K1 Structures and roles of fatty acids

Key Notes

Structure and properties

Fatty acids have a long hydrocarbon chain with a terminal carboxylic acid group. Most fatty acids have an even number of carbon atoms in an unbranched chain. Saturated fatty acids have no double bonds between the carbon atoms, whereas mono- and polyunsaturated fatty acids have one or more double bonds. The properties of a fatty acid depend on the chain length and the number of double bonds.

Nomenclature

Fatty acids are named according to the number of carbon atoms in the chain and the number and position of any double bonds. Some of the more common fatty acids are palmitate (C16:0), stearate (C18:0), oleate (C18:1), linoleate (C18:2), linolenate (C18:3) and arachidonate (C20:4). The double bonds in a fatty acid are usually in the *cis* configuration.

Roles

Fatty acids have four major biological roles:

1. They are components of membranes (glycerophospholipids and sphingolipids);
2. Several proteins are covalently modified by fatty acids;
3. They act as energy stores (triacylglycerols) and fuel molecules;
4. Fatty acid derivatives serve as hormones and intracellular second messengers.

Prostaglandins

Prostaglandins and the other eicosanoids (prostacyclins, thromboxanes and leukotrienes) are derived from arachidonate. These compounds all act as local hormones. Aspirin reduces inflammation by inhibiting prostaglandin synthase, the enzyme that catalyzes the first step in prostaglandin synthesis.

Related topics

Membrane lipids (E1)
Membrane proteins and carbohydrate (E2)
Signal transduction (E5)
Fatty acid breakdown (K2)
Fatty acid synthesis (K3)
Triacylglycerols (K4)

Structure and properties

A fatty acid consists of a **hydrocarbon chain** and a **terminal carboxylic acid group** (*Fig. 1*). Most fatty acids found in biology have an **even number of carbon atoms** arranged in an **unbranched chain**. Chain length usually ranges from 14 to 24 carbon atoms, with the most common fatty acids containing 16 or 18 carbon atoms. A **saturated fatty acid** has all of the carbon atoms in its chain saturated with hydrogen atoms (*Fig. 1a*). This gives the general formula $CH_3(CH_2)_nCOOH$, where n is an even number. **Monounsaturated fatty acids** have one double bond in their structure (*Fig. 1b* and *c*), while **polyunsaturated**

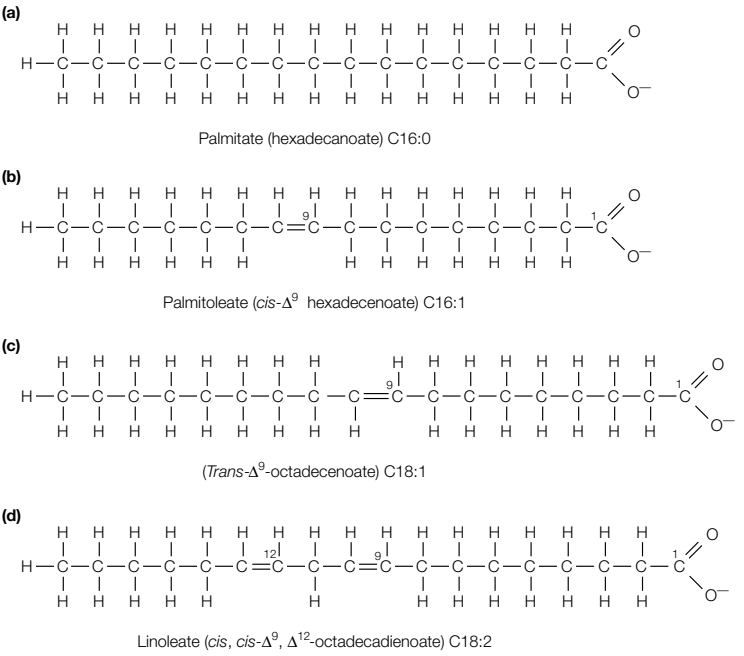

Fig. 1. Structures of (a) a saturated fatty acid (palmitate, C16:0); (b) a monounsaturated fatty acid with the double bond in the cis *configuration (palmitoleate, C16:1); (c) a monounsaturated fatty acid with the double bond in the* trans *configuration (C18:1); and (d) a polyunsaturated fatty acid (linoleate, C18:2).*

fatty acids have two or more double bonds (*Fig. 1d*). The double bonds in polyunsaturated fatty acids are separated by at least one methylene group.

The properties of fatty acids depend on their **chain length** and the **number of double bonds**. Shorter chain length fatty acids have lower melting temperatures than those with longer chains. Unsaturated fatty acids have lower melting temperatures than saturated fatty acids of the same chain length, whilst the corresponding polyunsaturated fatty acids have even lower melting temperatures (see Topic E1).

Nomenclature

Fatty acids are named according to the total number of carbon atoms, and to the number and position of any double bonds. The systematic names for fatty acids are made by adding 'oic acid' on to the name of the parent hydrocarbon. However, as fatty acids are ionized at physiological pH they are usually written as $RCOO^-$, and have names ending in 'ate' rather than 'oic acid'. A C18 saturated fatty acid would be called octadecanoate, a C18 monounsaturated fatty acid octadecenoate, and a C18 fatty acid with two double bonds octadecadienoate (see *Fig. 1*). However, many nonsystematic names are still in use (*Table 1*).

There is also a shorthand notation to show the number of carbon atoms and the number of any double bonds in the structure. A fatty acid with 18 carbons

Table 1. The names and formulae of some common fatty acids

Fatty acid	Formula	No. of double bonds	No. of carbon atoms
Palmitate	$CH_3(CH_2)_{14}COO^-$	None	16
Stearate	$CH_3(CH_2)_{16}COO^-$	None	18
Oleate	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO^-$	1	18
Linoleate	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COO^-$	2	18
Linolenate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^-$	3	18
Arachidonate	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^-$	4	20

and no double bonds is designated 18:0, while one with 18 carbons and two double bonds is 18:2. The carbon atoms in fatty acids are numbered from the carboxylic acid residue, and so the position of double bonds can be described using the number of the first carbon involved in the bond (e.g. Δ^9 shows a double bond between carbons 9 and 10 of the fatty acid chain; *Fig. 1b*). The configuration of the double bonds in most unsaturated fatty acids is ***cis***; so called because the two hydrogens on the carbon atoms either side of the double bond are on the same side of the molecule (*Fig. 1b*) (Latin, *cis* = on this side of). Thus, the full systematic name of linoleate (*Table 1*) is *cis*, *cis*-Δ^9, Δ^{12}-octadecadienoate (*Fig. 1d*). During the degradation of fatty acids (see Topic K2) some ***trans***-isomers are formed (*Fig. 1c*), where the hydrogens on the carbon atoms either side of the double bond are on opposite sides of the molecule (Latin, *trans* = across).

Roles

Fatty acids have four major biological roles:

1. They are used to make **glycerophospholipids** and **sphingolipids** that are essential components of biological membranes (see Topic E1);
2. Numerous proteins are **covalently modified** by fatty acids (see Topic E2). Myristate (C14:0) and palmitate (C16:0) are directly attached to some proteins, while phosphatidylinositol is covalently linked to the C terminus of other proteins via a complex glycosylated structure;
3. Fatty acids act as **fuel molecules**, being stored as **triacylglycerols**, and broken down to generate energy (see Topics K2 and K4);
4. Derivatives of fatty acids serve as **hormones** (such as the prostaglandins) and **intracellular second messengers** (such as DAG and IP_3) (see Topic E5).

Prostaglandins

Prostaglandins, and the structurally related molecules **prostacyclins**, **thromboxanes** and **leukotrienes**, are called **eicosanoids** because they contain 20 carbon atoms (Greek *eikosi* = 20). These hormones are relatively short-lived and hence act locally near to their site of synthesis in the body. They are derived from the common precursor **arachidonate** (*Fig. 2*). This polyunsaturated fatty acid is a derivative of linoleate (*Table 1*). Prostaglandins stimulate inflammation, modulate synaptic transmission between nerve cells, and induce sleep. Although **aspirin** (acetylsalicylic acid) has been used for centuries to decrease inflammation, pain and fever, it was not until 1974 that John Vane discovered how aspirin works. Aspirin inhibits the synthesis of prostaglandins by irreversibly inhibiting **prostaglandin synthase**. This enzyme catalyzes the first step in the synthesis of prostaglandins, prostacyclins and thromboxanes (*Fig. 2*).

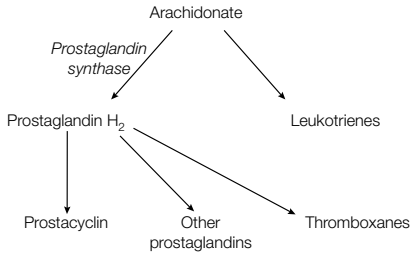

Fig. 2. Biosynthetic relationship of the eicosanoids.

K2 Fatty acid breakdown

Key Notes

Overview

Fatty acid breakdown (also called β-oxidation) brings about the oxidation of long-chain fatty acids with the production of energy in the form of ATP. The fatty acids are converted into their acyl CoA derivatives and then metabolized by the removal of two-carbon acetyl CoA units from the end of the acyl chain.

Activation

Fatty acid breakdown occurs in the cytosol of prokaryotes and in the mitochondrial matrix of eukaryotes. The fatty acid is activated by forming a thioester link with CoA before entering the mitochondria.

Transport into mitochondria

The inner mitochondrial membrane is not permeable to long-chain acyl CoA derivatives and so these are transported into the mitochondria as carnitine derivatives by carnitine/acyl carnitine translocase.

β-Oxidation pathway

Fatty acid breakdown involves a repeating sequence of four reactions:

1. Oxidation of the acyl CoA by FAD to form a *trans*-Δ^2-enoyl CoA;
2. Hydration to form 3-hydroxyacyl CoA;
3. Oxidation by NAD^+ to form 3-ketoacyl CoA;
4. Thiolysis by a second CoA molecule to form acetyl CoA and an acyl CoA shortened by two carbon atoms.

The $FADH_2$ and NADH produced feed directly into oxidative phosphorylation, while the acetyl CoA feeds into the citric acid cycle where further $FADH_2$ and NADH are produced. In animals the acetyl CoA produced in β-oxidation cannot be converted into pyruvate or oxaloacetate, and cannot therefore be used to make glucose. However, in plants two additional enzymes allow acetyl CoA to be converted into oxaloacetate via the glyoxylate pathway.

Oxidation of unsaturated fatty acids

Unsaturated fatty acids require the action of additional enzymes in order to be completely degraded by β-oxidation.

