FATTY ACIDS IN HUMAN METABOLISM

E. Tvrzická, A. Žák, M. Vecka, B. Staňková
4th Department of Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Keywords: polyunsaturated fatty acids n-6 and n-3 family, phospholipids, sphingomyeline, brain, blood, milk lipids, insulin, eicosanoids, plant oils, genomic control, atherosclerosis, tissue development.

Contents

Summary

Fatty acids are substantial components of lipids, which represent one of the three major components of biological matter (along with proteins and carbohydrates). Chemically lipids are esters of fatty acids and organic alcohols—cholesterol, glycerol and sphingosine. Pathophysiological roles of fatty acids are derived from those of individual lipids.

Fatty acids are synthesized *ad hoc* in cytoplasm from two-carbon precursors, with the aid of acyl carrier protein, NADPH and acetyl-CoA-carboxylase. Their degradation by β-oxidation in mitochondria is accompanied by energy-release.

Fatty acids in the mammalian organism reach chain-length 12-24 carbon atoms, with 0-6 double bonds. Their composition is species- as well as tissue-specific. Endogenous acids can be desaturated up to Δ9 position, desaturation to another position is possible only from exogenous (essential) acids [linoleic (n-6 series) and α-linolenic (n-3 series)].

Circulating lipids (in form of lipoproteins) consist of cholesteryl esters and triglycerides in nonpolar core and phosphatidylcholine and sphingomyeline in the polar envelope of lipoproteins. Non-esterified fatty acids (product of lipolysis and source for lipid synthesis) are bound to plasma albumin.

Membrane lipids, which ensure its fluidity and other functions, consist of phosphatidylcholine, phosphatidylethanolamine, sphingomyeline and some other (minor) phospholipids. Unsaturated fatty acids with 18-20 carbon atoms are precursors of prostaglandins, leucotrienes and thromboxanes, which have a broad scale of autocrine as well as paracrine effects. Fatty acids are ligands of several nuclear receptors, which take part in a number of metabolic pathways. Covalent modification of proteins by acylation enables their incorporation into membranes.

A number of pathological conditions is accompanied with changes in fatty acid composition, often expressed as decreased content of unsaturated and increased content of saturated fatty acids (e.g. dyslipidemia, malnutrition, inflammation and inherited diseases).

1. Introduction

Fatty acids (FA) play multiple roles in humans and other organisms. First and most important, FA are a substantial part of lipids, one of the three major components of biological matter (along with proteins and carbohydrates). Fatty acid containing lipids form the back bone of all cell membranes. Fatty acids are also important energy sources. They can be stored practically in unlimited quantities as shown in obese humans.

Unsaturated FA with 18-20 carbon atoms are precursors of prostaglandins, leucotrienes and thromboxanes, which have a broad scale of regulatory properties and have autocrine as well as paracrine effects. Fatty acids are ligands of several nuclear receptors, which take part in the subcellular control of a number of metabolic pathways. Covalent modification of proteins by FA acylation enables FA incorporation into membranes. Fatty acids with 20 and 22 carbon atoms are precursors of further autacoids—resolvins (resolution phase interaction products), lipoxins and neuroprotectins. Hydroxy FA are activators of some nuclear factors (e.g. NFκB, AP-1 and TNF-α) and are responsible for the expression of proinflammatory cytokines (e.g. IL-1, IL-6, IL-8 and TNF-α) and adhesion molecules (e.g. ICAM-1, VCAM-1 and ELAM-1).

Fatty acids are either saturated or unsaturated carboxylic acids with carbon chain varying between 2 and 36 carbon atoms. In higher animals and plants FA with 16 and 18 carbon atoms, i.e. palmitic, stearic, oleic and linoleic dominate. Fatty acids with chain length shorter than 14 and longer than 22 carbon atoms are present only in minor concentrations. Most FA have an even number of carbon atoms, as they are synthesized from two-carbon units. Approximately one half of FA in plants and animals are unsaturated and contain 1-6 double bonds. Polyunsaturated FA (PUFA) are characterized by pentadiene configuration of double bonds.

