

2. TISSUE - SPECIFIC METABOLISM

(Lenhinger, chapter 23, second part and chapter 17)

OVERVIEW

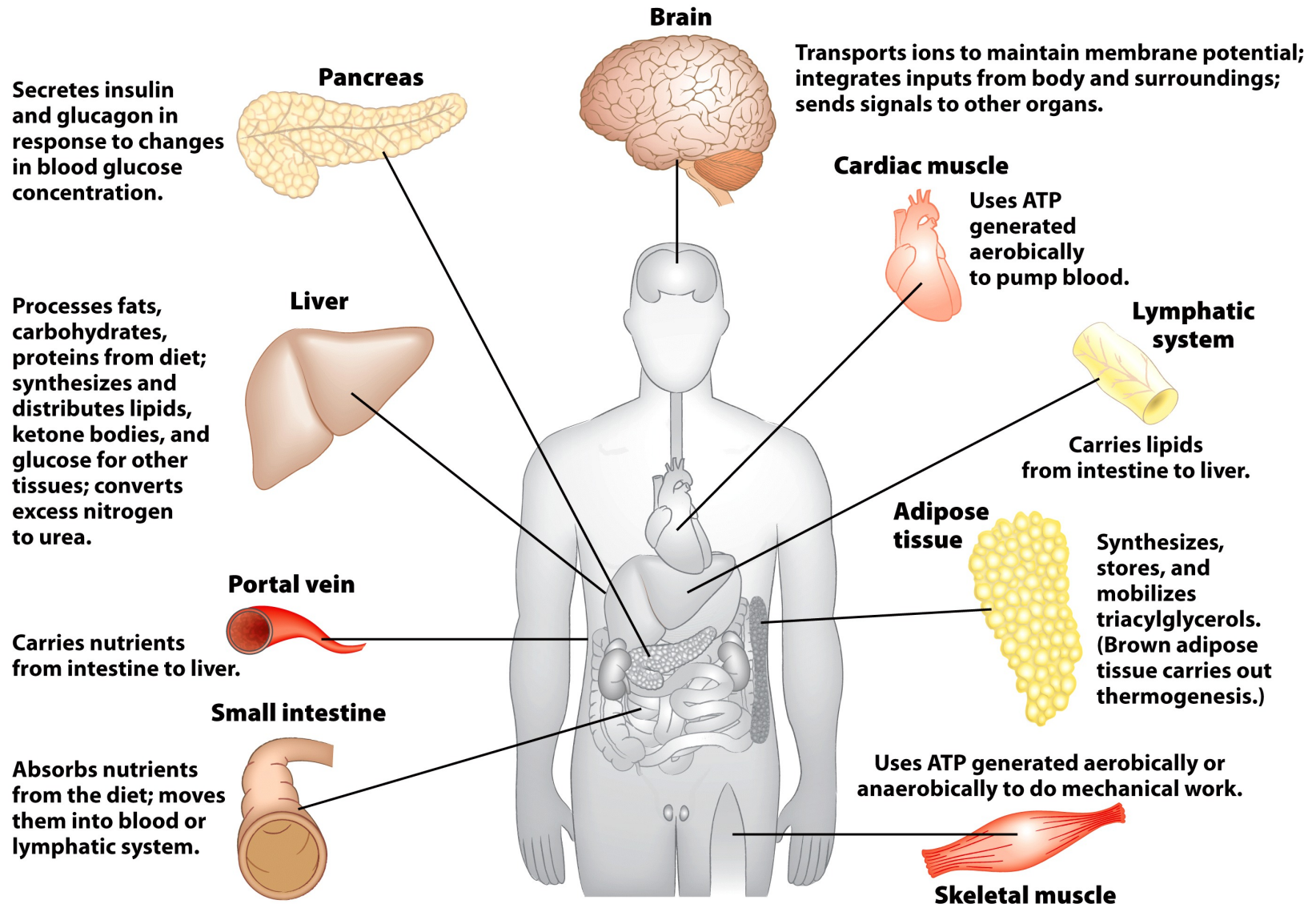


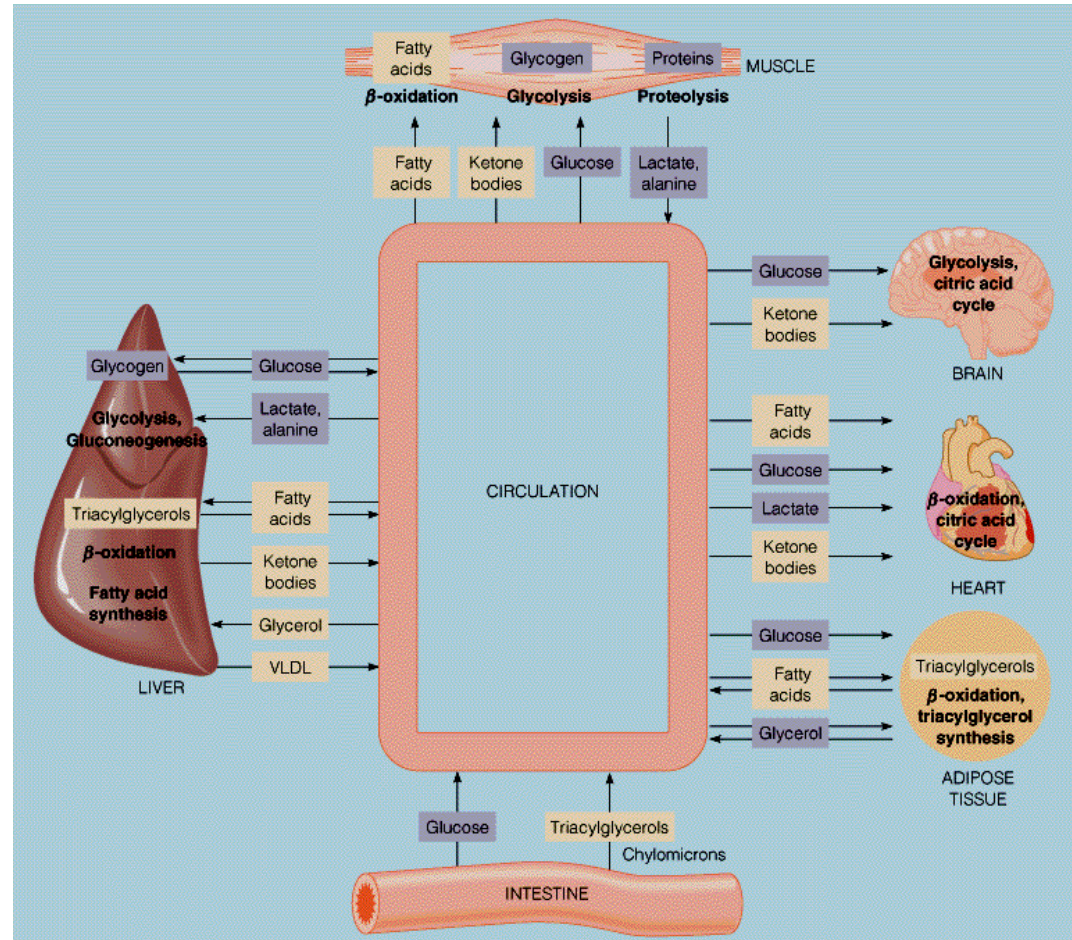
Figure 23-11

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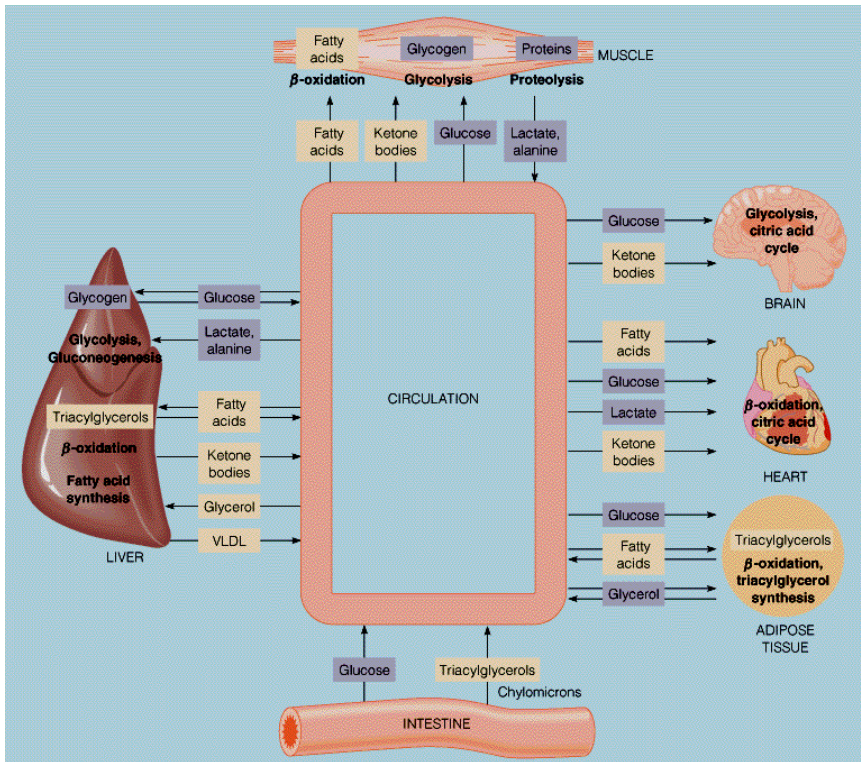
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OVERVIEW

- In mammals, nutrients (carbohydrates, lipids and proteins) are enzymatically hydrolyzed.
- Intestine epithelial cells absorb relatively small molecules that reach liver through blood circulation, mainly through portal vein.
- Hepatocytes transform diet compounds in compounds that generate energy or to precursors necessary for other tissues.
- These molecules reach their destination through blood circulation.
- To answer the organism needs, liver has a high **metabolic flexibility**.
- This flexibility derives in first instance from the 5-10 folds higher rate of modulation of the expression of hepatic enzymes involved in biosynthesis and degradation.



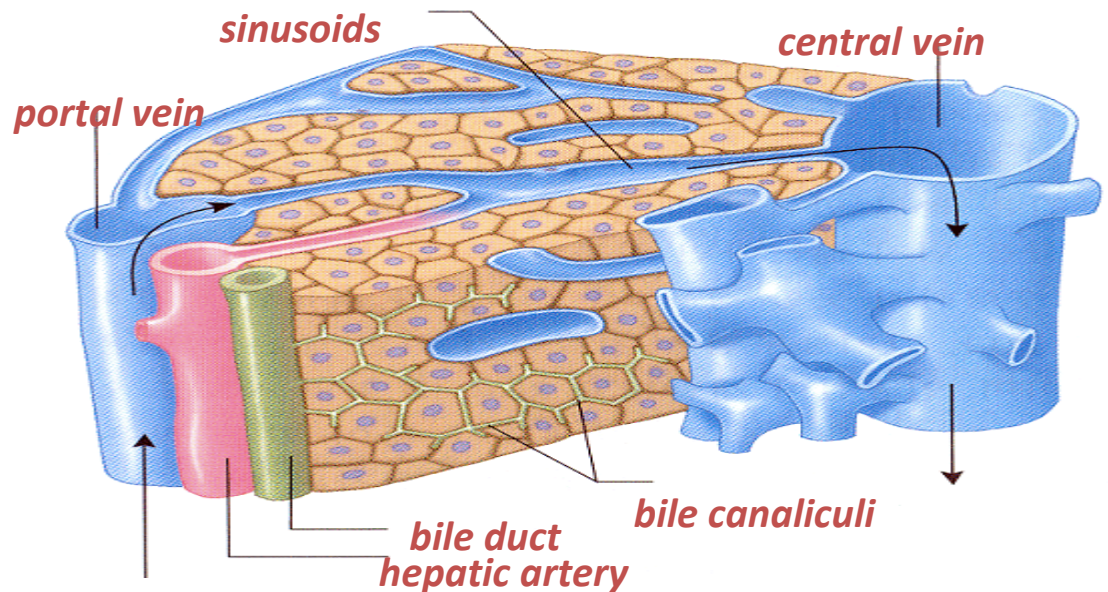
OVERVIEW



Tissue	Fuel Store	Preferred Fuel	Fuel Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (during exertion)	None	Glucose	Lactate, alanine
Heart muscle	None	Fatty acids	None
Adipose tissue	Triacylglycerols	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerols	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

METABOLISM IN THE LIVER

- Major function is to provide fuel for the brain, muscle and other tissues
- Metabolic hub of the body
- Most compounds absorbed from diet must first pass through the liver, which regulates blood levels of metabolites
- Regulation of storage and production of energy
- Synthesis of molecules for other tissues
- Interconversion of nutrients
- Storage of some substances
- Formation and secretion of bile
- Destruction of toxic substances
- Depot of iron, vitamins



METABOLISM OF CARBOHYDRATES IN THE LIVER

- Glycolysis
- Metabolism of fructose and galactose
- Gluconeogenesis
- Release of glucose into blood (maintain the stable glucose concentration in blood)
- Conversion of pyruvate into acetyl CoA
- Tricarboxylic acid cycle
- Pentose phosphate pathway
- Glycogenolysis, glycogenogenesis
- Cori cycle and glucose-alanine cycle
- Transformation of saccharides to glucose
- Synthesis of amino-saccharides
- Synthesis of uronic acids
- Degradation of insulin and glucagon

METABOLISM OF CARBOHYDRATES IN THE LIVER: GLUCOSE

- GLUT2 transporter of hepatocytes allows passive and rapid diffusion of glucose so that extra- and intracellular concentrations are similar.
- Glucose is then phosphorylated by hexokinase IV (glucokinase).
- Hexokinase IV is regulated at genic level
- The enzyme has a high K_M for glucose (10 mM) compared to the other isoforms of the enzyme present in other cells.
- Hepatocytes keep phosphorylating glucose when glucose 6-phosphate levels are so high that other isoforms are blocked (inhibited by glucose 6-P).
- Glucose phosphorylation is reduced when glucose levels are low, so that it is directed toward other tissues.