Oxidation of odd-chain fatty acids

Fatty acids having an odd number of carbon atoms give rise to acetyl CoA (two carbon atoms) and propionyl CoA (three carbon atoms) in the final round of fatty acid degradation.

Regulation

The rate of fatty acid degradation is controlled by the availability of free fatty acids in the blood which arise from the breakdown of triacylglycerols.

Energy yield

Complete degradation of palmitate (C16:0) in β-oxidation generates 35 ATP molecules from oxidation of the NADH and $FADH_2$ produced directly and 96 ATPs from the breakdown of the acetyl CoA molecules in the citric acid cycle. However, two ATP equivalents are required to activate the palmitate to its acyl CoA derivative prior to oxidation. Thus the net yield is 129 ATPs.

Ketone bodies

When in excess, acetyl CoA produced from the β-oxidation of fatty acids is converted into acetoacetate and D-3-hydroxybutyrate. Together with acetone, these compounds are collectively termed ketone bodies. Acetoacetate and D-3-hydroxybutyrate are produced in the liver and provide an alternative supply of fuel for the brain under starvation conditions or in diabetes.

Related topics

- Transport of small molecules (E3)
- Structures and roles of fatty acids (K1)
- Fatty acid synthesis (K3)
- Triacylglycerols (K4)
- Cholesterol (K5)
- Citric acid cycle (L1)
- Electron transport and oxidative phosphorylation (L2)

Overview

Fatty acid breakdown brings about the oxidation of long-chain fatty acids. The fatty acids are first converted to their **acyl coenzyme A (CoA) derivatives** and then degraded by the successive removal of two-carbon units from the end of the fatty acid as **acetyl CoA**. The pathway produces $FADH_2$ and NADH directly. The acetyl CoA produced can also enter the citric acid cycle and produce further $FADH_2$ and NADH (see Topic L1). The $FADH_2$ and NADH are then oxidized by the respiratory electron transport chain to yield energy in the form of ATP (see Topic L2).

Activation

Fatty acid breakdown occurs in the cytosol of prokaryotes, in peroxisomes in plants and in the mitochondrial matrix of all other eukaryotes. Before entering the **mitochondrial matrix**, the fatty acid is **activated** by forming a **thioester link** with **CoA** (*Fig. 1*). This reaction is catalyzed by **acyl CoA synthase** (also called **fatty acid thiokinase**) which is present on the outer mitochondrial membrane, and uses a molecule of ATP. The overall reaction is irreversible due to the subsequent hydrolysis of PP_i to two molecules of P_i.

Transport into mitochondria

Small- and medium-chain acyl CoA molecules (up to 10 carbon atoms) are readily able to cross the **inner mitochondrial membrane** by diffusion. However, longer chain acyl CoAs do not readily cross the inner mitochondrial membrane, and require a specific transport mechanism. To achieve this, the longer chain acyl CoAs are conjugated to the polar **carnitine** molecule which is found in both plants and animals. This reaction, catalyzed by an enzyme on the outer face of the inner mitochondrial membrane (**carnitine acyltransferase I**), removes the CoA group and substitutes it with a carnitine molecule (*Fig. 2*). The acylcarnitine is then transported across the inner mitochondrial membrane by a **carnitine/acylcarnitine translocase**. This integral membrane transport protein (see Topic E3) transports acylcarnitine molecules into the mitochondrial matrix and free carnitine molecules out. Once inside the mitochondrial matrix the acyl

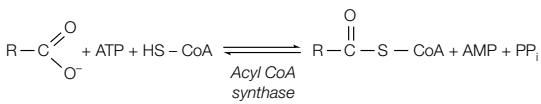

Fig. 1. Activation of a fatty acid.

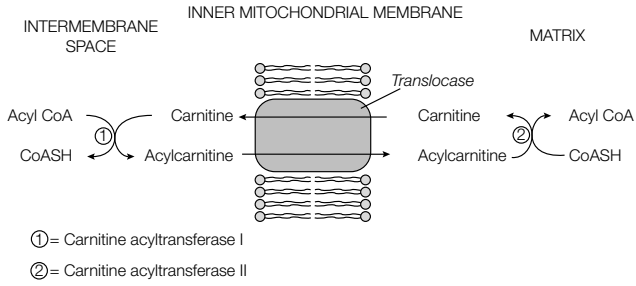

Fig. 2. Transport of fatty acids across the inner mitochondrial membrane.

group is transferred back on to CoA, releasing free carnitine, by the enzyme **carnitine acyltransferase II** which is located on the matrix side of the inner mitochondrial membrane (*Fig. 2*).

ß-Oxidation pathway

The individual reactions involved in the degradation of fatty acids by β-oxidation are as follows (*see Fig. 3*):

1. **Oxidation** of the fatty acyl CoA to enoyl CoA forming a *trans* Δ^2-double bond on the fatty acyl chain and producing $FADH_2$ (catalyzed by **acyl CoA dehydrogenase**).
2. **Hydration** of the *trans* Δ^2-enoyl CoA to form 3-hydroxyacyl CoA (catalyzed by **enoyl CoA hydratase**).
3. **Oxidation** of 3-hydroxyacyl CoA to 3-ketoacyl CoA producing NADH (catalyzed by **hydroxyacyl CoA dehydrogenase**).
4. Cleavage, or **thiolysis**, of 3-ketoacyl CoA by a second CoA molecule, giving acetyl CoA and an acyl CoA shortened by two carbon atoms (catalyzed by **β-ketothiolase**).

Thus, the breakdown of individual fatty acids occurs as a repeating sequence of four reactions: **oxidation** (by FAD), **hydration**, **oxidation** (by NAD^+) and **thiolysis**. These four reactions form one 'round' of fatty acid degradation (*Fig. 3*) and their overall effect is to remove two-carbon units sequentially in the form of acetyl CoA from the fatty acid chain. The cleavage of the Δ^2 (or β) bond of the fatty acyl chain (see *Fig. 3*, top structure, for nomenclature) gives fatty acid breakdown its alternative name, **β-oxidation**. The shortened acyl CoA then undergoes further cycles of β-oxidation until the last cycle, when the acyl CoA with four carbon atoms is split into two molecules of acetyl CoA. Thus a C16 saturated acyl CoA, such as palmitoyl CoA, would be completely degraded into eight molecules of acetyl CoA by seven rounds of degradation, leading to the overall equation:

$$\text{Palmitoyl CoA} + 7\,\text{FAD} + 7\,\text{NAD}^+ + 7\,\text{CoA} + 7\,\text{H}_2\text{O} \rightarrow 8\,\text{acetyl CoA} + 7\,\text{FADH}_2 + 7\,\text{NADH} + 7\,\text{H}^+$$

Mitochondria contain three **acyl CoA dehydrogenases** which act on short-, medium- and long-chain acyl CoAs, respectively. In contrast, there is just one each of the enzymes enoyl CoA hydratase, hydroxyacyl CoA dehydrogenase and β-ketothiolase which all have a broad specificity with respect to the length of the acyl chain.

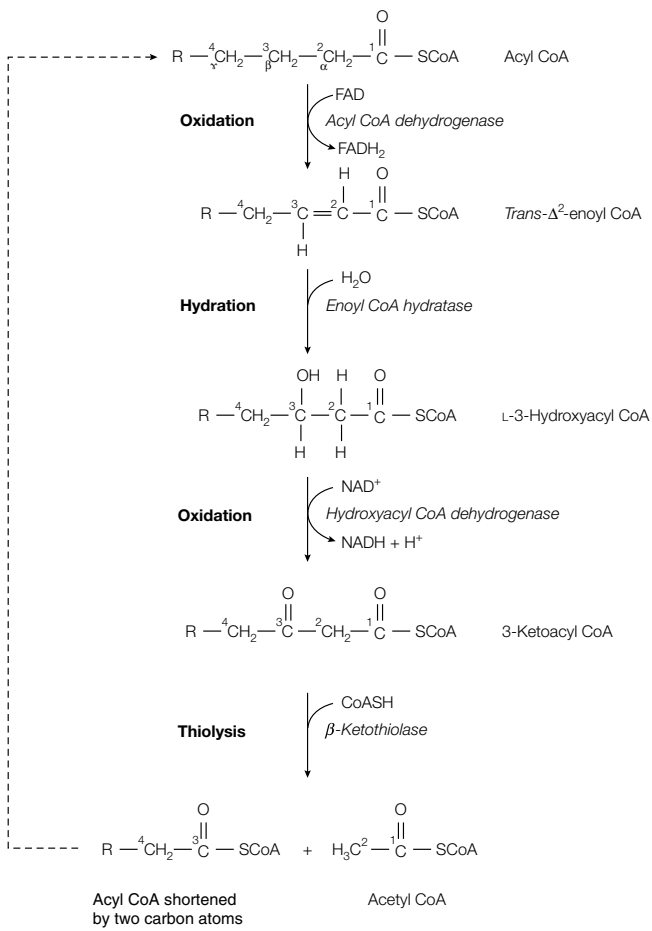

Fig. 3. Summary of the reactions involved in the degradation of fatty acids.

In animals the acetyl CoA produced from fatty acid degradation cannot be converted into pyruvate or oxaloacetate. Although the two carbon atoms from acetyl CoA enter the citric acid cycle, they are both oxidized to CO_2 in the reactions catalyzed by isocitrate dehydrogenase and α-ketoglutarate dehydrogenase (see Topic L1). Thus, **animals cannot convert fatty acids into glucose**. In contrast, plants have two additional enzymes, isocitrate lyase and malate synthase, that enable them to convert the carbon atoms of acetyl CoA into oxaloacetate. This is accomplished via the **glyoxylate pathway**, a route involving enzymes of both the mitochondrion and the glyoxysome, a specialized membranous plant organelle.

Oxidation of unsaturated fatty acids

Unsaturated fatty acids require some additional processing before they can be degraded completely by β-oxidation. Unsaturated fatty acyl CoAs with double bonds at odd-numbered carbon atoms (i.e. between, for example, C-9 and C-10 as in palmitoleate; see Topic K1, *Fig. 1b*) are acted on in the normal way by the degradation mechanism until the acyl CoA dehydrogenase encounters the *cis*-Δ^3-enoyl CoA formed at the end of the third round. The presence of the double bond between C-3 and C-4 prevents the formation of another double bond between C-2 and C-3. To overcome this problem an **isomerase** converts the *cis*-Δ^3 bond into a *trans*-Δ^2 double bond, and the resulting *trans*-Δ^2-enoyl CoA can then continue down the β-oxidation pathway (see *Fig. 4*).