Fatty acids are often expressed by the schematic formula CN:p n-x, where CN (carbon number) represents total number of carbon atoms, p - number of double bonds, and x – position of the first double bond from the methyl group (n). Structure formulas as well as types of shorthand notations are shown in Figure 1. Fatty acids relevant for metabolic pathways are summarized in Table 1.

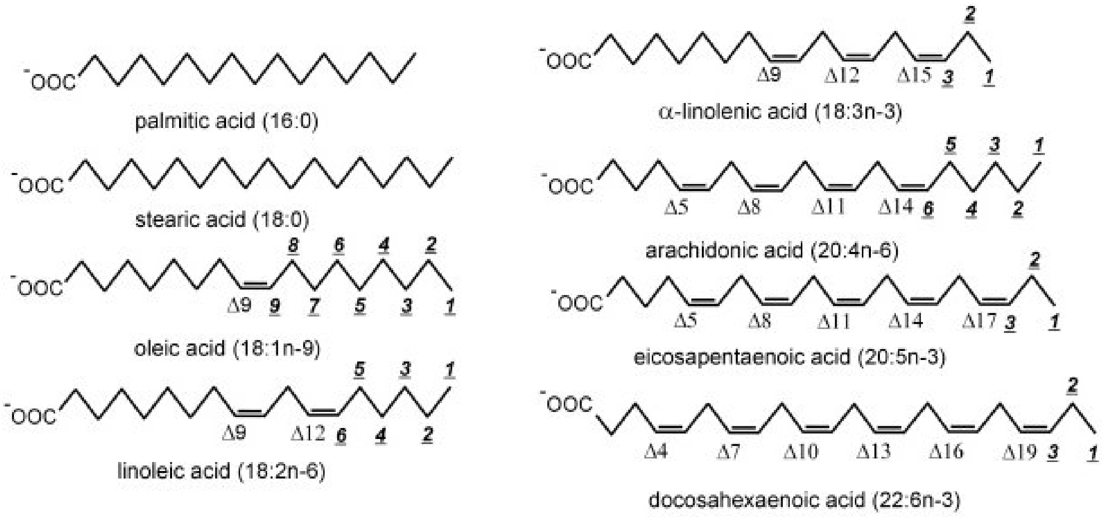

Figure 1. Structure formulas and types of shorthand notations of fatty acids.

Notation	**Systematic name by IUPAC**	**Trivial name**	**Abbrev.** [c]
12:0	dodecanoic acid	lauric acid	
14:0	tetradecanoic acid	myristic acid	MA
14:1n-5	*cis*-9-tetradecenoic acid	myristoleic acid	MOA
16:0	hexadecanoic acid	palmitic acid	PA
16:1n-9	*cis*-7-hexadecenoic acid		
16:1n-7	*cis*-9-hexadecenoic acid	palmitoleic acid	POA
18:0	octadecanoic acid	stearic acid	SA
18:1n-9	*cis*-9-octadecenoic acid	oleic acid	OA
18:1n-7	*cis*-11-octadecenoic acid	vaccenic acid	VA
18:2n-6	*cis, cis*-9,12-octadecadienoic acid	linoleic acid	LA
18:3n-6	*cis,cis,cis*-6,9,12-octadecatrienoic acid	-linolenic acid	GLA
18:3n-3	*cis,cis,cis*-9,12,15-octadecatrienoic acid	-linolenic acid	ALA
18:4n-3	*cis,cis,cis,cis*-6,9,12,15-octadecatetraenoic acid	stearidonic acid	
20:0	icosanoic acid	arachidic acid	
20:1n-11	*cis*-9-icosenoic acid	gondoleic acid	
20:1n-9	*cis*-11-icosenoic acid	gondoic acid	
20:2n-6	*cis,cis*-11,14-icosadienoic acid		
20:3n-9	*cis,cis,cis*-5,8,11-icosatrienoic acid	Mead acid	
20:3n-6	*cis,cis,cis*-8,11,14-icosatrienoic acid	dihomo- -linolenic acid	DHGLA
20:4n-6	*cis,cis,cis,cis*-5,8,11,14-icosatetraenoic acid	arachidonic acid	AA
20:5n-3	*cis,cis,cis,cis,cis*-5,8,11,14,17-icosapentaenoic acid	timnodonic acid	EPA
22:0	docosanoic acid	behenic acid	
22:1n-11	*cis*-11-docosenoic acid	cetoleic acid	
22:1n-9	*cis*-13-docosenoic acid	erucic acid	
22:4n-6	*cis,cis,cis,cis*-7,10,13,16-docosatetraenoic acid	adrenic acid	DTA
22:5n-3	*cis,cis,cis,cis,cis*-7,10,13,16,19-docosapentaenoic acid		DPA-3
22:5n-6	*cis,cis,cis,cis,cis*-4,7,10,13,16-docosapentaenoic acid		DPA-6
22:6n-3	*cis,cis,cis,cis,cis,cis*-4,7,10,13,16,19-docosahexaenoic acid	clupadonic acid	DHA

