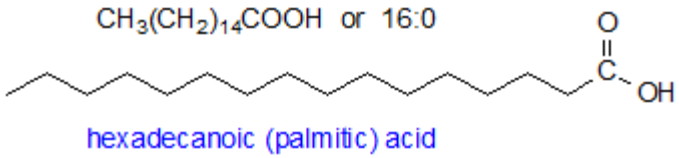
Fatty Acids: Straight-Chain Saturated

1. Structure, Nomenclature and Occurrence

Straight- or normal-chain, saturated components (even-numbered) make up 10 to 40% of the total fatty acids in most natural lipids. The most abundant saturated fatty acids in animal and plant tissues are straight-chain compounds with 14, 16 and 18 carbon atoms, but all the possible odd- and even-numbered homologues with 2 to 36 carbon atoms have been found in nature in esterified form. They are named systematically from the saturated hydrocarbon with the same number of carbon atoms, the final 'e' being changed to 'oic'. Thus, the fatty acid with 16 carbon atoms and the structural formula -



- is systematically named 'hexadecanoic acid', although it is more usual to see the trivial name 'palmitic acid' in the literature. It can be termed a 'C_{16}' fatty acid or with greater precision - '16:0', the number before the colon specifying the number of carbon atoms, and that after the colon, the number of double bonds. A list of saturated fatty acids together with their trivial names and shorthand designations is given in the table below. Trivial names are best avoided, and I have not listed the more obscure of these. However, this advice is perhaps too pedantic for the more common ones.

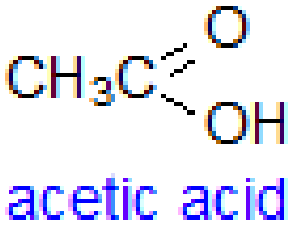
Table 1. Systematic and trivial names for saturated fatty acids.

Systematic name	Trivial name	Shorthand designation	Systematic name	Trivial name	Shorthand designation
ethanoic	acetic	2:0	octadecanoic	stearic	18:0
propanoic	propionic	3:0	nonadecanoic		19:0
butanoic	butyric	4:0	eicosanoic	arachidic	20:0
pentanoic	valeric	5:0	heneicosanoic		21:0
hexanoic	caproic	6:0	docosanoic	behenic	22:0
heptanoic		7:0	tricosanoic		23:0

octanoic	caprylic	8:0	tetracosanoic	lignoceric	24:0
nonanoic		9:0	pentacosanoic		25:0
decanoic	capric	10:0	hexacosanoic	cerotic	26:0
undecanoic		11:0	heptacosanoic		27:0
dodecanoic	lauric	12:0	octacosanoic	montanic	28:0
tridecanoic		13:0	nonacosanoic		29:0
tetradecanoic	myristic	14:0	triacontanoic		30:0
pentadecanoic		15:0	hentriacontanoic		31:0
hexadecanoic	palmitic	16:0	dotriacontanoic		32:0
heptadecanoic	margaric	17:0			

Although there is no internationally accepted definition, short-chain fatty acids are usually considered to be C_1 to C_6 in chain-length, while medium-chain are C_7 to C_{12}. Long-chain saturated fatty acids are C_{14} to C_{20}, while those with even longer chains are designated very-long-chain fatty acids. As saturated long-chain fatty acids have relatively high melting points, animal fats and seed oils such as palm oil in which these components are especially abundant tend to be solids at room temperature. Such saturated fatty acids in esterified form also increase the rigidity of membranes. Short- and medium chain fatty acids are weakly acidic with pK_a values around 4.8 and they have relatively high solubilities in water.

Not everyone would consider **formic** or methanoic acid (1:0) to be a fatty acid, not least because of its solubility in water, but it has been identified in esterified form in phosphatidylcholine from human neutrophils, with 16:0, 18:0 or 18:1 as the other fatty acid. It has also been found esterified to aliphatic alcohols in acarid mites.



Acetic or ethanoic acid (2:0) is of great importance in living tissues, as a source of energy and as the biosynthetic precursor of fatty acids and innumerable other lipids and organic molecules. However, it only occasionally found in association with fatty acids of higher molecular weight in esterified form in lipid molecules, although it does occur esterified to

glycerol in ruminant milk fats (presumably in position *sn*-3). Acetylated triacylglycerols accumulate in the pupae of a type of insect, the goldenrod gall fly; these remain liquid during winter when the pupa of the insect is frozen so can serve as a source of energy to maintain life. It is also the most common fatty acid linked to **platelet-activating factor**. In seed oils, acetic acid occurs in position *sn*-3 of triacylglycerols of *Euonymus verrucosus*, and related species, while in *Polygala virgata* it is in position *sn*-2. In other vegetable oils, it has been detected in linkage to the hydroxyl group of a hydroxy fatty acid, which is in turn esterified to glycerol, i.e. as an estolide.