Another enzyme, in addition to the isomerase, is required for the oxidation of **polyunsaturated fatty acids** which have a double bond at an even-numbered carbon atom. In this case the 2,4-dienoyl intermediate resulting from the action of acyl CoA dehydrogenase is acted on by **2,4-dienoyl CoA reductase** to form *cis*-Δ^3-enoyl CoA (*Fig. 4*). This is then converted by the isomerase into the *trans* form which continues down the pathway. These reactions are important since over half the fatty acids of plant and animal lipids are unsaturated (and often polyunsaturated).

Oxidation of odd-chain fatty acids

Fatty acids having an **odd number of carbon atoms** (which are relatively rare in nature) are also degraded by the β-oxidation pathway in the same way as those with an even number of carbon atoms. The only difference is that in the final

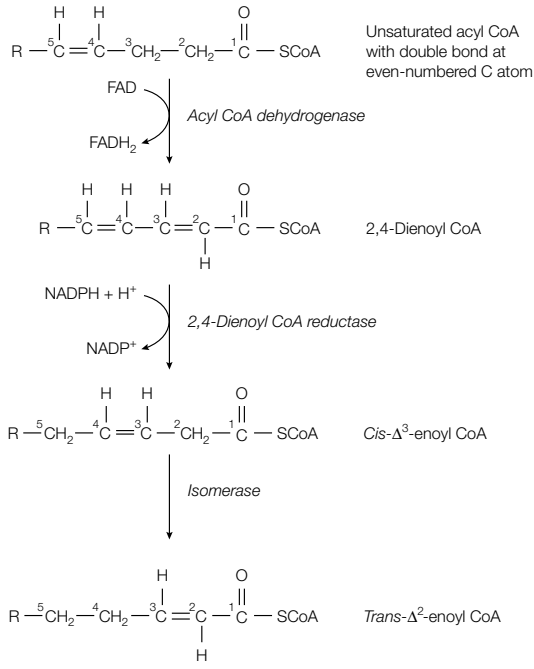

Fig. 4. Accessory enzymes required for the metabolism of unsaturated fatty acids.

round the five carbon acyl CoA intermediate is cleaved into one molecule of the C3 **propionyl CoA** and one molecule of the C2 acetyl CoA. The propionyl CoA is then converted into succinyl CoA which enters the citric acid cycle (see Topic L1).

Regulation

The major point of control of β-oxidation is the availability of fatty acids. The major source of free fatty acids in the blood is from the breakdown of **triacylglycerol** stores in adipose tissue which is regulated by the action of hormone-sensitive triacylglycerol lipase (see Topic K4). Fatty acid breakdown and fatty acid synthesis are coordinately controlled so as to prevent a futile cycle (see Topic K3).

Energy yield

For each round of degradation, one $FADH_2$, one NADH and one acetyl CoA molecule are produced. Each NADH generates three ATP molecules, and each $FADH_2$ generates two ATPs during oxidative phosphorylation (see Topic L2). In addition, each acetyl CoA yields 12 ATPs on oxidation by the citric acid cycle (see Topic L1). The total yield for each round of fatty acid degradation is therefore 17 ATP molecules.

The complete degradation of palmitoyl CoA (C16:0) requires seven rounds of degradation and hence produces 7 x 5 = 35 ATP molecules. A total of eight acetyl CoA molecules are produced and hence another 8 x 12 = 96 ATP. Thus the total ATP yield per molecule of palmitate degraded is 35 + 96 = 131 ATP. However, one ATP is hydrolyzed to AMP and PP_i in the activation of palmitate to palmitoyl CoA, resulting in two high-energy bonds being cleaved. Thus the net yield is **129 ATPs** (*Table 1*).

The yield of ATP is reduced slightly for unsaturated fatty acids, since the additional metabolic reactions which enable them to be degraded by the β-oxidation pathway either involve using NADPH or bypass an $FADH_2$-producing reaction (see *Fig. 4*).

Ketone bodies

When the level of acetyl CoA from β-oxidation increases in excess of that required for entry into the citric acid cycle, the acetyl CoA is converted into **acetoacetate** and **D-3-hydroxybutyrate** by a process known as **ketogenesis**. D-3-hydroxybutyrate, acetoacetate and its nonenzymic breakdown product **acetone** are referred to collectively as **ketone bodies** (*Fig. 5*).

Two molecules of acetyl CoA initially condense to form acetoacetyl CoA in a reaction which is essentially the reverse of the thiolysis step in β-oxidation. The acetoacetyl CoA reacts with another molecule of acetyl CoA to form **3-hydroxy-3-methylglutaryl CoA (HMG CoA)** (*Fig. 5*). This molecule is then cleaved to form acetoacetate and acetyl CoA. (HMG CoA is also the starting point for cholesterol biosynthesis; see Topic K5.) The acetoacetate is then either reduced

Table 1. Calculation of the ATP yield from the complete oxidation of palmitate

Degradative step	ATP yield
7 x 5 ATP for oxidation of NADH and $FADH_2$ produced by each round of degradation	35
8 x 12 ATP for the breakdown of acetyl CoA by the citric acid cycle	96
–2 ATP equivalents for the activation of palmitate	–2
	Total = 129

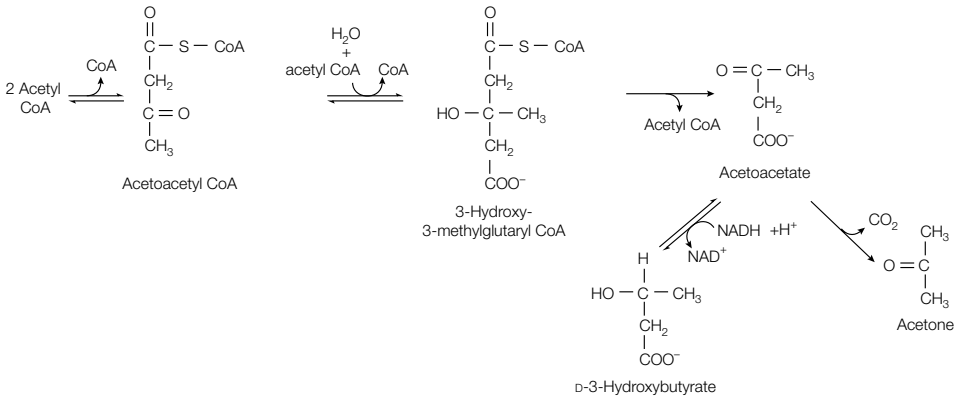

Fig. 5. Conversion of acetyl CoA to the ketone bodies acetoacetate, acetone and D-3-hydroxybutyrate.

to D-3-hydroxybutyrate in the mitochondrial matrix or undergoes a slow, spontaneous decarboxylation to acetone (*Fig. 5*). In diabetes, acetoacetate is produced faster than it can be metabolized. Hence untreated diabetics have high levels of ketone bodies in their blood, and the smell of acetone can often be detected on their breath.

Acetoacetate and D-3-hydroxybutyrate are produced mainly in the liver and are not just degradation products of little physiological value. They are used in preference to glucose as an energy source by certain tissues such as the heart muscle and kidney cortex. Although glucose is normally the major fuel for the brain, under conditions of starvation or diabetes this organ can switch to using predominantly acetoacetate.

K3 Fatty acid synthesis

Key Notes

Overview

Fatty acid synthesis involves the condensation of two-carbon units, in the form of acetyl CoA, to form long hydrocarbon chains in a series of reactions. These reactions are carried out on the fatty acid synthase complex using NADPH as reductant. The fatty acids are covalently linked to acyl carrier protein (ACP) during their synthesis.

Transport into the cytosol

Since fatty acid synthesis takes place in the cytosol, the acetyl CoA produced from pyruvate has to be transported out of the mitochondria. However, the inner mitochondrial membrane is not permeable to this compound, so it is first combined with oxaloacetate to form citrate which readily crosses the membrane. In the cytosol the citrate is cleaved to regenerate the acetyl CoA.

The pathway

The first committed step in fatty acid biosynthesis is the carboxylation of acetyl CoA to form malonyl CoA which is catalyzed by the biotin-containing enzyme acetyl CoA carboxylase. Acetyl CoA and malonyl CoA are then converted into their ACP derivatives. The elongation cycle in fatty acid synthesis involves four reactions: condensation of acetyl-ACP and malonyl-ACP to form acetoacetyl-ACP releasing free ACP and CO_2, then reduction by NADPH to form D-3-hydroxybutyryl-ACP, followed by dehydration to crotonyl-ACP, and finally reduction by NADPH to form butyryl-ACP. Further rounds of elongation add more two-carbon units from malonyl-ACP on to the growing hydrocarbon chain, until the C16 palmitate is formed. Further elongation of fatty acids takes place on the cytosolic surface of the smooth endoplasmic reticulum (SER).

Formation of double bonds

The enzymes for introducing double bonds into the acyl chain are also present on the cytosolic surface of the SER. The polyunsaturated fatty acids linoleate and linolenate cannot be synthesized by mammals and are therefore termed essential fatty acids as they have to be ingested in the diet.

Regulation

The key control point of fatty acid synthesis is acetyl CoA carboxylase which catalyzes the formation of malonyl CoA. Acetyl CoA carboxylase is inactivated by phosphorylation by an AMP-activated protein kinase. Thus when the energy charge of the cell is low (high AMP, low ATP) acetyl CoA carboxylase is inactive. It is reactivated by dephosphorylation by protein phosphatase 2A. Glucagon and epinephrine inhibit fatty acid synthesis by inhibiting protein phosphatase 2A, whereas insulin stimulates fatty acid synthesis by activating the phosphatase. Acetyl CoA carboxylase is also allosterically regulated: citrate activates the enzyme, whereas palmitoyl CoA inhibits it.

Related topics

Regulation of enzyme activity (C5)
Pentose phosphate pathway (J5)
Structures and roles of fatty acids (K1)
Fatty acid breakdown (K2)
Triacylglycerols (K4)
Citric acid cycle (L1)

Overview

Fatty acids are synthesized by the condensation of two-carbon units. However, in terms of the enzymic steps involved, the process is not the reverse of β-oxidation (see Topic K2). **Fatty acid synthesis** involves a separate series of reactions to build up long-chain hydrocarbons from **acetyl CoA** units. The key differences between fatty acid synthesis and breakdown are:

- fatty acid synthesis occurs in the **cytosol** of both prokaryotes and eukaryotes whereas their degradation occurs in the mitochondria of eukaryotes;
- fatty acid synthesis uses **NADPH** as the reductant whereas NADH is produced in β-oxidation;
- during their synthesis, fatty acids are covalently linked to an **acyl carrier protein (ACP)** as opposed to CoA in their degradation;
- the enzyme activities of fatty acid synthesis in higher organisms are present in a single, multifunctional polypeptide chain (as a dimer) called **fatty acid synthase**, whereas in β-oxidation the individual activities are present on separate enzymes.

