Integration Of Metabolism
Metabolism Consist of Highly Interconnected Pathways

• The basic strategy of catabolic metabolism is to form **ATP, NADPH, and building blocks** for biosyntheses.

1. **ATP is the universal currency of energy**

Energy source in muscle contraction, active transport, signal amplification, and biosyntheses.
2. **ATP is generated by the oxidation of fuel molecules such as glucose, fatty acids, and amino acids.**

The common intermediate in most of these oxidations is acetyl CoA. The carbon atoms of the acetyl unit are completely oxidized to CO₂ by the citric acid cycle with the concomitant formation of NADH and FADH2. These electron carriers then transfer their high potential electrons to the respiratory chain.
3. **NADPH is the major electron donor in reductive biosyntheses.**

In most biosyntheses, the products are more reduced than the precursors, and so reductive power is needed as well as ATP. The high-potential electrons required to drive these reactions are usually provided by NADPH. The **pentose phosphate pathway** supplies much of the required NADPH.
4. **Biomolecules are constructed from a small set of building blocks**

The metabolic pathways that generate ATP and NADPH also provide building blocks for the biosynthesis of more-complex molecules. For example, *acetyl CoA*, the common intermediate in the breakdown of most fuels, supplies a two-carbon unit in a wide variety of biosyntheses, such as those leading to fatty acids, prostaglandins, and cholesterol.
5. **Biosynthetic and degradative pathways are almost always distinct**

For example, the pathway for the synthesis of fatty acids is different from that of their degradation. This separation enables both biosynthetic and degradative pathways to be thermodynamically favorable at all times.
Anabolism and catabolism must be precisely coordinated.

1. *Allosteric interactions*

Enzymes that catalyze essentially irreversible reactions are likely control sites, and the first irreversible reaction in a pathway (the committed step) is nearly always tightly controlled.
2. **Covalent modification**

Some regulatory enzymes are controlled by covalent modification in addition to allosteric interactions. For example, the catalytic activity of glycogen phosphorylase is enhanced by phosphorylation, whereas that of glycogen synthase is diminished.
3. **Enzyme levels**

The amounts of enzymes, as well as their activities, are controlled. The rates of synthesis and degradation of many regulatory enzymes are altered by hormones.
Figure 24.1
Control mechanisms of metabolism and some typical response times. [Note: Response times may vary according to the nature of the stimulus and from tissue to tissue.]
4. *Compartmentation*

The metabolic patterns of eukaryotic cells are markedly affected by the presence of compartments. The fates of certain molecules depend on whether they are in the cytosol or in mitochondria, and so their flow across the inner mitochondrial membrane is often regulated.
Compartmentation of the Major Pathways of Metabolism

Cytosol:
- Glycolysis
- Pentose phosphate pathway
- Fatty acid synthesis

Mitochondrial matrix
- Citric acid cycle
- Oxidative phosphorylation
- $\beta$-Oxidation of fatty acids
- Ketone-body formation

Interplay of both compartments:
- Gluconeogenesis
- Urea synthesis
5. Metabolic specializations of organs. 

Regulation in higher eukaryotes is enhanced by the existence of organs with different metabolic roles. Metabolic specialization is the result of differential gene expression.
Major Metabolic Pathways and Control Sites

1. Glycolysis
2. Citric acid cycle and oxidative phosphorylation
3. Pentose phosphate pathway
4. Gluconeogenesis
5. Glycogen synthesis and degradation
6. Fatty acid synthesis and degradation
7. Nucleotide metabolism
1. *Glucose 6-phosphate.*

Stored as glycogen, degraded to pyruvate, or converted into ribose 5-phosphate. Glucose 6-phosphate can be formed by the mobilization of glycogen or it can be synthesized from pyruvate and glucogenic amino acids by the gluconeogenic pathway.
Metabolic Fates of Glucose 6-Phosphate

- Glucose
- Glucose 6-phosphate
- Glucose 1-phosphate
- Fructose 6-phosphate
- Pyruvate
- 6-Phosphogluconate
- Ribose 5-phosphate
- Glycogen
2. Pyruvate

Primarily from glucose 6-phosphate, alanine, and lactate. Pyruvate can be reduced to lactate by LDH to regenerate NAD+. This reaction enables glycolysis to proceed transiently under anaerobic conditions in active tissues such as contracting muscle. The lactate formed in active tissue is subsequently oxidized back to pyruvate, in other tissues. The essence of this interconversion buys time and shifts part of the metabolic burden of active muscle to other tissues.
Another readily reversible reaction in the cytosol is the transamination of pyruvate, an $\alpha$-ketoacid, to alanine, the corresponding amino acid.