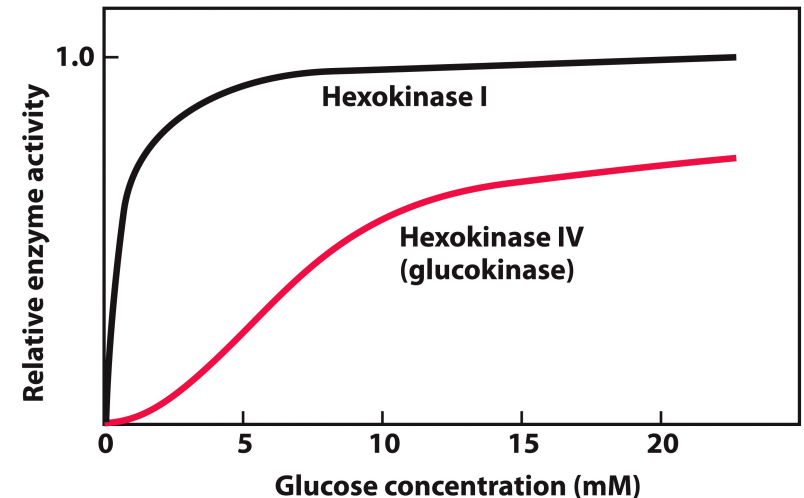


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Hexokinase IV regulatory protein (inhibitory effect) attracts the enzyme into the nucleus when fructose 6-P is high in the liver (high glycolysis, low gluconeogenesis=low levels of glucose) whereas it releases the enzyme in the cytosol when glucose levels are high.

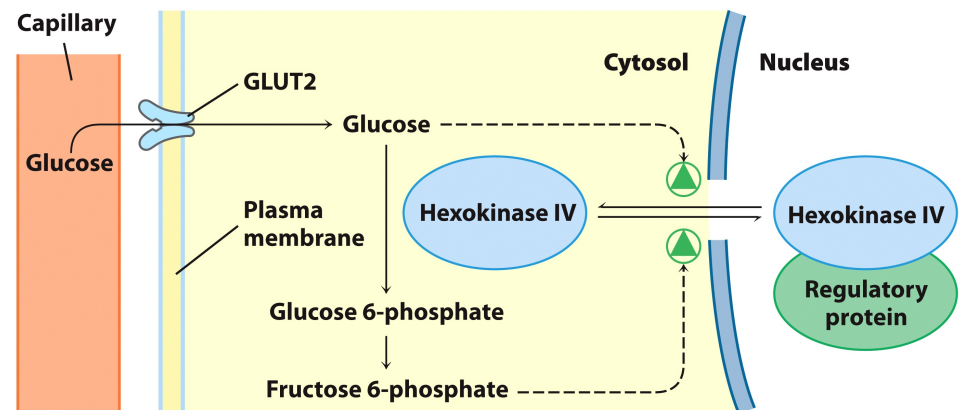


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METABOLISM OF CARBOHYDRATES IN THE LIVER: GLUCOSE

1. Glucose is required to maintain blood correct levels (4 mM) to supply energy for brain and other tissues.
2. If glucose-6-phosphate is not dephosphorylated, it is incorporated into glycogen.
3. Hepatic glycolysis produces pyruvate, acetyl-CoA and energy, even if the preferred fuel in liver cells for ATP production are fatty acids.
4. Acetyl-CoA can be used for fatty acids biosynthesis
5. Alternatively, glucose 6-phosphate can enter the pentose phosphate pathway, that produces both reducing power (NADPH) and D-ribose 5-phosphate.
6. NADPH is also an essential cofactor for xenobiotics detoxification by human liver enzymes.

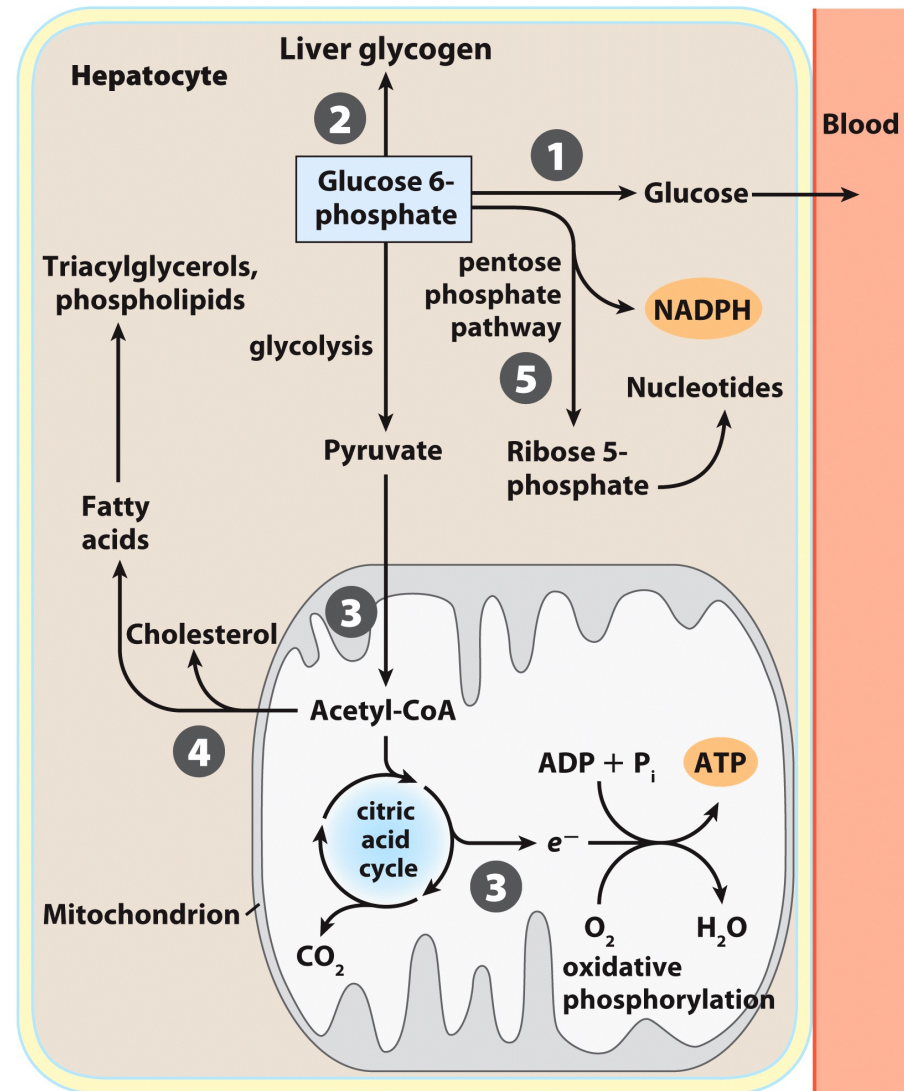


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METABOLISM OF FATTY ACIDS IN THE LIVER

1. They can be converted into lipids.
2. In most cases, they are the fuel for energy production in the liver.
3. Acetyl-CoA enters the citric acid cycle and oxidation reactions lead to ATP production through oxidative phosphorylation.
4. Extra acetyl-CoA is converted in ketone bodies, that can pass through the blood-brain barrier and supply up to 60-70% of energy required by brain.
5. Part of acetyl-CoA is used for the biosynthesis of cholesterol that is the precursor for steroid hormones and bile salts, necessary for lipids absorption.
6. Fatty acids are converted into phospholipids and triacylglycerols that are transported by blood lipoproteins (VLDL and HDL) to adipose tissue.
7. Part of fatty acids binds to albumin to be transported to heart and skeletal muscle for energy production.
8. Part of fatty acids binds to albumin to be transported to heart and skeletal muscle for energy production.

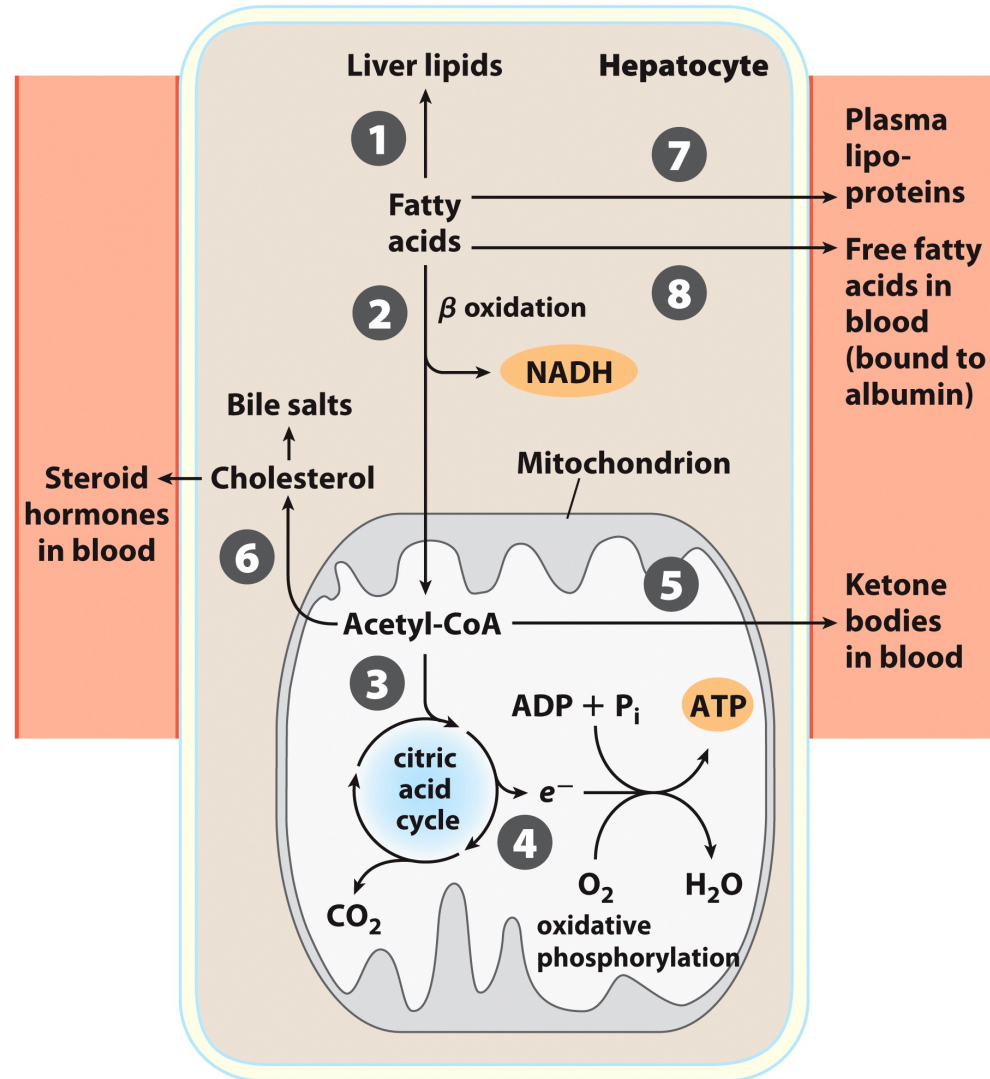


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METABOLISM OF FATTY ACIDS IN THE LIVER

- Ketone bodies are exported as fuels for other tissues (brain)

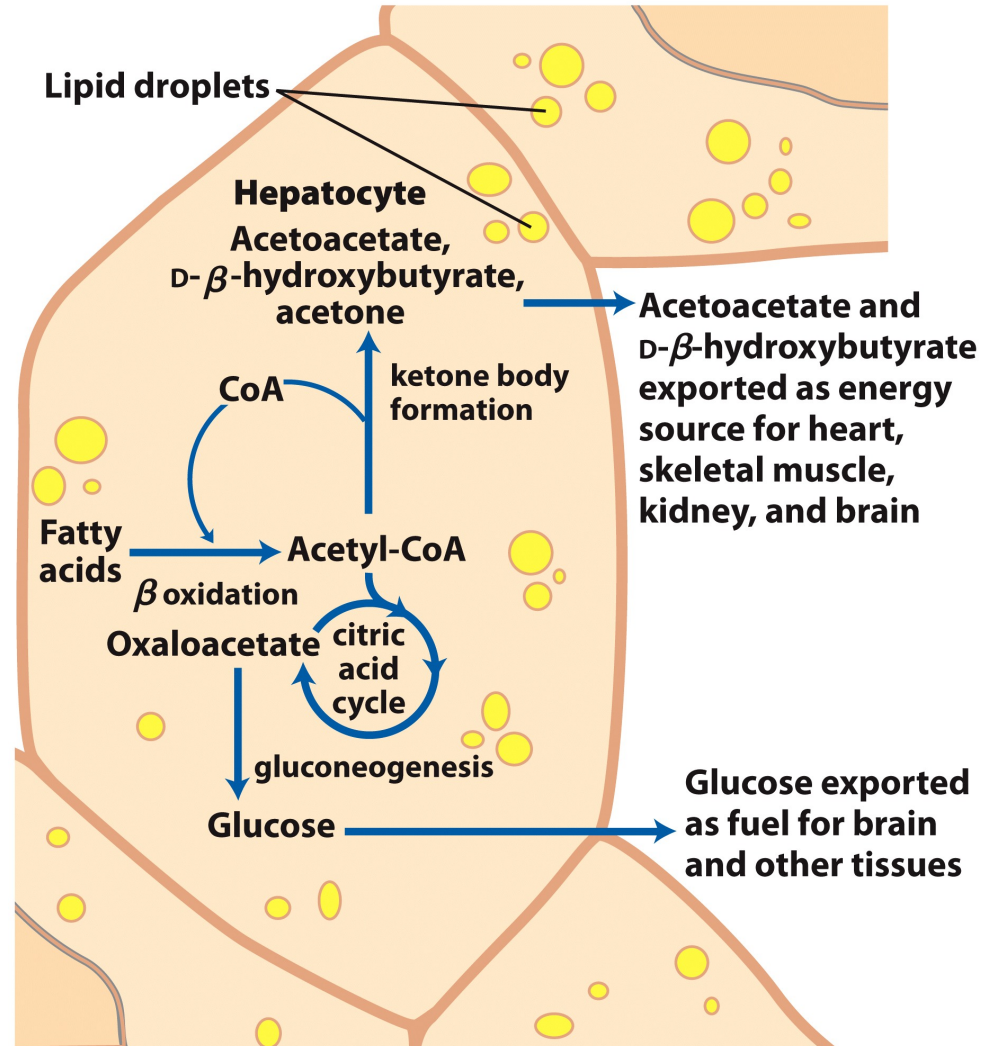
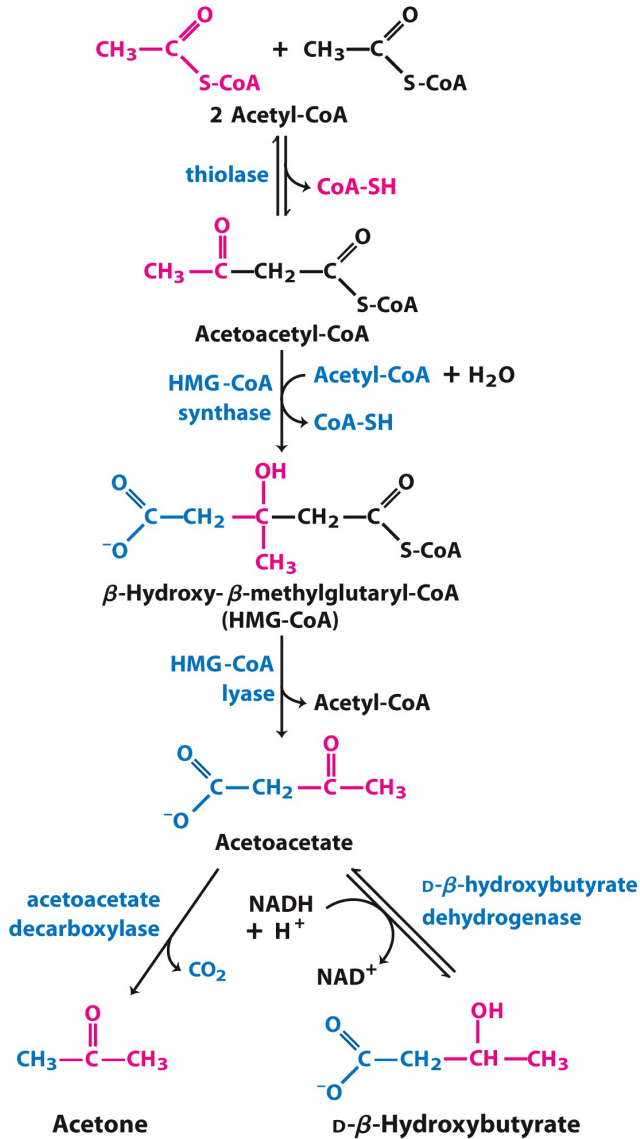