Transport into the cytosol

Fatty acids are synthesized in the cytosol, but acetyl CoA is produced from pyruvate in the mitochondria (see Topic L1). Thus the acetyl CoA must be transferred from the mitochondria into the cytosol to allow fatty acid synthesis to occur. However, the **inner mitochondrial membrane** is not readily permeable to this molecule. This problem is overcome by the condensation of acetyl CoA with oxaloacetate to form **citrate** (*Fig. 1*). This is then transported into the cytosol where it is cleaved to regenerate acetyl CoA and oxaloacetate by **ATP-citrate lyase** in an energy-requiring process. The oxaloacetate, which also cannot cross the inner mitochondrial membrane, is returned to the mitochondrial matrix through conversion first to malate (catalyzed by **malate dehydrogenase**) and then to pyruvate (catalyzed by **$NADP^+$-linked malate enzyme**) (*Fig. 1*). This latter decarboxylation reaction generates NADPH which can be used in fatty acid synthesis. The remaining NADPH required for fatty acid synthesis is provided by the pentose phosphate pathway (see Topic J5). Once back in the

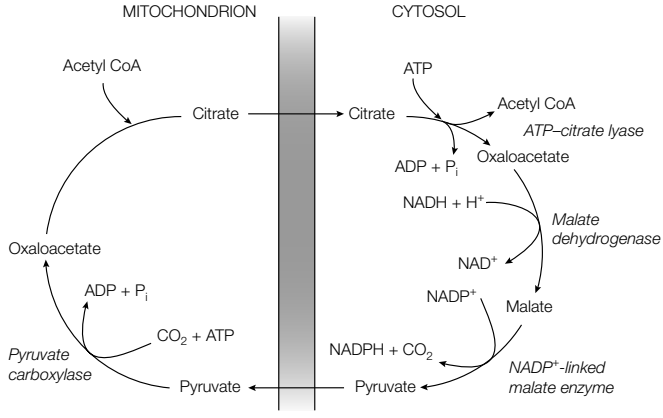

Fig. 1. Transport of acetyl CoA from the mitochondrial matrix into the cytosol.

mitochondrial matrix, pyruvate is carboxylated to form oxaloacetate by **pyruvate carboxylase** with the hydrolysis of a further molecule of ATP (*Fig. 1*).

The pathway

The **first committed step** in fatty acid biosynthesis is the carboxylation of acetyl CoA to form **malonyl CoA** using CO_2 in the form of bicarbonate HCO_3^- (*Fig. 2*). This reaction is catalyzed by the enzyme **acetyl CoA carboxylase** which has **biotin** as a prosthetic group, a common feature in CO_2-binding enzymes. One molecule of ATP is hydrolyzed in the reaction, which is irreversible. The **elongation steps** of fatty acid synthesis all involve intermediates linked to the terminal sulfhydryl group of the **phosphopantetheine** reactive unit in **ACP**; phosphopantetheine is also the reactive unit in CoA. Therefore, the next steps are the formation of acetyl-ACP and malonyl-ACP by the enzymes **acetyl transacylase** and **malonyl transacylase**, respectively (*Fig. 2*). (For the synthesis of fatty acids with an odd number of carbon atoms the three-carbon propionyl-ACP is the starting point instead of malonyl-ACP.)

The elongation cycle of fatty acid synthesis has four stages for each round of synthesis (*Fig. 3*). For the first round of synthesis these are:

1. **Condensation** of acetyl-ACP and malonyl-ACP to form acetoacetyl-ACP, releasing free ACP and CO_2 (catalyzed by acyl-malonyl-ACP condensing enzyme).
2. **Reduction** of acetoacetyl-ACP to form D-3-hydroxybutyryl-ACP, using NADPH as reductant (catalyzed by β-ketoacyl-ACP reductase).
3. **Dehydration** of D-3-hydroxybutyryl-ACP to produce crotonyl-ACP (catalyzed by 3-hydroxyacyl-ACP dehydratase).
4. **Reduction** of crotonyl-ACP by a second NADPH molecule to give butyryl-ACP (catalyzed by enoyl-ACP reductase).

This first round of elongation produces the four-carbon butyryl-ACP. The cycle now repeats with malonyl-ACP adding two-carbon units in each cycle to the lengthening acyl-ACP chain. This continues until the 16-carbon **palmitoyl-ACP** is formed. This molecule is not accepted by the acyl-malonyl-ACP condensing enzyme, and so cannot be elongated further by this process. Instead it is hydrolyzed by a thioesterase to give palmitate and ACP.

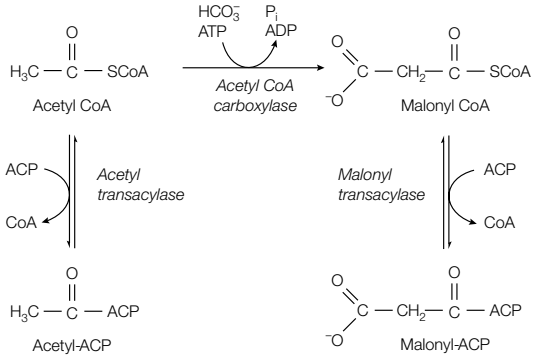

Fig. 2. Formation of acetyl- and malonyl-acyl carrier protein (ACP).

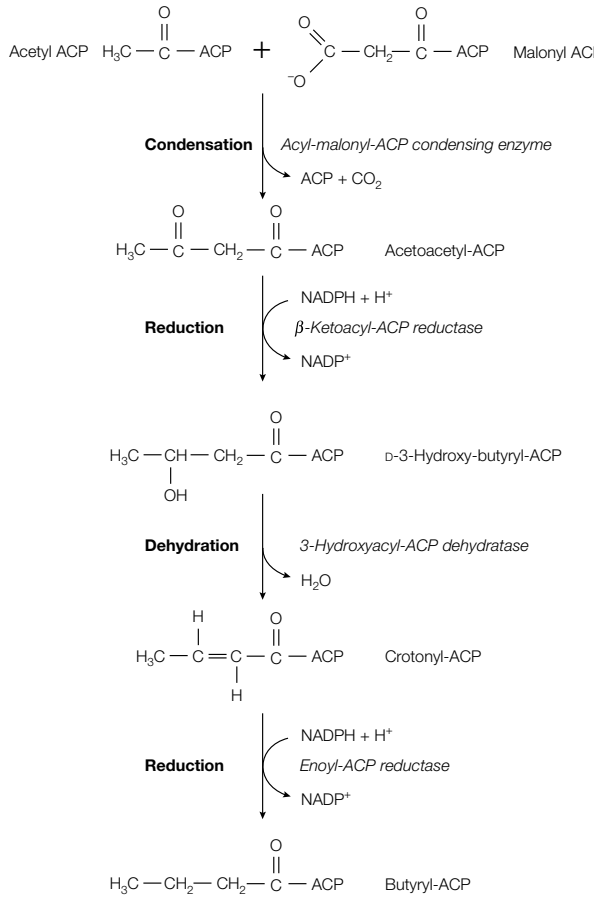

Fig. 3. The elongation cycle of fatty acid synthesis.

The overall stoichiometry for the synthesis of palmitate is:

$$8 \text{ acetyl CoA} + 7 \text{ ATP} + 14 \text{ NADPH} + 6 \text{ H}^+ \rightarrow$$
$$\text{palmitate} + 14 \text{ NADP}^+ + 8 \text{ CoA} + 6 \text{ H}_2\text{O} + 7 \text{ ADP} + 7 \text{ P}_\text{i}$$

For each of the seven rounds of fatty acid elongation, one ATP is used in the synthesis of malonyl-CoA and two NADPH are used in the reduction reactions.

In eukaryotes the elongation of fatty acids beyond C16 palmitate is carried out by enzymes located on the cytosolic surface of the **smooth endoplasmic reticulum (SER)**. Malonyl CoA is used as the two-carbon donor, and the fatty acid is elongated as its CoA derivative rather than its ACP derivative.

In prokaryotes, each of the reactions of fatty acid synthesis is catalyzed by a separate enzyme. However, in eukaryotes, the enzymes of the fatty acid synthesis elongation cycle are present in a single polypeptide chain, multifunctional enzyme complex, called **fatty acid synthase**. The fatty acid synthase complex exists as a dimer, with the ACP moiety shuttling the fatty acyl chain

between successive catalytic sites, and from one subunit of the dimer to the other. It is, in effect, a highly efficient production line for fatty acid biosynthesis.

Formation of double bonds

In eukaryotes the SER has enzymes able to introduce **double bonds** into fatty acyl CoA molecules in an oxidation reaction that uses molecular oxygen. This reaction is catalyzed by a membrane-bound complex of three enzymes: NADH-cytochrome b_5 reductase, cytochrome b_5 and a desaturase. The overall reaction is:

$$\text{saturated fatty acyl CoA} + \text{NADH} + \text{H}^+ + \text{O}_2 \rightarrow$$
$$\text{monounsaturated acyl CoA} + \text{NAD}^+ + 2\,\text{H}_2\text{O}$$

The reaction may be repeated to introduce more than one double bond into a fatty acid.

Mammals lack the enzymes to insert double bonds at carbon atoms beyond C-9 in the fatty acid chain. Thus they cannot synthesize **linoleate** and **linolenate**, both of which have double bonds later in the chain than C-9 (linoleate has *cis*, *cis* Δ^9, Δ^{12} double bonds, and linolenate has all-*cis* Δ^9, Δ^{12}, Δ^{15} double bonds). Hence, in mammals linoleate and linolenate are called **essential fatty acids** since they have to be supplied in the diet. These two unsaturated fatty acids are also the starting points for the synthesis of other unsaturated fatty acids, such as **arachidonate**. This C20:4 fatty acid is the precursor of several biologically important molecules, including the prostaglandins, prostacyclins, thromboxanes and leukotrienes (see Topic K1).

Regulation

The synthesis of fatty acids takes place when carbohydrate and energy are plentiful and when fatty acids are scarce. The key enzyme in the regulation of fatty acid synthesis is **acetyl CoA carboxylase** which synthesizes malonyl CoA. This is a good example of **control at the committed step** of a metabolic pathway. Acetyl CoA carboxylase is inactivated by the **phosphorylation** of a single serine residue by an **AMP-activated protein kinase** (*Fig. 4*) (see Topic C5). Unlike cAMP-dependent protein kinase (protein kinase A) (see Topic K4), this kinase is not affected by cAMP, but instead is stimulated by AMP and inhibited by ATP. Thus when the energy charge of the cell is low (i.e. there is a high AMP:ATP ratio) fatty acid synthesis is switched off. **Protein phosphatase 2A** removes the phosphate group from inactivated acetyl CoA carboxylase (*Fig. 4*), thereby reactivating it.