24:0	tetracosanoic acid	lignoceric acid	
24:1n-9	*cis*-15-tetracosenoic acid	nervonic acid	NA
26:0	hexacosanoic acid	cerotic acid	
28:0	oktacosanoic acid	montanic acid	
30:0	triacontanoic acid	melissic acid	

Table 1. Fatty acids relevant in metabolic pathways in vertebrates.

In this chapter the basic properties of fatty acids, their roles in normal metabolism and some aspects of their role in pathophysiology will be discussed.

2. Physico-Chemical Properties of Fatty Acids

The melting point of fatty acids increases with the length of the hydrocarbon chain (i.e. CN), and it decreases with the number of double bonds. This property is reflected also in the compounds, where FA represent an important component (phospholipids, triglycerides), as well as in higher organized structures (plasma membranes, lipoproteins). Double bonds have under physiological conditions preferably cis-configuration, which causes a 30° deflection of the carbon chain. This prevents the chain from effectively filling the space, decreasing van der Waals interactions and thus the melting point.

Degree of desaturation (number of double bonds in cis configuration) significantly influences microviscosity of cell membranes, their thickness and consequently also the function of associated proteins (enzymes, cell receptors, membrane transporters and ion channels).

Water solubility of FA decreases with chain length. In diluted solutions FA are present as monomers, in higher concentrations they form micelles. The concentration, above which FA associate into micelles, is called the critical micellar concentration. In the micelles, the carboxyl sides are oriented into water phase, while hydrophobic (aliphatic) parts are packed within the centre. Micelles and liposomes are schematically shown in Figure 2.

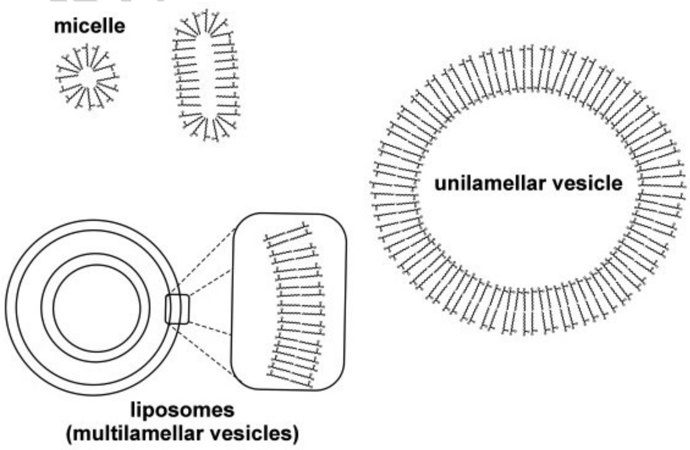

Figure 2. Schematic structure of micelles and liposomes.

