Integration of metabolism

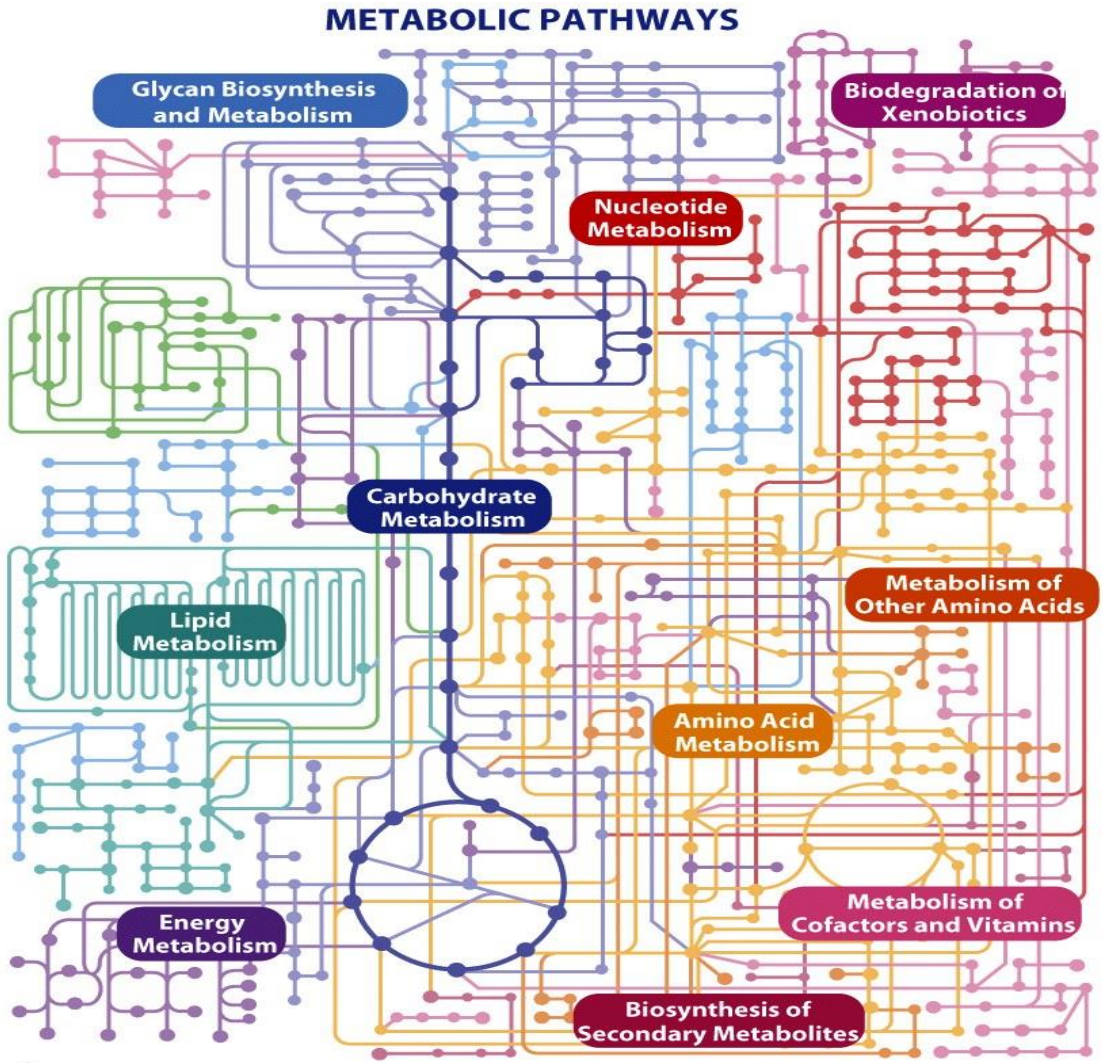

Figure 15-1
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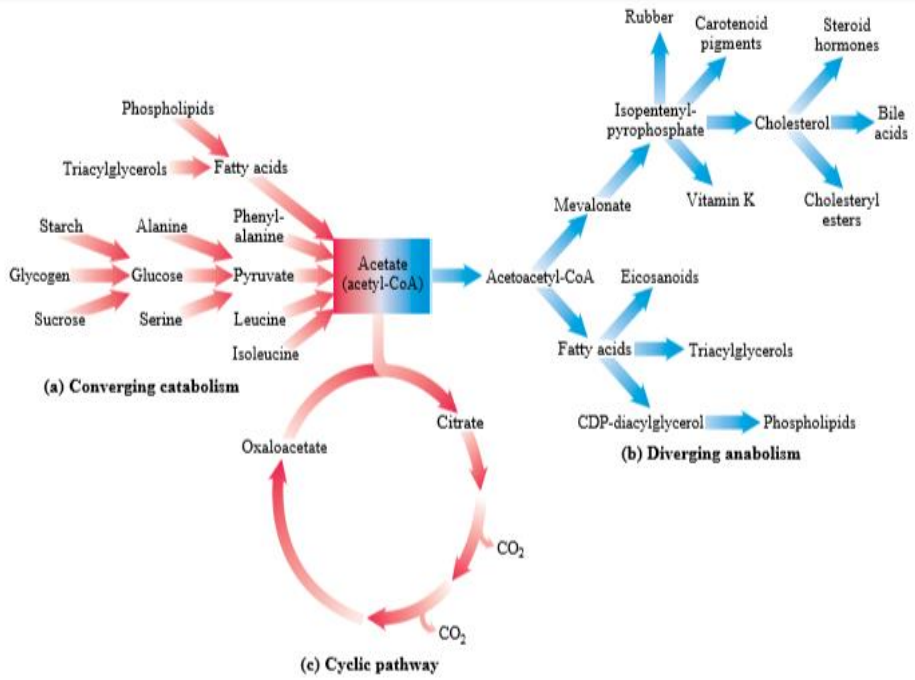
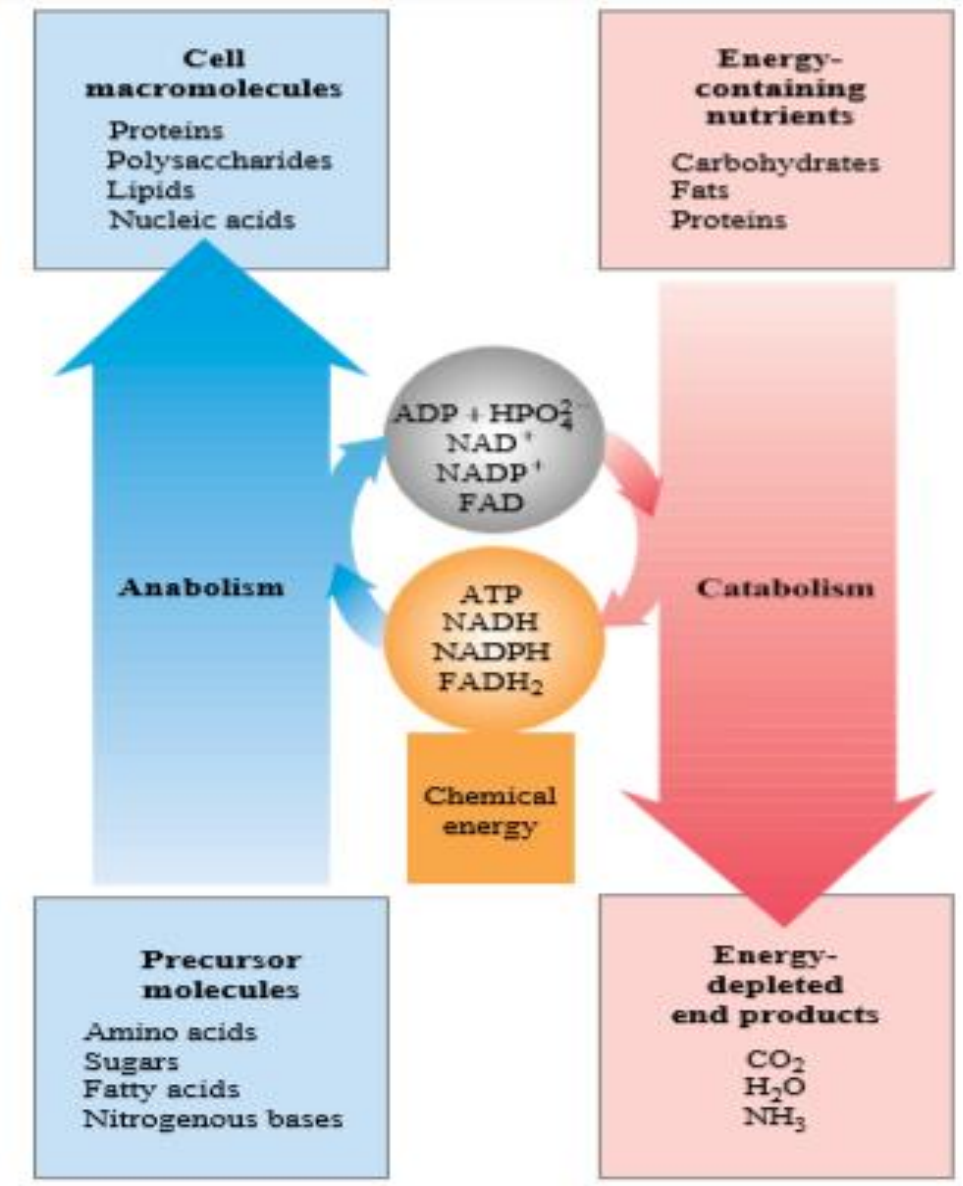
Objectives of integration of metabolism