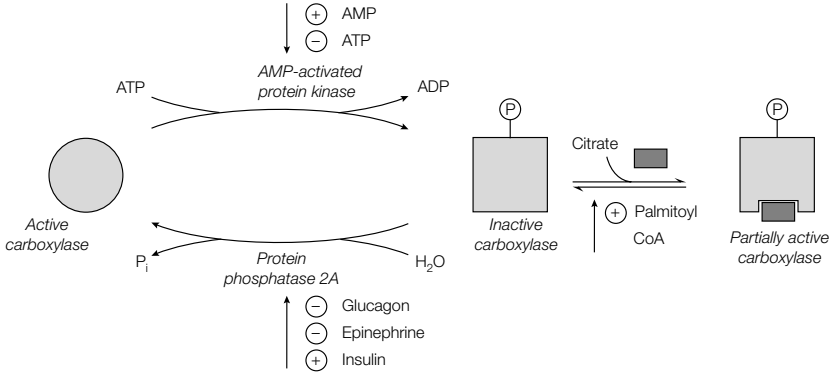

Fig. 4. Summary of the control of acetyl CoA carboxylase by phosphorylation and allosteric regulation.

Acetyl CoA carboxylase is also subject to hormonal regulation. When energy is required, **glucagon** and **epinephrine** inhibit protein phosphatase 2A, thus keeping acetyl CoA carboxylase in the inactive form (*Fig. 4*) and blocking fatty acid synthesis. In the well-fed state, when blood glucose levels are high, **insulin** stimulates acetyl CoA carboxylase, possibly by activating protein phosphatase 2A (*Fig. 4*), thereby leading to an increase in fatty acid synthesis.

As well as its control by phosphorylation/dephosphorylation, acetyl CoA carboxylase is also **allosterically regulated** (for a fuller description of allosteric regulation see Topic C5). The citric acid cycle intermediate **citrate**, the level of which is high when both acetyl CoA and ATP are abundant, allosterically stimulates acetyl CoA carboxylase. This results in the conversion of the inactive phosphorylated form into a partially active form that is still phosphorylated (*Fig. 4*), thereby activating fatty acid synthesis so that the excess acetyl CoA is 'stored' as fatty acid residues within triacylglycerol in adipose tissue. In contrast, high levels of **palmitoyl CoA**, which is abundant when there is an excess of fatty acids, antagonize the effect of citrate on acetyl CoA carboxylase, reducing its activity (*Fig. 4*) and switching off further fatty acid synthesis.

K4 TRIACYLGLYCEROLS

Key Notes

Structure and function

Triacylglycerols (fats or triglycerides) consist of three fatty acid chains esterified to a glycerol backbone. Simple triacylglycerols have three identical fatty acids, mixed triacylglycerols have two or three different fatty acids. Triacylglycerols are the major energy store and the major dietary lipid in humans. They are insoluble in water and are stored in specialized adipose (fat) cells.

Synthesis

Triacylglycerols are synthesized from glycerol 3-phosphate, which is derived from the glycolytic intermediate dihydroxyacetone phosphate, and fatty acyl CoAs. Acyl CoA molecules are added on to glycerol 3-phosphate to form first lysophosphatidic acid and then phosphatidic acid. The phosphate group is then removed to form diacylglycerol (DAG), which is further acylated to triacylglycerol. The energy for the synthesis of triacylglycerols comes from the hydrolysis of the high-energy thioester bond in acyl CoA.

Breakdown

The fatty acids in triacylglycerols are released from the glycerol backbone by the action of lipases. The free fatty acids can then be degraded by β-oxidation to produce energy. The glycerol is converted into dihydroxyacetone phosphate which enters glycolysis.

Regulation

The concentration of free fatty acids in the blood is controlled by the rate at which hormone-sensitive triacylglycerol lipase hydrolyzes the triacylglycerols stored in adipose tissue. Glucagon, epinephrine and norepinephrine cause an increase in the intracellular level of cAMP which allosterically activates cAMP-dependent protein kinase. The kinase in turn phosphorylates hormone-sensitive lipase, activating it, and leading to the release of fatty acids into the blood. Insulin has the opposite effect; it decreases the level of cAMP which leads to the dephosphorylation and inactivation of hormone-sensitive lipase.

Related topics

- Membrane lipids (E1)
- Signal transduction (E5)
- Fatty acid breakdown (K2)
- Fatty acid synthesis (K3)
- Cholesterol (K5)
- Lipoproteins (K6)

Structure and function

Triacylglycerols (also called **fats** or **triglycerides**) consist of three fatty acid chains esterified to a glycerol backbone. **Simple triacylglycerols** have three identical fatty acids esterified to the glycerol backbone, while **mixed triacylglycerols** have two or three different fatty acid chains (*Fig. 1*). Triacylglycerols constitute the **major fuel store** and the **major dietary lipid** in humans. Triacylglycerols are a highly concentrated **energy store**. The energy yield from the complete oxidation of fatty acids is about 39 kJ g^{-1}, compared with an energy yield of 13 kJ g^{-1} of carbohydrate or protein. The hydrophobic properties of fats

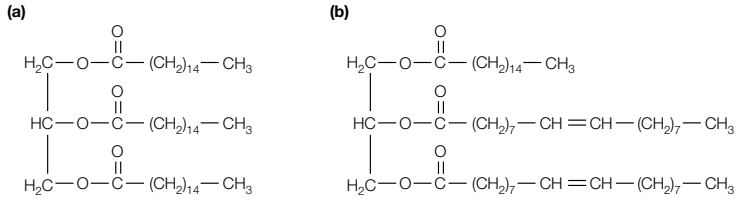

Fig. 1. Structure of (a) a simple triacylglycerol (1,2,3-tripalmitoyl-glycerol) and (b) a mixed triacylglycerol (1-palmitoyl-2,3-dioleoyl-glycerol).

make them insoluble in water, and fats are stored in specialized cells called **adipose cells** (fat cells), which consist almost entirely of triacylglycerol. These cells are specialized for the synthesis and storage of triacylglycerols and for their mobilization into fuel molecules. Triacylglycerols are transported round the body in large lipid–protein particles called **lipoproteins** (see Topic K6).

Synthesis

Triacylglycerols are synthesized from **fatty acyl CoAs** and **glycerol 3-phosphate** (*Fig. 2*). The glycolytic intermediate **dihydroxyacetone phosphate** is first reduced to glycerol 3-phosphate which is, in turn, acylated by glycerol-3-phosphate acyltransferase to form **lysophosphatidic acid**. This is then reacted with a further acyl CoA molecule to form **phosphatidic acid**. Removal of the phosphate group from phosphatidic acid generates **diacylglycerol (DAG)**, which is further acylated with a third acyl CoA molecule to form **triacylglycerol** (*Fig. 2*). ATP is not involved in the biosynthesis of triacylglycerols. Instead the reactions are driven by the cleavage of the high-energy thioester bond between the acyl moiety and CoA. Both phosphatidic acid (phosphatidate) and DAG are also used in the synthesis of membrane phospholipids (see Topic E1) and DAG is also used as a second messenger in cell signaling (see Topic E5).

Breakdown

The initial event in the utilization of both stored fat and dietary fat as energy sources is the hydrolysis of triacylglycerol by **lipases**. These enzymes release the three fatty acid chains from the glycerol backbone (*Fig. 3*). The fatty acids can then be broken down in **β-oxidation** to generate energy (see Topic K2). The glycerol backbone is also utilized, being transformed into dihydroxyacetone phosphate, an intermediate in glycolysis (*Fig. 4*). This requires two enzymes, glycerol kinase, which uses ATP to phosphorylate glycerol, producing L-glycerol 3-phosphate, and glycerol 3-phosphate dehydrogenase which produces dihydroxyacetone phosphate.

In the intestine, dietary fats are hydrolyzed by **pancreatic lipase** and the released fatty acids taken up into the **intestinal cells**. Both the digestion and uptake processes are aided by the detergent-like properties of the **bile salts** (see Topic K5).

Regulation

The breakdown of fatty acids in β-oxidation (see Topic K2) is controlled mainly by the concentration of free fatty acids in the blood, which is, in turn, controlled by the hydrolysis rate of triacylglycerols in adipose tissue by **hormone-sensitive triacylglycerol lipase**. This enzyme is regulated by **phosphorylation** and **dephosphorylation** (*Fig. 5*) in response to hormonally controlled levels of the intracellular second messenger **cAMP** (see Topic E5). The catabolic hormones

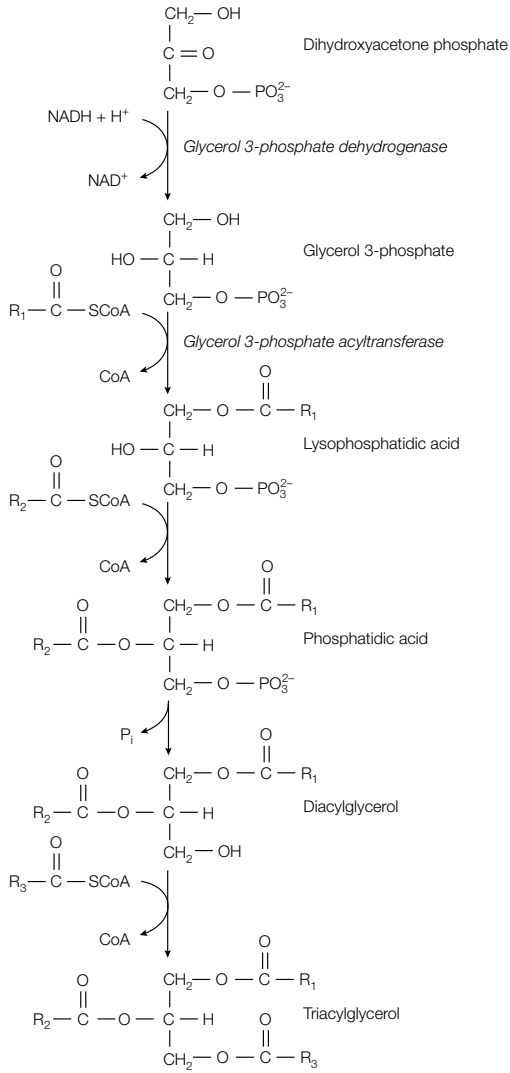

Fig. 2. Synthesis of triacylglycerols.

glucagon, **epinephrine** and **norepinephrine** bind to receptor proteins on the cell surface and increase the levels of cAMP in adipose cells through activation of **adenylate cyclase** (see Topic E5 for details of the signal transduction pathway). The cAMP allosterically activates **cAMP-dependent protein kinase** (otherwise known as **protein kinase A**) which phosphorylates various intracellular enzymes including hormone-sensitive lipase. Phosphorylation of hormone-sensitive lipase activates it, thereby stimulating the hydrolysis of triacylglycerols,

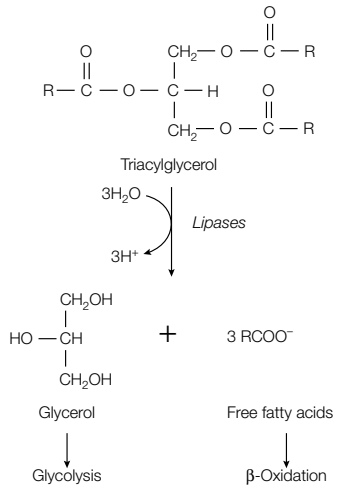

Fig. 3. Breakdown of triacylglycerols.

raising the levels of fatty acids in the blood, and subsequently activating β-oxidation in tissues such as muscle and liver. Glucagon and epinephrine also prevent the dephosphorylation, and therefore activation, of **acetyl CoA carboxylase**, so that fatty acid synthesis is inhibited (see Topic K3).