3. Biosynthesis of Fatty Acids

Fatty acids are synthesized from two or three carbon precursors, with the aid of acyl carrier protein, NADPH and acetyl-CoA-carboxylase. The elongation is using malonyl-CoA in the microsomal system and acetyl-CoA in the mitochondrial system. Their degradation by β-oxidation in mitochondria is accompanied by energy-release. Approximately 60 FA have been identified in blood plasma and tissues, however, only some of them are relevant from the biological point of view. Composition of FA is partially species as well as tissue specific.

Human (mammalian) tissues are able to synthesize saturated FA, preferably with straight chain and even CN. Monounsaturated FA (MFA) are formed by introducing double bond in position Δ9 from the carboxyl carbon. The reaction is catalyzed by the enzyme Δ9 desaturase. Desaturation of stearic acids (18:0) results in oleic acid (18:1 n-9) and that of palmitic acid (16:0) in palmitoleic one (16:1 n-7). Monounsaturated FA n-9 family with CN 20-24 are elongation products of oleic acid, those of n-11 family are desaturation and elongation products of FA 20:0, as shown schematically in Figure 3.

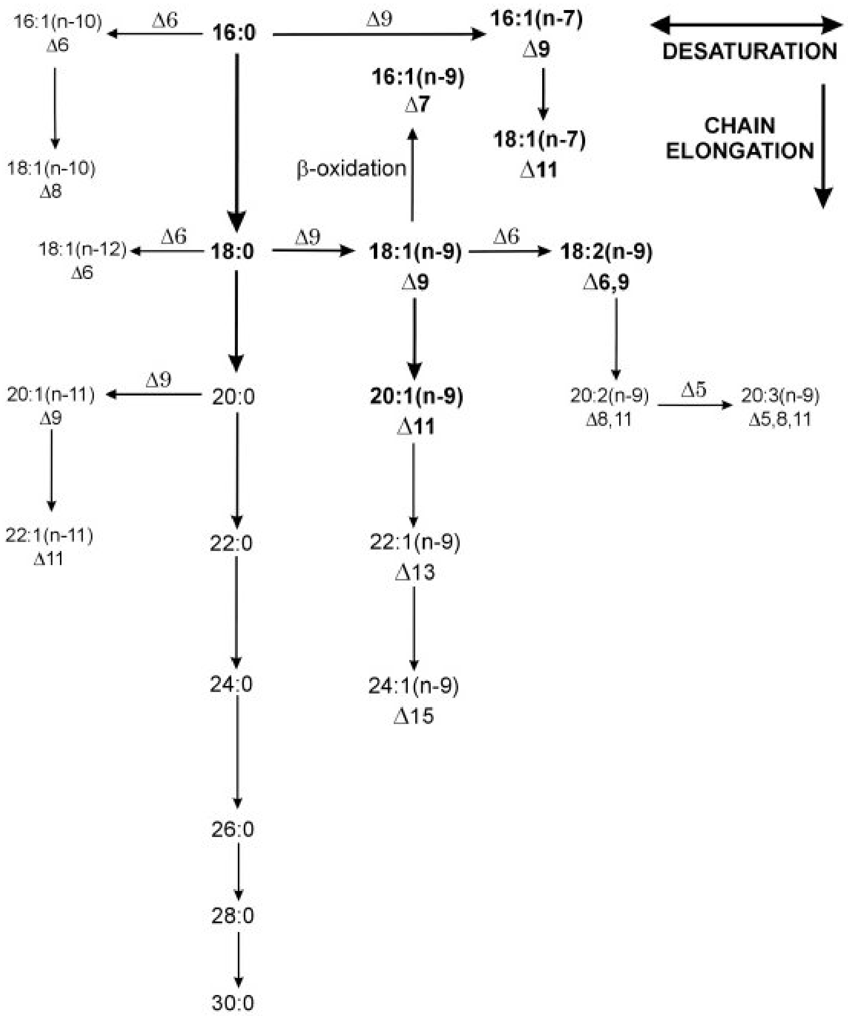

Figure 3. Elongation and desaturation of endogenous fatty acids.

Further desaturation (Δ6, Δ5) and elongation of oleic acid produces mead acid (20:3 n-9), which is produced by human organism only when dietary intake of essential FA (EFA) is not sufficient.

