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FATTY ACIDS AS BIOCOMPOUNDS: THEIR ROLE IN HUMAN METABOLISM, HEALTH AND DISEASE – A REVIEW. PART 1: CLASSIFICATION, DIETARY SOURCES AND BIOLOGICAL FUNCTIONS

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Background. Fatty acids are substantial components of lipids and cell membranes in the form of phospholipids. This review consists of two parts. The present part aims at describing fatty acid classification, dietary sources and biological functions. The second part will focus on fatty acid physiological roles and applications in human health and disease.

Results. In humans, not all fatty acids can be produced endogenously due to the absence of certain desaturases. Thus, specific fatty acids termed essential (linoleic, alpha-linolenic) need to be taken from the diet. Other fatty acids whose synthesis depends on essential fatty acid intake include eicosapentaenoic acid and docosahexaenoic acid, found in oily fish. Dietary sources of saturated fatty acids are animal products (butter, lard) and tropical plant oils (coconut, palm), whereas sources of unsaturated fatty acids are vegetable oils (such as olive, sunflower, and soybean oils) and marine products (algae and fish oils). Saturated fatty acids have been related to adverse health effects, whereas unsaturated fatty acids, especially monounsaturated and n-3 polyunsaturated, are thought to be protective. In addition, *trans* fatty acids have been shown to have negative effects on health, whereas conjugated fatty acids might be beneficial. Lastly, fatty acids are the main components of lipid classes (triacylglycerols, phospholipids, cholesteryl esters, non-esterified fatty acids).

Conclusion. Fatty acids are important biocompounds which take part in complex metabolic pathways, thus having major biological roles. They are obtained from various dietary sources which determine the type of fat consumed and consequently health outcome.

INTRODUCTION

Dietary modifications that have occurred over time include changes in the type of fat consumed toward increased consumption of saturated animal fat in particular, and lower intake of unsaturated fat (plant and marine sources) (ref.[1,2]). This change in the composition of diet may have a great effect on the fatty acid composition of human tissues and affect metabolism and health[3].

Fatty acids (FA) play multiple roles in humans and other organisms. Most importantly, FA are substantial part of lipids, one of the three major components of biological matter (along with proteins and carbohydrates) (ref.[4]). Fatty acids are also important energy substrates comprising around 30% of total energy intake for humans. They can be stored in excess amounts in adipose tissue, especially when increased dietary intake of fat and energy occurs resulting in obesity.

Fatty acids are either saturated or unsaturated carboxylic acids with carbon chains varying between 2 and 36 carbon atoms. Polyunsaturated FA (PUFA) are characterized by pentadiene configuration of double bonds. Most FA have an even number of carbon atoms, as they are synthesized from two-carbon units. Specifically, fatty acids are synthesized *ad hoc* in the 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 acid composition is species as well as tissue specific. In animal and plant tissues, the most abundant FA are those with 16 and 18 carbon atoms, i.e. palmitic, stearic, oleic and linoleic. Fatty acids in mammalian organisms reach a chain-length of 12-24 carbon atoms, with 0-6 double bonds. However, fatty acids with chain lengths shorter than 14 and longer than 22 carbon atoms are present only in minor concentrations. Approximately half of the FA in plants and animals are unsaturated and contain 1-6 double bonds.

Fatty acids can be desaturated endogenously up to the Δ9 position due to lack of certain enzymes in humans (Δ12- and Δ15-desaturases). For this reason linoleic (LA; 18:2n-6) and α-linolenic (ALA; 18:3n-3) acids must be taken from the diet and are termed essential. Further elongation and desaturation of these fatty acids to produce long-chain (LC) PUFA, including eicosapentaenoic acid (EPA; 20:5n-3), docosahexaenoic acid (DHA; 22:6n-3) and arachidonic acid (AA; 20:4n-6), is possible but not very efficient in humans. Thus, these fatty acids may be characterized as conditionally essential depending on essential fatty acid availability. Recommendations for minimum dietary intake of EPA plus DHA vary between 250-450 mg/day, especially for pregnant women and those

of reproductive age[5,6]. Rich sources of these LC n-3 PUFA are fish oils and the flesh of oily fish.

From a chemical point of view, lipids are esters of fatty acids with organic alcohols – cholesterol, glycerol and sphingosine. Lipids circulate in the blood stream in the form of lipoproteins, which are composed of cholesteryl esters, triacylglycerols, and phospholipids. Non-esterified fatty acids are bound to plasma albumin. Fatty acids in the form of phospholipids (mainly phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin) form the back bone of all cell membranes and are essential for their fluidity and functionality.

The present review on the role of FA as biocompounds consists of two parts. The first part aims at presenting and discussing FA nomenclature, physicochemical properties, biosynthesis, classification according to saturation, dietary sources, and biological function, as well as the structure and role of lipid classes. The second part of this review (to be published in the next volume of Biomedical Papers) will focus on FA physiological roles and applications in human health and disease as growth and development, cardiovascular health, cancer, and immune system disorders.