The anabolic hormone **insulin** has the opposite effect to glucagon and epinephrine. It stimulates the formation of triacylglycerols through decreasing the level of cAMP, which promotes the dephosphorylation and inactivation of

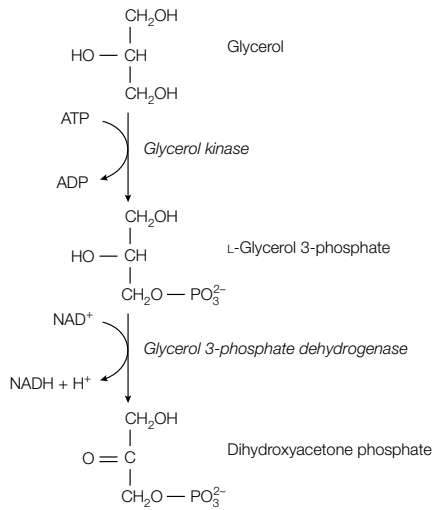

Fig. 4. Conversion of glycerol into the glycolytic intermediate dihydroxyacetone phosphate.

hormone-sensitive lipase (*Fig. 5*). Insulin also stimulates the dephosphorylation of acetyl CoA carboxylase, thereby activating fatty acid synthesis (see Topic K3). Thus fatty acid synthesis and degradation are **coordinately controlled** so as to prevent a futile cycle.

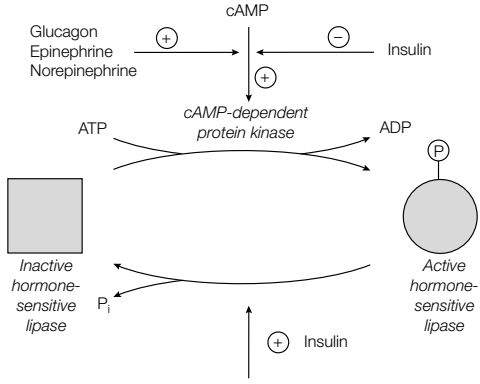

Fig. 5. Summary of the control of hormone-sensitive triacylglycerol lipase.

K5 CHOLESTEROL

Key Notes

Functions of cholesterol

Cholesterol is a component of cell membranes and is the precursor of steroid hormones and the bile salts.

Biosynthesis of cholesterol

All 27 carbon atoms of cholesterol are derived from acetyl CoA. First acetyl CoA and acetoacetyl CoA combine to form 3-hydroxy-3-methylglutaryl CoA (HMG CoA) which, in turn, is reduced to mevalonate by HMG CoA reductase. Mevalonate is converted into the five-carbon isoprene compounds 3-isopentenyl pyrophosphate and its isomer dimethylallyl pyrophosphate. These two compounds condense to form the C10 geranyl pyrophosphate, which is elongated to the C15 farnesyl pyrophosphate by the addition of another molecule of isopentenyl pyrophosphate. Two molecules of farnesyl pyrophosphate condense to form the C30 squalene, which is then converted via squalene epoxide and lanosterol to cholesterol.

Regulation of cholesterol biosynthesis

Cholesterol can either be obtained in the diet or synthesized in the liver. High levels of cholesterol and its metabolites decrease the amount and inhibit the activity of HMG CoA reductase, the enzyme that catalyzes the committed step in cholesterol biosynthesis. This enzyme can also be inhibited therapeutically by the compound lovastatin.

Bile salts

Bile salts (bile acids) are the major excretory form of cholesterol. These polar compounds are formed in the liver by converting cholesterol into the activated intermediate cholyl CoA and then combining this compound with either glycine, to form glycocholate, or taurine, to form taurocholate. The detergent-like bile salts are secreted into the intestine where they aid the digestion and uptake of dietary lipids.

Vitamin D

Vitamin D is derived via cholesterol in a series of reactions, one of which requires the action of UV light to break the bond between two carbon atoms. Deficiency of vitamin D causes rickets in children and osteomalacia in adults.

Steroid hormones

The steroid hormones are derived from cholesterol by a series of reactions that involve the heme-containing cytochrome P450 enzymes. These mono-oxygenases require both O_2 and NADPH to function. There are five classes of steroid hormones: (1) the progestagens; (2) the androgens; (3) the estrogens; (4) the glucocorticoids; and (5) the mineralocorticoids.

Related topics

Regulation of enzyme activity (C5)
Membrane lipids (E1)
Membrane proteins and carbohydrate (E2)
Protein glycosylation (H5)
Fatty acid breakdown (K2)
Fatty acid synthesis (K3)
Triacylglycerols (K4)
Lipoproteins (K6)
Hemes and chlorophylls (M4)

Functions of cholesterol

Cholesterol is a **steroid**. It is an important constituent of **cell membranes**, where, in mammals, it modulates their fluidity (see Topic E1). Cholesterol is also the precursor of **steroid hormones** such as progesterone, testosterone and cortisol, and the **bile salts** (see below).

Biosynthesis of cholesterol

Animals are able to synthesize cholesterol *de novo* by an elegant series of reactions in which all 27 carbon atoms of cholesterol are derived from **acetyl CoA**. The acetate units are first converted into **C5 isoprene units**, that are then condensed to form a linear precursor to the cyclic cholesterol.

The first stage in the synthesis of cholesterol is the formation of **isopentenyl pyrophosphate** (*Fig. 1*). Acetyl CoA and acetoacetyl CoA combine to form

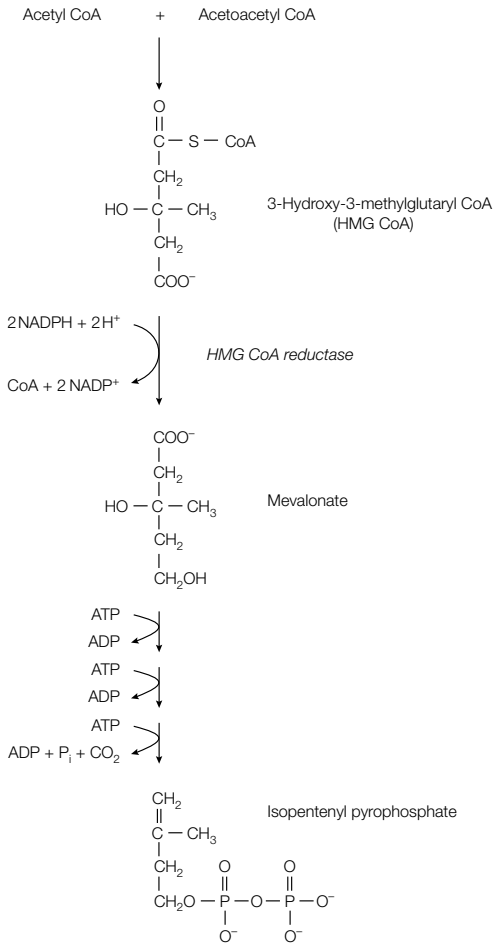

Fig. 1. Synthesis of isopentenyl pyrophosphate.

3-hydroxy-3-methylglutaryl CoA (HMG CoA). This process takes place in the liver, where the HMG CoA in the mitochondria is used to form ketone bodies during starvation (see Topic K2), whereas that in the cytosol is used to synthesize cholesterol in the fed state (under the influence of cholesterol). HMG CoA is then reduced to **mevalonate** by **HMG CoA reductase** (*Fig. 1*). This is the committed step in cholesterol biosynthesis and is a key control point. Mevalonate is converted into **3-isopentenyl pyrophosphate** by three consecutive reactions each involving ATP, with CO_2 being released in the last reaction (*Fig. 1*).

The C5 isoprene units in isopentenyl pyrophosphate are then condensed to form the C30 compound squalene (*Fig. 2*). First, isopentenyl pyrophosphate isomerizes to **dimethylallyl pyrophosphate** (*Fig. 2a*), which reacts with another molecule of isopentenyl pyrophosphate to form the C10 compound **geranyl pyrophosphate** (*Fig. 2b*). Another molecule of isopentenyl pyrophosphate then reacts with geranyl pyrophosphate to form the C15 compound **farnesyl pyrophosphate**. Next, two molecules of farnesyl pyrophosphate condense to form **squalene** (*Fig. 2b*).

Squalene is then converted into **squalene epoxide** in a reaction that uses O_2 and NADPH (*Fig. 2b*). The squalene epoxide cyclizes to form **lanosterol**, and finally cholesterol is formed from lanosterol by the removal of three methyl groups, the reduction of one double bond by NADPH, and the migration of the other double bond (*Fig. 2b*).

Farnesyl pyrophosphate and the C20 compound **geranylgeranyl pyrophosphate** (which is formed by the condensation of another isopentenyl pyrophosphate with farnesyl pyrophosphate) are covalently linked to cysteine residues in a number of proteins, giving rise to **prenylated proteins**, promoting their association with membranes (see Topic E2). **Dolichol**, which contains some 20 isoprene units is used to carry the biosynthetic precursor of the N-linked oligosaccharides that are subsequently attached to proteins (see Topic H5).