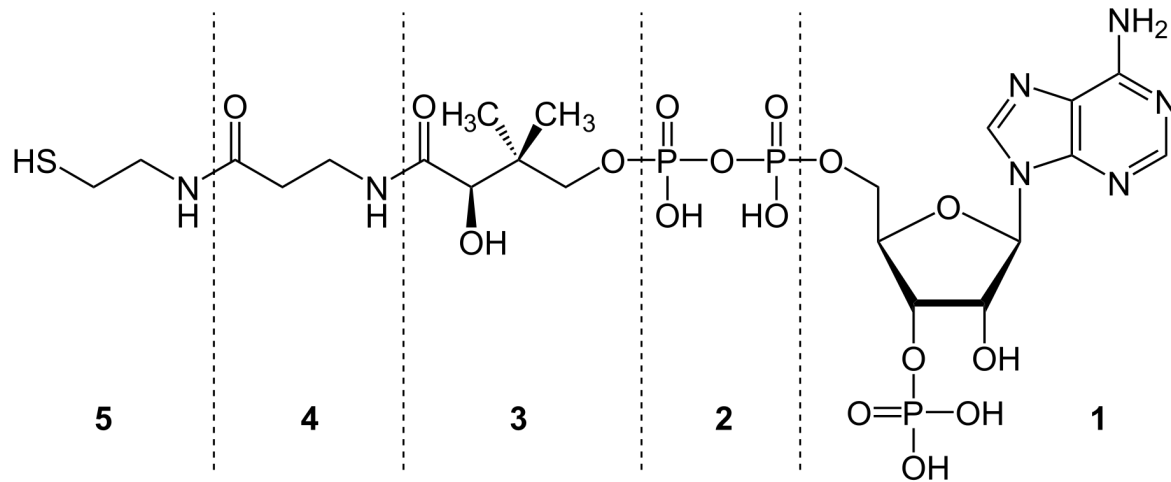
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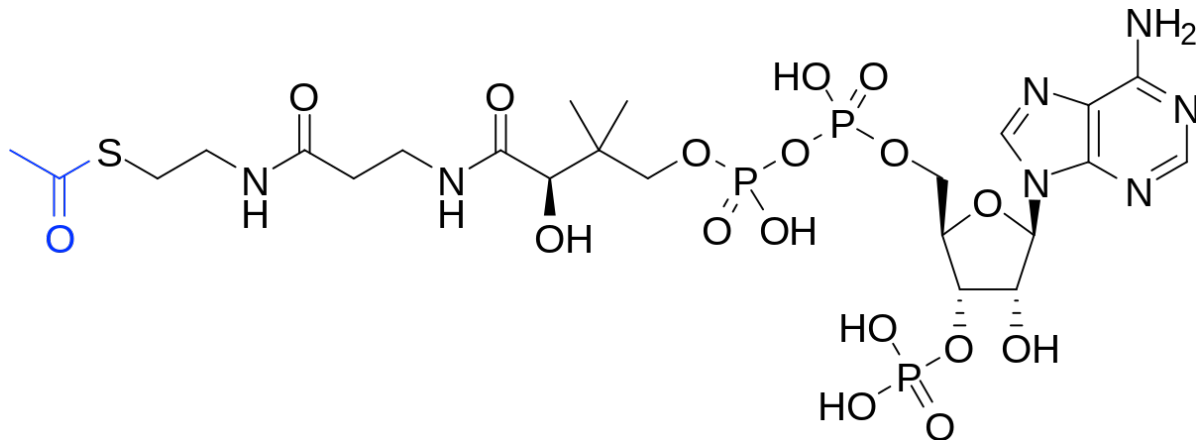
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Acetyl-CoA



Structure of coenzyme A: 1: 3'-phosphoadenosine. 2: diphosphate, organophosphate anhydride. 3: pantoic acid. 4: β-alanine. 5: cysteamine.



Structure of acetyl-coenzyme A

METABOLISM OF AMINO ACIDS IN THE LIVER

1. Precursors of liver and blood protein biosynthesis (high turnover).
2. They can exit from liver cells and go through blood circulation to other tissues for protein synthesis.
3. They can be the precursors for biosynthesis of nucleotides, hormones and other nitrogen-containing compounds in the liver or other tissues.
4. A) They can be transaminated or deaminated to become pyruvate or other intermediates of TCA. B) NH_4 is converted to urea.
5. Pyruvate can be converted into glucose and glycogen in gluconeogenesis.
6. or in Acetyl-CoA (see 7, 8, 9, 10).

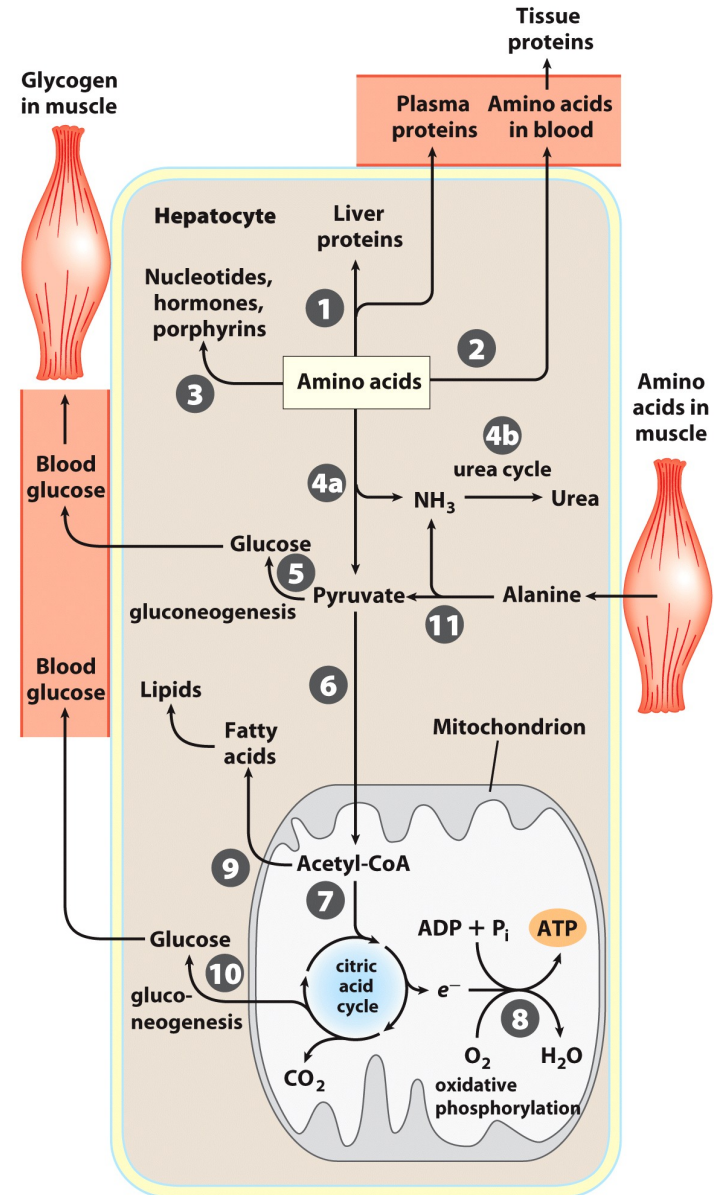


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METABOLISM OF AMINO ACIDS IN THE LIVER

- During starving, amino acids from muscle proteins are degraded.
- They donate amino groups to pyruvate that becomes alanine that is transported to liver.

11. Alanine is deaminated to produce pyruvate that forms glucose through gluconeogenesis.

This is the glucose-alanine cycle and it has the role to maintain constant glucose in the blood.

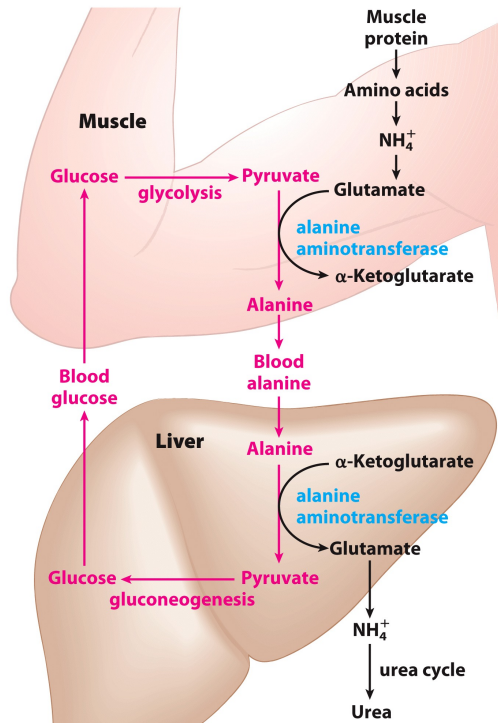


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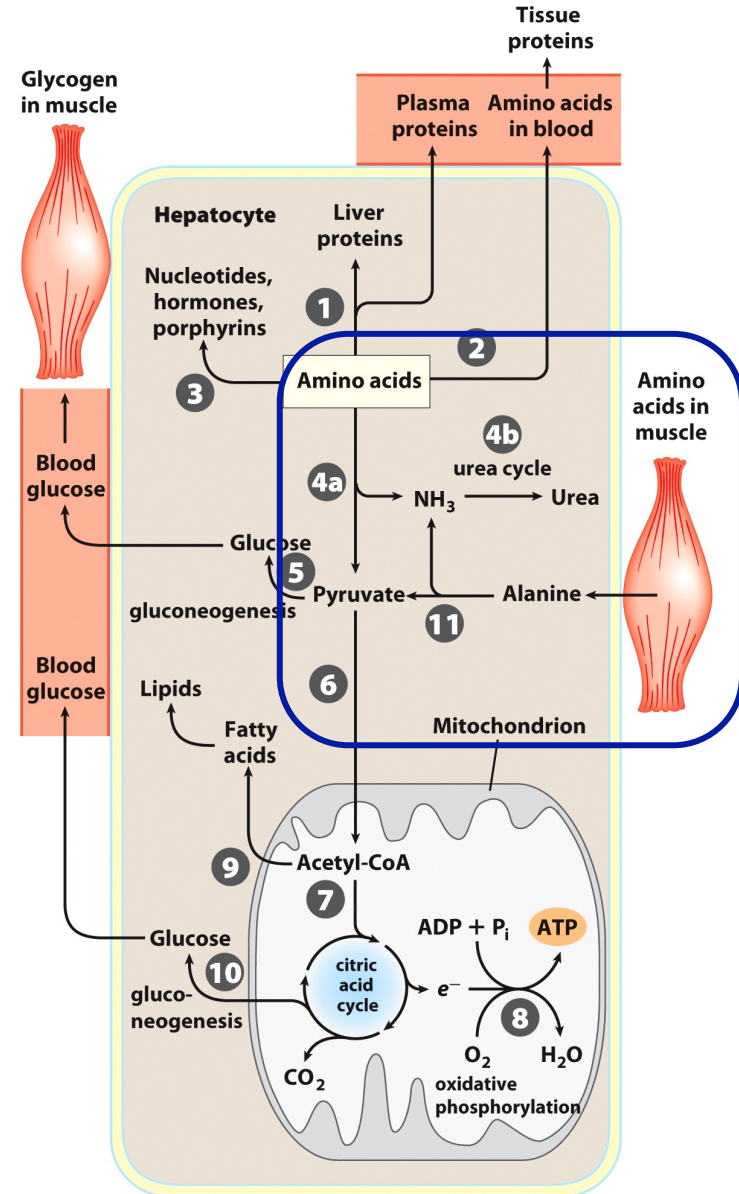


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METABOLISM OF AMINO ACIDS IN THE LIVER