1. Explain what is meant by anabolic, catabolic, and amphibolic metabolic pathways.
2. Describe in outline the metabolism of carbohydrates, lipids, and amino acids at the level of tissues and organs, and at the subcellular level, and the interconversion of metabolic fuels.
3. Describe the ways in which flux of metabolites through metabolic pathways is regulated.
4. Describe how a supply of metabolic fuels is provided in the fed and fasting states; the formation of metabolic fuels reserves in the fed state and their mobilization in fasting.



Metabolism : Anabolism & Catabolism



- **Metabolism,** the sum of all the chemical transformations taking place in a cell or organism, occurs through a series of enzyme-catalyzed reactions that constitute metabolic pathways.
- **Anabolism**, also called biosynthesis: small, simple precursors are built up into larger complex molecules. Anabolic reactions require an input of energy.
- **Catabolism** is the degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats, and proteins) are converted into smaller, simpler end products (such as CO_2, H_2O, NH_3). Catabolism generates/release energy i.e. ATP or heat.

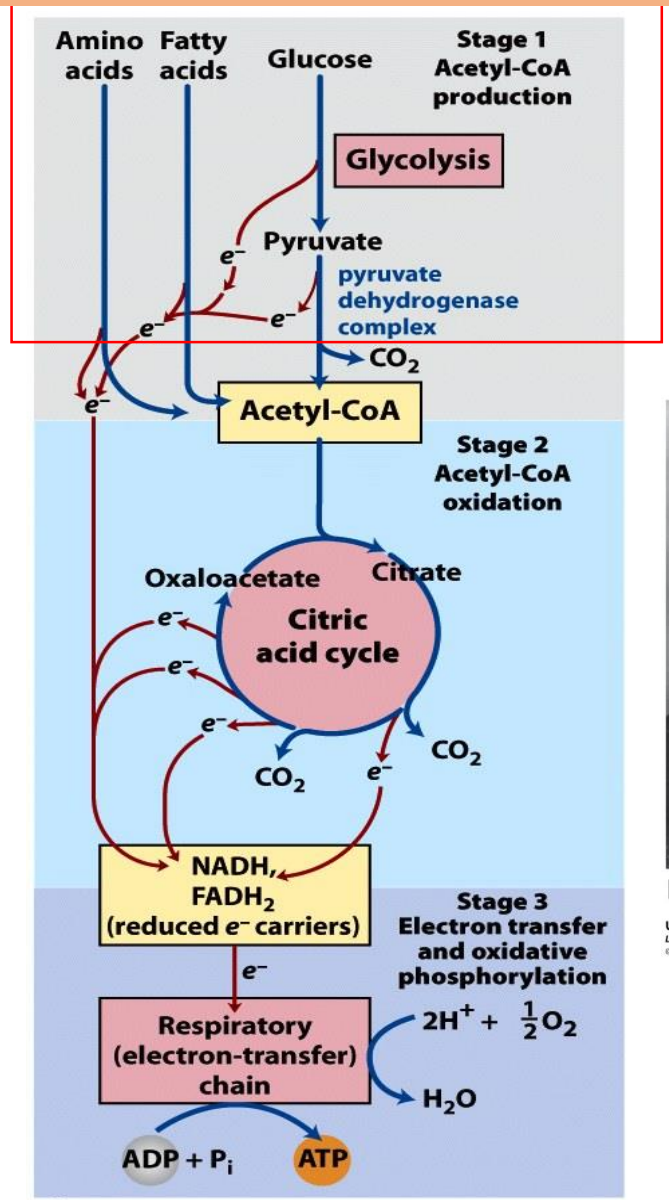
The metabolism of carbohydrates, lipid and protein

Catabolism of proteins, fats, and carbohydrates occur in the three stages of cellular respiration.

Stage 1: oxidation of fatty acids, glucose, and some amino acids yields acetyl-CoA.

Stage 2: oxidation of acetyl groups in the citric acid cycle includes four steps in which electrons are abstracted.