FATTY ACID NOMENCLATURE

Fatty acids are carboxylic acids with a typical RCOOH structure, containing a methyl end, a hydrocarbon chain (R) and a carboxylic terminus. Fatty acids have both a systematic and a common name (e.g. octadecanoic and stearic). They are also often expressed as a schematic formula (shorthand notation) as in CN:p n-x, where CN (carbon number) represents total number of carbon atoms, p – number of double bonds, x – position of the first double bond from the methyl terminus (n) (ref.[7]). For example, the shorthand notation for linoleic acid (9,12-octadecadienoic acid) is 18:2n-6 since it has 18 carbon atoms, and 2 double bonds of which the first one is on the sixth carbon atom counted from the methyl end. A different way of expressing the position of the first double bond is counting from the carboxylic terminus and this is indicated as the Δ position. An example would be that the position of the first double bond in α-linolenic acid (18:3n-3) counting from the carboxylic group is Δ9. The structural formulas as well as types of shorthand notations are shown in (Fig. 1). Important fatty acids[8] involved in metabolic pathways are summarized in (Table 1).

PHYSICOCHEMICAL 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 also reflected in compounds where FA represent an important component (phospholipids, triacylglycerols), as well as in higher organized structures (plasma membranes, lipoproteins). Under physiological conditions, double bonds preferably have a *cis*-configuration, which causes a 30° deflection (curve) of the carbon chain. This results in the *cis*-unsaturated chain occupying greater space, decreasing van der Waals interactions and thus the melting point[9].

Moreover, the degree of unsaturation (number of double bonds in *cis*-configuration) significantly influences cell membrane microviscosity and thickness, and consequently also the function of associated proteins (enzymes, cell receptors, membrane transporters and ion channels).

The water solubility of FA decreases as the chain lengthens. In diluted solutions, FA are present as monomers. However, in higher concentrations they form micelles. The concentration, above which FA associate into micelles, is called the critical micellar concentration. In

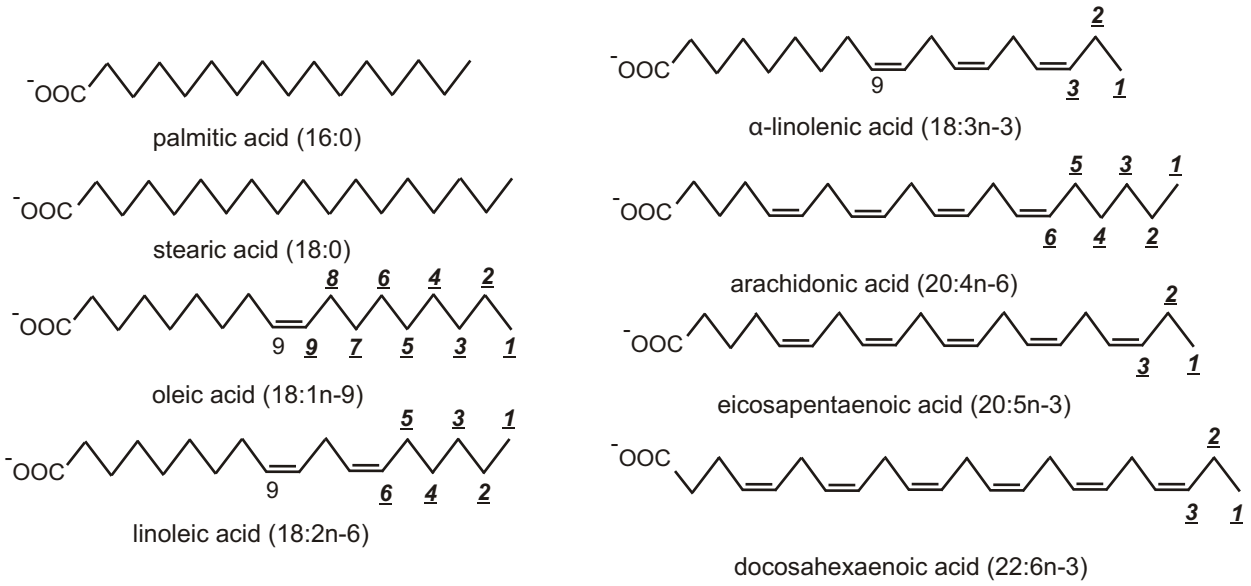

Fig. 1. Structural formulas and types of shorthand notations of fatty acids.