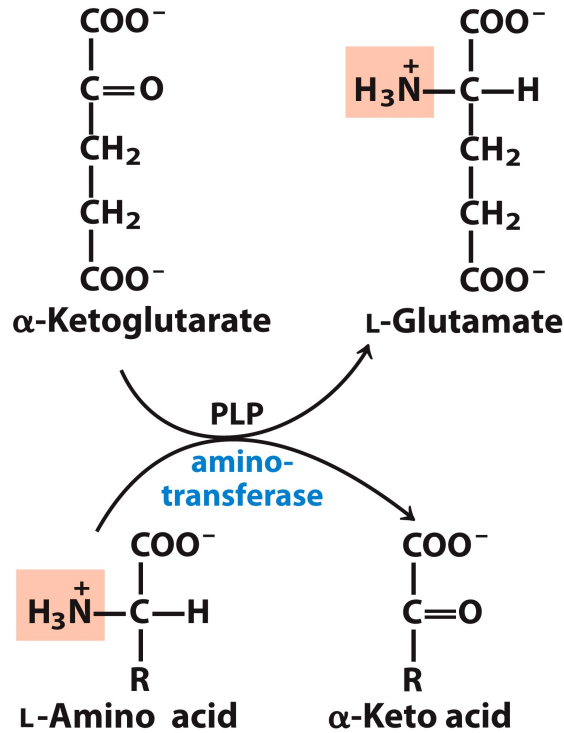


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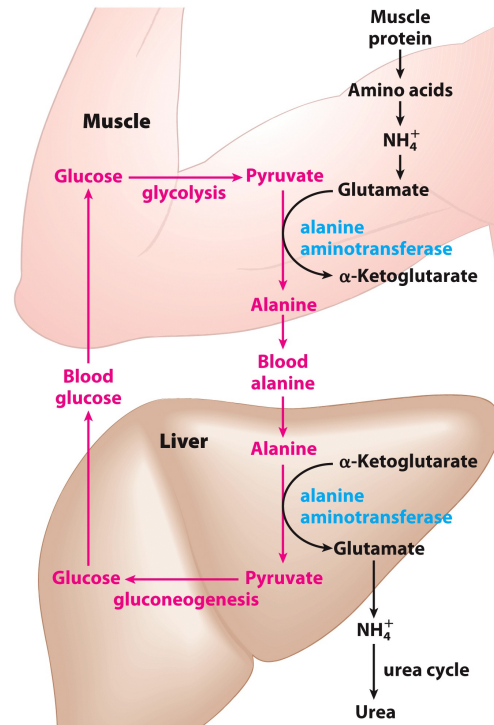


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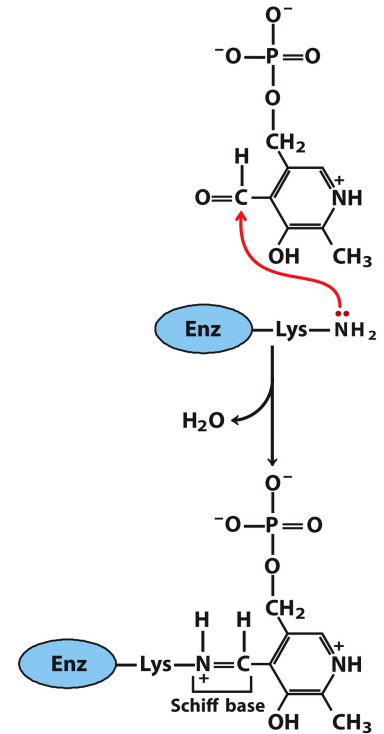


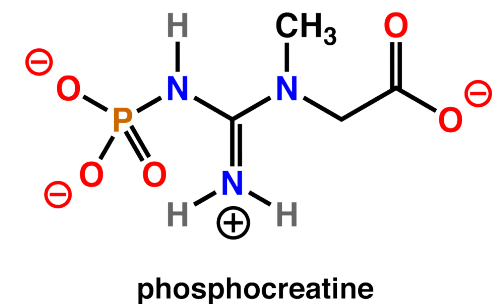
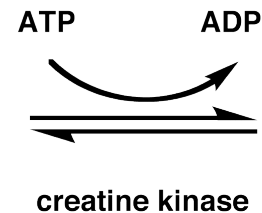
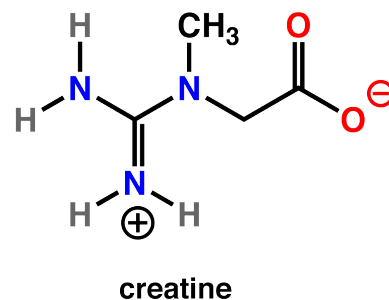
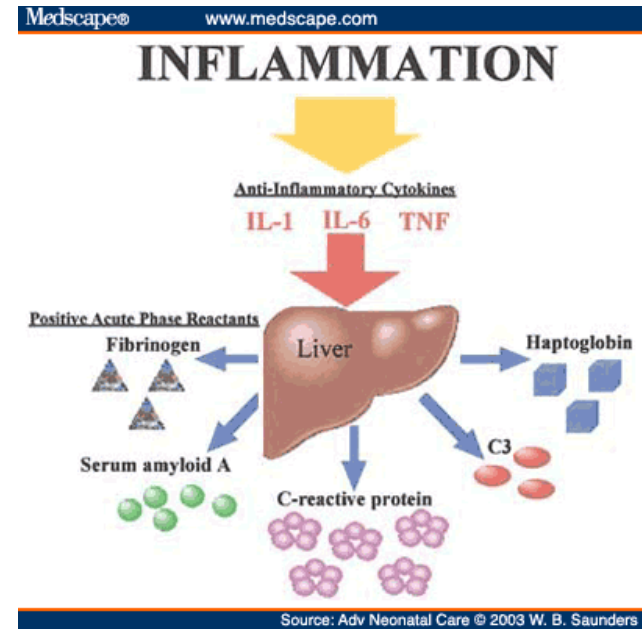
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Pyridoxal phosphate (PLP, vitamin B6) is the cofactor for transaminases)

The glucose-alanine cycle (also known as Cahill cycle) ultimately serves as a method of ridding the muscle tissue of the toxic ammonium ion

METABOLISM OF N-CONTAINING COMPOUNDS IN THE LIVER

- synthesis of **plasma proteins (except Ig)**
- synthesis of **coagulation factors**
- synthesis of **acute phase reactants**
- degradation of amino „N“ (**urea, Gln**)
- synthesis of non-essential **amino acids**
- metabolism of aromatic AAs
- degradation of purines to **uric acid**
- synthesis of **creatine**
- conjugation and excretion of **bilirubin**



Muscle

Metabolism of vitamins

- provitamins → vitamins, storage of vitamins
- carotenes → vitamin A
- 25-hydroxylation of provitamin D
- cleavage of side chain of vitamin K
- storage of vitamin B₁₂
- synthesis of nicotinic acid from Trp
- formation of coenzymes from B vitamins

Metabolism of minerals

- storage of iron (ferritin)
- storage and metabolism of other trace elements (Cu, Mn, Co, Mo, Zn,..)
- synthesis of transport proteins
(transferrin, ceruloplasmin for Cu)
- deiodation of thyroidal hormones → I⁻ (iodide)

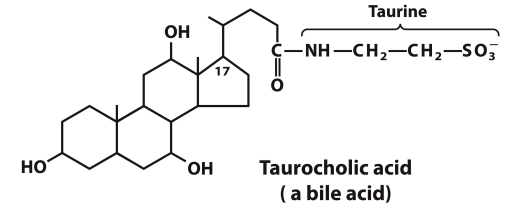
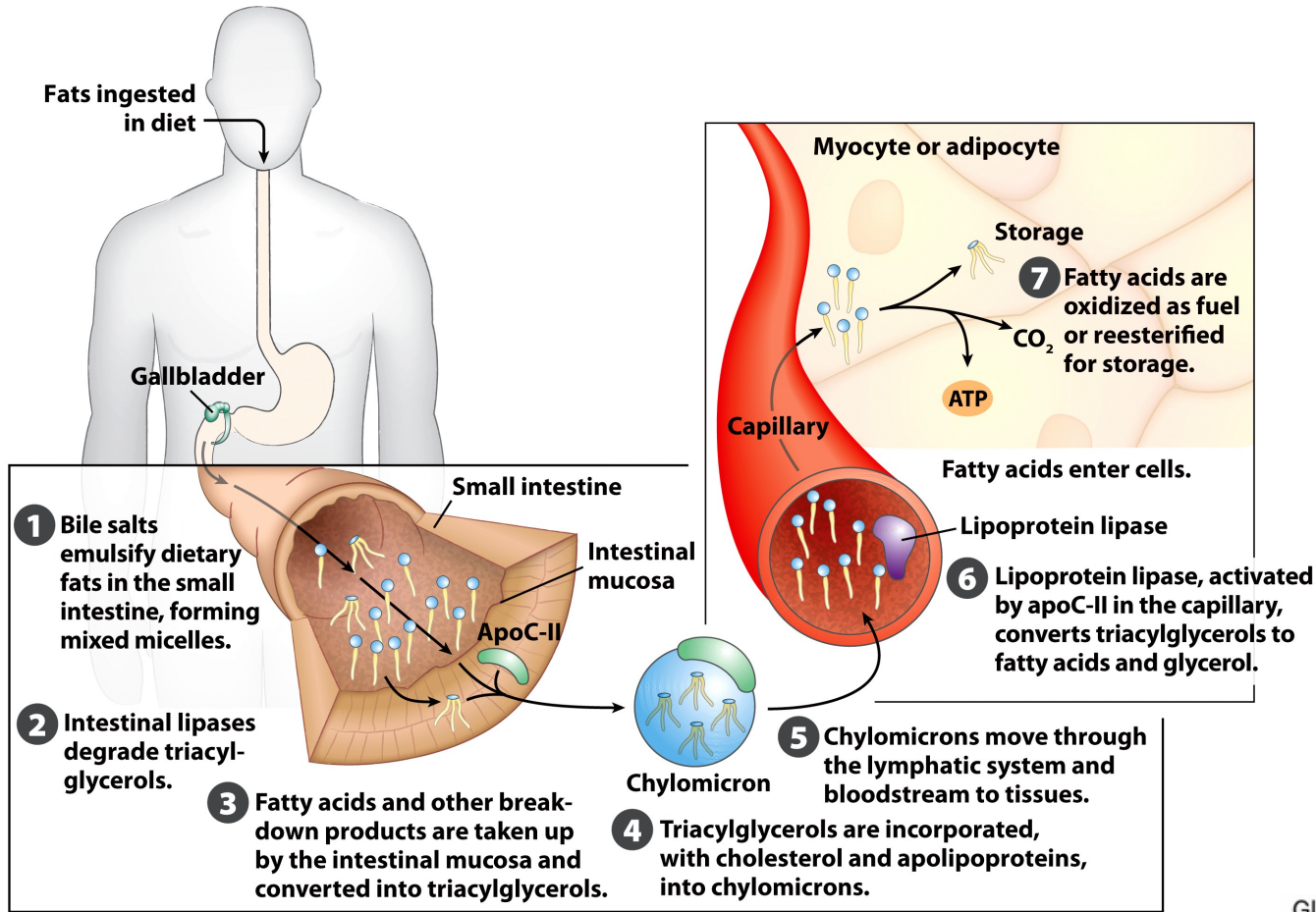
Metabolism of hormones

- degradation and excretion

Metabolism of xenobiotics

Prof. Sadeghi lectures

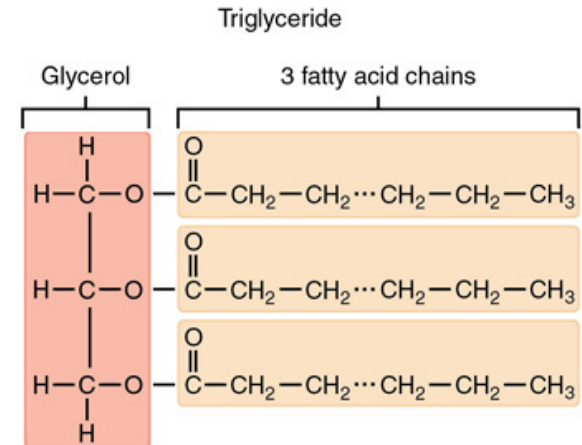
METABOLISM IN THE ADIPOSE TISSUE



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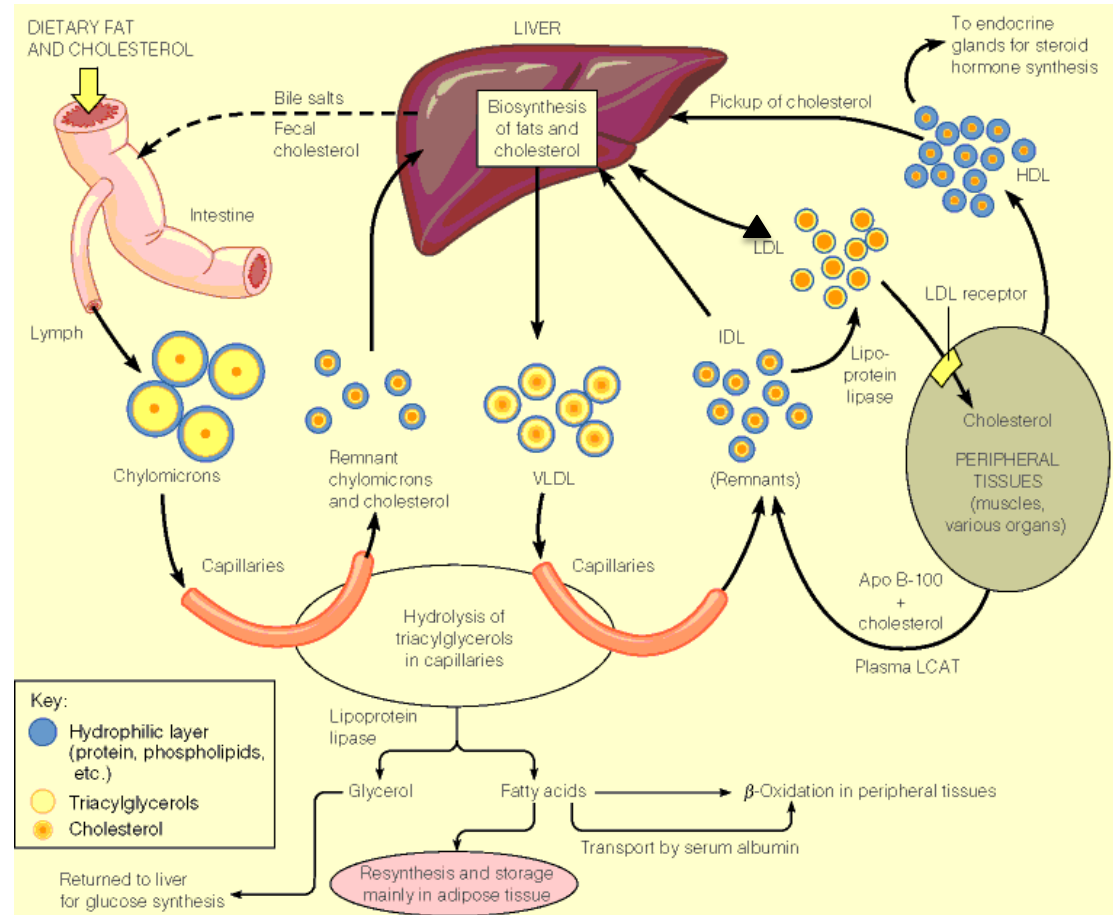
Figure 17-1
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- Enormous stores of triacylglycerols
- Fatty acids imported into adipocytes from chylomicrons and VLDLs as free fatty acids
- Once in the cell they are esterified to glycerol backbone.
- Glucagon/epinephrine stimulate reverse process