Several amino acids can be converted into pyruvate. Thus, *transamination is a major link between amino acid and carbohydrate metabolism.*
A third fate of pyruvate is its carboxylation to oxaloacetate inside mitochondria, the first step in gluconeogenesis. This reaction and the subsequent conversion of oxaloacetate into phosphoenolpyruvate bypass an irreversible step of glycolysis and hence enable glucose to be synthesized from pyruvate.
A fourth fate of pyruvate is its **oxidative decarboxylation** to acetyl CoA. This irreversible reaction inside mitochondria is a decisive reaction in metabolism: it commits the carbon atoms of carbohydrates and amino acids to oxidation by the citric acid cycle or to the synthesis of lipids.
Major Metabolic Fates of Pyruvate and Acetyl CoA in Mammals

- Pyruvate can be converted to glucose 6-phosphate, oxaloacetate, lactate, alanine, and 3-hydroxy-3-methylglutaryl CoA.
- Acetyl CoA can be further converted to cholesterol, ketone bodies, CO₂, and fatty acids.
3. **Acetyl CoA.**

The major sources of this activated two-carbon unit are the oxidative decarboxylation of pyruvate and the β-oxidation of fatty acids. Acetyl CoA is also derived from ketogenic amino acids. The fate of acetyl CoA, in contrast with that of many molecules in metabolism, is quite restricted. The acetyl unit can be completely oxidized to \( \text{CO}_2 \) by the citric acid cycle.
Alternatively, 3-hydroxy-3-methylglutaryl CoA can be formed from three molecules of acetyl CoA. This six-carbon unit is a precursor of cholesterol and of *ketone bodies*, which are *transport* forms of acetyl units released from the liver for use by some peripheral tissues. A third major fate of acetyl CoA is its export to the cytosol in the form of *citrate* for the synthesis of fatty acids.
Regulation of Glycolysis

Fructose 6-phosphate

ATP → Phosphofructokinase
Activated by F-2,6-BP
Activated by AMP
Inhibited by ATP and citrate

ADP → Fructose 1,6-bisphosphate
Regulation of Gluconeogenesis

Fructose 1,6-bisphosphate

\[ \text{H}_2\text{O} \rightarrow \text{Fructose 1,6-bisphosphatase} \]

Activated by citrate
Inhibited by AMP
Inhibited by F-2,6-BP

Fructose 6-phosphate
Regulation of the Pentose Phosphate Pathway

Glucose 6-phosphate

\[
\text{NADP}^+ \quad \text{Glucose 6-phosphate dehydrogenase} \quad \text{NADPH}
\]

6-Phosphoglucono-δ-lactone

\[
\text{H}_2\text{O} \quad \text{Lactonase} \quad 6\text{-Phosphogluconate}
\]
Regulation of Fatty Acid Synthesis

Acetyl CoA

\[ \text{H}_3\text{C} \text{S} \text{CoA} \]

\[ \text{HCO}_3^- + \text{ATP} \]

\[ \text{Acetyl CoA carboxylase} \]

\[ \text{Activated by citrate} \]

\[ \text{ATP} + P_i \]

\[ \text{Inhibited by palmitoyl CoA} \]

Malonyl CoA

\[ \text{H}_2\text{C} \text{S} \text{CoA} \]
Control of Fatty Acid Degradation

Carnitine acyltransferase I

Carnitine

Inhibited by malonyl CoA

Acyl carnitine

Acyl CoA

CoASH
Each Organ Has a Unique Metabolic Profile

1. **Brain.** *Glucose is virtually the sole fuel for the human brain, except during prolonged starvation.*

It consumes about 120 g daily, which corresponds to an energy input of about 420 kcal, accounting for some **60%** of the utilization of glucose by the whole body in the resting state. Much of the energy, estimates suggest from 60% to 70%, is used to power transport mechanisms that maintain the Na+-K+ membrane potential required for the transmission of the nerve impulses.
This danger point is reached when the plasma-glucose level drops below about 2.2 mM /L (40 mg/dl)

Fatty acids do not serve as fuel for the brain, because they are bound to albumin in plasma and so do not traverse the blood-brain barrier. In starvation, *ketone bodies* generated by the liver partly replace glucose as fuel for the brain.
Of the fuels circulating in the blood, only glucose can penetrate the blood-brain barrier.

