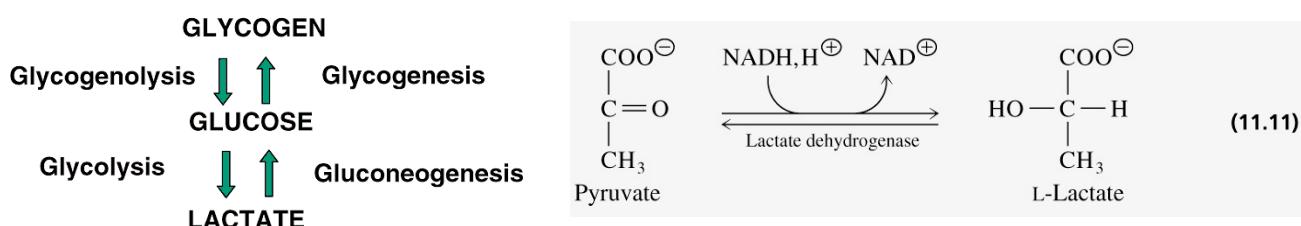




**Figure 15-12 Concepts in Biochemistry, 3/e**  
 © 2006 John Wiley & Sons

## Interaction of glycolysis and gluconeogenesis: The Cori Cycle

- The Cori Cycle operates during exercise, when aerobic metabolism in muscle cannot keep up with energy needs.
- Glucose synthesized in liver and transported to muscle and blood.
- A highly exercising muscle generates a lot of NADH from glycolysis but without oxygen there is no way to regenerate NAD<sup>+</sup> from the NADH (need NAD<sup>+</sup>!)
- Lactic acidosis can and would result from insufficient oxygen (an increase in lactic acid and decrease in blood pH)
- So, the NADH is reoxidized by reduction of **pyruvate to lactate** by enzyme **lactate dehydrogenase**; Results in replenishment of NAD<sup>+</sup> for glycolysis



- Then the lactate formed in skeletal muscles during exercise is transported to liver where it is used for **gluconeogenesis**
  - Lactate is transported through the bloodstream to the liver
  - Lactate is oxidized to pyruvate in the liver
  - Liver lactate dehydrogenase reconverts lactate to pyruvate since has high NAD<sup>+</sup>/NADH ratio
  - Pyruvate is used to remake glucose by gluconeogenesis
- Glucose is transported back to the muscles via the bloodstream