Stage 3: electrons carried by NADH and $FADH_2$ are funneled into a chain of mitochondrial (or, in bacteria, plasma membrane-bound) electron carriers—the respiratory chain—ultimately reducing O_2 to H_2O.This electron flow drives the production of ATP.



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Acetyl-CoA is a common degradation product

Hans Krebs, 1900–1981

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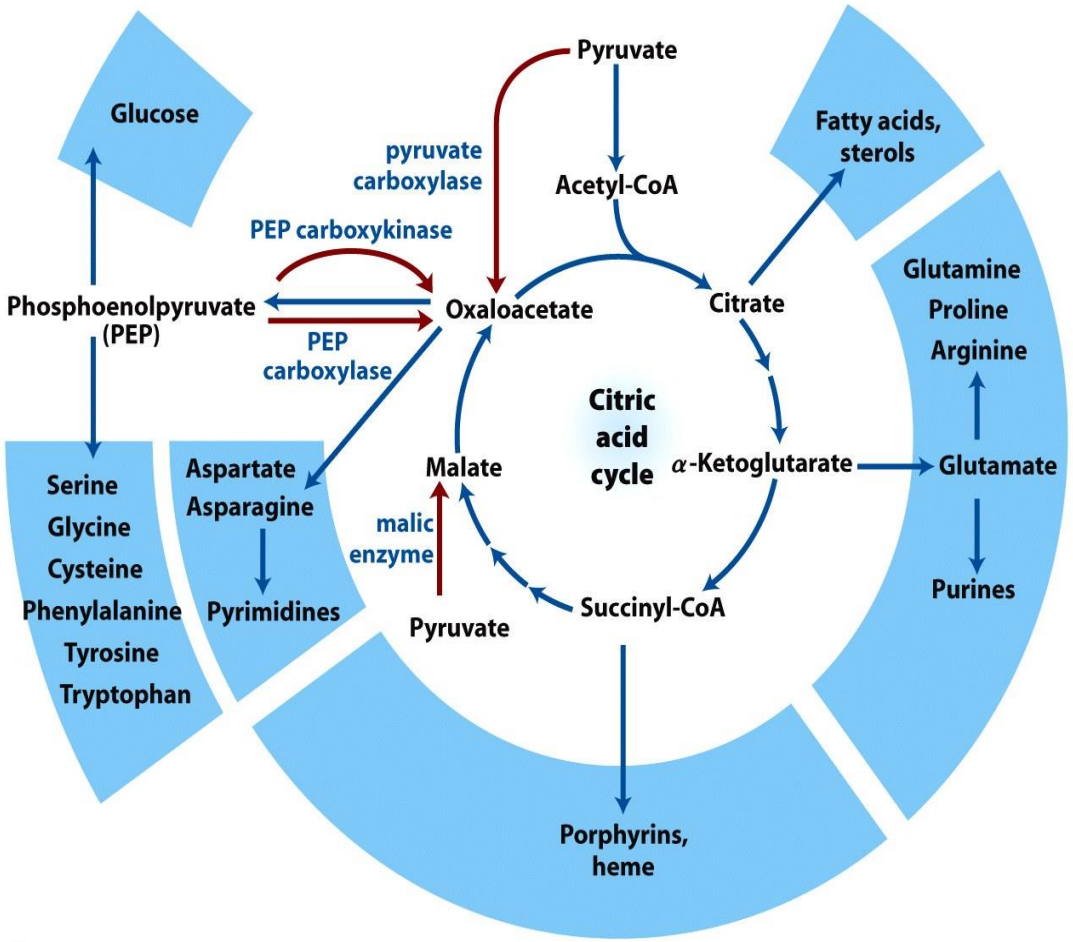
Metabolic pathways fall into 3 categories

Metabolic pathways fall into 3 types, anabolic, catabolic, and amphibolic pathways



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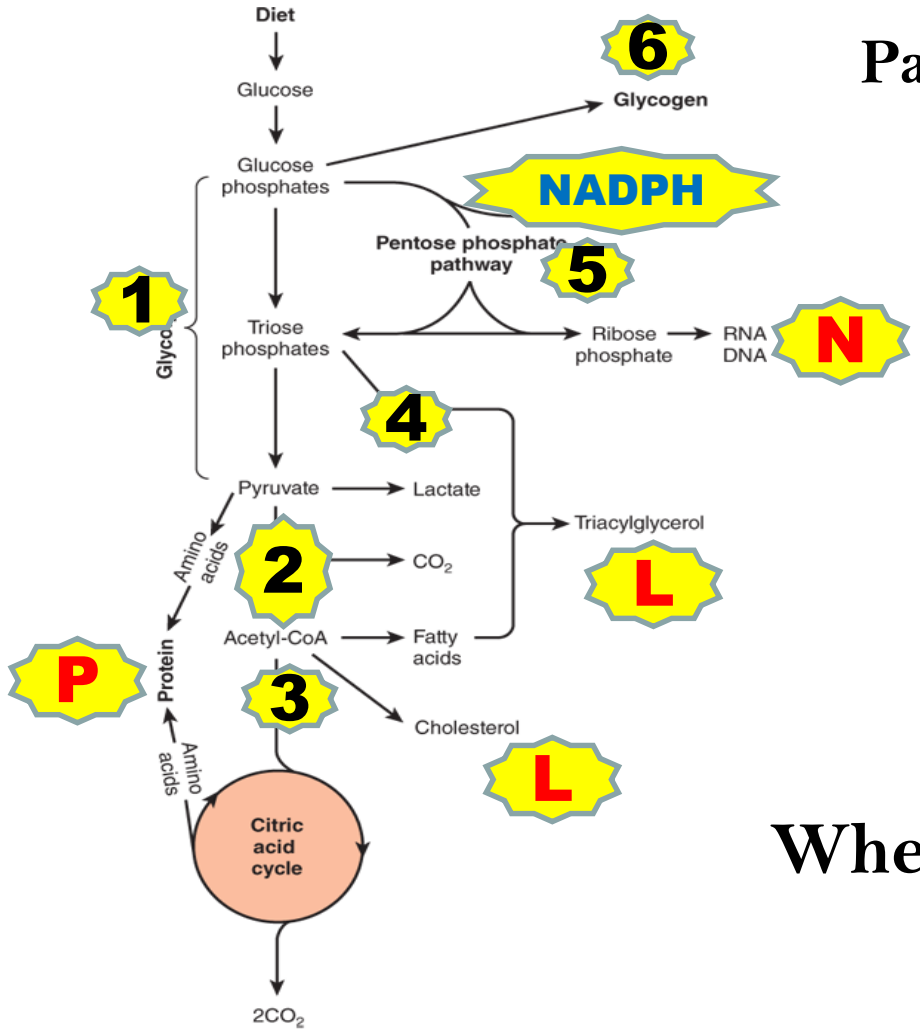
Citric acid cycle is an amphibolic pathway, serving both catabolic and anabolic pathways.