Figure 24.7
Major metabolic pathways in brain in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate metabolism.]
2. Muscle

The major fuels for muscle are glucose, fatty acids, and ketone bodies.

Muscle differs from the brain in having a large store of glycogen (1200 kcal. In fact, about 3/4 of all the glycogen in the body is stored in muscle. This glycogen is readily converted into glucose-6-P for use within muscle cells.

Muscle, like the brain, lacks glucose 6-phosphatase, and so it does not export glucose. Rather, muscle retains glucose, its preferred fuel for bursts of activity.
In actively contracting skeletal muscle, the rate of glycolysis far exceeds that of the citric acid cycle, and much of the pyruvate formed is reduced to lactate, some of which flows to the liver, where it is converted into glucose. These interchanges, known as the Cori cycle shift part of the metabolic burden of muscle to the liver.
In addition, a large amount of alanine is formed in active muscle by the transamination of pyruvate. Alanine, like lactate, can be converted into glucose by the liver. Why does the muscle release alanine? Muscle can absorb and transaminate branched-chain amino acids; however, it cannot form urea. Consequently, the nitrogen is released into the blood as alanine.
Metabolic Interchanges between Muscle and Liver
3. Heart

- Unlike skeletal muscle, heart muscle functions almost exclusively aerobically, as evidenced by the density of mitochondria in heart muscle. Moreover, the heart has virtually no glycogen reserves. **Fatty acids** are the heart's main source of fuel, although **ketone bodies** as well as **lactate** can serve as fuel for heart muscle. In fact, heart muscle consumes acetoacetate in preference to glucose.
4. Adipose tissue
The triacylglycerols stored in adipose tissue are an enormous reservoir of metabolic fuel.

In a typical 70-kg man, the 11 kg of triacylglycerols have an energy content of 100,000 kcal. Adipose tissue is specialized for the esterification of fatty acids and for their release from triacylglycerols.

In human beings, the liver is the major site of fatty acid synthesis. Recall that these fatty acids are esterified in the liver to glycerol phosphate to form triacylglycerol and are transported to the adipose tissue in lipoprotein particles, such as VLDL.
Triacylglycerols are not taken up by adipocytes; rather, they are first hydrolyzed by an extracellular lipoprotein lipase for uptake. This lipase is stimulated by processes initiated by insulin. After the fatty acids enter the cell, the principal task of adipose tissue is to activate these fatty acids and transfer the resulting CoA derivatives to glycerol in the form of glycerol 3-phosphate. This essential intermediate in lipid biosynthesis comes from the reduction of the glycolytic intermediate dihydroxyacetone phosphate. Thus, adipose cells need glucose for the synthesis of triacylglycerols.
Triacylglycerols are hydrolyzed to fatty acids and glycerol by *intracellular lipases*. The release of the first fatty acid from a triacylglycerol, the rate-limiting step, is catalyzed by a hormone-sensitive lipase that is reversibly phosphorylated. The hormone *epinephrine* stimulates the formation of cyclic AMP, the intracellular messenger in the amplifying cascade.
Synthesis and Degradation of Triacylglycerols by Adipose Tissue
5. Kidneys

- The kidneys require large amounts of energy to accomplish the reabsorption. Although constituting only 0.5% of body mass, kidneys consume 10% of the oxygen used in cellular respiration. Much of the glucose that is reabsorbed is carried into the kidney cells by the sodium-glucose cotransporter.
During starvation, the kidney becomes an important site of gluconeogenesis and may contribute as much as $\frac{1}{2}$ of the blood glucose.
6. Liver

- The metabolic activities of the liver are essential for providing fuel to the brain, muscle, and other peripheral organs.
- Indeed, the liver, which can be from 2% to 4% of body weight, is an organism's metabolic hub (center of metabolism).
- Most compounds absorbed by the intestine first pass through the liver, which is thus able to regulate the level of many metabolites in the blood.
END of Metabolism
Part I >>
Food Intake and Starvation Induce Metabolic Changes

• This nightly starved fed cycle has three stages: the postabsorptive state after a meal, the early fasting during the night, and the refed state after breakfast. A major goal of the many biochemical alterations in this period is to maintain glucose homeostasis that is, a constant blood-glucose level.
• What happened in the well-fed, or postabsorptive, state?
1. The well-fed, or postabsorptive, state