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

Notation	Systematic name by IUPAC	Trivial name	Abbreviation[c]	Molecular mass	Melting point (°C)
4:0	tetranoic	butyric		88.11	–7.9–5.1
6:0	hexanoic	caproic		116.16	–3.4–3.9
8:0	octanoic	caprylic		144.22	16.3–16.7
10:0	decanoic	capric		172.27	31.2–31.6
12:0	dodecanoic	lauric		200.32	44.0–44.2
14:0	tetradecanoic	myristic	MA	228.38	53.9–54.4
14:1n-5	*cis*-9-tetradecenoic	myristoleic	MOA	226.37	
16:0	hexadecanoic	palmitic	PA	256.43	62.5–63.1
16:1n-9	*cis*-7-hexadecenoic			254.411	
16:1n-7	*cis*-9-hexadecenoic	palmitoleic	POA	254.411	–0.5
18:0	octadecanoic	stearic	SA	284.48	67–69.6
18:1n-9	*cis*-9-octadecenoic	oleic	OA	282.47	16.3
18:1n-9	*trans*-9-octadecenoic	elaidic		282.47	44–46
18:1n-7	*cis*-11-octadecenoic	vaccenic	VA	282.47	43–44
18:2n-6	*cis, cis*-9,12-octadecadienoic	linoleic	LA	280.46	–5 (–9)
18:3n-6	all *cis*-6,9,12-octadecatrienoic	γ-linolenic	GLA	278.44	
18:3n-3	all *cis*-9,12,15-octadecatrienoic	α-linolenic	ALA	278.44	–11 (–17)
18:4n-3	all *cis*-6,9,12,15-octadecatetraenoic	stearidonic		276.417	
20:0	eicosanoic	arachidic	AA	312.54	75.3–75.4 (74–76)
20:1n-11	*cis*-9-eicosenoic	gondoleic		310.518	
20:1n-9	*cis*-11-eicosenoic	gondoic		310.518	
20:2n-6	*cis,cis*-11,14-eicosadienoic			308.502	
20:3n-9	all *cis*-5,8,11-eicosatrienoic	Mead		306.487	
20:3n-6	all *cis*-8,11,14-eicosatrienoic	dihomo-γ-linolenic	DHGLA	306.487	
20:4n-6	all *cis*-5,8,11,14-eicosatetraenoic	arachidonic	AA	304.471	–49.5
20:5n-3	all *cis*-5,8,11,14,17-eicosapentaenoic	timnodonic	EPA	302.455	–54
22:0	docosanoic	behenic		340.60	79.9–80.0 (74–78)
22:1n-11	*cis*-11-docosenoic	cetoleic		338.58	
22:1n-9	*cis*-13-docosenoic	erucic		338.58	33.8
22:2n-6	*cis,cis*-13,16-docosadienoic acid			336.556	
22:3n-6	all *cis* 10,13,16-docosatrienoic acid			334.540	
22:4n-6	all *cis*-7,10,13,16-docosatetraenoic	adrenic		332.524	
22:5n-3	all *cis*-7,10,13,16,19-docosapentaenoic		DPA-3	330.509	
22:5n-6	all *cis*-4,7,10,13,16-docosapentaenoic		DPA-6	330.509	
22:6n-3	all *cis*-4,7,10,13,16,19-docosahexaenoic	clupadonic	DHA	328.493	–44.7, –44.5
24:0	tetracosanoic	lignoceric		368.641	75–83
24:1n-9	*cis*-15-tetracosenoic	nervonic	NA	366.625	42–43
26:0	hexacosanoic	cerotic		396.7	87–88
28:0	octacosanoic	montanic		424.7	90.9
30:0	triacontanoic	melissic		452.8	93–94

micelles, the carboxyl sides are oriented into the water phase, while hydrophobic (aliphatic) parts are packed within the centre[10]. Fatty acids esterified in phospholipids can form liposomes which are widely used in medicine[11] as well as in other fields (cosmetics). Micelles and liposomes are schematically shown in (Fig. 2) (based on Nelson & Cox, 2005) (ref.[12]).

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[4]. The elongation is via malonyl-CoA in the microsomal system and acetyl-CoA in the mitochondrial system. Their degradation by