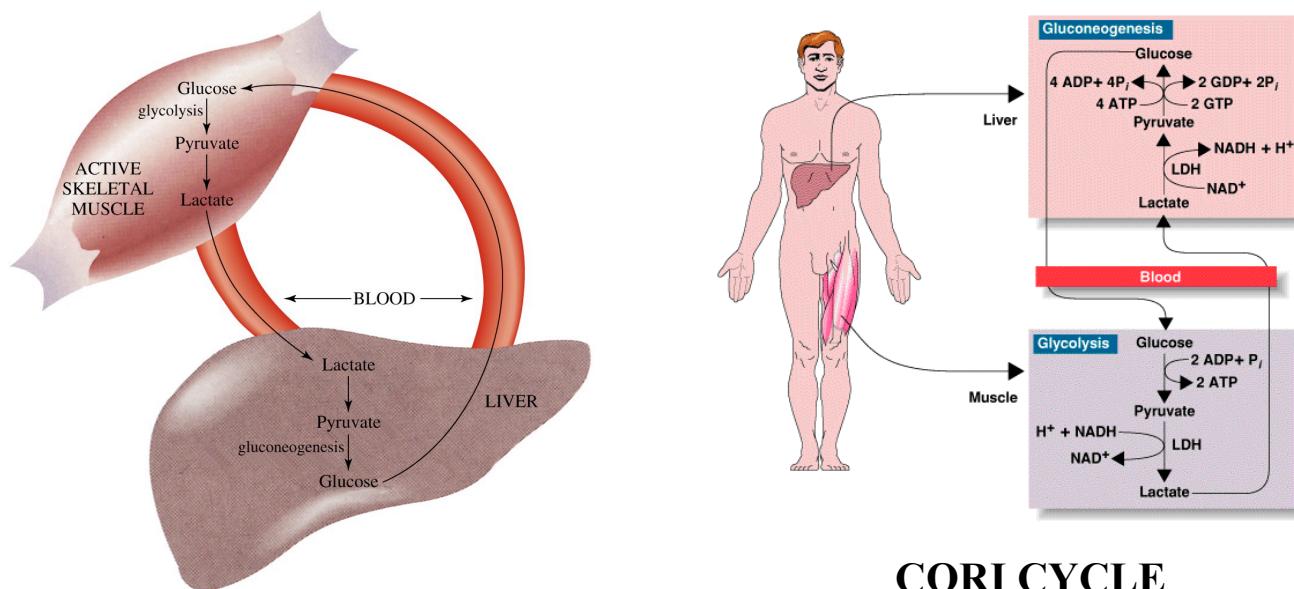


Figure 15-7 Concepts in Biochemistry, 3/e  
© 2006 John Wiley & Sons

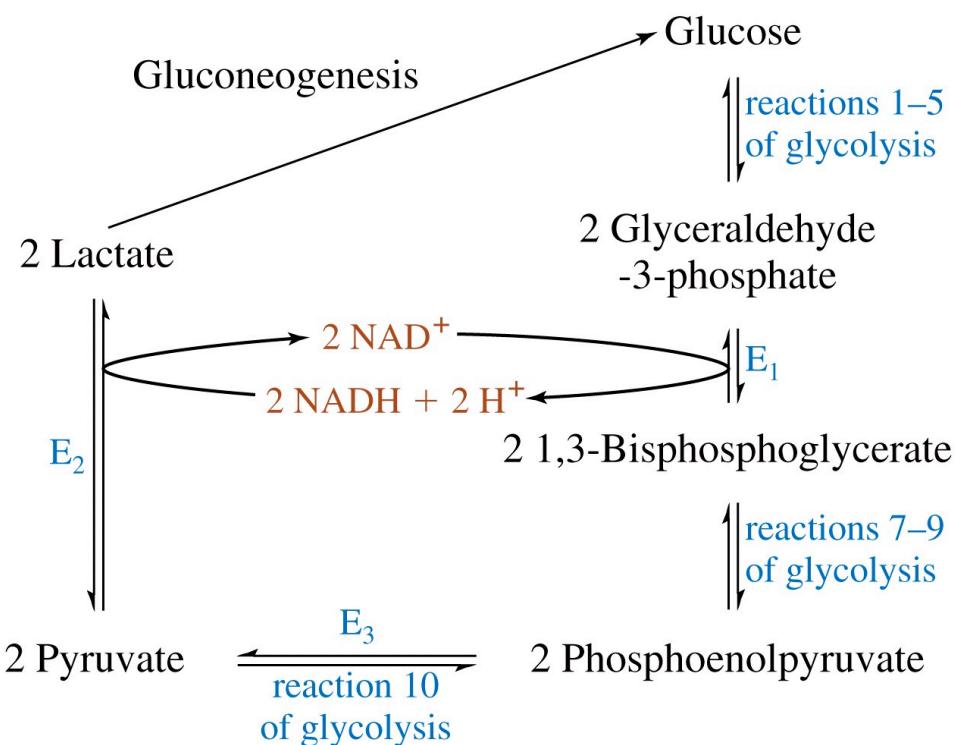


Figure 15-6 Concepts in Biochemistry, 3/e  
© 2006 John Wiley & Sons

## ETHANOL METABOLISM:

- Metabolism of ethanol alters the **NAD<sup>+</sup>/NADH ratio** in cells
- Primary site of ethanol metabolism is **LIVER**
- Some in stomach, kidneys, bone marrow
- Ethanol → Acetate by TWO enzymes in liver
  1. **Alcohol Dehydrogenase** (cytosol)
  2. **Aldehyde Dehydrogenase** (mitochondrial matrix)