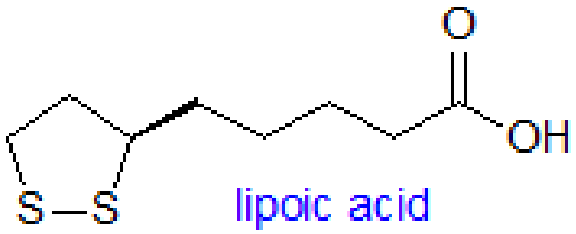
Acetates of long-chain alcohols are found in plant and insect waxes and as insect pheromones. A novel sphingomyelin, isolated from a cyanobacterium, *Scytonema julianum*, contains acetate in an estolide linkage, i.e. with the acetyl group esterified to an ω-1 hydroxyl group in a long-chain fatty acid. An acetylated cerebroside derivative has been found in rat brain myelin, i.e. with an acetyl group linked at the C3 hydroxyl of the sphingosine base. Indeed, acetate is a common constituent of complex sphingolipids, usually in amide linkage to glucosamine, galactosamine, neuraminic acid or even sphingosine.

Propanoic acid (3:0) is important as the biosynthetic precursor of some amino acids. It is rarely found in esterified form in natural lipids, and to my knowledge the only exception is for molecules related to platelet-activating factor.

Butanoic or butyric acid (4:0) comprises 3-4% by weight (much more in molar terms) of the total fatty acids in cow's milk, where it is found exclusively in position 3 of the triacyl-*sn*-glycerols. It is found in milk fats of other ruminants, but not in the lipids of other tissues of these species (it is a major product of fermentation in ruminant animals). In most animals, it is produced by microbial fermentation of dietary fibers in the lower intestinal tract, where it is absorbed for transport to other tissues. It is reported to have a role in signalling with effects upon epithelial cell proliferation, apoptosis and differentiation, and it is the main energy source for colonocytes. In other tissues, it is an anti-inflammatory agent, primarily inhibiting the activation of the transcription factor NF-κB and acts as signal molecules by binding to Free Fatty Acid Receptor 2 (FFAR2, GPR43) and FFAR3 (GPR41) (see our web page on **unesterified fatty acids**). It may even affect brain function as it is reported to be an antidepressant in animal models of depression and chronic mild stress.

Odd-chain fatty acids from **5:0 to 11:0** have been detected at trace levels in the triacylglycerols of ruminant milks, but not elsewhere in conventional esterified form in these species. More generally, they are found as oxidation products of long-chain fatty acids, together with a range of even-numbered components (2:0 to 12:0) as urinary acylcarnitines.

Hexanoic acid (6:0) comprises 1-2% of the total fatty acids in ruminant milk triacylglycerols, where most of it is esterified to position 3 of the triacyl-*sn*-glycerols. It is also found as a minor component of certain seed oils rich in medium-chain saturated fatty acids (see below). Other than these, the commonest source of short-chain fatty acids in the human diet is microbial metabolism in the gut.



Medium-chain fatty acids, such as **octanoic** (8:0), **decanoic** (10:0) and **dodecanoic** (12:0), are found in esterified form in most milk fats, including those of non-ruminants, though usually as minor components, but not elsewhere in animal tissues in significant amounts. They are never detected in membrane lipids, for example. They are absent from most vegetable fats, but with important exceptions. Thus, they are major components of such seed oils as coconut oil, palm kernel oil and *Cuphea* species. Octanoic acid is esterified to a serine residue in the active form of the peptide hormone ghrelin, as discussed in our web page on **proteolipids**. It is also the biosynthetic precursor of lipoic acid, which acts as a cofactor of bioenergetic mitochondrial enzymes and is a natural antioxidant.

Odd-chain fatty acids from **13:0 to 19:0** are found in esterified form in the lipids of many bacterial species, and they can usually be detected at trace levels in most animal tissues, presumably having been taken up as part of the food chain. In particular, they occur in appreciable amounts (5% or more) in the tissues of ruminant animals where a high proportion is derived from the rumen microflora.

Myristic acid (14:0) is a ubiquitous component of lipids in most living organisms, but usually at levels of 1 to 2% only. However, it is more abundant in cow's milk fat, some fish oils and in those seed oils enriched in medium-chain fatty acids (e.g. coconut and palm kernel, and of course those of the family Myristicaceae, e.g. nutmeg oil). This fatty acid is found very specifically in certain **proteolipids**, where it is linked via an amide bond to an *N*-terminal glycine residue, and is essential to the function of the protein components.