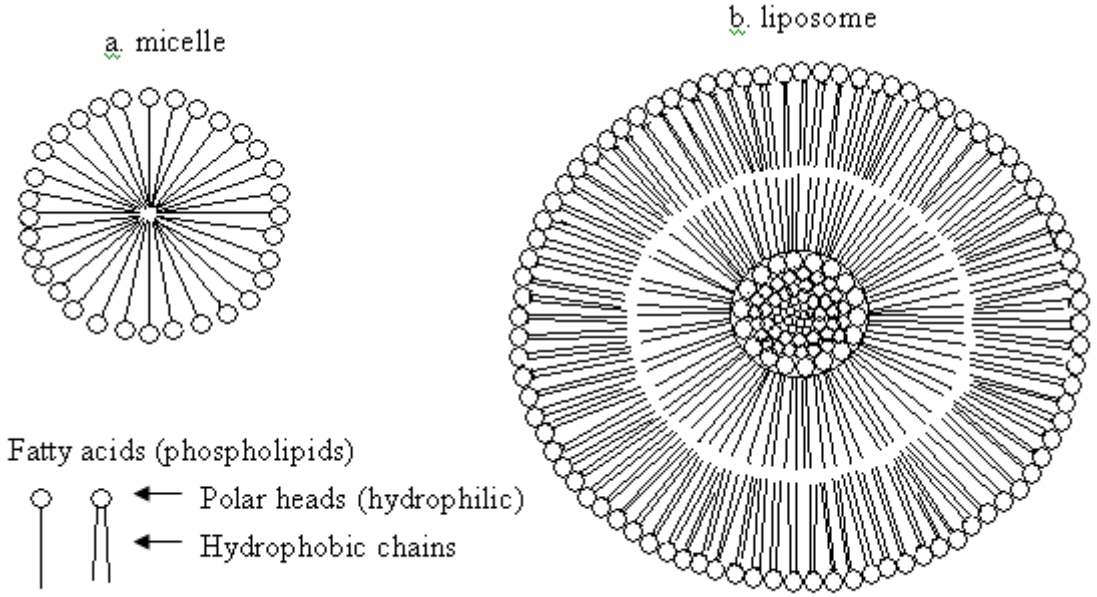

Fig. 2. Schematic structure of micelles (a) and liposomes (b). In micelles, the hydrophobic chains of fatty acids are turned inwardly towards the core of the sphere, whereas polar heads are on the outer layer. There is virtually no water in the interior. Liposomes are three-dimensional hollow vesicles enclosing an aqueous cavity. They are formed when the two-dimensional bilayer folds on itself.

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 important from a biological point of view.

The composition of FA in individual species is predominately determined genetically but can be modified by diet. Mammals, including humans, are able to synthesize saturated FA, preferably with straight chain and even number of carbon atoms. Monounsaturated FA (MFA) are formed by introducing a double bond in position Δ9 counting from the carboxyl carbon. The reaction is catalyzed by the enzyme Δ9-desaturase[4]. Polyunsaturated FA contain 2-6 double bonds in pentadiene configuration (i.e. methylene interruption of the double bonds).

Typically, desaturation of stearic acid (18:0) results in oleic acid (18:1 n-9) and that of palmitic acid (16:0) in palmitoleic acid (16:1 n-7). As shown schematically in (Fig. 3), MFA of the n-9 with 20-24 carbon atoms are elongation products of oleic acid, whereas those of the n-11 family are desaturation and elongation products of arachidic acid (20:0). Further desaturation (Δ6, Δ5) and elongation of oleic acid produces Mead acid (20:3 n-9), which is produced in humans only when dietary intake of essential FA (EFA) is not sufficient[13,14]. Essential FA include LA for n-6 family, and ALA for n-3 family. Essential FA are PUFA which have their first double bond located on the third (n-3 family) or the sixth (n-6 family) carbon atom counting from the methyl terminus of the hydrocarbon chain. Essential FA cannot be synthesized in humans due to lack of Δ12- and Δ15-desaturases which are present only in plants and marine algae[4], and thus, the human organism is completely dependent on their dietary intake. Further elongation and desaturation of these fatty acids to produce LC PUFA, including EPA, DHA and AA, is performed but not that efficiently in humans. Thus, these fatty acids may be characterized as conditionally essential depending on essential fatty acid availability. The metabolic pathways of EFA are schematically shown in (Fig. 4). It should be noted that fatty acids in individual metabolic pathways differ in their affinity to enzymes and their ability to inhibit desaturases (the FA affinity ratio is n-3 : n-6 : n-9 ~ 10 : 3 : 1).

FATTY ACID CLASSIFICATION, DIETARY SOURCES AND BIOLOGICAL FUNCTIONS

Total fat, as well as the type of fat, determine the effect of their consumption on health[15,16]. Fatty acids can be divided into several groups with respect to their structure, physiological role and biological effects. In the following paragraphs fatty acids are classified according to their structure as saturated and unsaturated.

Saturated fatty acids

Saturated FA (SFA) do not contain any double bonds and can be divided into subgroups according to their chain length:

Short chain (saturated) fatty acids (SCFA), include acetic (2:0), propionic (3:0), and butyric (4:0) acids, which are formed during fibre fermentation in the proximal colon. They are quickly absorbed, and acetic and partially also propionic acids are resorbed by portal circulation, transported to the liver and transformed into glucose (propionic acid) and FA (acetic acid). This process can cover 10-20% of resting energy expenditure (REE)