- Alcohol consumption leads to excess NADH production
- Excess NADH *inhibits* NAD<sup>+</sup> requiring reactions in metabolic pathways because less of it is around, notably **gluconeogenesis** and **fatty acid metabolism**

### Consequences:

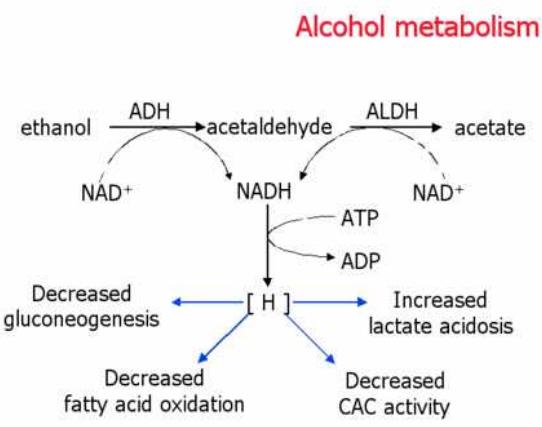
1. **Inhibiting fatty acid oxidation** leads to elevated TAG levels in liver
  - TAG's accumulate as fatty deposits and ultimately contribute to cirrhosis of the liver ("Fatty Liver")
  - Fatty acid synthesis is increased and there is an increase in triacylglyceride production by the liver.
2. **Inhibition of gluconeogenesis leads to:**
  - Buildup of substrate lactate (lactic acid) causing acidosis (rarely overt)
  - Hypoglycemia (low blood sugar) in undernourished people. Can lead to irreversible CNS damage

Too much NADH greatly favors the conversion of pyruvate to lactate. Therefore, lactate, which is converted to pyruvate, cannot be used for gluconeogenesis. Glycerol is converted to DHAP via a reaction that needs NAD<sup>+</sup> and is inhibited by NADH; therefore glycerol cannot be used for gluconeogenesis.

3. **Acetaldehyde** can escape from the liver into blood and form adducts with protein –NH<sub>2</sub> groups, nucleic acids and other compounds which may impair function. The results of which are the toxic side effects (the **hangover**) - **Acetaldehyde** is **VERY** reactive

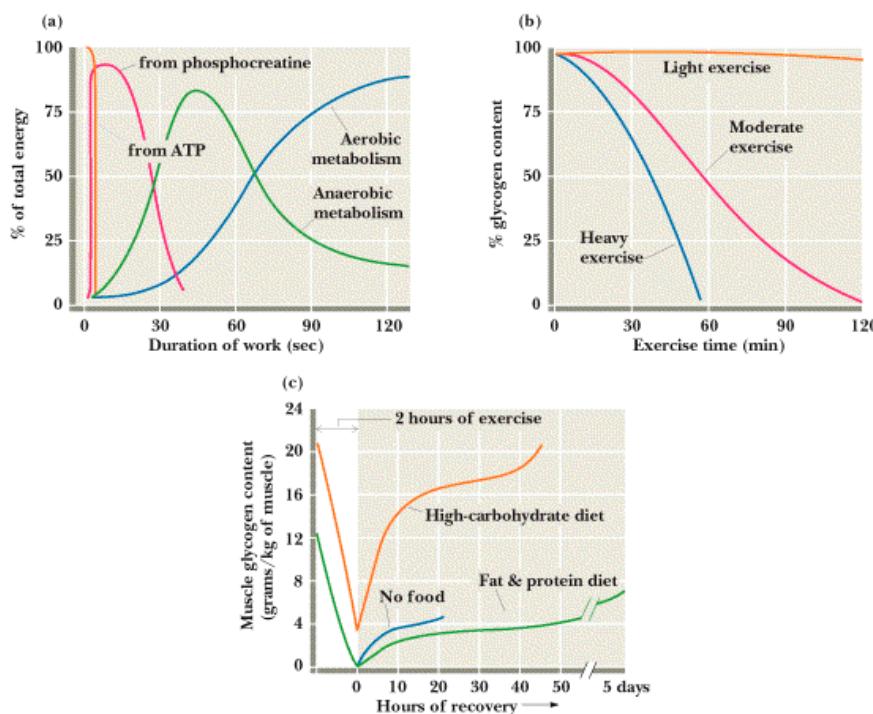
### **DON'T TAKE TYLENOL (acetaminophen) WITH ALCOHOL!!!**