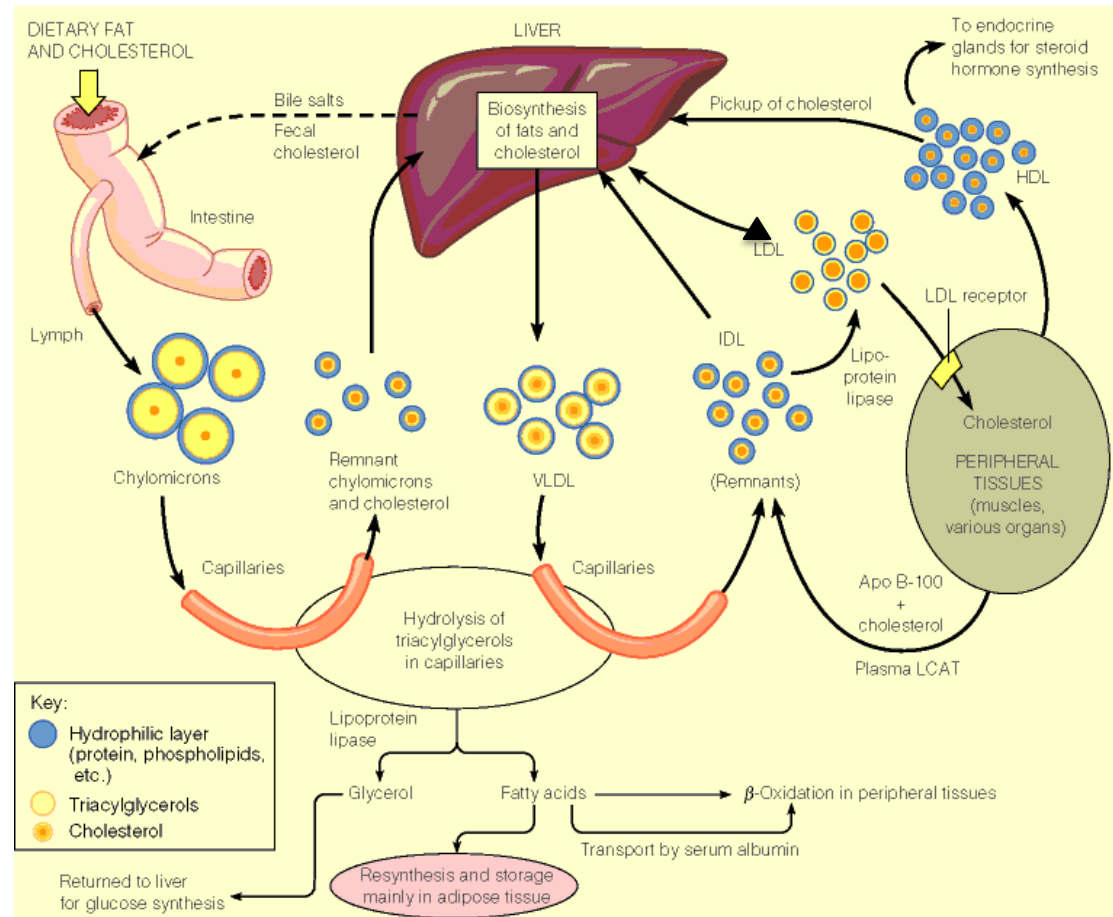
METABOLISM IN THE ADIPOSE TISSUE

- Dietary fat is hydrolyzed in the lumen of the small intestine (mostly by pancreatic lipase) to yield glycerol, free fatty acids, monoacylglycerols, and diacylglycerols.
- The hydrolysis products of this digestion are combined back into triacylglycerols (fats) in the endoplasmic reticula and Golgi complexes of the intestinal mucosa cells.
- Fats are combined with apoproteins to form chylomicrons, which transport the fats through blood and lymph.
- Chylomicrons are thus the transport vehicle for dietary cholesterol. Free fatty acids are rarely found in the bloodstream. Rather, they are complexed to serum albumin.



METABOLISM IN THE ADIPOSE TISSUE

- The liver also plays an important role in fat metabolism. Fats synthesized in the liver are combined with another set of apoproteins to form very low density lipoproteins (VLDLs), which are hydrolyzed en route to peripheral tissues at the inner surface of capillaries.
- Hydrolysis of fats in capillaries by lipoprotein lipase yields intermediate-density lipoproteins (IDLs) from VLDLs and chylomicron remnants from chylomicrons.
- IDLs are taken up by the liver and further processed to low-density lipoproteins (LDLs).
- LDLs are the primary form by which cholesterol is transported to tissues and high-density lipoproteins (HDLs) serve to transport cholesterol from tissues back to the liver.



METABOLISM IN THE ADIPOSE TISSUE

TABLE 21-1 Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Source: Modified from Kritchevsky, D. (1986) Atherosclerosis and nutrition. *Nutr. Int.* 2, 290–297.

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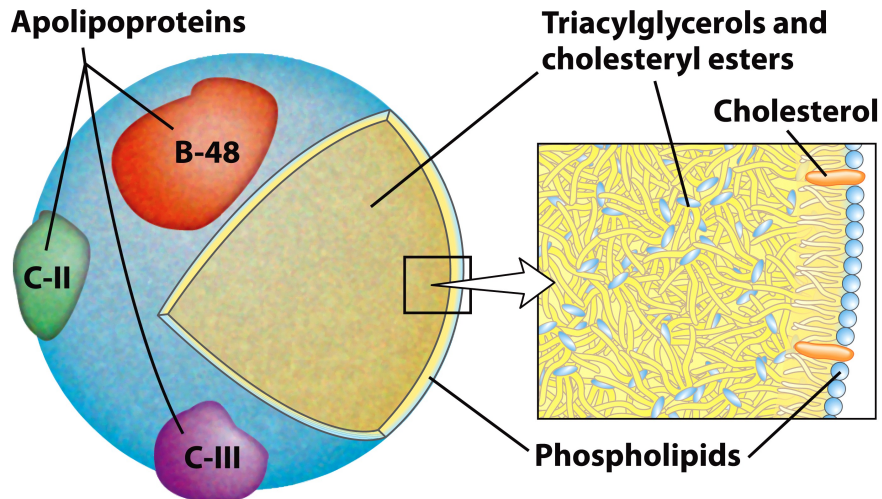
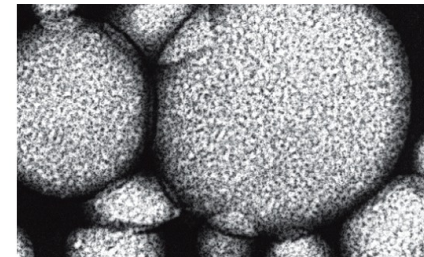
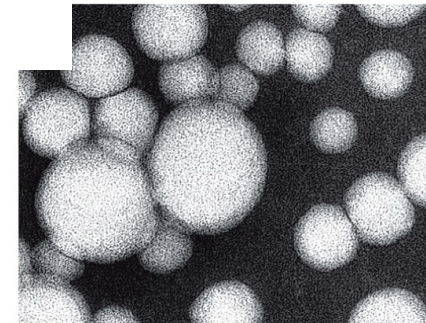


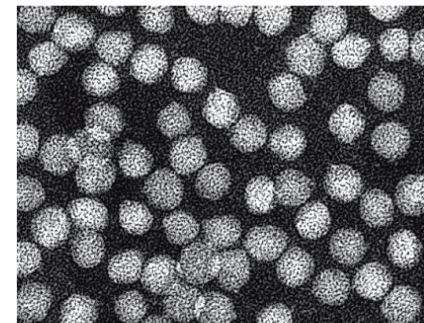
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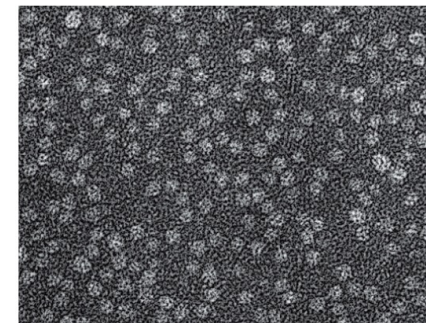
Chylomicrons (×60,000)



VLDL (×180,000)



LDL (×180,000)

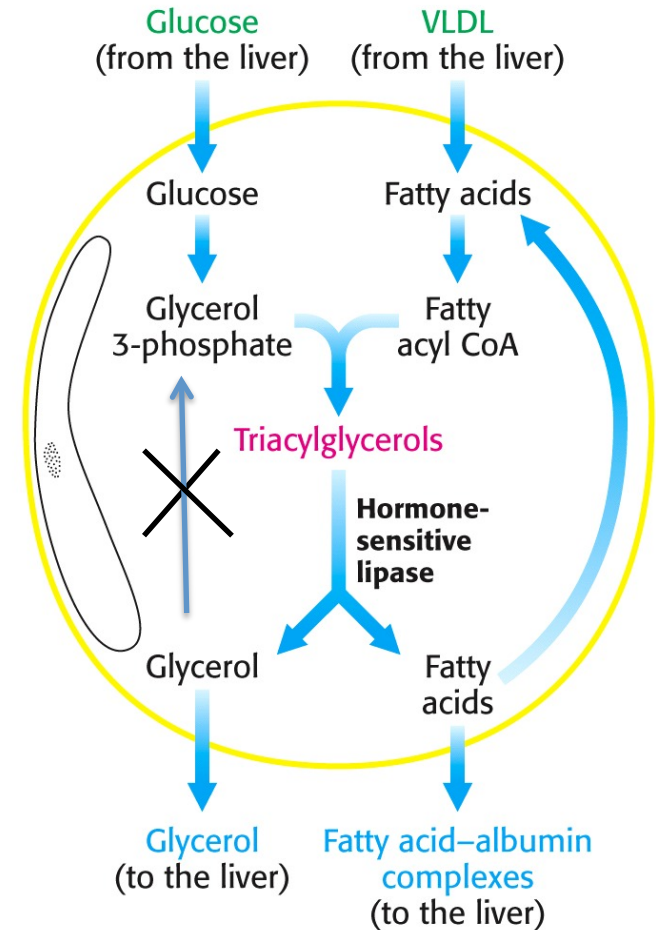


HDL (×180,000)

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METABOLISM IN THE ADIPOSE TISSUE

- Adipose tissue is the major fuel storage tissue for an animal. The total stored triacylglycerols amount to some 565,000 kJ (135,000 kcal) in an average-sized human.
- This is enough fuel, metabolic complications aside, to sustain life for a couple of months in the absence of further caloric intake.
- The adipocyte, or fat cell, is designed for continuous synthesis and breakdown of triacylglycerols, with breakdown controlled largely via the activation of **hormone-sensitive lipase**.
- Because adipocytes **lack** the enzyme **glycerol kinase**, they cannot rebuild a fat from glycerol generated by hydrolysis of another fat.
- Some glucose catabolism must occur for triacylglycerol synthesis to take place—specifically, the formation of dihydroxyacetone phosphate, for reduction to glycerol-3-phosphate.



METABOLISM IN THE ADIPOSE TISSUE

- Glucose acts as a sensor in adipose tissue metabolism.
- When glucose levels are adequate, the production of dihydroxyacetone phosphate generates enough glycerol-3-phosphate for the resynthesis of triacylglycerols from the released fatty acids.
- When intracellular glucose levels fall, the concentration of glycerol-3-phosphate falls also, and fatty acids are released from the adipocyte as the albumin complex for export to other tissues.

1. Low levels of glucose cause glucagon release.
2. Glucagon binds its receptor on adipocyte membrane and 3) activates PKA through cAMP.
4. PKA phosphorylates and activates hormone sensitive lipase (HSL) and activates perilipin molecules on lipid droplet surface.
5. Perilipin phosphorylation induces CGI dissociation and its association to adipocyte triacylglycerol lipase (ATGL) that converts tri- into diacylglycerols (6).
7. Perilipin-P associates to HSL-P allowing its access to the lipid droplet surface where it converts di- into monoacylglycerols.
8. A third lipase (monoacylglycerol lipase, MGL) hydrolyse them.
9. Fatty acids exit adipocytes, bind to albumin and 10) enter miocytes through a specific fatty acids transporter.