Palmitic acid (16:0) is usually considered the most abundant saturated fatty acid in nature, and it is found in appreciable amounts in the lipids of animals, plants and lower organisms. It is the primary product of the fatty acid synthase and comprises 20 to 30% of the lipids in most animal tissues and lipid classes. In seed oils, it is present in amounts that vary from 10 to 40%, and among commercial sources, it is most abundant in palm oil (40% or more). It is the biosynthetic precursor of **sphingoid bases** and thence of all sphingolipids, and it has a vital function in cells in specific **proteolipids**, where it is linked to internal cysteine residues via thioester bonds. However, many negative effects as a nutrient upon health have been reported, especially when it is consumed in excess, and for example, it is pro-inflammatory as an agonist for the toll-like receptors TLR2 and TLR4.

Stearic acid (18:0) is the second most abundant saturated fatty acid in nature, and again it is found in the lipids of most living organisms. In lipids of some commercial importance, it occurs in the highest concentrations in ruminant fats (milk fat and tallow) or in vegetable oils

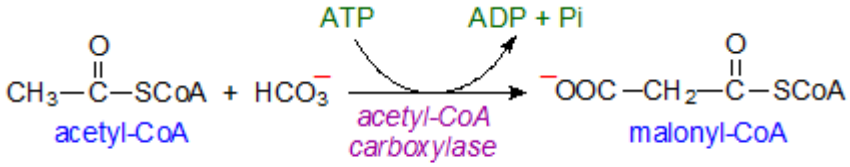
such as cocoa butter, and of course in industrially hydrogenated fats. It can comprise 80% of the total fatty acids in **gangliosides**. Relatively high proportions of stearic acid in comparison to other saturated fatty acids are subjected to enzymatic desaturation to produce oleic acid in animal tissues

Eicosanoic acid (20:0) can be detected at low levels in most lipids of animals, and often in those of plants and microorganisms. Saturated fatty acids from **20:0 to 26:0** in amide linkage to long-chain bases are normal and important constituents of animal and plant **sphingolipids**. While very-long-chain saturated fatty acids (**22:0 to 32:0**) are not usually considered to be common constituents of lipids, they do occur in many plant **waxes**, which by some estimates are the most abundant lipids in living tissues on earth, and they are also found in some animal waxes such as wool and meibum wax.

2. Biosynthesis and Metabolism of Saturated Fatty Acids

Animals obtain fatty acids both from the diet and from synthesis *de novo*, and some parasitic organisms acquire them from their hosts, but most forms of life must synthesise all their fatty acids from short-chain precursors. As fatty acids are even numbered, it was easily deduced that a two-carbon precursor then shown to be acetate or more accurately its **Coenzyme A ester** was involved, but when it was found that the reaction required carbon dioxide, the experimental evidence soon pointed to malonyl-CoA as the chain-extender. In animals, most of the acetate is derived from glucose metabolism via pyruvate. In some plants, it may be formed similarly in the plastids, but in others acetate is formed from pyruvate in mitochondria and must diffuse to the plastids before conversion to the CoA ester. The following account presents the basic details only of the biosynthetic processes in different organisms.

Acetyl-CoA carboxylase: Malonyl-CoA is formed from acetyl CoA by the activity of the enzyme acetyl-CoA carboxylase in which biotin is the prosthetic group (and thus can be inhibited by avidin). Four different components are required for activity: biotin carboxylase, biotin carboxyl carrier protein, and α- and β-carboxyltransferases. In the first step in the ATP-dependent reaction, a carboxyl group derived from bicarbonate (HCO_3^-) is transferred to biotin, which serves as a temporary carrier of CO_2 before transferring it to acetyl-CoA in a second step to yield malonyl-CoA.



Biosynthesis of malonyl-CoA

In prokaryotes and primitive plants, the enzyme complex comprises four dissociable proteins, i.e. it is heteromeric, but in animals, the enzyme is a single multifunctional or homomeric

complex that exists in two main isoforms (ACC1 and ACC2). ACC1 is expressed most actively in the cytosol of lipogenic tissues, such as liver, adipose tissue and lactating mammary gland, and the malonyl-CoA produced is used for fatty acid synthesis. The ACC2 isoform is expressed more in highly metabolic organs such as skeletal muscle and the heart, where the malonyl-CoA produced is involved in the regulation of fatty acid oxidation by inhibiting the carnitine palmitoyl-CoA transferase-1 (see our web page on **β-oxidation**). The two pools are highly segregated and do not mix. When there is increased energy demand, the protein kinase AMPK is activated and phosphorylates both ACC1 and ACC2 to inactivate them; ACC2 inhibition tends to increase fatty acid β-oxidation, while ACC1 inhibition decreases fatty acid biosynthesis.