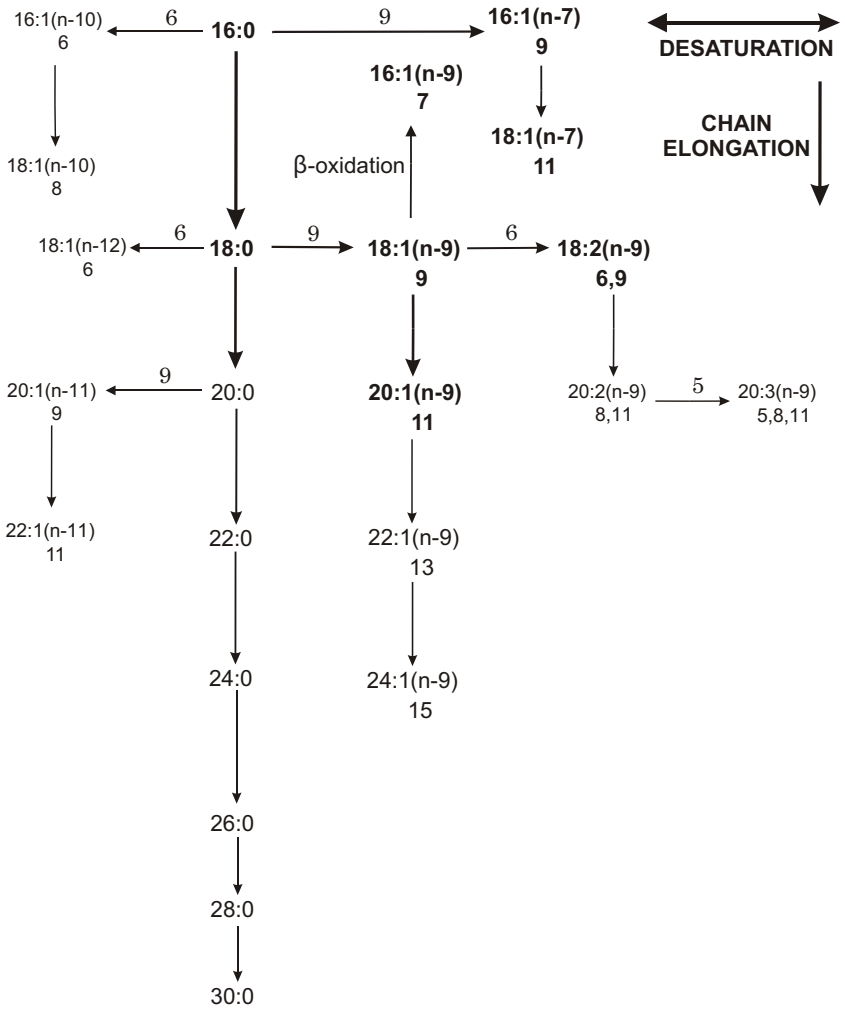

Fig. 3. Elongation and desaturation of endogenous fatty acids.

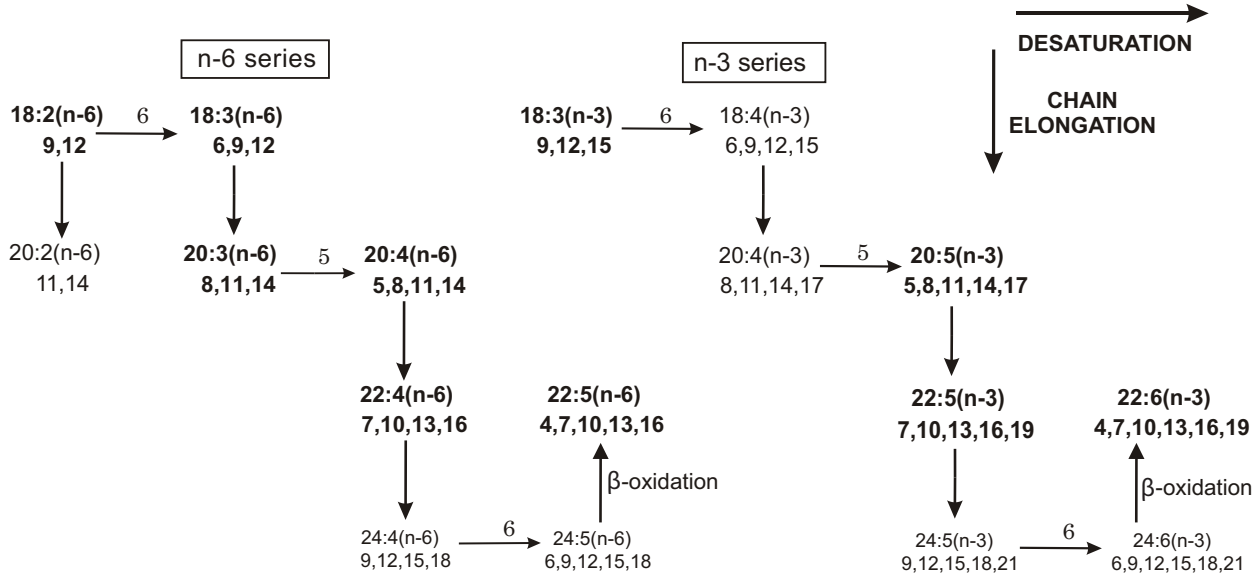

Fig. 4. Elongation and desaturation of essential fatty acids of the n-3 and n-6 families. In human tissues these pathways are rather slow.

of the human body. Importantly, butyric and partially also propionic acids are used in metabolism, proliferation and restoration (cell replication) of colonocytes.

Other functions of SFA in the colon also include stimulation of:

1) water, sodium, chloride and bicarbonate absorption
2) blood flow through mucous membrane of the colon
3) colonocyte proliferation
4) mucus production
5) limited reproduction of saprophytic bacteria and putrefication due to decreased acidity[17].