After we consume and digest an evening meal, glucose and amino acids are transported from the intestine to the blood. The dietary lipids are packaged into chylomicrons and transported to the blood by the lymphatic system. This fed condition leads to the secretion of insulin, which is one of the two most important regulators of fuel metabolism, the other regulator being glucagon.
<table>
<thead>
<tr>
<th>Metabolic Process</th>
<th>Location</th>
<th>Effect</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose uptake</td>
<td>Muscle</td>
<td>Increases</td>
<td>GLUT4 transporter</td>
</tr>
<tr>
<td>Glucose breakdown</td>
<td>Liver</td>
<td>Increases</td>
<td>Glucokinase</td>
</tr>
<tr>
<td>Glycolysis</td>
<td>Muscle and liver</td>
<td>Increases</td>
<td>PFK-1</td>
</tr>
<tr>
<td>Acetyl-CoA production</td>
<td>Muscle and liver</td>
<td>Increases</td>
<td>Pyruvate dehydrogenase</td>
</tr>
<tr>
<td>Glycogen synthesis</td>
<td>Muscle and liver</td>
<td>Increases</td>
<td>Glycogen synthase</td>
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<tr>
<td>Glycogen breakdown</td>
<td>Muscle and liver</td>
<td>Decreases</td>
<td>Glycogen phosphorylase</td>
</tr>
<tr>
<td>Fatty-acid synthesis</td>
<td>Liver and muscle</td>
<td>Increases</td>
<td>Acetyl-CoA varboxylase</td>
</tr>
<tr>
<td>Triacylglycerol synthesis</td>
<td>Adipocytes</td>
<td>Increases</td>
<td>Lipoprotein lipase</td>
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</tbody>
</table>
The liver helps to limit the amount of glucose in the blood during times of plenty by storing it as glycogen so as to be able to release glucose in times of scarcity. How is the excess blood glucose present after a meal removed? Insulin accelerates the uptake of blood glucose into the liver by GLUT2. The level of glucose 6-phosphate in the liver rises because only then do the catalytic sites of glucokinase become filled with glucose.
• The high insulin level in the fed state also promotes the entry of glucose into muscle and adipose tissue. Insulin stimulates the synthesis of glycogen by muscle as well as by the liver. The entry of glucose into adipose tissue provides glycerol 3-phosphate for the synthesis of triacylglycerols. The action of insulin also extends to amino acid and protein metabolism. Insulin promotes the uptake of branched-chain amino acids (valine, leucine, and isoleucine) by muscles.
• What happened in the early fasting state?
2. The early fasting state

- The blood-glucose level begins to drop several hours after a meal, leading to a decrease in insulin secretion and a rise in glucagon secretion; glucagon is secreted by the α cells of the pancreas in response to a low blood-sugar level in the fasting state. Just as insulin signals the fed state, glucagon signals the starved state. It serves to mobilize glycogen stores when there is no dietary intake of glucose. The main target organ of glucagon is the liver.
Figure 24.9
Metabolic fuels present in a 70 kg man at the beginning of a fast.
• The large amount of glucose formed by the hydrolysis of glucose 6-phosphate derived from glycogen is then released from the liver into the blood. The entry of glucose into muscle and adipose tissue decreases in response to a low insulin level. The diminished utilization of glucose by muscle and adipose tissue also contributes to the maintenance of the blood glucose level. The net result of these actions of glucagon is to markedly increase the release of glucose by the liver.
Both muscle and liver use fatty acids as fuel when the blood-glucose level drops. Thus, the blood-glucose level is kept at or above 80 mg/dl by three major factors:

1. the mobilization of glycogen and the release of glucose by the liver,
2. the release of fatty acids by adipose tissue, and
3. the shift in the fuel used from glucose to fatty acids by muscle and the liver.
• What happened in the refed state?
What are the biochemical responses to a breakfast? Fat is processed exactly as it is processed in the normal fed state. However, this is not the case for glucose. The liver does not initially absorb glucose from the blood, but rather leaves it for the peripheral tissues. Moreover, the liver remains in a gluconeogenic mode. Now, however, the newly synthesized glucose is used to replenish the liver's glycogen stores. As the blood-glucose levels continue to rise, the liver completes the replenishment of its glycogen stores and begins to process the remaining excess glucose for fatty acid synthesis.
• What are the adaptations if fasting is prolonged to the point of starvation? A typical well-nourished 70-kg man has fuel reserves totaling about 161,000 kcal. The energy need for a 24-hour period ranges from about 1600 kcal to 6000 kcal, depending on the extent of activity. Thus, stored fuels sufficient to meet caloric needs in starvation for 1 to 3 months. However, the carbohydrate reserves are exhausted in only a day.
• What is the first priority in starvation & why?
The first priority