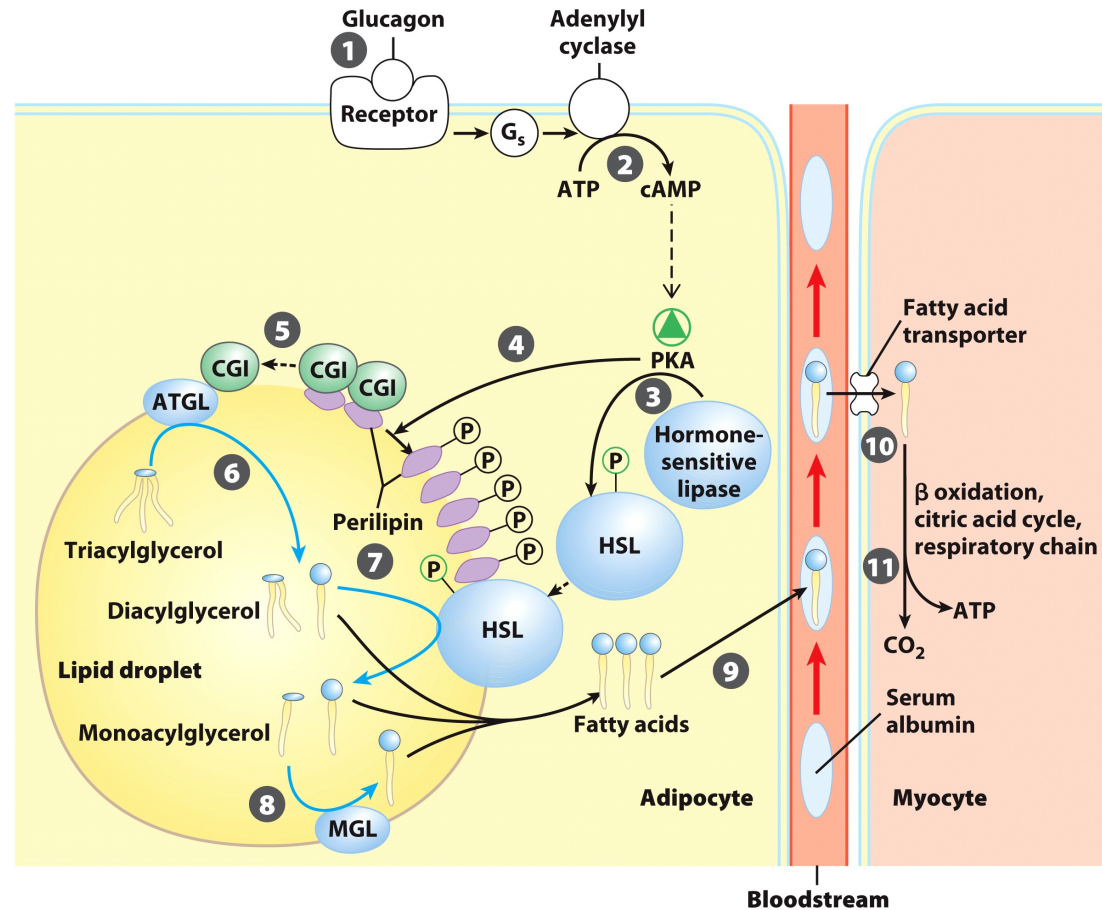
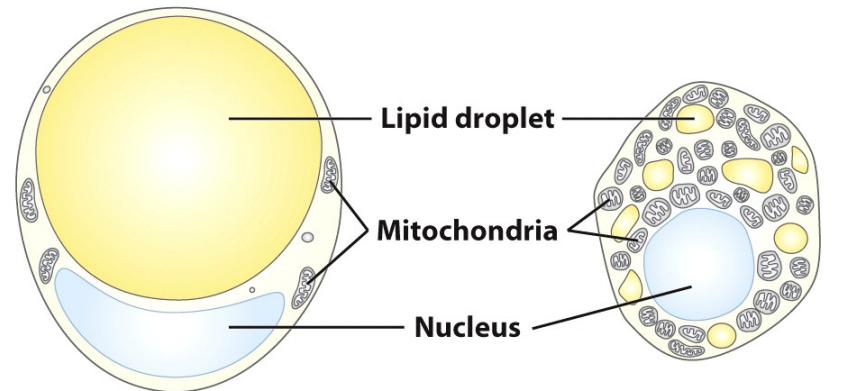


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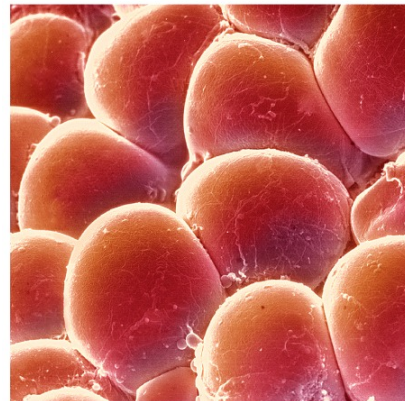
METABOLISM IN THE ADIPOSE TISSUE

- Two kinds of adipose tissues, white (WAT) and brown (BAT)
- WAT cells (30-70 μm) contain a single drop of lipids (triglycerides)
- BAT has smaller cells (20-40 μm) that store triglycerides but contain more mitochondria.
- They express *UCP1* gene coding for thermogenin, responsible for the key role of these cells: thermogenesis.



(a) White adipocyte

(b) Brown adipocyte

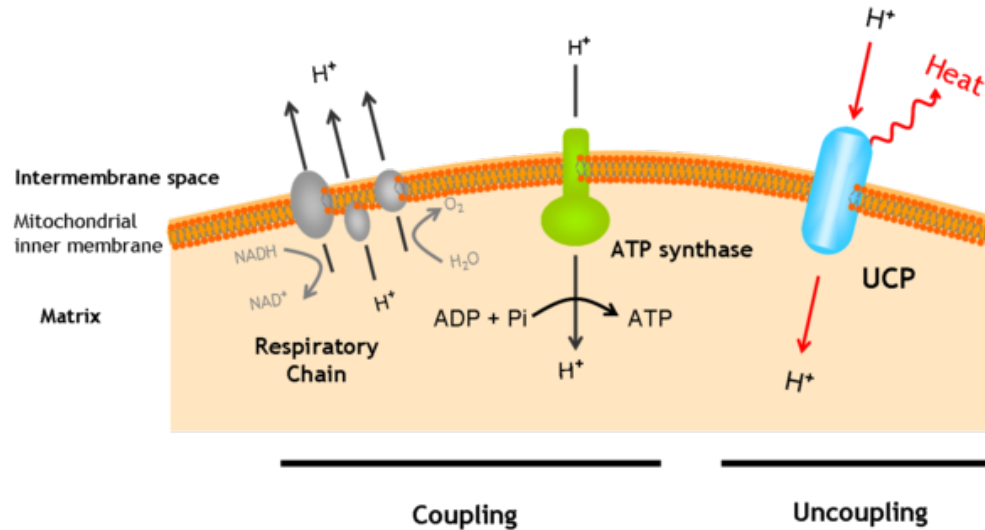


(c)



(d)

METABOLISM IN THE ADIPOSE TISSUE



•Expression of the UCP1 gene is stimulated by catecholamines. Catecholamines also activate the UCP1 protein, through a mechanism involving cyclic AMP, hormone sensitive lipase, and free fatty acids.

•In the brown adipose tissue of mammals, UCP1 induces a drastic uncoupling, allowing dissipation of the electrochemical gradient energy as heat.



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Box 17-1 Figure 1
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METABOLISM IN MUSCLE

- Glucose, fatty acids and ketone bodies are fuels for muscles
- Muscles have large stores of glycogen (3/4 of body glycogen in muscle)
- Muscles do not export glucose (no glucose-6-phosphatase)
- In active muscle glycolysis exceeds citric acid cycle, therefore lactic acid formation occurs
- **Cori Cycle** required
- Muscles can't do urea cycle. So excrete large amounts of alanine to get rid of ammonia (Glucose Alanine Cycle)

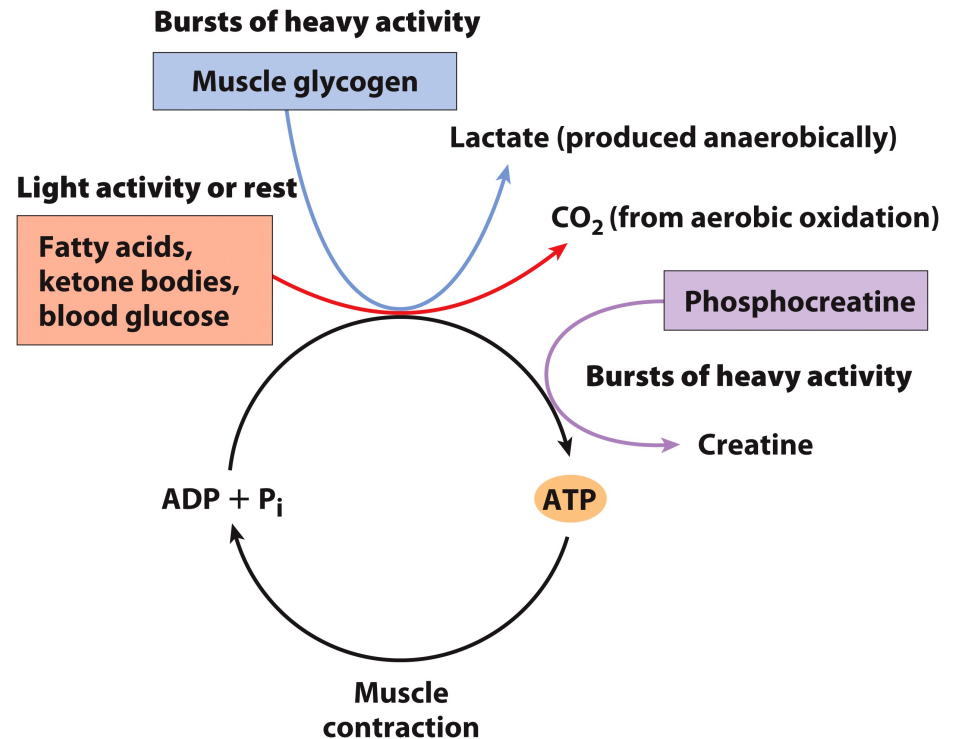
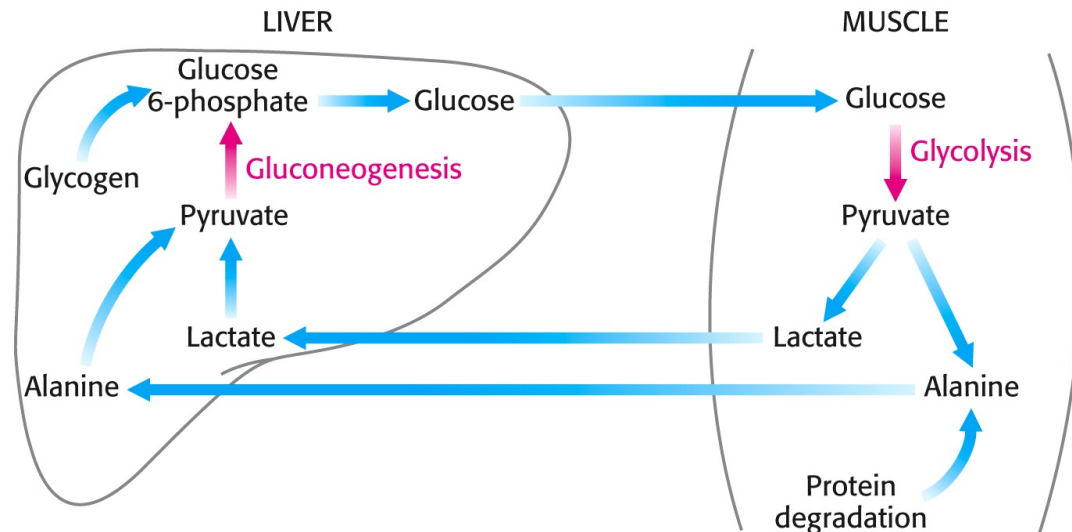


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METABOLISM IN MUSCLE

- Muscle can utilize a variety of fuels—glucose, fatty acids, and ketone bodies. Skeletal muscle varies widely in its energy demands and the fuels it consumes, in line with its wide variations in activity.
- In resting muscle, fatty acids represent the major energy source; during exertion, glucose is the primary source. Early in a period of exertion, glucose comes from mobilization of the muscle's glycogen reserves.
- Muscle contains another readily mobilizable source of energy, its own protein. However, the breakdown of muscle protein to meet energy needs is both energetically wasteful and harmful to an animal, which must move about in order to survive.
- Protein breakdown is regulated so as to minimize amino acid catabolism except in starvation.
- Muscle has an additional energy reserve in creatine phosphate, which generates ATP without the need for metabolizing fuels. This reserve is exhausted early in a period of exertion and must be replenished, along with glycogen stores, as muscle rests after prolonged exertion.



METABOLISM IN MUSCLE: CORI CYCLE

- The Cori cycle is an organismal mechanism for meeting the glucose needs of a body at exercise.
- Muscles at work produce lactate from glycolysis when oxygen becomes limiting.
- Lactate is transported from the muscles to the liver via the bloodstream.
- In the liver, lactate is converted (via gluconeogenesis) back to glucose, where it is dumped back into the bloodstream for transport to muscle.