Medium chain (saturated) fatty acids (MCFA) include caproic (6:0), caprylic (8:0), and capric (10:0) acids, which are resorbed directly and transported by the portal vein. Their intramitochondrial transfer does not need the presence of carnitine or carnitine palmitoyl transferases. Fat emulsions containing medium chain triacylglycerols (MCT) are used as nutritional support in enteral nutrition. These have shorter biological half-time and higher stability to lipoperoxidation. These emulsions also inhibit decrease of REE during caloric restriction. Thus they are recommended in some cases of restrictive dietary regimen for obese individuals[18].

Long chain (saturated) fatty acids (LCFA) include lauric (12:0), myristic (14:0), palmitic (16:0), and stearic (18:0) acids have significant atherogenic and thrombogenic potential. These FA, originating mainly in coconut oil *(Cocos/Nucifera)*, palm kernel oil *(Elaeis guineensis)*, cocoa butter *(Theobroma cacao)*, shea butter *(Butyrospermum parkii,* synonymous to *Vitellaria paradoxa) (*ref.[19,20]) and illipe butter *(Bassia latifolia),* represent 80-90% of total SFA from food intake. The last three sources, which are substantial components of chocolate products, also contain approximately 35% of oleic acid. Animal sources of LCFA are butter, lard and beef tallow[21]. A variation of canola oil producing plant has been cultivated to have a high content of stearic acid (up to 40%) which is advantageous when margarines are produced. Table 2 shows the percentage of individual FA for fats and oils rich in SFA (ref.[22]).

Consumption of saturated LCFA increases levels of cholesterol, namely that of low density lipoprotein (LDL)-cholesterol, which is connected with increased coronary heart disease (CHD) mortality[23]. The effect of saturated LCFA in increasing LDL-cholesterol decreases in the direction 12:0 - 14:0 - 16:0 (ref.[24,25]). On the other hand, the high density lipoprotein (HDL)-cholesterol lowering effect of saturated LCFA decreases in the direction 14:0-12:0-16:0 (ref.[26,27]). In contrast, some studies have shown that stearic acid (18:0) decreases LDL- and increases HDL-cholesterol, which may suggest that it has

Table 2. Average percentage of individual fatty acids in oils and fats rich in saturated fatty acids.

Fatty acid	Coconut	Palm kernel	Palm fruit pulp	Cocoa	Shea	Illipe	Lard	Butter
4:0	–	–	–	–	–	–	–	3.2
6:0	0.5		–	–	–	–	–	2.0
8:0	7.8	3.3	–	–	–	–	–	1.2
10:0	6.7	3.4	–	–	–	–	–	2.5
12:0	47.5	48.2	0.1	–	–	–	–	2.6
14:0	18.1	16.2	1.0	–	–	–	–	7.4
16:0	8.8	8.4	44.3	25.0	4.3	17.0	26.5	21.7
16:1n-7	–	–	–	–	–	–	3.0	–
18:0	2.6	2.5	4.6	38.0	38.1	45.0	13.0	10.0
18:1n-9	6.2	15.3	38.7	32.0	48.6	35.0	45.5	17.0
18:2n-6	1.6	2.3	10.5	3.0	7.1	1.0	8	2.2
18:3n-6	–	–	0.3	–	0.3	–	–	–
18:3n-3	–	–	–	–	–	–	–	0.3
20:0	–	–	–	–	1.2	–	–	0.1
SFA	92.0	82.0	50.0	63.0	43.6	62.0	40.5	50.7
MFA	6.2	15.3	38.7	32.0	48.6	35.0	48.5	17.0
PUFA n-6	1.6	2.3	10.8	3.0	7.4	1.0	8.0	2.2
PUFA n-3	–	–	–	–	–	–	–	0.3
TOTAL	99.8	99.6	99.5	98.0	99.6	98.0	97.0	70.2

SFA, saturated fatty acids; MFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

Source: U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference[22]

Note: Percentages may not add up too 100% due to some FA traces not listed; where % FA varied average values were used.

antiatherogenic properties[28,29]. Also, it has been shown that stearic acid did not increase postprandial inflammation[30]. However, it has been suggested that stearic acid has the highest prothrombotic potential compared to other saturated LCFA, although this is under debate[31]. The significance of the increased content of saturated fatty acids in membrane lipid rafts is not yet quite clear[32].

The atherogenic and thrombogenic potentials of FA can be expressed as atherogenic (AI) and thrombogenic (TI) indices[33]:

$AI = [4 \times 14:0 + 16:0 \times [n\text{-}6PUFA + n\text{-}3PUFA + MFA]^{-1}$;

$TI = [14:0 + 16:0 + 18:0] \times [0.5 \times MFA + 0.5 \times n\text{-}6PUFA + 3 \times n\text{-}3PUFA + n\text{-}3PUFA / n\text{-}6PUFA]^{-1}$

Very long chain (saturated) fatty acids (VLCFA) include arachidic (20:0), behenic (22:0), lignoceric (24:0), cerotic (26:0), montanic (28:0) and melissic (30:0) acids, which appear in significant concentrations in inherited metabolic diseases, e.g. Zellweger syndrome, X-linked adrenoleucodystrophy, Refsum's disease, Menkes' disease[34]. Individuals suffering from these disorders may benefit from administration of n-3 PUFA.