Regulation of cholesterol biosynthesis

Cholesterol can be obtained either from the diet or it can be synthesized *de novo*, mainly in the liver. Cholesterol is transported round the body in **lipoprotein** particles (see Topic K6). The rate of synthesis of cholesterol is dependent on the cellular level of cholesterol. High levels of cholesterol and its metabolites control cholesterol biosynthesis by:

- feedback-inhibiting the activity of **HMG CoA reductase**, the enzyme which catalyzes the committed step in cholesterol biosynthesis (see Topic C5);
- decreasing the amount of HMG CoA reductase by reducing the synthesis and translation of its mRNA;
- decreasing the amount of HMG CoA reductase by increasing its rate of degradation.

In addition, HMG CoA reductase, like acetyl CoA carboxylase in fatty acid synthesis (see Topic K3), is inactivated by phosphorylation by an AMP-activated protein kinase, retained in this form under the influence of glucagon during starvation.

HMG CoA reductase can be inhibited therapeutically by administering the drug **lovastatin**, based on the fungal products **mevinolin** and **compactin,** which competitively inhibit the enzyme and hence decrease the rate of cholesterol biosynthesis. Therefore, these compounds are routinely used for the treatment of **hypercholesterolemia** (high levels of blood cholesterol) (see Topic K6).

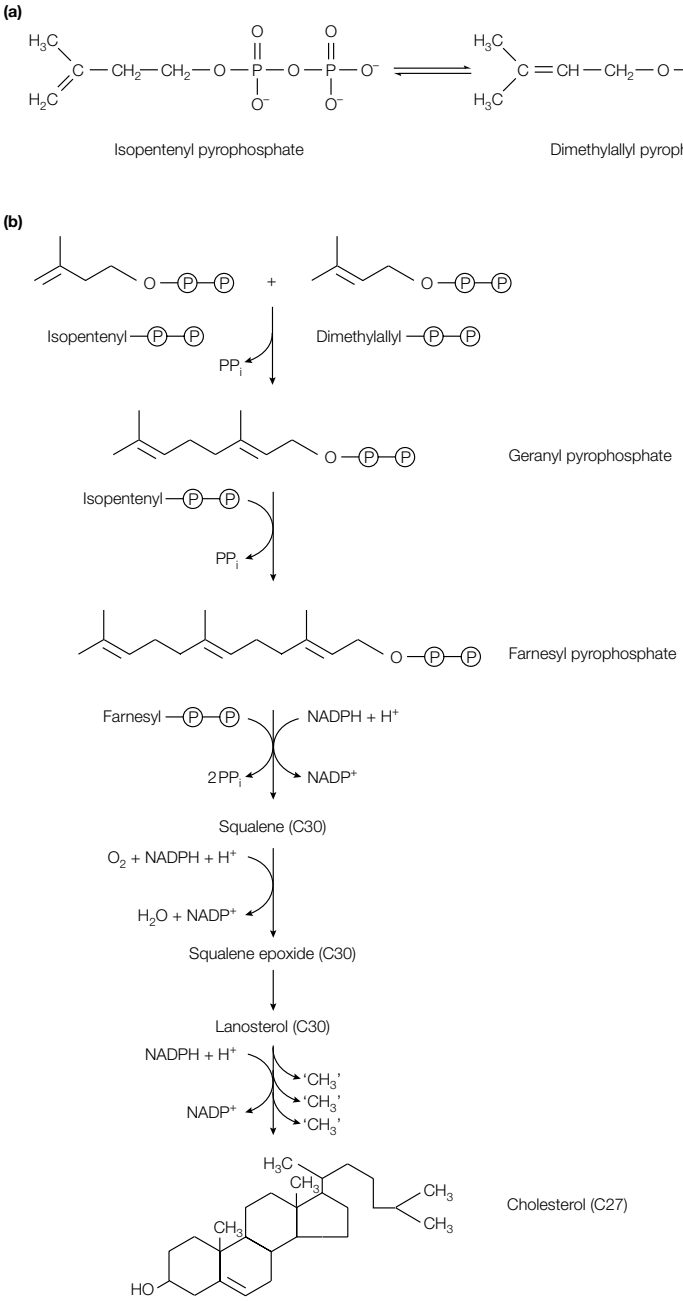

Fig. 2 Synthesis of squalene and cholesterol from isopentenyl pyrophosphate. (a) Isomerization of isopentenyl pyrophosphate to dimethylallyl pyrophosphate; (b) synthesis of cholesterol.

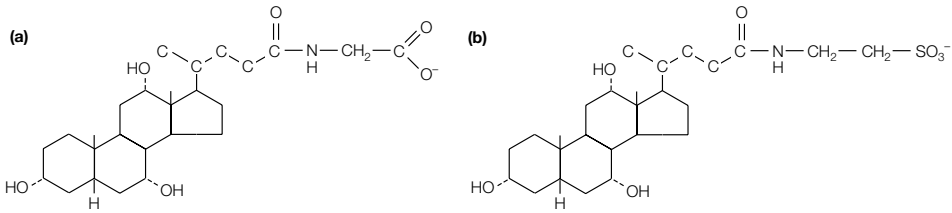

Fig. 3. Structures of the bile salts (a) glycocholate and (b) taurocholate.

Bile salts

Bile salts (or bile acids) are polar derivatives of cholesterol and constitute the major pathway for the excretion of cholesterol in mammals. In the liver, cholesterol is converted into the activated intermediate **cholyl CoA** which then reacts either with the amino group of glycine to form **glycocholate** (*Fig. 3a*), or with the amino group of taurine (H_2N-CH_2-CH_2-SO_3^-, a derivative of cysteine) to form **taurocholate** (*Fig. 3b*). After synthesis in the liver, the bile salts glycocholate and taurocholate are stored and concentrated in the gall bladder, before release into the small intestine. Since they contain both polar and nonpolar regions (that is are amphipathic molecules), the bile salts are very effective detergents and act to solubilize dietary lipids. The resulting increase in the surface area of the lipids aids their hydrolysis by lipases and their uptake into intestinal cells (see Topic K4). The intestinal absorption of the **lipid-soluble vitamins** A, D, E and K also requires the action of the bile salts.

Vitamin D

Vitamin D is derived from 7-dehydrocholesterol by the action of the **UV** component of sunlight on the skin. UV light brings about photolysis of 7-dehydrocholesterol between C-9 and -10, leading to a rearrangement of the double bonds of the molecule to form **previtamin D_3** (*Fig. 4*). This molecule spontaneously isomerizes to form **vitamin D_3** (**cholecalciferol**). Subsequent hydroxylation reactions take place in the liver and kidneys to produce 1,25-dihydroxycholecalcerol (1,25(OH)D_3), the active hormone (*Fig. 4*). **Rickets**, which is caused by a deficiency of vitamin D, was historically a common disease of childhood in Britain due to the low vitamin D content of the national diet, and lack of exposure to sunlight. Even today, people whose cultures require the body to be clothed so that no skin is exposed to sunlight have problems in

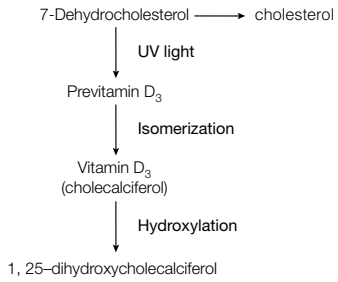

Fig. 4. Formation of vitamin D.

Table 1. Classes of steroid hormone

Class	Site of synthesis	Hormone	Action
Progestagens	Corpus luteum	Progesterone	Prepares uterine lining for egg implantation; maintenance of pregnancy
Androgens	Testis	Testosterone	Development of male secondary sex characteristics
Estrogens	Ovary	Estrone	Development of female secondary sex characteristics
Glucocorticoids	Adrenal cortex	Cortisol	Promotes gluconeogenesis and glycogen formation; enhances fat and protein degradation
Mineralocorticoids	Adrenal cortex	Aldosterone	Increases reabsorption of Na^+ and excretion of K^+ and H^+ by kidney tubules

maintaining an adequate vitamin D level. In adults this takes the form of **osteomalacia** – the softening or weakening of the bones.

Steroid hormones

Cholesterol is the precursor of the five major classes of **steroid hormones** (*Table 1*). The synthesis of steroid hormones is initiated by the removal of a six-carbon unit from carbon 20 of the cholesterol side chain to form **pregnenolone**, the common precursor of all steroid hormones (*Fig. 5*). A series of reactions catalyzed by **cytochrome P450** modify pregnenolone to give rise to the individual hormones (*Fig. 5*).

The cytochrome P450s are a group of **heme-containing enzymes** (see Topic M4) that get their name from the wavelength maximum of their absorbance spectra when bound to carbon monoxide. They are present in both the mitochondria and the SER of many cells, and consist of a family of structurally related enzymes with different substrate specificities. The enzymes all catalyze so-called **mono-oxygenase** reactions, in which one oxygen atom from molecular oxygen is inserted into the substrate molecule, and the other oxygen atom forms water. The electrons required to bring about the reduction of oxygen to form water are supplied by specialized electron transport chains which are functionally linked to the P450 enzymes. These electron transport chains usually have NADPH as the ultimate electron donor, so a cytochrome P450-catalyzed reaction is often characterized by the involvement of both O_2 and NADPH.

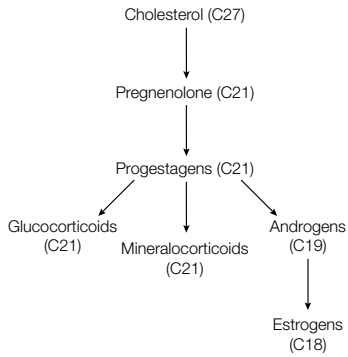

Fig. 5. Biosynthetic pathway for the synthesis of the steroid hormones.

K6 LIPOPROTEINS

Key Notes

Structure and function

Lipoproteins are globular, micelle-like particles consisting of a hydrophobic core of triacylglycerols and cholesterol esters surrounded by an amphipathic coat of protein, phospholipid and cholesterol. The apolipoproteins (apoproteins) on the surface of the lipoproteins help to solubilize the lipids and target the lipoproteins to the correct tissues. There are five different types of lipoprotein, classified according to their functional and physical properties: chylomicrons, very low density lipoproteins (VLDLs), intermediate density lipoproteins (IDLs), low density lipoproteins (LDLs), and high density lipoproteins (HDLs). The major function of lipoproteins is to transport triacylglycerols, cholesterol and phospholipids around the body.

Chylomicrons

Chylomicrons are synthesized in the intestine and transport dietary triacylglycerols to skeletal muscle and adipose tissue, and dietary cholesterol to the liver. At these target tissues the triacylglycerols are hydrolyzed by lipoprotein lipase on the surface of the cells and the released fatty acids are taken up either for metabolism to generate energy or for storage. The resulting cholesterol-rich chylomicron remnants are transported in the blood to the liver where they are taken up by receptor-mediated endocytosis.