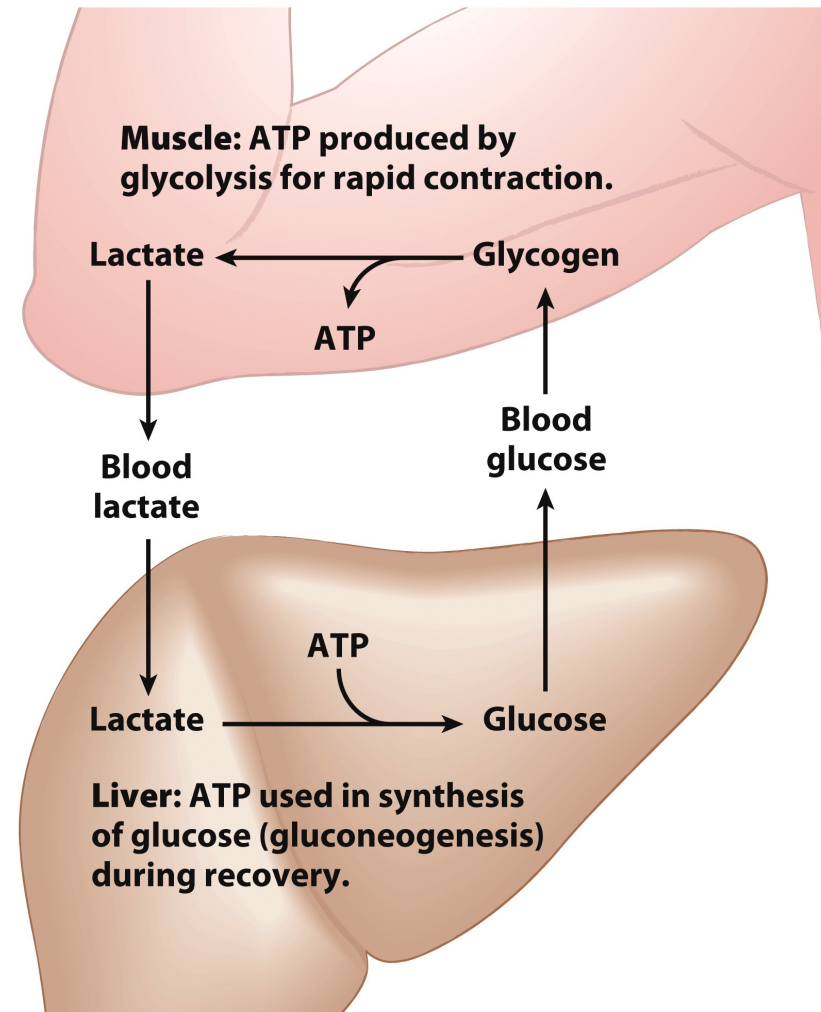
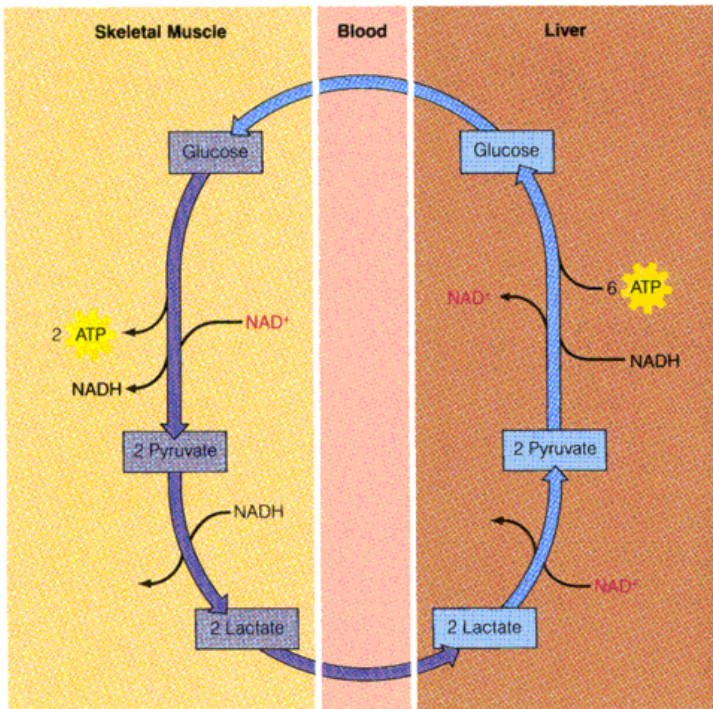


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METABOLISM IN MUSCLE: GLUCOSE-ALANINE CYCLE

- During starving, amino acids from muscle proteins are degraded.
 - They donate amino groups to pyruvate that becomes alanine that is transported to liver.
11. Alanine is deaminated to produce pyruvate that forms glucose through gluconeogenesis.

This is the glucose-alanine cycle and it has the role to maintain constant glucose in the blood.

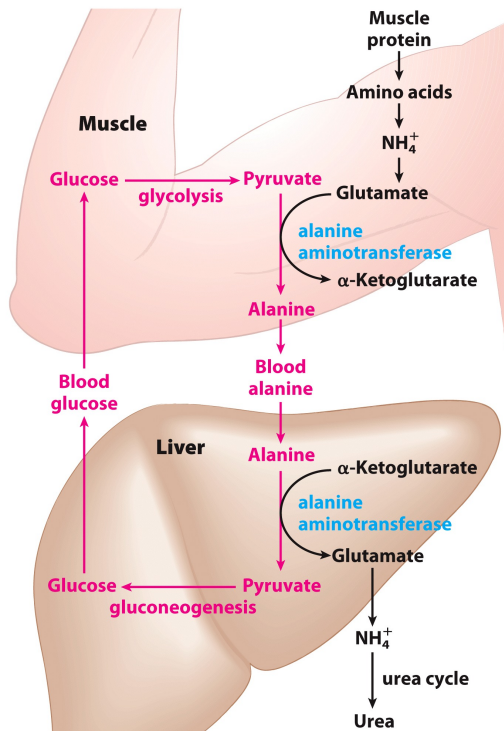


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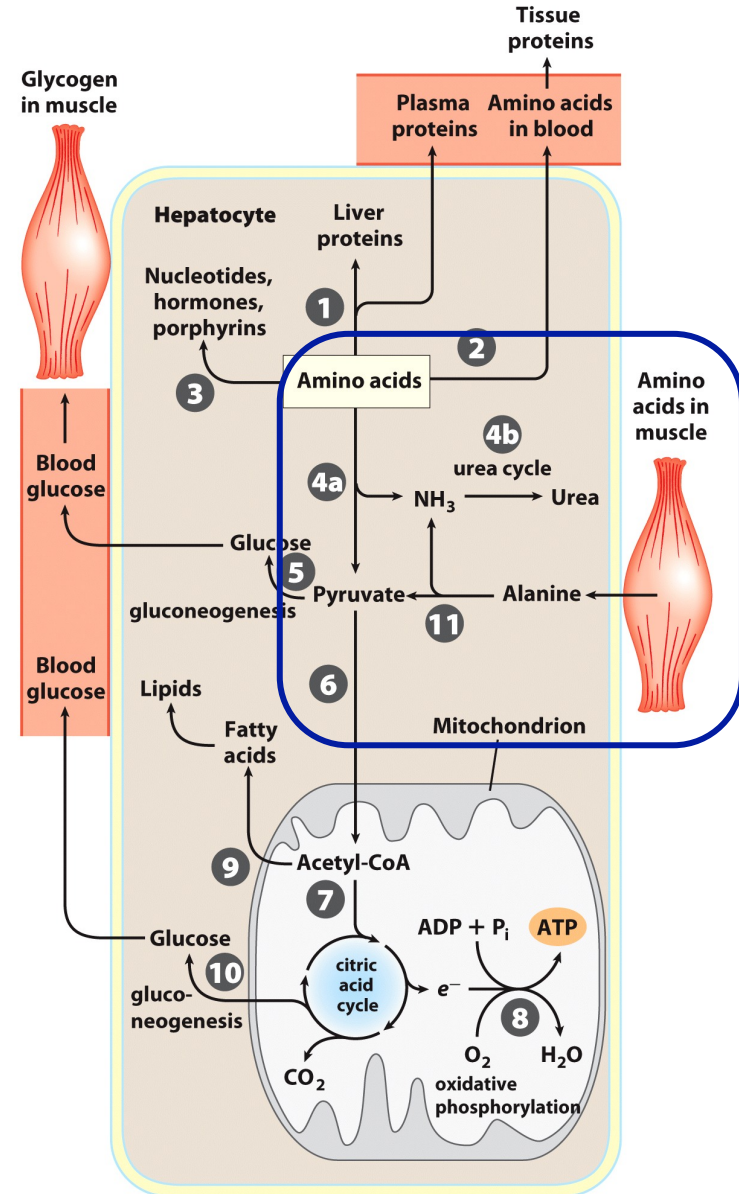
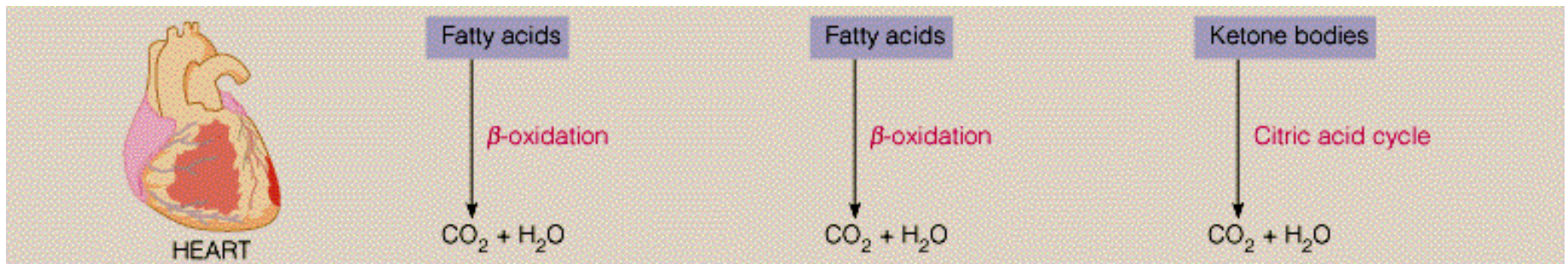


Figure 23-13
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METABOLISM IN HEART MUSCLE

- The heart uses a variety of fuels-mainly fatty acids but also glucose, lactate, and ketone bodies.
- Metabolism of heart muscle differs from that of skeletal muscle in three important respects:
 1. The variation in work output is far less than that seen in skeletal muscle. That is, the heart must work steadily and continuously in order to keep the organisms alive.
 2. The heart is a completely aerobic tissue, whereas skeletal muscle can function anaerobically for limited periods. **Mitochondria** are much more densely packed in heart than in other cells, making up nearly half the volume of a heart cell.
 3. The heart contains negligible energy reserves as glycogen or lipid, although there is a small amount of creatine phosphate.
- The supply of both oxygen and fuels from the blood to the heart must be continuous to meet its unending energy demands.



METABOLISM IN BRAIN

- The brain's need for about 120 grams of glucose per day is equivalent to 1760 kJ-about 15% of the total energy consumed each day.
- The brain's quantitative requirement for glucose remains quite **constant**, even when an animal is at rest or asleep.
- The brain is a highly aerobic organ, too, and its metabolism utilizes some 20% of the total oxygen consumed by a human.
- Because the brain has no significant glycogen or other fuel reserves, the supply of both oxygen and glucose cannot be interrupted, even for a short time. Otherwise, anoxic brain damage results.
- However, the brain can adapt during fasting to use ketone bodies instead of glucose as a major fuel.

Starvation

Ketone bodies

Normal diet

Glucose

**CO₂ from
aerobic
oxidation**

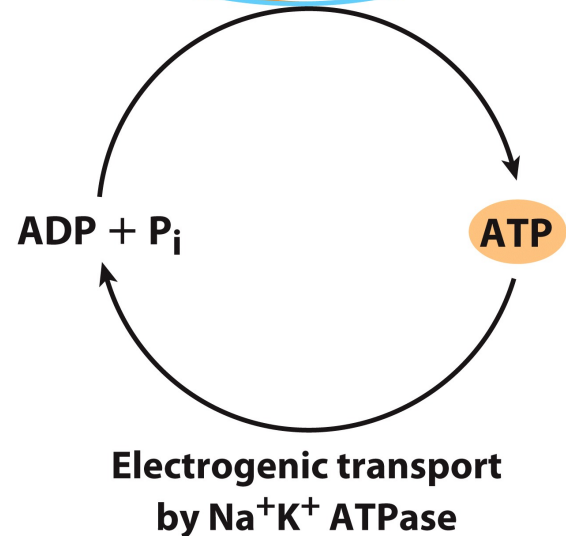
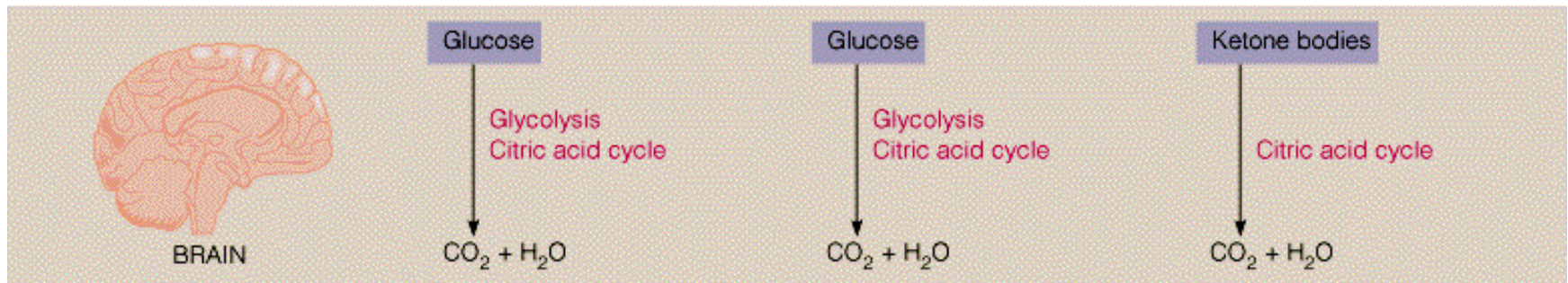


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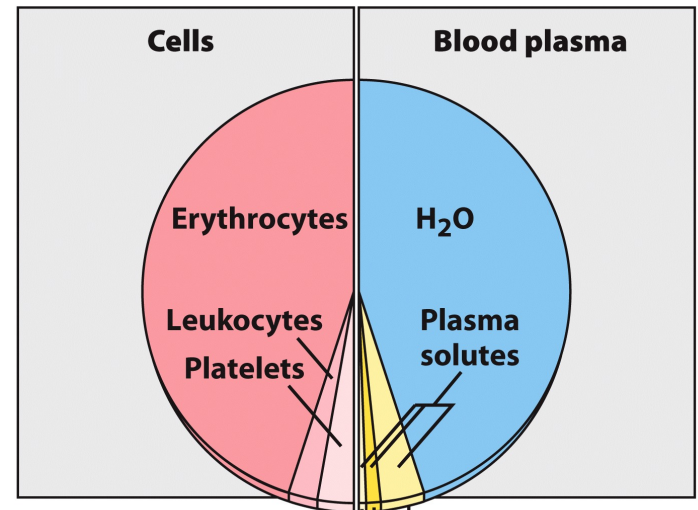
METABOLISM IN BRAIN

- Glucose is the primary fuel for the brain
- Brain lacks fuel stores, requires constant supply of glucose
- Consumes 60% of whole body glucose in resting state. Required to maintain Na^+ and K^+ membrane potential in nerve cells
- Fats can't serve as fuel because blood brain barrier prevents **albumin access**.
- Under starvation ketone bodies can be used.