Polyunsaturated FA contain 2-6 double bonds in pentadiene configuration. Essential FA are PUFA with the first double bond localized on the third (n-3 family) or the sixth (n-6 family) carbon atom from the methyl group. Essential FA cannot be synthesized by mammals and thus, the organism is completely dependent on their dietary intake. There are two basic precursors, so called parent FA – linoleic acid (18:2 n-6) for n-6 family, and α-linolenic acid (18:3 n-3) for n-3 family. Metabolic pathways of EFA are schematically shown in Figure 4.

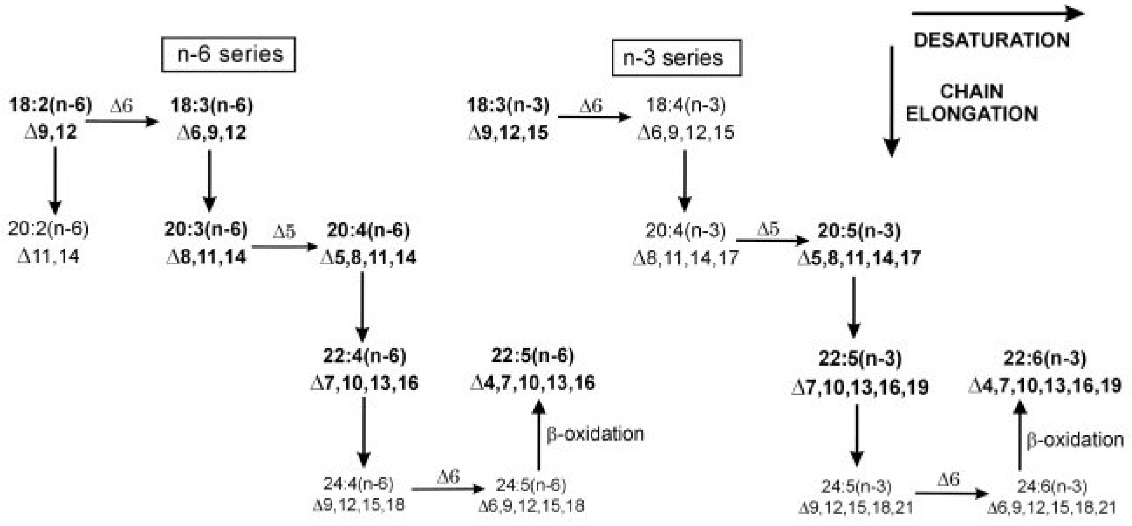

Figure 4. Elongation and desaturation of essential fatty acids of n-3 and n-6 families. In human tissues this reactions are rather slow.

Fatty acids in individual metabolic pathways differ in their affinity to enzymes and ability to inhibit desaturases (affinity ratio FA n-3 : FA n-6 : FA n-9 ~ 10 : 3 : 1).

-
-
-

Bibliography

Bitman J., Wood L., Mehta N.R., Hamosh P. and Hamosh M. (1984). Comparison of the phospholipid composition of breast milk from mothers of term and preterm infants during lactation. *Am. J. Clin. Nutr.*

84, 1103-1119. [Valuable information on mother´s milk and its role in the development of tissues in babies.]

Brenna T.J. (2002). Efficiency of conversion of α-linolenic acid to long chain n-3 fatty acids in man. *Curr. Opin. Clin. Nutr. Metab. Care*, 5, 127-132. [External sources of EPA and DHA are important as in humans the conversion over α-linolenic acid is slow.]

Dyerberg J. (1986). Linolenate-derived polyunsaturated fatty acids and prevention of atherosclerosis. *Nutr. Rev.* 44, 125-134. [One of the first reviews on the pathophysiology and roles of n-3 FA.]

Fernandez M.L. and West K.L. (2005). Mechanisms by which dietary fatty acids modulate plasma lipids. *J. Nutr.* 135(9), 2075-8. [Explains mode of action of EFA.]