VLDLs, IDLs and LDLs

VLDLs are synthesized in the liver and transport triacylglycerols, cholesterol and phospholipids to other tissues, where lipoprotein lipase hydrolyzes the triacylglycerols and releases the fatty acids for uptake. The VLDL remnants are transformed first to IDLs and then to LDLs as all of their apoproteins other than apoB-100 are removed and their cholesterol esterified. The LDLs bind to the LDL receptor protein on the surface of target cells and are internalized by receptor-mediated endocytosis. The cholesterol, which is released from the lipoproteins by the action of lysosomal lipases, is either incorporated into the cell membrane or re-esterified for storage. High levels of intracellular cholesterol decrease the synthesis of the LDL receptor, reducing the rate of uptake of cholesterol, and inhibit HMG CoA reductase, preventing the cellular synthesis of cholesterol.

HDLs

HDLs are synthesized in the blood and extract cholesterol from cell membranes, converting it into cholesterol esters. Some of the cholesterol esters are then transferred to VLDLs. About half of the VLDLs and all of the HDLs are taken up into the liver cells by receptor-mediated endocytosis and the cholesterol disposed of in the form of bile salts.

Atherosclerosis

Atherosclerosis is characterized by cholesterol-rich arterial thickenings (atheromas) that narrow the arteries and cause blood clots to form. If these blood clots block the coronary arteries supplying the heart, the result is a myocardial infarction, or heart attack.

Familial hypercholesterolemia

This is an inherited disorder in which individuals have a lack of functional LDL receptors preventing cholesterol from being taken up by the tissues. The resulting high blood cholesterol level leads to an increase in the formation of atheromas and can cause death from myocardial infarction during childhood.

Related topics

Membrane lipids (E1)
Transport of macromolecules (E4)
Triacylglycerols (K4)
Cholesterol (K5)

Structure and function

Triacylglycerols (see Topic K4), phospholipids (see Topic E1) and cholesterol (see Topic K5) are relatively insoluble in aqueous solution. Hence, they are transported around the body in the blood as components of **lipoproteins**. These globular, micelle-like particles consist of a hydrophobic core of triacylglycerols and cholesterol esters surrounded by an amphipathic coat of protein, phospholipid and cholesterol. The protein components of lipoproteins are called **apolipoproteins** (or **apoproteins**). At least 10 different apoproteins are found in the different human lipoproteins. Their functions are to help solubilize the hydrophobic lipids and to act as cellular targeting signals. Lipoproteins are classified into five groups on the basis of their physical and functional properties (*Table 1*):

- **Chylomicrons** are the largest and least dense lipoproteins. They transport dietary (exogenous) triacylglycerols and cholesterol from the intestines to other tissues in the body.
- **Very low density lipoproteins** (VLDLs), **intermediate density lipoproteins** (IDLs) and **low density lipoproteins** (LDLs) are a group of related lipoproteins that transport internally produced (endogenous) triacylglycerols and cholesterol from the liver to the tissues.
- **High density lipoproteins** (HDLs) transport endogenous cholesterol from the tissues to the liver.

Chylomicrons

Chylomicrons, the largest of the lipoproteins, are synthesized in the intestine. They transport ingested triacylglycerols to other tissues, mainly skeletal muscle and adipose tissue, and transport ingested cholesterol to the liver (*Fig. 1*). At the target tissues the triacylglycerols are hydrolyzed by the action of **lipoprotein lipase**, an enzyme located on the outside of the cells that is activated by **apoC-II**, one of the apoproteins on the chylomicron surface. The released fatty acids and monoacylglycerols are taken up by the tissues, and either used for energy

Table 1. Characteristics of the five classes of lipoproteins

Lipoprotein	Molecular mass (kDa)	Density (g ml^{-1})	% Protein	Major lipids	Apoproteins
Chylomicrons	> 400 000	< 0.95	1.5–2.5	TG	A, B-48, C, E
VLDLs	10 000–80 000	<1.006	5–10	TG, PL, CE	B-100, C, E
IDLs	5000–10 000	1.006–1.019	15–20	CE, TG, PL	B-100, C, E
LDLs	2300	1.019–1.063	20–25	CE, PL	B-100
HDLs	175–360	1.063–1.210	40–55	PL, CE	A, C, D, E

C, cholesterol; CE, cholesterol ester; TG, triglyceride; PL, phospholipid.

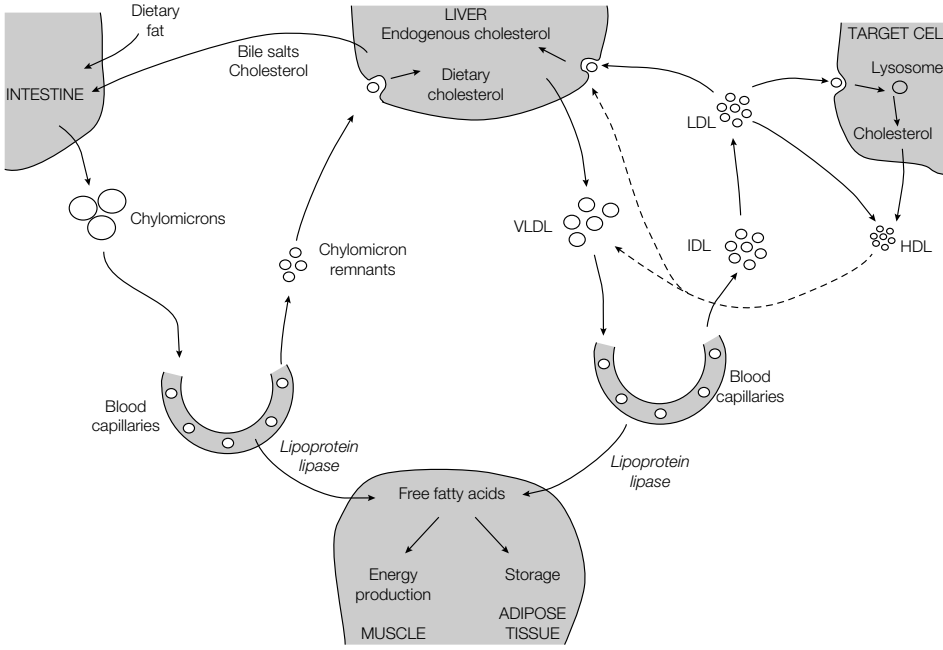

Fig. 1. The transport of triacylglycerol and cholesterol by lipoproteins.

production or re-esterified to triacylglycerol for storage. As their triacylglycerol content is depleted, the chylomicrons shrink and form cholesterol-rich **chylomicron remnants** which are transported in the blood to the liver (*Fig. 1*). Here they bind to a specific cell-surface remnant receptor and are taken up into the liver cells by **receptor-mediated endocytosis** (see Topic E4).

VLDLs, IDLs and LDLs

VLDLs are synthesized in the liver and transport a variety of lipids (see *Table 1*) to other tissues, again mainly adipose tissue and skeletal muscle. As with chylomicrons, the triacylglycerols in VLDLs are acted on by **lipoprotein lipase** and the released fatty acids taken up by the tissues (*Fig. 1*). The VLDL remnants remain in the blood, first as IDLs and then as LDLs. In the transformation to LDLs, much of the cholesterol is esterified on its hydroxyl group on C-3 by the addition of a fatty acid chain from phosphatidylcholine (lecithin) by the enzyme **lecithin–cholesterol acyl transferase (LCAT)**. In addition, all of the apoproteins other than **apoB-100** are removed.

LDLs are then taken up by target cells through **receptor-mediated endocytosis** (see Topic E4). The **LDL receptor**, a transmembrane glycoprotein on the surface of the target cells, specifically binds apoB-100 in the LDL coat. The receptors then cluster into clathrin-coated pits and are internalized (see Topic E4, *Fig. 3*). Once in the lysosomes, the LDLs are digested by lysosomal enzymes, with the cholesterol esters being hydrolyzed by a lysosomal lipase to release the cholesterol (*Fig. 1*). This is then incorporated into the cell membrane and any excess is re-esterified for storage by **acyl CoA cholesterol acyltransferase** (ACAT).

To prevent the build up of cholesterol and its ester derivatives in the cell, high levels of cholesterol:

- decrease the synthesis of the LDL receptor, thereby reducing the rate of uptake of cholesterol by receptor-mediated endocytosis, and
- inhibit the cellular biosynthesis of cholesterol through inhibition of HMG CoA reductase (see Topic K5).

HDLs

HDLs have the opposite function to that of LDLs in that they remove cholesterol from the tissues. The HDLs are synthesized in the blood mainly from components derived from the degradation of other lipoproteins. HDLs then acquire their cholesterol by extracting it from cell membranes and converting it into cholesterol esters by the action of LCAT (*Fig. 1*). The HDLs are then either taken up directly by the liver or transfer their cholesterol esters to VLDLs, of which about half are taken up by the liver by receptor-mediated endocytosis (*Fig. 1*). The liver is the only organ that can dispose of significant quantities of cholesterol, primarily in the form of **bile salts** (see Topic K5).

Atherosclerosis

Atherosclerosis, the most common type of **hardening of the arteries**, is characterized by the presence of cholesterol-rich arterial thickenings (**atheromas**). This progressive disease begins with the intracellular deposition of lipids, mainly cholesterol esters, in the smooth muscle cells of the arterial wall. These lesions become fibrous, calcified plaques that narrow and can eventually block the arteries. **Blood clots** are also more likely to occur which may stop the blood flow and deprive the tissues of oxygen. If these blockages occur in the coronary arteries, those supplying the heart, the result is a **myocardial infarction** or **heart attack**, which is the most common cause of death in Western industrialized countries. Blood clots in cerebral arteries cause stroke, while those in peripheral blood vessels in the limbs can lead to possible gangrene and amputation.

Familial hypercholesterolemia

Familial hypercholesterolemia is an inherited disorder in which homozygotes have a markedly elevated level of cholesterol in their blood, whilst in heterozygotes the level is twice that of normal individuals. Not only does this result in the deposition of cholesterol in the skin as yellow nodules known as **xanthomas**, but also in the formation of **atheromas** that can cause death from **myocardial infarction** during childhood. The molecular defect in familial hypercholesterolemia is the lack of functional **LDL receptors**. Thus, the LDL cholesterol cannot be taken up by the tissues and results in a high concentration in the blood. Homozygotes can be treated by liver transplantation, while heterozygotes can be treated by inhibiting HMG CoA reductase with lovastatin (see Topic K5) and reducing the intestinal re-absorption of bile salts, thereby decreasing the blood cholesterol level.