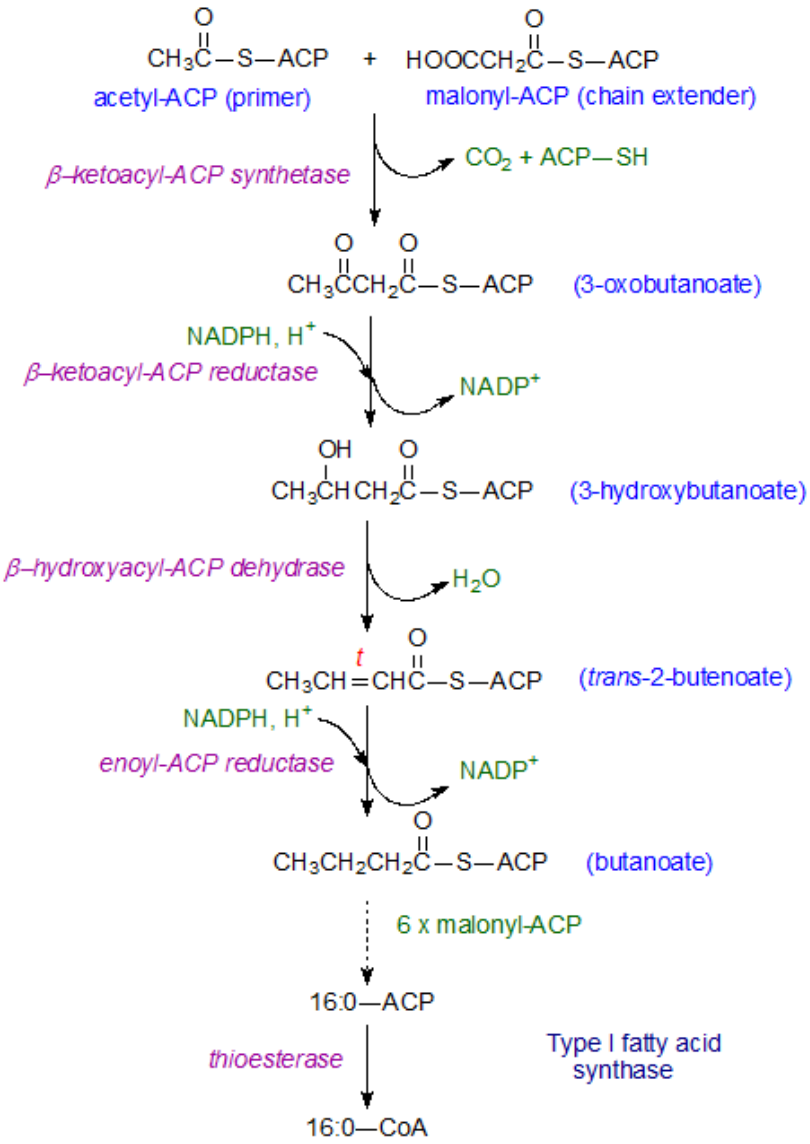
In higher plants, acetyl-CoA carboxylase exists in two molecular forms: as multi-protein complexes in the plastids and as multifunctional proteins in the cytosol, although there are some differences among plant genera. As acetyl-CoA carboxylase is the first committed step in lipid biosynthesis, its acute regulation is especially important. Among a number of factors, including transcription and phosphorylation, it is promoted by citrate from the Krebs cycle (not in yeasts), and it is inhibited by the long-chain acyl-CoAs formed by the fatty acid synthases.

Successive molecules of malonyl-CoA are then added to the single primer molecule of acetyl-CoA in a sequence of reactions catalysed by a multifunctional enzyme complex, the **fatty acid synthase**, which can be of three types.

Type I fatty acid synthases (FAS I): In this enzyme complex found in animals, the various sub-units carrying out each step of the reaction are discrete domains of a single protein entity that is the product of one gene. In yeast and fungi, there are two genes that produce polypeptide products, which then coalesce to form a multifunctional Type I fatty acid synthase complex. **Mycobacteria** contain both FAS 1 and FAS II (see below) systems. Type I fatty acid synthases are generally considered to be more efficient than type II, because all the enzymatic activities are linked in a single polypeptide template from which the intermediates cannot easily diffuse.

