Integration Of Metabolism
Learning Objectives

1. What happens in metabolism in the well fed state?
2. What happens in metabolism in the fasting state?
3. Metabolic adaptation in prolonged starvation. What are the priorities?
POST-ABSORPTIVE PHASE 1

Liver

Adipose tissue

Muscle

Protein

Glycogen

Lactate

Erythrocyte

Energy

Brain

Blok 1.5 (2013)
POST-ABSORPTIVE PHASE 1

liver
- Energy
- Keto acids
- Amino acids
- Amino acids
- Glucose
- Lactate
- Glycogen

adipose tissue
- Triacylglyceride
- Glycerol
- Fatty acid
- Glucose

blood
- Energy
- Lactate
- Protein

muscle
- Amino acids
- Glucose
- Glycogen

erythrocyte
- Glucose
- Lactate

brain
- Glucose
- Energy
POST-ABSORPTIVE PHASE 1

effect of insulin

liver

energy

keto acids

amino acids

amino acids

lactate

glucose

glycogen

TAG

Adipose tissue

TAG

glycerol

fatty acids

blood

energy

lactate

protein

muscle

erythrocyte

brain

aminoc acids

+ glucose

+ fatty acids

+ glycogen

+ glucose

+ lactate
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.
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.
SUBSTRATE SATURATION CURVES FOR HEXOKINASE & GLUCOKINASE

Hexokinase

Glucokinase

Glucose + ATP → Glucose-6-P

Devlin, chapter 15, fig 14
• 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.
Hormonal control in the postabsorptive phase

- Effect
  - insuline
  - glucagon
  - adrenaline

Plasma glucose

Glucose uptake

Glycogenolysis

Gluconeogenesis

Lipolysis (FFA)
• 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.

Fat: 15 kg = 135,000 Kcal

Protein: 6 kg
= 24,000 kcal

Glycogen: 0.2 kg
= 800 kcal
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?
3. 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.
How is the loss of muscle curtailed?

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.
Fuel Choice During Starvation

- **Glucose** levels decrease over time during starvation.
- **Ketone bodies** and **fatty acids** levels increase over time during starvation.

Plots show:
- **X-axis**: Days of starvation
- **Y-axis**: Plasma level (mM)
# Fuel metabolism in starvation

## Amount formed or consumed in 24 hours (grams)

<table>
<thead>
<tr>
<th>Fuel exchanges and consumption</th>
<th>3d day</th>
<th>40th day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fuel use by the brain</strong></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>100</td>
<td>40</td>
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<tr>
<td>Ketone bodies</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>All other use of glucose</td>
<td>50</td>
<td>40</td>
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<td><strong>Fuel mobilization</strong></td>
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<tr>
<td>Adipose-tissue lipolysis</td>
<td>180</td>
<td>180</td>
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<td>Muscle-protein degradation</td>
<td>75</td>
<td>20</td>
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<tr>
<td><strong>Fuel output of the liver</strong></td>
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<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>150</td>
<td>80</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>150</td>
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</tbody>
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