

## FATTY ACIDS IN HUMAN METABOLISM

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### Contents

1. Introduction
2. Physico-Chemical Properties of Fatty Acids
3. Biosynthesis of Fatty Acids
4. Classification and Biological Function of Fatty Acids
5. Fatty Acids as Constitutional Components of Lipids
6. Physiological Roles of Fatty Acids
7. Milk Lipids and Developing Brain
8. Pathophysiology of Fatty Acids
9. Therapeutic Use of Polyunsaturated Fatty Acids

Acknowledgements

Glossary

Bibliography

Biographical Sketches

### 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  $\beta$ -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  $\Delta 9$  position, desaturation to another position is possible only from exogenous (essential) acids [linoleic (n-6 series) and  $\alpha$ -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. NF $\kappa$ B, AP-1 and TNF- $\alpha$ ) and are responsible for the expression of proinflammatory cytokines (e.g. IL-1, IL-6, IL-8 and TNF- $\alpha$ ) 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.

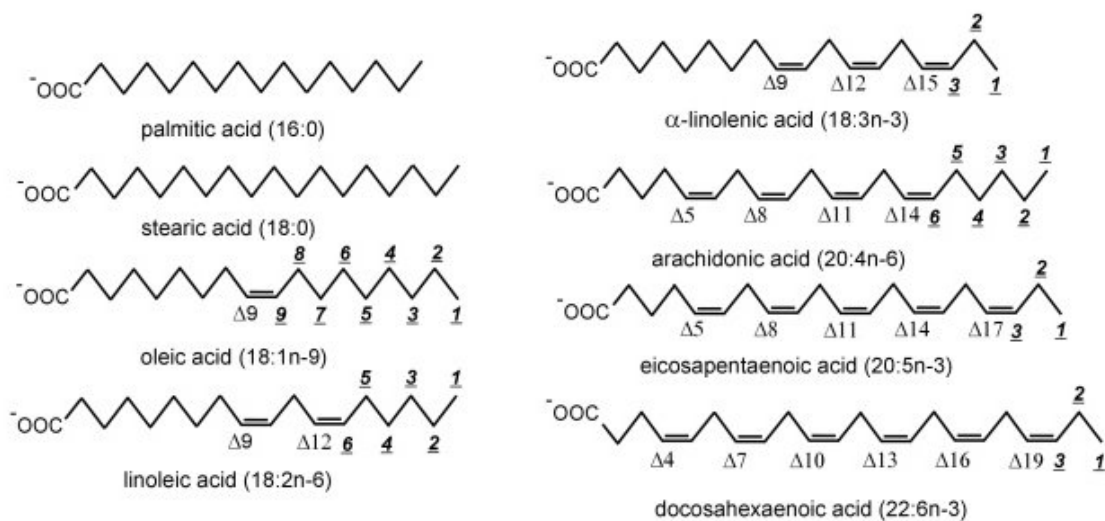


Figure 1. Structure formulas and types of shorthand notations of fatty acids.

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

|         |                                   |                 |    |
|---------|-----------------------------------|-----------------|----|
| 24:0    | tetracosanoic acid                | lignoceric acid |    |
| 24:1n-9 | <i>cis</i> -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.

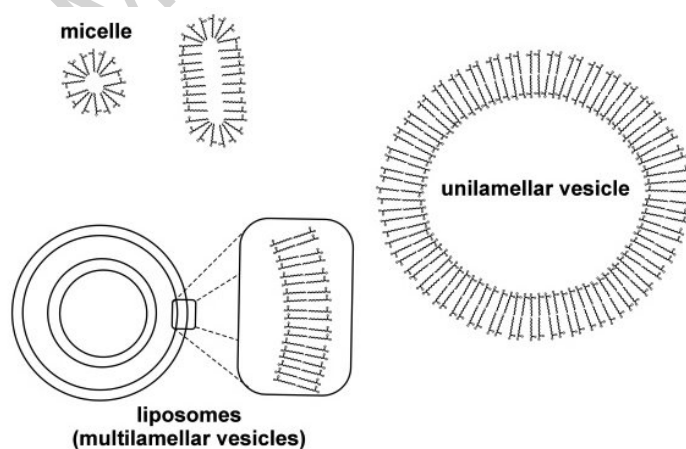


Figure 2. Schematic structure of micelles and liposomes.

### 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  $\beta$ -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  $\Delta 9$  from the carboxyl carbon. The reaction is catalyzed by the enzyme  $\Delta 9$  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.