THE ROLE OF BLOOD

- Glycolysis in the erythrocyte is the most prominent pathway in the energy metabolism of blood.
- Blood cells constitute nearly half the volume of blood, and erythrocytes constitute more than 99% of blood cells.
- Mammalian **erythrocytes** contain no mitochondria and depend exclusively upon **anaerobic glycolysis** to meet their energy needs.
- Blood also plays a role in transporting compounds metabolized in other tissues as follows:
 1. Blood transports waste products/fuels. The bloodstream transports what may be one organ's waste product but another organ's fuel (for example, lactate from muscle to liver).
 2. Blood transports oxygen from lungs to tissues, enabling exergonic oxidative pathways to occur, followed by transport of the resultant CO_2 back to the lungs for exhalation.
 3. The lipoprotein components of blood plasma play indispensable roles in transporting lipids.
 4. Blood is also the medium of transport of hormonal signals from one tissue to another, and of exit for metabolic end products, such as urea, via the kidneys.



Inorganic components (10%)

NaCl, bicarbonate, phosphate, CaCl_2 , MgCl_2 , KCl, Na_2SO_4

Organic metabolites and waste products (20%)

glucose, amino acids, lactate, pyruvate, ketone bodies, citrate, urea, uric acid

Plasma proteins (70%)

Major plasma proteins: serum albumin, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), immunoglobulins (hundreds of kinds), fibrinogen, prothrombin, many specialized transport proteins such as transferrin

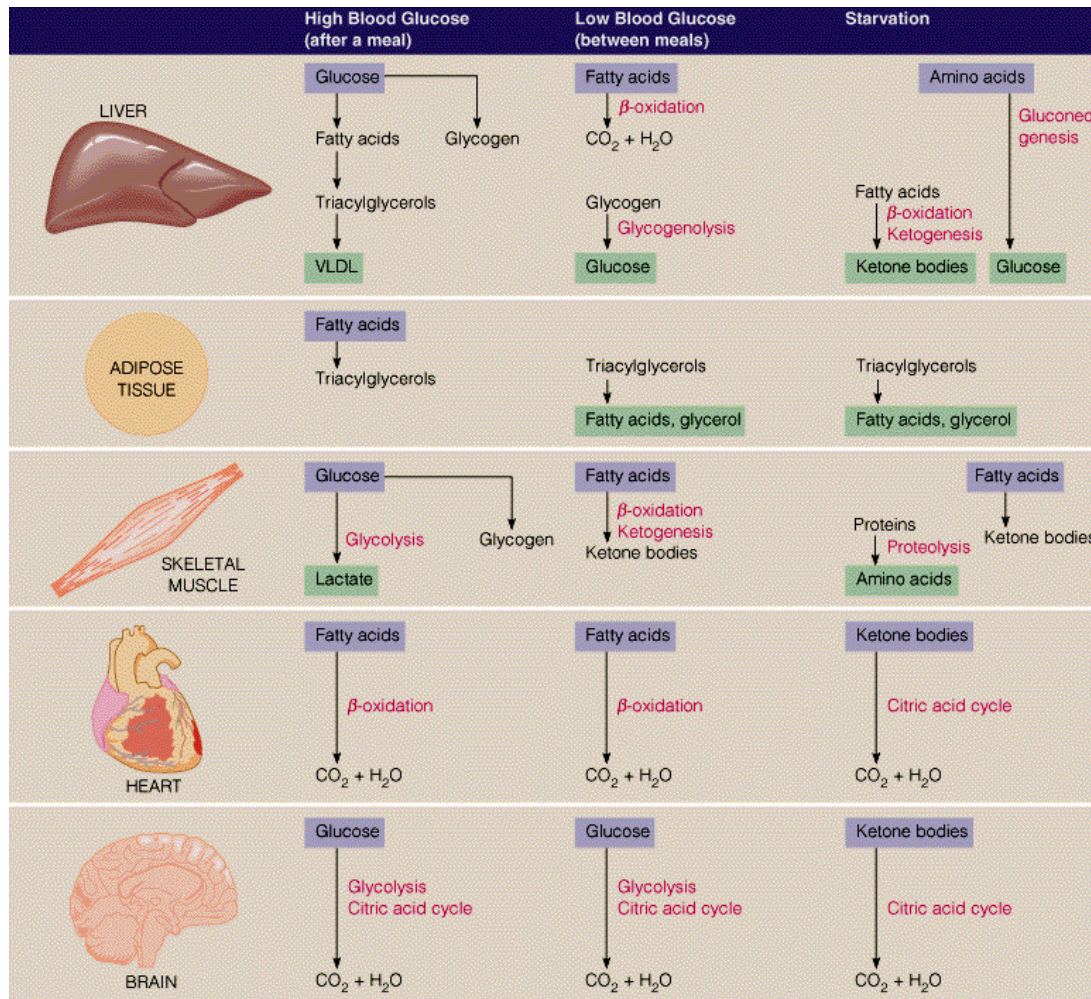
Figure 23-23

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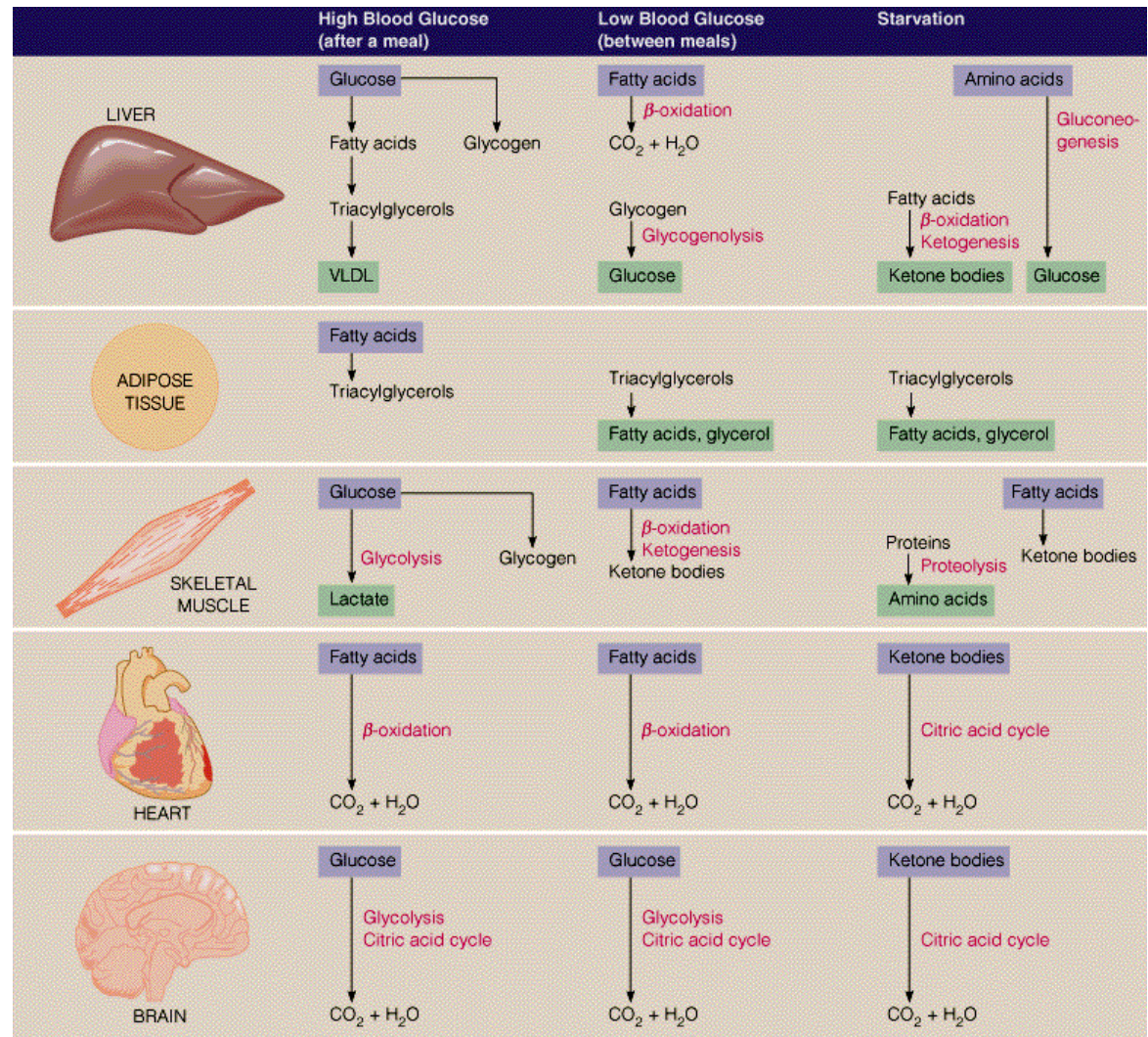
Well-Fed State

- Glucose and amino acids enter blood stream, triacylglycerol packed into chylomicrons
- Insulin is secreted, stimulates storage of fuels
- Stimulates glycogen synthesis in liver and muscles
- Stimulates glycolysis in liver which generates acetyl-CoA for fatty acid synthesis



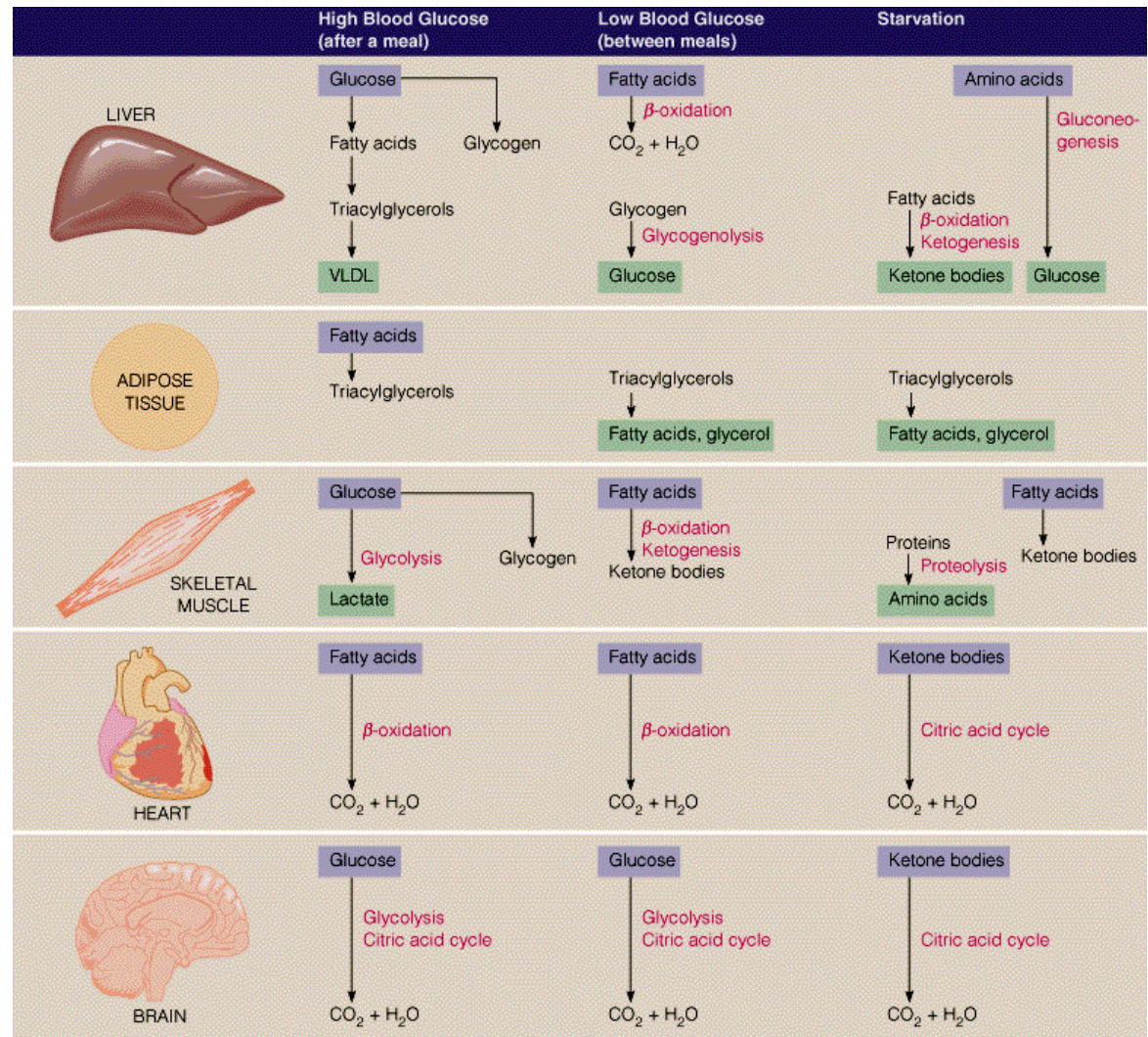
Early Fasting State

- Blood glucose levels begin to drop, glucagon is secreted
- Stimulates mobilization of fuels
- Stimulates glycogen breakdown in liver and glucose is released to the blood stream
- Glucose is not taken up by muscle tissues but used primarily to fuel the brain
- Glucagon stimulates release of fatty acids from adipose tissues and the shift of muscle fuel from glucose to fatty acids.
- Gluconeogenesis is stimulated in liver, glucose made from carbon skeletons coming from TAG and amino acid catabolism. New glucose exported to bloodstream



Refed State

- Liver initially does not absorb glucose, lets glucose go to peripheral tissues, and stays in gluconeogenesis mode
- Newly synthesized glucose goes to replenish glycogen stores
- As blood glucose levels rise, liver completes replenishment of glycogen stores.
- Excess glucose goes to fat production.



Starvation

- Fuels change from glucose to fatty acids to ketone bodies