As a first step, both the primer and extender substrates are attached to **acyl carrier protein (ACP)**, which has the same prosthetic group as Coenzyme A. The ACPs in this instance are tethered covalently to the megasynthase by flexible linkers in the peptide chain, allowing them to carry their cargo from one enzyme or enzymatic domain to another during the iterative cycles of fatty acid biosynthesis. This enables the sequence of reactions in which the chain is extended and butanoate is formed in the first turn of the cycle, as illustrated. First, 3-oxobutanoate is produced by a reaction catalysed by β-ketoacyl-ACP synthetase, this is reduced to 3-hydroxy-butanoate by β-ketoacyl-ACP reductase, which is in turn dehydrated to *trans*-2-butenoate by β-hydroxyacyl-ACP hydratase before it is reduced to butanoate by enoyl-ACP reductase. The process then continues with the addition of a further six units of malonyl-ACP by successive cycles of these reactions until palmityl-ACP is formed. At this point, a thioesterase removes the fatty acyl product as the free acid (with the mammalian

enzyme), and it must be converted to the CoA-ester before it can enter into the various biosynthetic pathways for the production of specific lipids. With the fungal fatty acid synthase, the finished acid is attached directly to CoA using a malonoyl/palmitoyl transacylase domain.



The chain-length of the final product is believed to be controlled by two factors. Firstly, the condensing enzymes have a limited space available for the growing chain, so elongation is inhibited when the chain reaches an appropriate length. Secondly, the lengthening hydrophobic tail of the growing chain has an affinity for the enzymes that terminate the reaction to release the acyl chain, for example as CoA esters or unesterified fatty acids. Medium-chain fatty acids are usually produced by enzymes in which the specificity of the thioesterase component differs from normal, i.e. the chain-elongation cycle is terminated prematurely. In addition, shorter chain fatty acids can be produced in some tissues, such as the mammary gland, by a separate chain-termination enzyme, thioesterase II, which is able to modify the specificity of the fatty acids synthase.

In the production of odd-chain fatty acids, the primer molecule can be propanyl-CoA, but these can also be produced from even-numbered components by alpha-oxidation. Similarly, short- and medium-chain fatty acids can be produced as by-products of oxidative processes.

It has long been known that for activity the mammalian fatty acid synthases exists as a dimer, while the fungal forms are hexameric, but the exact nature and requirement for the polymeric states were not known until X-ray crystal structures of the enzymes were obtained. With the mammalian enzyme, the two monomers are in a head-to-head arrangement (not head-to-tail as previously believed) and dimerization seems to be dictated by the structure of the β-ketoacyl synthase domain, i.e. the component responsible for the key chain-elongation step. This amazing dodecameric enzyme complex contains 48 active centres held together by linkage units in a single barrel shaped structure. Although the structure of the fungal FAD I is very different, it appears that the β-ketoacyl synthase domain is again the dominant factor controlling polymerization. The mammalian fatty acid synthase is primarily a cytoplasmic enzyme complex, but it can be located on intracellular membranes. It is phosphorylated by kinases and this regulation may be important for both activity of the enzyme and its subcellular location.

Type II fatty acid synthases (FAS II) have been characterized in bacteria (e.g. *E. coli*), parasites, algae, higher plants and perhaps surprisingly mitochondria in animals. They consist of separate proteins encoded by different genes that each catalyse a separate step analogous to those by FAS I enzymes, and these proteins can be dissociated and purified although they normally operate in concert. Similarly, the ACPs are discrete proteins that transport the growing fatty acyl chain to the reaction partners while sequestering the reactive intermediates within a hydrophobic core to protect against possible side reactions. In plastids of plants, three types of β-ketoacyl-ACP synthases (KASs) catalyse the elongation of malonyl-ACP to fatty acids, i.e. KAS III (FabH) catalyses the initial condensation reaction to generate butyryl-ACP, while KAS I (FabB) catalyses the condensation of butyroyl and subsequent intermediate ACPs to myristoyl-ACP (C_{14}). KAS II (FabF) catalyses a range of chain-elongation reactions but notably the condensation of C_{14} and C_{16}-ACPs with malonyl-ACP, and it determines the ratio of 16:0 to 18:0 (stearate). The reaction is terminated by a thioesterase.

Variant FatB forms in selected species, including those in *Cuphea* species, are able to release fatty acids earlier to generate seed oils enriched in medium-chain fatty acids, although variant forms of the acyltransferases are required also to insert these into triacylglycerols.