Catabolic pathway: oxidize acetyl CoA (from carbohydrate, protein, lipid) to CO_2 and ATP.

Anabolic pathway : intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways such as citrate for fatty acids synthesis.

Overview of carbohydrate metabolism



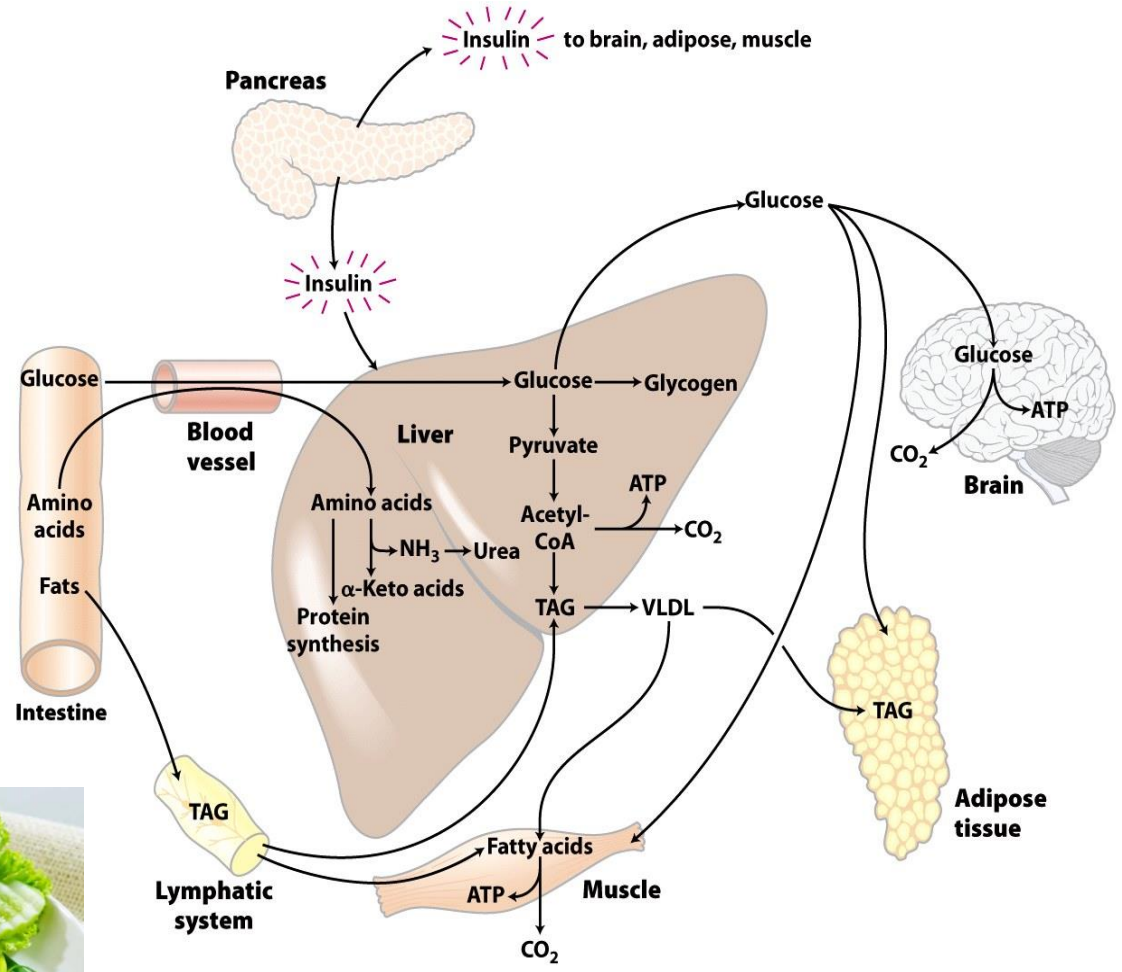
Source: V.W. Rodwell, D.A. Bender, K.M. Botham, P.J. Kennelly P.A. Weil: Harper's Illustrated Biochemistry, 31st Edition

Pathways of carbohydrate metabolism

1. Glycolysis (glucose → pyruvate)
2. Pyruvate → Acetyl CoA
3. Krebs' cycle → ETS → Energy (ATP)
4. Anaerobic glycolysis (Pyruvate → lactate)
5. Oxidation of glucose for NADPH, R-5-P (Pentose phosphate pathway)
6. Glycogenesis

Where does the integration of metabolism occur ?

The well-fed state: the lipogenic liver



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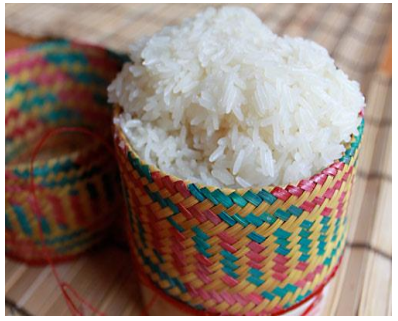
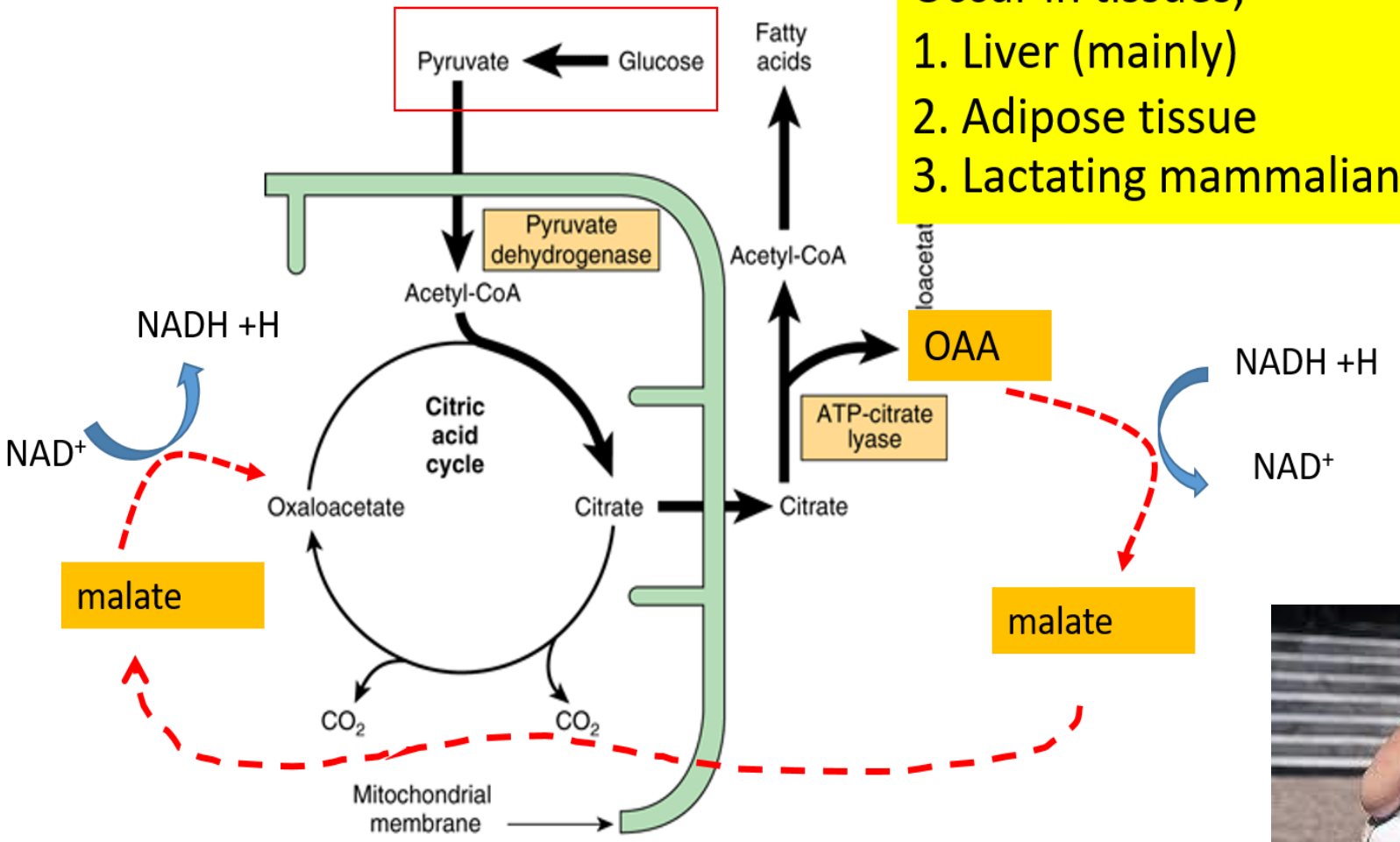
The well-fed state: the lipogenic liver.
Immediately after a calorie-rich meal, glucose, fatty acids, and amino acids enter the liver.