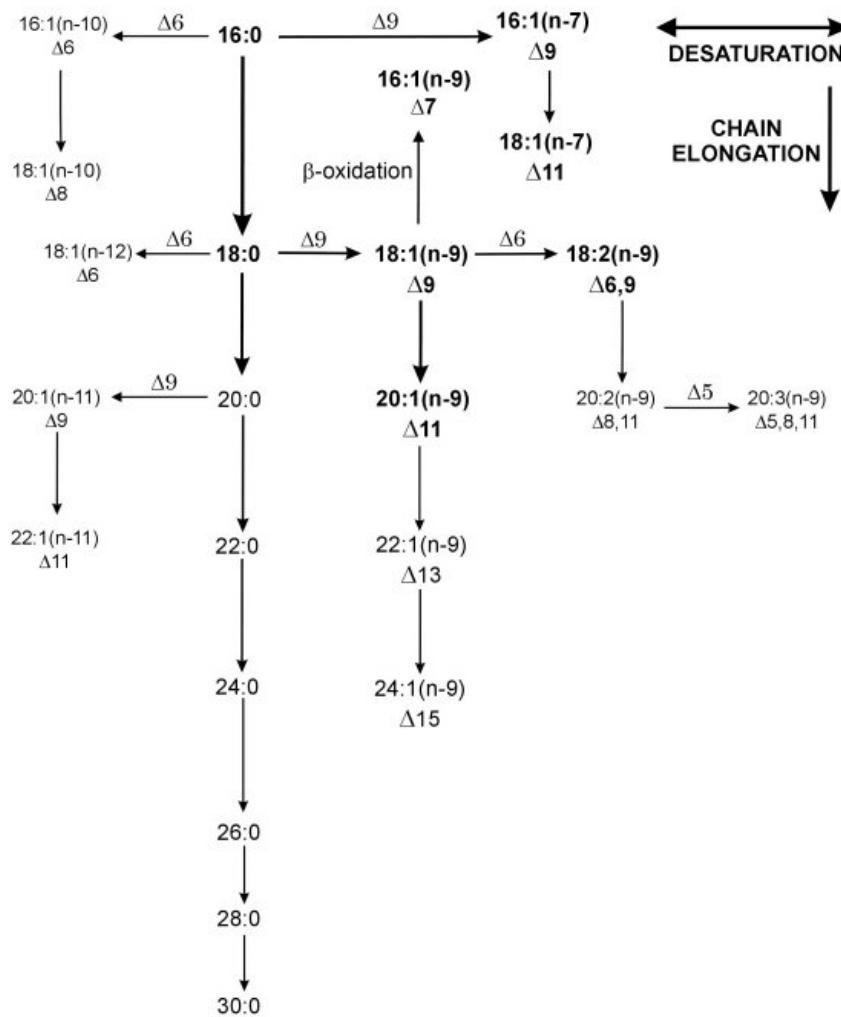


Figure 3. Elongation and desaturation of endogenous fatty acids.

Further desaturation ( $\Delta 6$ ,  $\Delta 5$ ) 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  $\alpha$ -linolenic acid (18:3 n-3) for n-3 family. Metabolic pathways of EFA are schematically shown in Figure 4.

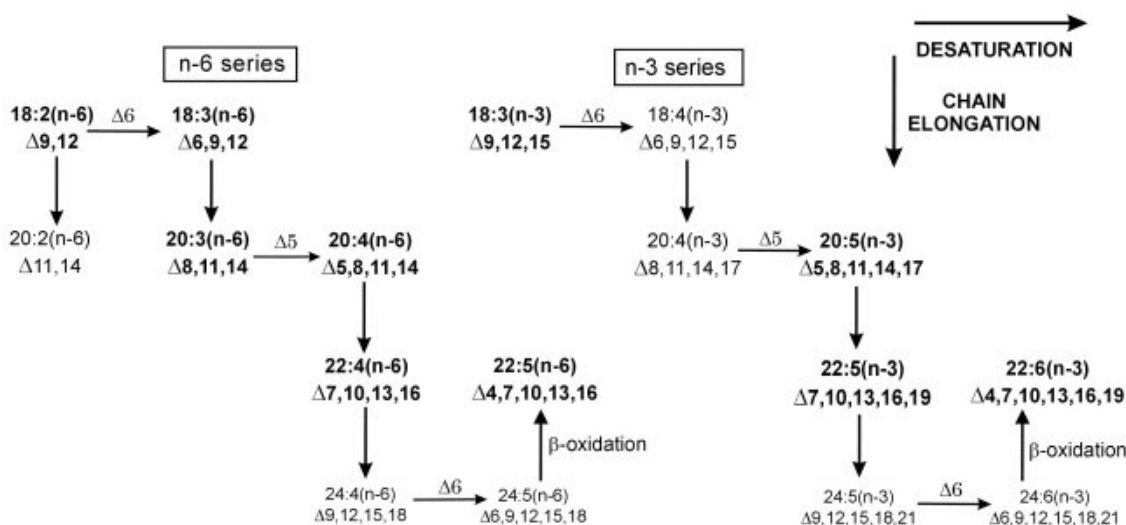


Figure 4. Elongation and desaturation of essential fatty acids of n-3 and n-6 families. In human tissues this reactions are rather slow.

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).

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### 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, 1<sup>st</sup> 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 1<sup>st</sup> 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 1<sup>st</sup> School of Medicine, Prague. He has been on the staff of the 4<sup>th</sup> Department of Medicine, 1<sup>st</sup> 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 1<sup>st</sup> 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 1<sup>st</sup> 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 1<sup>st</sup> Faculty of Medicine, Charles University Prague, 4<sup>th</sup> 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