Jensen R.G. (2002). Invited review: The composition of bovine milk lipids: January 1995 to December 2000. *J. Dairy Sci.* 85, 295-300. [An excellent review on milk composition, lipid classes incuding.]

Lombardo Y.B. and Chicco A.G. (2006). Effects of dietary polyunsaturated n-3 fatty acids on dyslipidemia and insulin resistence in rodents and humans. A review. *J. Nutr. Biochem.* 17, , 1-13. [New review on pathophysiology and role of EFA.]

Martinez M. (2000). The fundamentals and practice of docosahexaenoic acid therapy in peroxisomal disorders. *Curr. Opin. Clin. Nutr. Metab. Care*, 3, 101-108. [Unsaturated FA may offer benefits in treating human pathologies.]

Simopoulos A.P. (1991). Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.*, 54, 438-463. [Still valuable overview on the important role of nutritional EFA.]

Vance D.E. and Vance J.E. (2002). Biochemistry of lipids, lipoproteins and membranes. 4th Edition, Amsterdam, Elsevier. [Useful basic textbook.]

Vergroesen A.J. and Crawford M., Eds. (1989). The role of fats in human nutrition., Academic Press, London. [Useful book on human nutrition and lipids.]

Biographical Sketches

RNDr. Eva Tvrzická, PhD, is an Assistant Professor at Charles University, Prague, Czech Republic. After having finished studies in the Faculty of Science, Charles University, Prague and completing PhD studies (1974), she was employed as a chemist-specialist. She currently occupies the position of a senior research scientist, 1st Faculty of Medicine, Research Angiologic Laboratory, that is focused on the application of chromatographic methods in lipid and lipoprotein research, studies on lipid metabolism under different pathological conditions, serum and tissue lipids under various pathological states, risk factors of atherosclerosis, and new methodologies for the studying of lipids as well as lipoproteins. She is author and co-author of more than 100 publications and more than 140 scientific presentations.

Aleš Žák, MD, DSc, is an Associate Professor at Charles University, Prague, Czech Republic**.** Finished his studies at the School of General Medicine (now the 1st School of Medicine), Charles University, Prague in 1975. He was approved as an assistant professor (1982) and associated professor of medicine (1999). Assoc. prof. Žák has a PhD (1995) and a DSc (2001) degree from the 1st School of Medicine, Prague. He has been on the staff of the 4th Department of Medicine, 1st School of Medicine, Charles University in Prague as an assistant registrar (1976 - 1982), registrar (1982 - 1985), head of the biochemical laboratory (1985 – 1998), head of ICU (1995), and a head of the Department (2001 - present). His research projects and teaching activities cover studies on lipid transport disorders with respect to influence of essential fatty acids and with respect to atherosclerotic vascular disease, changes in cholesterol and fatty acid metabolism in protein-calorie malnutrition and teaching students of the 1st School of Medicine (internal medicine, pathobiochemistry). He is an author and co-author of 150 publications and more than 200 scientific presentations at various congresses and symposia.

Marek Vecka, MSc, was born in Domažlice, Czech Republic, in 1976. After obtaining his BSc. degree in chemistry (1997) and MSc. degree in biochemistry (1999) from the Faculty of Science in Charles University in Prague, he passed his doctoral examination (2001) in biochemistry and pathobiochemistry. He is currently a postgraduate student of the 1st Faculty of Medicine in Charles University, Prague, with a position of research specialist. His major areas of interest include sterol and fatty acid metabolism. He is author or co-author of 25 publications and more than 40 scientific presentations.

Barbora Staňková, MSc, was born in Ostrava, Czech Republic, in 1973. She completed her BSc. Degree at the University of Pardubice in Clinical Biology and Biochemistry, and six years later a master degree at Charles University, Faculty of Sciences in Biochemistry. She currently occupies the position of Lab research worker at 1st Faculty of Medicine, Charles Univesity Prague, 4th Medical Department. Her scientific interests include fatty acids in different pathological stages, studies on lipoprotein particle size in patients with disturbances in lipid metabolism. She is the author or co-author of approx. 50 scientific papers