- Insulin released in response to the high blood glucose concentration stimulates glucose uptake by the tissues.
- Some glucose is exported to the brain for its energy needs, and some to adipose and muscle tissue.
- In the liver, excess glucose is oxidized to acetyl-CoA, which is used to synthesize fatty acids for export as triacylglycerols in VLDLs to adipose and muscle tissue.
- The NADPH necessary for lipid synthesis is obtained by oxidation of glucose in the pentose phosphate pathway.
- Excess amino acids are converted to pyruvate and acetyl-CoA, which are also used for lipid synthesis.
- Dietary fats move via the lymphatic system, as chylomicrons, from the intestine to muscle and adipose tissues.

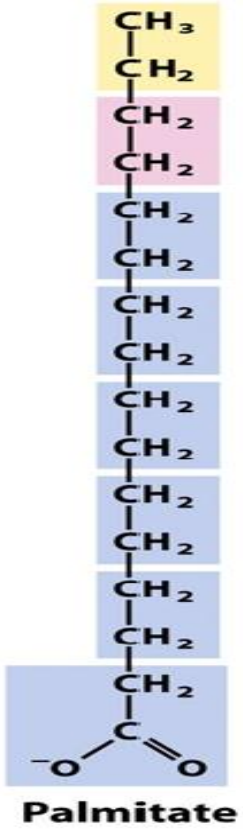
Glucose is the major source for fatty acids synthesis



Occur in tissues;
1. Liver (mainly)
2. Adipose tissue
3. Lactating mammalian gland