Unsaturated fatty acids

Monounsaturated fatty acids in cis configuration

The *cis* term is used when the two hydrogens at the double bond are on the same side of the molecule as each other. This leads to a different orientation of the adjoining carbons across the double bond resulting in the molecule having a curved structure. Main representatives in this group are oleic (18:1n-9*c*), vaccenic[35] (18:1n-7*c*) and palmitoleic (16:1n-7*c*) acids. Other MFA synthesized endogenously – myristoleic (14:1n-5*c*), gondoic (20:1n-9*c*), erucic (22:1n-9*c*) and nervonic (24:1n-9*c*) acids – are present only in minor concentrations. Monounsaturated FA not synthesized *de novo* include gadoleic (20:1n-11*c*) and cetoleic (22:1n-11*c*) acids. Erucic acid, substantial part of noncultivated rapeseed oil *(Brassica napus)*, is suggested to be cardiotoxic[36]. Experiments with erucic acid on rats have shown increased deposition of fat which is followed by the formation of myocardial lesions[37,38]. In human studies, dietary erucic acid was found to reduce the number of platelets and their membrane anisotropy[39]. These findings have initiated the cultivation of rapeseed oil with low content in erucic acid[40].

Oleic acid (18:1n-9*c*) has antiatherogenic and antithrombotic properties as it has been shown to increase the HDL-/LDL-cholesterol ratio and decrease aggregation of thrombocytes. Incorporation of oleic acid into cholesteryl esters, triacylglycerols and phospholipids of lipoprotein particles increases their resistance to lipoperoxidation. Replacement of SFA by oleic acid (about 7% of total energy intake (TEI), when total fat is maximum 30% of TEI) decreased concentration of triacylglycerols (TAG), LDL-cholesterol, and increased concentration of HDL-cholesterol, and regulated insulin sensitivity[41]. Olive oil has also been tested experimentally for its protective role in carcinogenesis[42] and for its effect on the inflammatory response[43]. Olive oil *(Olea europaea)* is the main dietary source of oleic acid, however, it can also be found in canola oil (Canadian oil, low acid; cultivated *Brassica campestris, Brassica napus, or Brassica juncea*), hybrid safflower oil *(Carthamus/Tinctorius)*, cultivated rapeseed oil *(Brassica campestris)*, peanut oil *(Arachis hypogaea)*, hazelnut oil *(Corylus americana)*, sweet almond oil *(Prunus*

Table 3. Average percentage of individual fatty acids in oils rich in monounsaturated fatty acids.

Fatty acid	Olive	Rape seed*	Rape seed**	Canola	Almond	Avocado fruit pulp	Peanut	Hazelnut
12:0	–	–	–	–	–	–	–	–
14:0	–	–	–	–	–	–	–	–
16:0	11.0	2.7	4.0	4.0	7	10.6	9.5	5.2
18:0	2.0	1.0	7.0	2.0	2	0.7	2.2	2
18:1n-9	71.0	11	52.0	62.0	69	67.9	44.8	77.8
18:2n-6	10.0	13.8	30.0	18.6	17	12.5	32	10.1
18:3n-6	–	–	–	–	–	–	–	–
18:3n-3	1.0	6.2	7.0	9.0	–	0.9	–	–
20:0	–	–	–	–	–	–	–	–
SFA	13.0	3.7	11.0	6.0	9.0	11.3	11.7	7.2
MFA	71.0	52.0*	52.0	62.0	69	67.9	44.8	77.8
PUFA n-6	10.0	13.8	30.0	18.6	17	12.5	32	10.1
PUFA n-3	1.0	6.2	7.0	9.0	–	0.9	–	–
TOTAL	95.0	75.7	100	95.6	95.0	92.6	88.5	95.1

SFA, saturated fatty acids; MFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

Source: U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference[22]

Note: Percentages may not add up too 100% due to some FA traces not listed; where % FA varied average values were used.

*Non-cultivated rape seed (mustard seed) oil (*Brassica napus*); contains about 41% erucic acid (22:1n-9)

**Cultivated rape seed oil (*Brassica campestris*)

amygdalus dulcis) and avocado oil *(Persea gratissima)*. Lower content of oleic acid (40-50%) is found in palm oil *(Elaeis guineensis)*, rice bran oil *(Oryza sativa)*, corn oil *(Zea mays)* and sesame oil *(Sesamum indicum)*. High content of hydroxyoctadecenoic acid, 18:1-OH, is found in castor oil *(Ricinus communis)*. A number of oil producing plants have been genetically modified to have an increased content of oleic acid[21]. (Table 3) shows the percentage of individual FA for oils rich in MFA (ref.[22]).