- Ethanol induces production of cytochrome P450's that catalyze the oxidation of Tylenol to facilitate excretion
- However, with Tylenol, the oxidized product is **MORE** toxic than the parent compound
- Liver damage can result



24-85

## FUELS USED DURING EXERCISE



### PANEL A:

#### The Immediate Energy System

- Provides energy rapidly but for only a short period of time
- It is used to fuel activities that last for about **10 or fewer seconds**
- For example weight lifting and picking up a bag of groceries
- Components includes existing cellular ATP stores and creatine phosphate (CP)

#### The Nonoxidative (Anaerobic ) Energy System

- Used at the start of an exercise session and for high intensity activities lasting for about **10 seconds to 2 minutes**
- Examples, 400 meter run or to dash up several flights of stairs
- Creates ATP by breaking down glucose and glycogen.
- Does not require oxygen
- 2 key limiting factors
  - body's supply of glucose and glycogen is limited
  - nonoxidative system results in the production of lactic acid

#### The Oxidative (Aerobic) Energy System

- Requires oxygen to generate ATP
- The aerobic production of energy does not produce any toxic waste products and so is the preferred system for prolonged exercise.
- Used during physical activity that lasts longer than ~2 minutes (e.g. distance running, hiking)
- ATP production takes place in cellular structures called mitochondria – can use carbohydrates (glucose and glycogen) or fats to produces ATP

The actual fuel source depends on:

- Intensity and duration of the activity
- Fitness status of the individual

### Glycogen Utilization

### Glycogen Recovery

**PANEL B:**

In general, carbohydrate use increases with increasing intensity and falls with increasing duration of an activity. Fats are used for lower – intensity exercise.

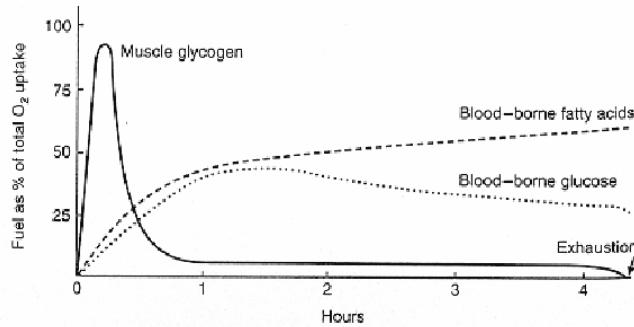
Glycogen stores are finite, and inevitably become depleted during long continuous exercise lasting in excess of 70-92 minutes (the more intensive the exercise, the quicker the glycogen is depleted). This applies not only to endurance events, such as marathon running but also to intermittent exercise sports such as soccer and rugby. When glycogen stores have been used up, the muscles attempt to cover their energy needs from fat metabolism. Unfortunately, because fat cannot supply energy at as rapid a rate as carbohydrate, the competitor is forced to slow down or reduce his/her rate of work to the level at which energy expenditure and energy synthesis are matched.

This situation is made worse by the fact that when glycogen stores in the muscles are used up, blood glucose (hypoglycemia) reduces the supply of glucose to the brain, contributing to the feeling of exhaustion and causing a decrease in technique and the ability to make correct decisions.