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com



Pentose phosphate pathway (PPP) supplies the NADPH for Fatty acid synthesis

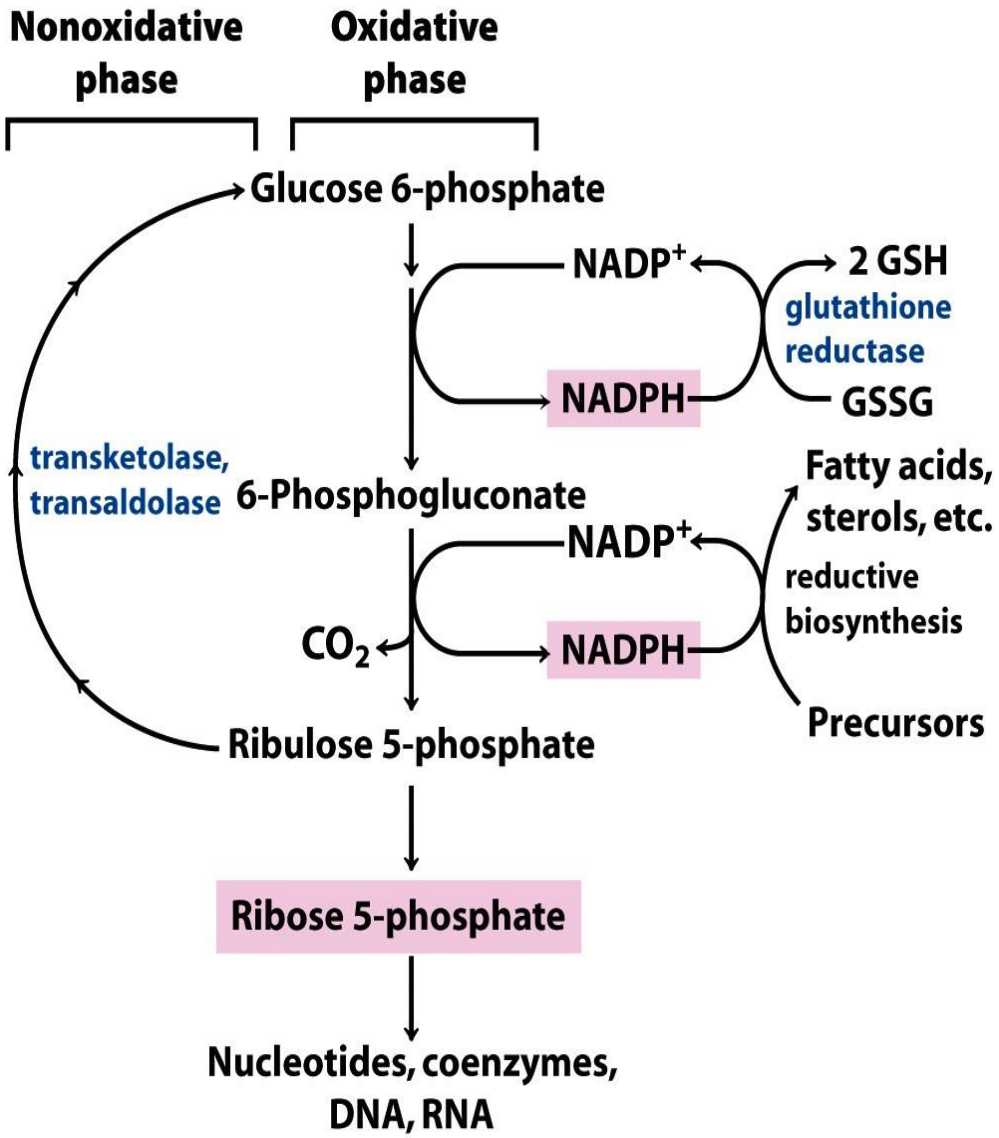


Figure 14-20
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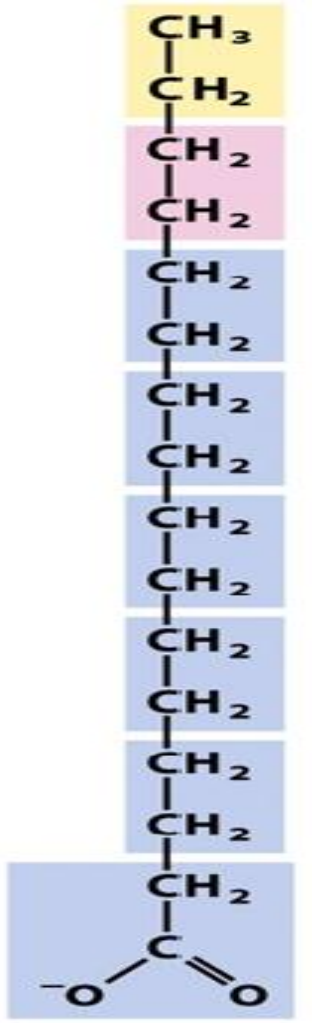

Palmitate

- NADPH formed in the oxidative phase is used to reduce glutathione, GSSG (oxidized form) and to support reductive biosynthesis.
- The other product of the oxidative phase is ribose 5-phosphate, which serves as a precursor for nucleotides, coenzymes, and nucleic acids.
- In cells that are not using ribose 5-phosphate for biosynthesis, the non-oxidative phase recycles six molecules of the pentose into five molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate (in six cycles) to CO_2.

Coordinated regulation of fatty acid synthesis and breakdown

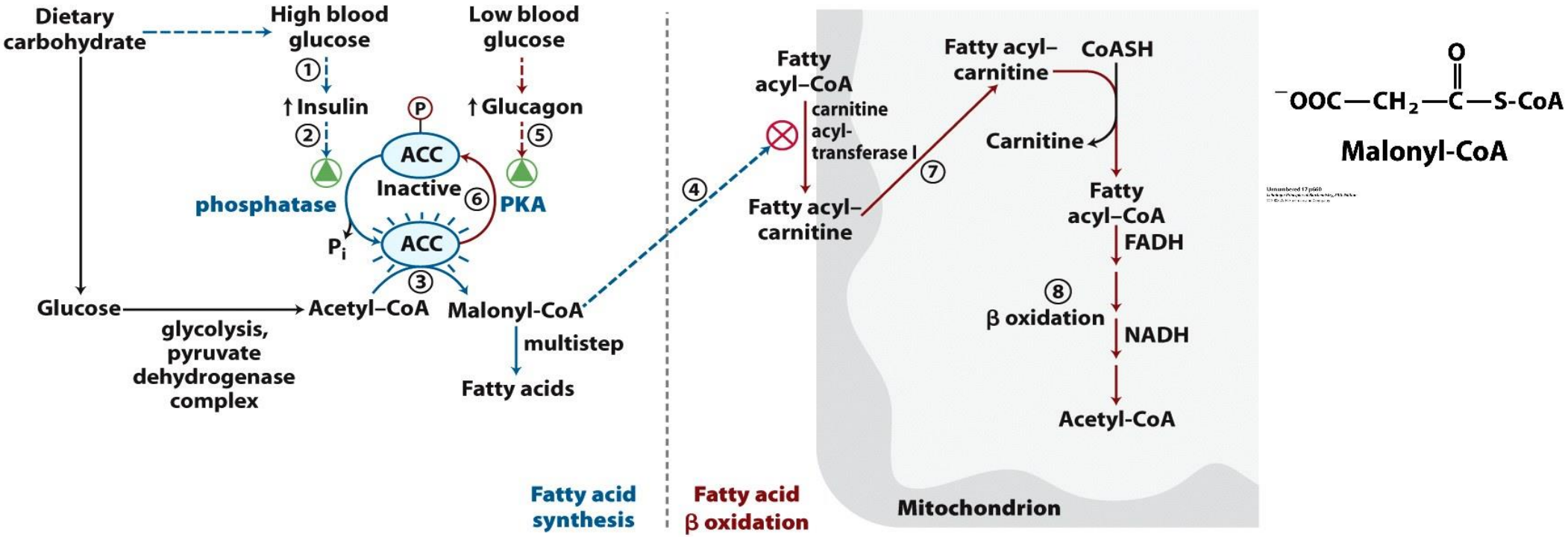

Figure 17-12
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Ingestion of a high-carbohydrate meal raises the blood glucose level and thus **1)** triggers the release of insulin. **2) Insulin-dependent protein** phosphatase dephosphorylates ACC, activating it. **3) ACC** catalyzes the formation of malonyl-CoA , and **4) malonyl-CoA** inhibits carnitine acyltransferase , thereby preventing fatty acid entry into the mitochondrial matrix.

When blood glucose levels drop between meals, 5) **glucagon** release activates cAMP-dependent protein kinase (PKA), **which 6)** phosphorylates and inactivates ACC. The concentration of malonyl-CoA falls, the inhibition of fatty acid entry into mitochondria is relieved, **and 7) fatty acids enter** the mitochondrial matrix and **8)** become the major fuel.

Storage energy

Available Metabolic Fuels in a Normal-Weight 70 kg Man

TABLE 23–5 Available Metabolic Fuels in a Normal-Weight 70 kg Man and in an Obese 140 kg Man at the Beginning of a Fast

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival (months)*
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

*Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.

Table 23-5
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What make a 70 kg person differ from a 140 kg one?

In case of prolonged starvation, theoretically, who should live longer? Why?