In general, the synthases in prokaryotes differ in that they do not use thioesterases, and instead acyltransferases terminate the reaction by esterifying new fatty acids directly to a lipid. The *E. coli* FAS II is not in fact typical of bacterial enzymes in that it is also capable of producing unsaturated fatty acids (see our web page on **monoenoic fatty acids**), and it has only recently been recognized that the Archaea have a non-typical fatty acid synthase.

In contrast to type I, type II fatty acid synthases can produce many different products for cellular metabolism, including fatty acids of different chain lengths, and unsaturated, *iso*-

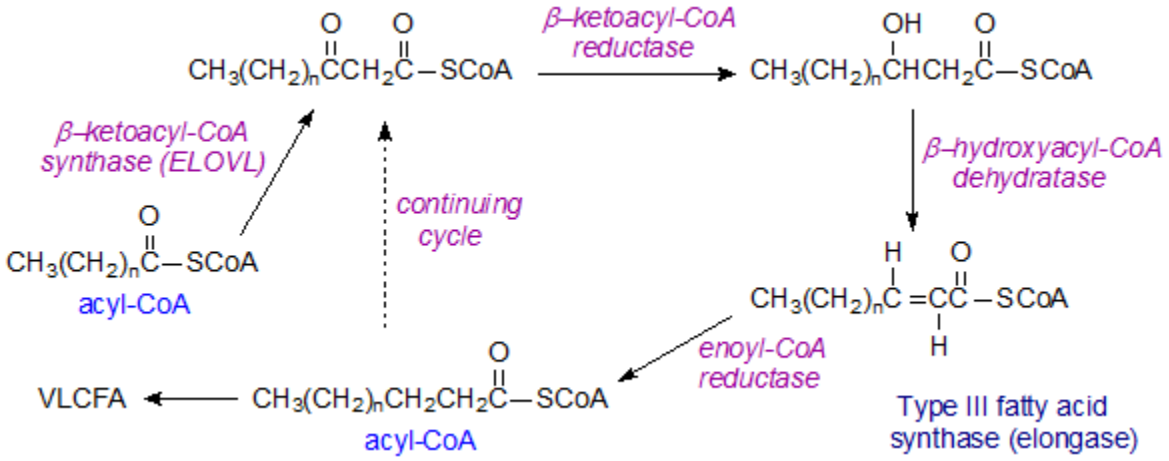
and *anteiso*-methyl-branched, and hydroxy fatty acids. In addition, ACP-intermediates from the process, which are diffusible discrete proteins that must deliver their acyl groups to independent catalytic partners, especially complex lipid synthesis, can be used for production of other important cellular constituents, such as lipoic acid synthesis and assembly of the electron transport chain complex.

Mitochondria in animals including humans and in yeasts contain FAS II enzymes, related to those in prokaryotes and entirely distinct from the cytoplasmic FAS I. Indeed, the components of this, such as malonyl-CoA:ACP transferase, β-ketoacyl synthase and 2-enoyl-ACP reductase, were first identified by their similarity to the corresponding bacterial and yeast proteins and can be regarded as orthologs. There does not appear to be a mitochondrial acetyl-CoA carboxylase in mammals, although a variant has been described in yeasts. While propionyl-CoA carboxylase, a mitochondrial enzyme in mammals, can catalyse carboxylation of acetyl-CoA also *in vitro*, the efficiency is low and it is possible that mitochondria import the required malonate. Fewer proteins are involved in fatty acid synthesis in mitochondria than in bacteria, and as an example a single KAS is responsible for all the condensation steps. Although many questions remain, it has been established that mitochondrial fatty acid synthesis is essential for cellular respiration and mitochondrial biogenesis. During β-oxidation of fatty acids, CoA acts as acyl-group carrier whereas ACP has this function in synthesis, an arrangement that separates the two metabolic pathways and prevents futile cycling. An important product of mitochondrial fatty acid synthesis is octanoyl-ACP for lipoic acid biosynthesis. Links between mitochondrial type II fatty acid synthases and RNA processing have also been uncovered in vertebrates and yeast, and this pathway may be involved in the coordination of intermediary metabolism in eukaryotic cells.