- Even under starvation conditions, the blood-glucose level must be maintained above 2.2 mM (40 mg/dl). The first priority of metabolism in starvation is to provide sufficient glucose to the brain and other tissues (such as red blood cells) that are absolutely dependent on this fuel.
• What is the second priority in starvation & why?
The second priority

- Thus, the second priority of metabolism in starvation is to preserve protein, which is accomplished by shifting the fuel being used from glucose to fatty acids and ketone bodies.
The metabolic changes on the first day of starvation are like those after an overnight fast. The low blood-sugar level leads to decreased secretion of insulin and increased secretion of glucagon. *The dominant metabolic processes are the mobilization of triacylglycerols in adipose tissue and gluconeogenesis by the liver. The liver obtains energy for its own needs by oxidizing fatty acids released from adipose tissue.*
The concentrations of **acetyl CoA** and **citrate** consequently increase, which switches off glycolysis. The uptake of glucose by muscle is markedly diminished because of the low insulin level, whereas fatty acids enter freely. Consequently, *muscle shifts almost entirely from glucose to fatty acids for fuel.*
• The β-oxidation of fatty acids by muscle halts the conversion of pyruvate into acetyl CoA, because acetyl CoA stimulates the phosphorylation of the pyruvate dehydrogenase complex, which renders it inactive.

• Hence, pyruvate, lactate, and alanine are exported to the liver for conversion into glucose. Glycerol derived from the cleavage of triacylglycerols is another raw material for the synthesis of glucose by the liver.
• Proteolysis also provides carbon skeletons for gluconeogenesis. During starvation, degraded proteins are not replenished and serve as carbon sources for glucose synthesis. Initial sources of protein are those that turn over rapidly, such as proteins of the intestinal epithelium and the secretions of the pancreas.
After about 3 days of starvation, the liver forms large amounts of acetoacetate and β-hydroxybutyrate (ketone bodies). Their synthesis from acetyl CoA increases markedly because the citric acid cycle is unable to oxidize all the acetyl units generated by the degradation of fatty acids. Gluconeogenesis depletes the supply of oxaloacetate, which is essential for the entry of acetyl CoA into the citric acid cycle. Consequently, the liver produces large quantities of ketone bodies, which are released into the blood.
• At this time, the brain begins to consume appreciable amounts of acetoacetate in place of glucose. After 3 days of starvation, about a $\frac{1}{3}$ of the energy needs of the brain are met by ketone bodies. The heart also uses ketone bodies as fuel.
After several weeks of starvation, ketone bodies become the major fuel of the brain. Acetoacetate is activated by the transfer of CoA from succinyl CoA to give acetoacetyl CoA. Cleavage by thiolase then yields two molecules of acetyl CoA, which enter the citric acid cycle. In essence, ketone bodies are equivalents of fatty acids that can pass through the blood-brain barrier. Only 40 g of glucose is then needed per day for the brain, compared with about 120 g in the first day of starvation.
The effective conversion of fatty acids into ketone bodies by the liver and their use by the brain markedly diminishes the need for glucose. Hence, less muscle is degraded than in the first days of starvation. The breakdown of 20 g of muscle daily compared with 75 g early in starvation is most important for survival.

A person's survival time is mainly determined by the size of the triacylglycerol depot.
• What happens after depletion of the triacylglycerol stores?
• The only source of fuel that remains is proteins. Protein degradation accelerates, and death inevitably results from a loss of heart, liver, or kidney function.

حسب عملك أما جنة أو إلى الجحيم وبئس المصير
Fuel Choice During Starvation

- **Glucose**: Decreases over days of starvation.
- **Ketone bodies**: Increases over days of starvation.
- **Fatty acids**: Increases over days of starvation.
## Fuel metabolism in starvation

<table>
<thead>
<tr>
<th>Fuel exchanges and consumption</th>
<th>3d day</th>
<th>40th day</th>
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<tbody>
<tr>
<td>Fuel use by the brain</td>
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<tr>
<td>Glucose</td>
<td>100</td>
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<tr>
<td>Ketone bodies</td>
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<td>100</td>
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<tr>
<td>All other use of glucose</td>
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<tr>
<td>Fuel mobilization</td>
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<tr>
<td>Adipose-tissue lipolysis</td>
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<td>180</td>
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<tr>
<td>Muscle-protein degradation</td>
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<td>20</td>
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<tr>
<td>Fuel output of the liver</td>
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<tr>
<td>Glucose</td>
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<tr>
<td>Ketone bodies</td>
<td>150</td>
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END of Metabolism
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