Regulation of triacylglycerol synthesis by insulin

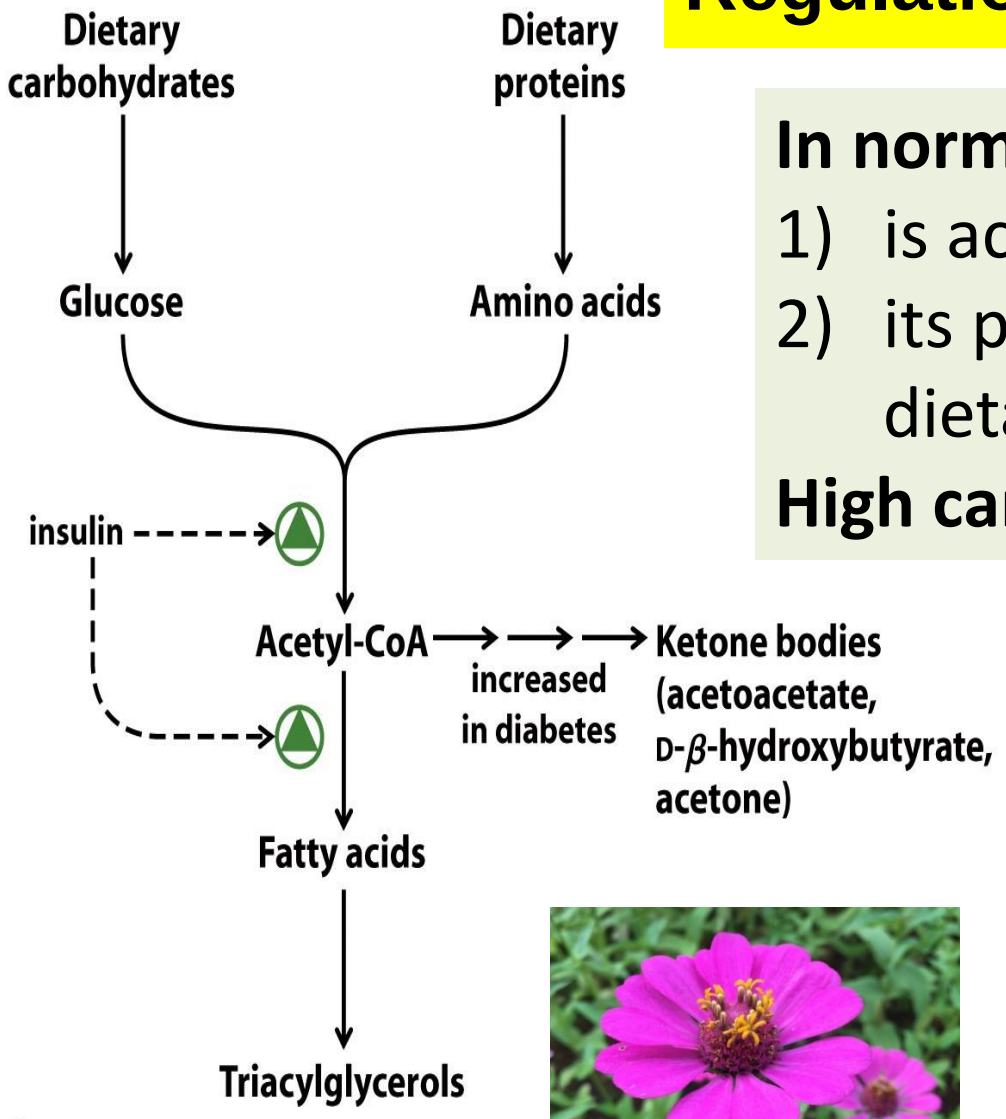

Figure 21-19
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In normal condition, Fatty acid synthesis

1) is activated by insulin hormone
2) its precursor is Acetyl-CoA which derived from dietary carbohydrates and proteins

High carbohydrate consumption induces obesity.

In patient with T1DM, FA synthesis is decreased but lipolysis is increased, resulting in acetyl-CoA accumulation and shunting for synthesis of ketone bodies. This higher rate of lipolysis making patient with T1DM become thin.

Prolonged starvation

How many days that they were trapped in the cave?

The fasting state: the glucogenic liver.