**PANEL C:**

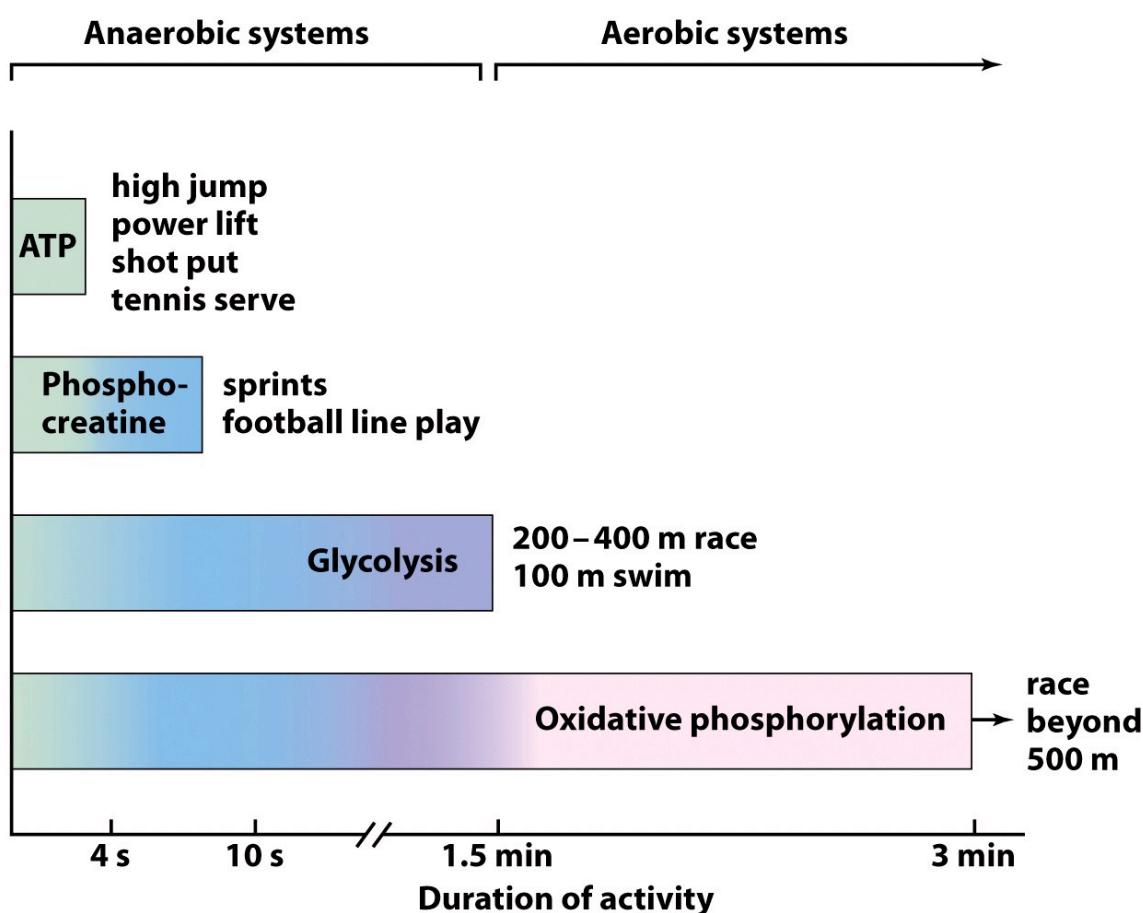
Choice of diet has a dramatic effect on glycogen recovery following exhaustive exercise. A diet consisting mainly of protein and far results in very little recovery of muscle glycogen even after 5 days! On the other hand a high carbohydrate diet provides faster restoration of muscle glycogen. Even though, however, complete recovery of glycogen stores takes about 2 days. During a prolonged exercise session, carbohydrates are the predominant fuel at the start of a workout, but fat utilizations (aerobic) increases over time.

Carbohydrate metabolism is an energy system that does not depend on oxygen, but is only available for a short period of time as it rapidly causes fatigue. One of the reasons for this fatigue is the accumulation of lactic acid which quickly reduces the ability of the muscles to contract effectively. Lactic acid in the muscles can cause discomfort both during and after exercise, and total recovery will not occur until the excess lactic acid produced during exercise has been fully degraded.

**Fuels Used During Exercise**

- the pattern of fuel utilization changes with the duration of the exercise

Remember, entry of glucose into muscles requires insulin! (Fed-state!)



© John Wiley & Sons, Inc. All rights reserved.