Type III fatty acid synthases - elongases: the latter term is more often used for enzymes on the cytosolic side of the endoplasmic reticulum that catalyse the addition of C_2 units to preformed fatty acids. For example, palmitoyl-CoA can be further elongated by C_2 units to form long- or very-long-chain fatty acids by such enzymes. Based on the presence of similar motifs in their gene structure, seven enzymes are recognized in mammals that have been termed **ELOVL 1 to 7** (Elongation of very-long-chain fatty acid) and are believed to perform the condensation reaction in the elongation cycle. Three of these (ELOVL 1, 3 and 6) are involved in the production of saturated and monoenoic fatty acids, while the remainder are elongases of **polyunsaturated fatty acids**, especially those of the essential *n*-6 and *n*-3 families. Of these, ELOVL1 is expressed ubiquitously in tissues and has been linked to the production of C_{24} fatty acids for sphingolipid biosynthesis; in the epidermis, it is regulated by ceramide synthases to produce C_{26} fatty acids, which can be further elongated by ELOV4 up to C_{36}; ELOV4 is also involved in docosahexaenoic acid metabolism in the retina. ELOV3 is expressed in sebaceous glands and brown adipose tissue. ELOVL6 appears to be the only enzyme capable of elongating palmitate to a significant extent (in addition to 12:0 and 14:0). A separate enzyme system that uses acetate as chain extender is present in mitochondria.

The cycle of fatty acid elongation is composed of four steps, the first of which is rate-limiting, i.e. condensation, reduction, dehydration and reduction again, to increase the chain-

length of an acyl-CoA ester by two. In the initial step, the CoA ester is condensed with malonyl-CoA in a reaction catalysed by the ELOVL enzyme (or β-ketoacyl-CoA synthase). The product is a 3-keto-acyl-CoA, which is reduced by a β-ketoacyl-CoA reductase, requiring NADPH as the source of reducing equivalents, to produce 3-hydroxyacyl-CoA. The elements of water are removed by a β-hydroxyacyl-CoA dehydratase to produce a *trans*-2,3-acyl-CoA, which is then reduced by enoyl-CoA reductase to produce a fatty acid two methylene groups longer than the starting molecule. Depending on the requirement of the organism at any particular time, the product can be incorporated into lipids or undergo additional cycles of elongation.



In higher plants such as *Arabidopsis thaliana*, the four components of the elongation system have been identified, but share little homology with the animal and yeast equivalents; they are believed to be organized in a single complex on the cytosolic side of the endoplasmic reticulum but this requires confirmation. The condensing enzyme provides the substrate specificity and determines the amount of product synthesised.

Some parasitic organisms produce all their fatty acids by using elongases. For example, *Trypanosoma brucei*, the human parasite that causes sleeping sickness, uses three elongases. The first converts C_4 to C_{10}, the second extends C_{10} to C_{14}, and the third elongates C_{14} to C_{18}. There are three fatty acid elongases in yeast also, all of which produce very-long-chain fatty acids.

Desaturation: In animal cells, most saturated fatty acids from 12:0 to 18:0 can be converted to monounsaturated products through the action of Δ9-desaturases, with the activity increasing the greater the chain-length (see our web page on **monoenoic fatty acids**). In addition to the formation of 9-16:1, palmitic acid can also be desaturated by a Δ6-desaturase in human sebaceous glands to produce sapienic acid (6-16:1), which may have antimicrobial activity. Similarly, in plants stearoyl-CoA can be desaturated to oleoyl-coA (or other isomers) in the endoplasmic reticulum, and then enter metabolic pathways whereby it is converted to linoleate and linolenate (see our web page on **polyunsaturated fatty acids**).

Catabolism: Fatty acids are broken down in animal tissues to produce energy by a multi-step process of β-oxidation. This is discussed in our web page on **carnitines**.

3. Saturated Fatty Acids in Health and Disease

In addition to being a source of energy in tissues, long-chain saturated fatty acids provide desirable properties to lipids in membranes by conferring rigidity where this is required, and in controlling the activities of membrane proteins through covalent bonding. They are essential especially for the function of sphingolipids, which are able to alter the thickness of the plasma membrane locally by varying the lengths of the fatty acid chains, This is a key factor also in the formation of **raft** domains in membranes and in the barrier properties of the **ceramides** in the epidermis of the skin. Similarly, saturated fatty acids are key components of the **wax** layer that protects the external surface of plants. As mentioned briefly above and discussed in much greater detail elsewhere in this web site, palmitic acid is the precursor of **sphingoid bases** and thence of all sphingolipids. Saturated fatty acids are also indispensable components of **proteolipids** (*S*-palmitoylation and *N*-myristoylation), as they direct specific proteins to their functional locations in membranes. Of course, they are also a source of **monounsaturated fatty acids** via the action of desaturases. Short- and medium chain saturated fatty acids are metabolized very differently from the those of longer chain-length; they are important substrates for energy metabolism and anabolic processes in mammals and some have signalling functions.