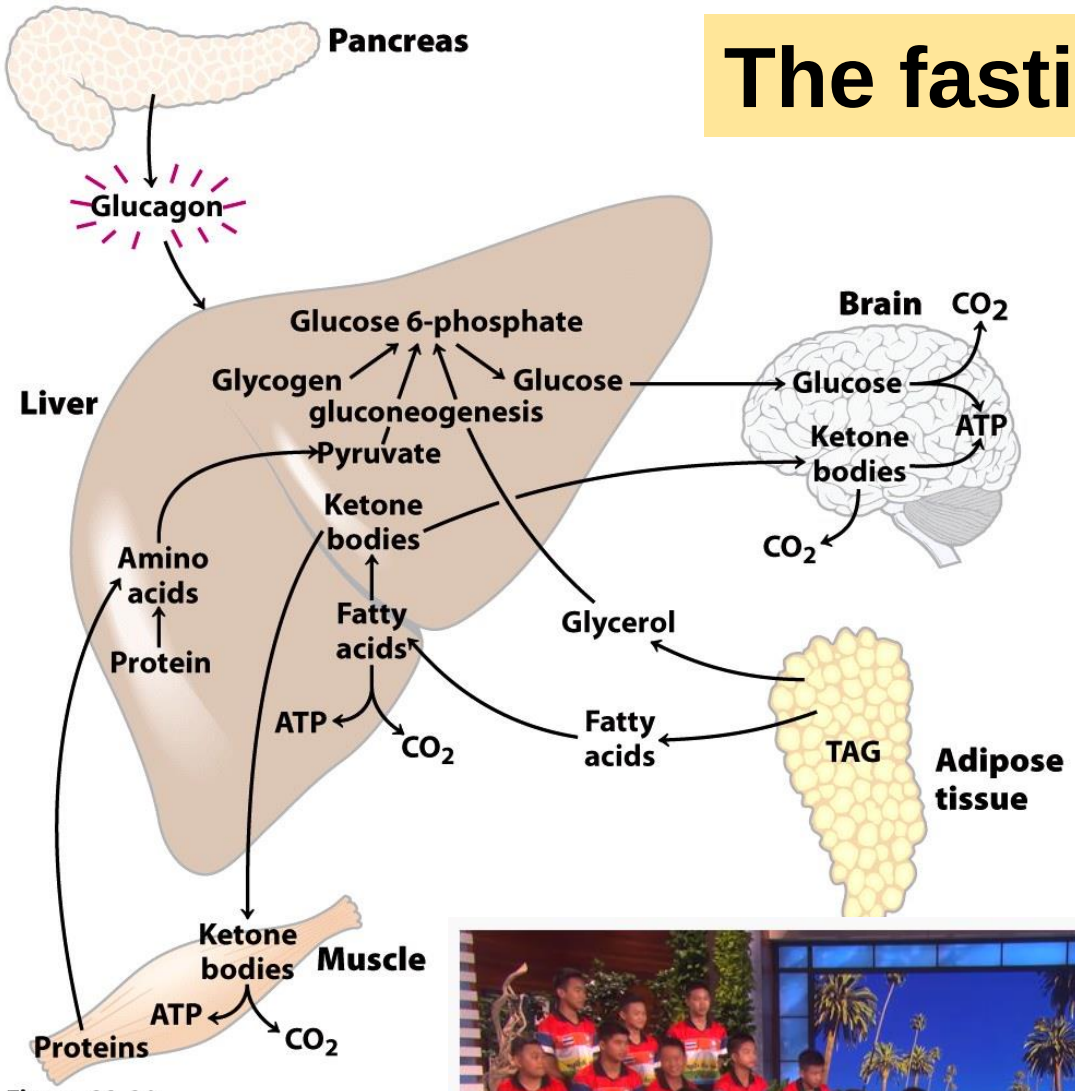

Figure 23-30
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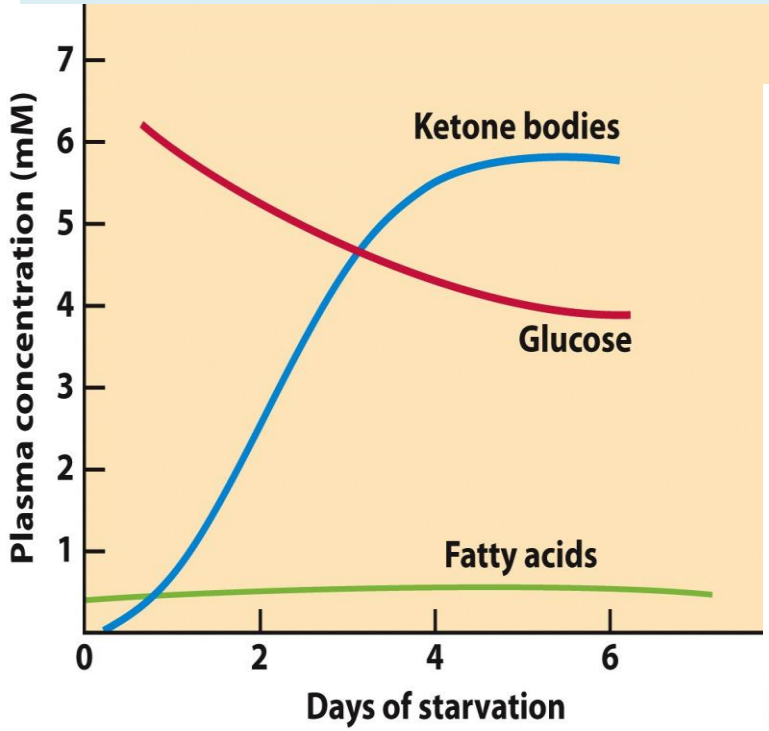
1. After some hours without a meal, the liver becomes the principal source of glucose for the brain. Liver glycogen is broken down, and the glucose 1-phosphate produced is converted to glucose 6-phosphate, then to free glucose, which is released into the bloodstream.

2. Amino acids from the degradation of proteins in liver and muscle, and glycerol from the breakdown of TAGs in adipose tissue, are used for gluconeogenesis.

The liver uses fatty acids as its principal fuel, and excess acetyl-CoA is converted to ketone bodies for export to other tissues; the brain is especially dependent on this fuel when glucose is in short supply.

Concentrations of fatty acids, glucose, and ketone bodies in plasma during the 1st week of starvation.



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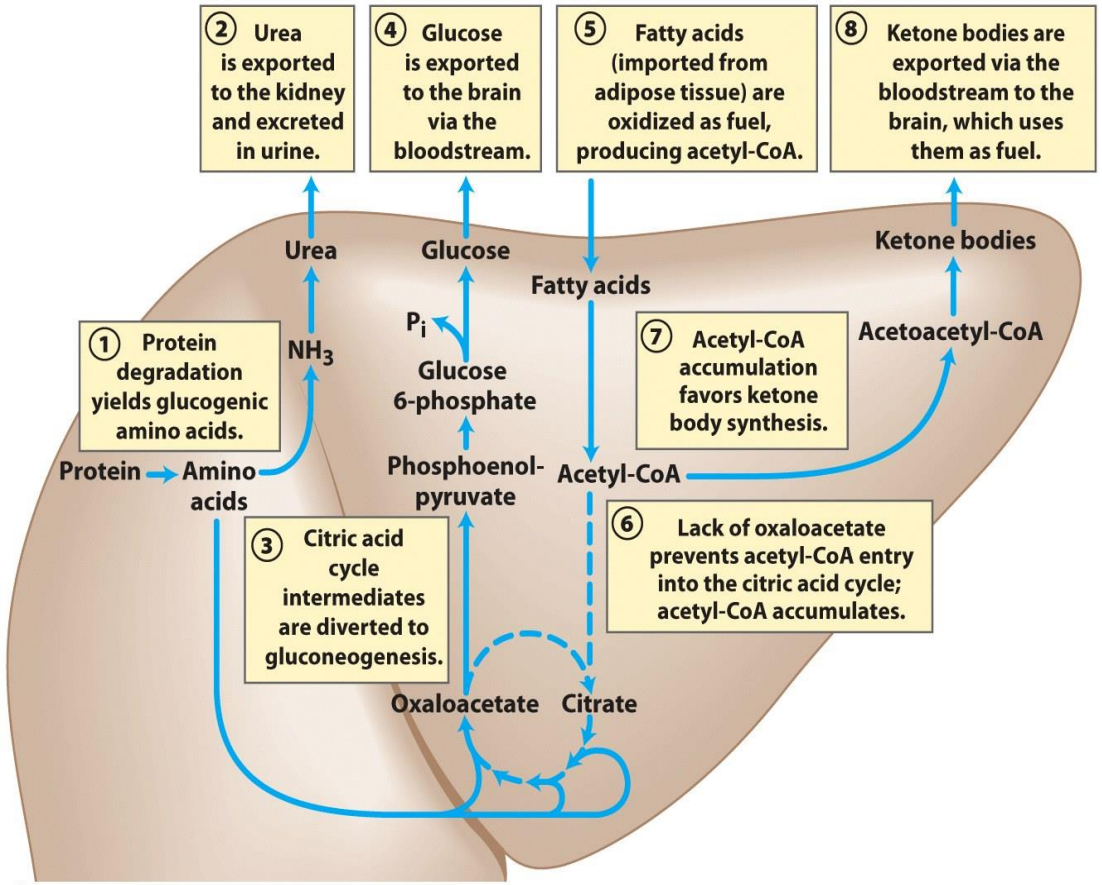

Figure 23-31
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Fuel metabolism in the liver during prolonged fasting or in uncontrolled diabetes mellitus.

1. After depletion of stored carbohydrates, proteins become an important source of glucose, produced from glucogenic amino acids by gluconeogenesis (1 to 4).
2. Fatty acids imported from adipose tissue are converted to ketone bodies for export to the brain (5 to 8).
3. Broken arrows represent reactions with reduced flux under these conditions.