In contrast, there is evidence that long-chain saturated fatty acids activate certain transcription factors that target lipogenic target genes, while in the unesterified (free) form they activate G protein-coupled receptors now termed **Free Fatty Acid Receptors (FFAR)**, sometimes leading to negative health effects. For example, palmitic acid can activate inflammatory pathways directly by stimulating macrophages to produce cytokines via toll-like receptors 2 and 4 (TLR2 and 4), and by stimulating such signalling molecules as protein kinase R. Excessive levels are believed to be contributory factors in the development of obesity, type 2 diabetes mellitus and cardiovascular diseases. Fatty acid synthesis is especially important in cancer as abnormally high levels of the fatty acid synthase are present in tumour tissues in patients at later stages of the disease, and this overexpression is a predictor of poor prognosis. Inhibiting the enzyme leads to the death of tumour cells while sparing normal cells, which do not depend on this enzyme for routine functions, and it restores membrane architecture enabling a better response to chemotherapies. One drug with this property has reached the stage of clinical studies in patients with solid tumours. While deregulation of fatty acid biosynthesis *de novo* can lead to innumerable metabolic problems, further treatment of the topic is best left to those with more medical knowledge; the reading list below may help.

The vital functions of saturated fatty acids are often forgotten when their nutritional properties are debated, but there is little doubt that there are many potentially deleterious

effects. The balance between the good and the bad is obviously critical. Most nutritionists recommend keeping dietary intakes of saturated fatty acids as low as possible, and synthesis *de novo* is probably sufficient for essential functions, but again I prefer to leave discussion of this complex and contentious topic to others.

Unsaturated Fatty Acids

An **unsaturated fat** is a fat or fatty acid in which there is at least one double bond within the fatty acid chain. A fatty acid chain is monounsaturated if it contains one double bond, and polyunsaturated if it contains more than one double bond.

Where double bonds are formed, hydrogen atoms are subtracted from the carbon chain. Thus, a saturated fat has no double bonds, has the maximum number of hydrogens bonded to the carbons, and therefore is "saturated" with hydrogen atoms. In cellular metabolism, unsaturated fat molecules contain somewhat less energy (i.e., fewer calories) than an equivalent amount of saturated fat. The greater the degree of unsaturation in a fatty acid (i.e., the more double bonds in the fatty acid) the more vulnerable it is to lipid peroxidation (rancidity). Antioxidants can protect unsaturated fat from lipid peroxidation

Double bonds may be in either a ***cis*** or **a *trans*** isomer, depending on the geometry of the double bond. In the *cis* isomer, hydrogen atoms are on the same side of the double bond; whereas in the *trans* isomer, they are on opposite sides of the double bond (see trans fat). Saturated fats are useful in processed foods because saturated fats are less vulnerable to rancidity and usually more solid at room temperature than unsaturated fats. Unsaturated chains have a lower melting point, hence these molecules increase the fluidity of cell membranes.

Although both monounsaturated and polyunsaturated fats can replace saturated fat in the diet, trans unsaturated fats should not. Replacing saturated fats with unsaturated fats helps lower levels of total cholesterol and LDL cholesterol in the blood. Trans unsaturated fats are an exception because the double bond stereochemistry predisposes the carbon chains to assume a linear conformation, which conforms to rigid packing as in plaque formation. The geometry of the cis double bond induces a bend in the molecule, thereby precluding rigid formations. Natural sources of fatty acids are rich in the cis isomer.

Although polyunsaturated fats are protective against cardiac arrhythmias, a study of post-menopausal women with a relatively low fat intake showed that polyunsaturated fat is positively associated with progression of coronary atherosclerosis, whereas monounsaturated fat is not. This probably is an indication of the greater vulnerability of polyunsaturated fats to lipid peroxidation, against which vitamin E has been shown to be protective.

Examples of unsaturated fatty acids are palmitoleic acid, oleic acid, myristoleic acid, linoleic acid, and arachidonic acid. Foods containing unsaturated fats include avocado, nuts, olive oils, and vegetable oils such as canola. Meat products contain both saturated and unsaturated fats.

Although unsaturated fats are conventionally regarded as 'healthier' than saturated fats, the United States Food and Drug Administration (FDA) recommendation stated that the amount

of unsaturated fat consumed should not exceed 30% of one's daily caloric intake. Most foods contain both unsaturated and saturated fats. Marketers advertise only one or the other, depending on which one makes up the majority. Thus, various unsaturated fat vegetable oils, such as olive oils, also contain saturated fat.

In chemical analysis, fatty acids are separated by gas chromatography of methyl esters; additionally, a separation of unsaturated isomers is possible by argentation thin-layer chromatography.