Monounsaturated fatty acids in trans configuration

These are molecules that have one double bond in which the hydrogens are on the opposite side to one another resulting in a non-curved structure and thus, to physicochemical properties close to those of SFA, affecting cell membrane properties similarly to SFA. Main *trans* MFA are elaidic (18:1n-9*t*) and trans-vaccenic (18:1n-7*t*) acids. *Trans* FA are of exogenous origin. Their atherogenic effect[44] is assumed to be greater than that of SFA. Also, *trans* MFA are twice as active in raising LDL-cholesterol and decreasing HDL-cholesterol than SFA. The different effects of *trans* FA and SFA on human metabolism are still being studied[45,46]. Main dietary sources of *trans* FA are hardenings or shortenings (such as margarines from hydrogenated plant oils using an improper catalyst) and butter (*trans* FA in milk originate from the gastrointestinal tract of ruminants). Hydrogenated fats are used mainly in pastry and the "fast-food" industry[47]. However, advances in technology used by the food processing industry have now reduced the production of *trans* fatty acids.

Polyunsaturated fatty acids

Polyunsaturated FA contain two or more double bonds in the molecule. In general, the more double bonds there in the fatty acid, the more prone they are to lipoperoxidation[48]. Endogenous PUFA mostly belong to the n-9 family, synthesized in increased amounts when there is a lack of EFA (LA, ALA) (ref[49]). These FA are termed essential because they cannot be synthesized *de novo* in humans and they are considered parental FA for the n-3 and n-6 PUFA families[50]. Essential FA exert beneficial antiatherogenic as well as antithrombotic effects. This is a result of their impact on lipoprotein concentration, membrane fluidity, function of membrane enzymes and receptors, modulation of eicosanoid production, regulation of blood pressure and metabolism of minerals[51].

n-3 Polyunsaturated fatty acids

In the n-3 PUFA family the parent fatty acid is ALA. Its main metabolic products are EPA (timnodonic acid) and DHA (clupadonic acid), and to a lesser extent docosapentaenoic acid (DPA, 22:5n-3). These metabolites are termed LC n-3 PUFA. Dietary sources of ALA are seeds and leaves of some plants – soybeans *(Glycine max)*, linseed *(Linum usitatissimum)*, blackcurrant seeds *(Ribes nigrum)* and borage leaves *(Borago officinalis)*, as well as their oils[21]. Its metabolites, EPA and DHA, can be taken from the diet through oily fish which are excellent sources containing approximately 2 g of EPA plus DHA per portion of fish (150 g). Among other fish, oily fish include sardines, mackerel, trout, salmon, fresh (not canned) tuna, and herring. Other sources of LC n-3 PUFA include fish oils, the liver of non-oily fish (such as cod and haddock), and the flesh of some white non-oily fish but in much lower amounts[5]. Conversion of ALA into 20-22 CN metabolites is much more effective in marine animals than in human species. Thus, EPA and DHA are in humans mostly of exogenous source[52,53]. The high content of DHA in nervous tissues and the retina is extremely important. Also, the unique properties of this FA play a role in the mechanism of signal transduction, probably by regulation of G-protein signaling[54,55].

As ligands of peroxisome proliferator-activated receptor (PPAR-α), n-3 PUFA have a number of pleiotropic effects on lipid and energy metabolism. They are thought to activate PPAR-α and decrease lipogenesis and very low density lipoprotein (VLDL) secretion[56] by suppression of sterol response element binding protein (SREBP-1). Also, other potential effects of n-3 PUFA are to increase the activity of lipoprotein lipase, decrease concentrations of apo C-III and potentiate reverse cholesterol transport[57,58]. In the form of high concentration oil supplements, n-3 PUFA are thought to induce expression of uncoupling proteins (UCP) and increase density of mitochondria by β-oxidation of FA in muscles[59-62]. The immunomodulative properties of LC n-3 PUFA are connected with their ability to suppress the activation of T-lymphocytes[63]. This activation demands acylated proteins, localized in cell membrane lipid rafts, which leave the raft after increased exposure to (and thus content of) LC n-3 PUFA (ref.[57,64]).

n-6 Polyunsaturated fatty acids

In the n-6 PUFA family the parent fatty acid is LA. Its metabolic products are γ-linolenic (GLA; 18:3n-6), dihomo-γ-linolenic (DHGLA; 20:3n-6) and arachidonic acids, and in minor amounts also adrenic (22:4n-6) and docosapentaenoic (22:5n-6) acids. High concentrations of n-6 PUFA (>60%) are found in soybean oil *(Glycine soja)*, sunflower seed oil *(Helianthus annuus)*, safflower oil *(Carthamus tinctorius)*, evening primrose oil *(Oenothera biennis)*, grape seed oil *(Vitis vinifera)*, poppy seed oil *(Populus nigra)*, borage seed oil *(Borago officinalis)*, blackcurrant seed oil *(Ribes nigrum),* and lower concentrations (40-50%) in wheat germ oil *(Triticum vulgare)*, corn oil *(Zea mays)*, walnut oil *(Juglans regia)*, cottonseed oil *(Gossypium)* and sesame oil *(Sesamum indicum)*, as well as the seeds of some of these plants[21]. (Table 4) shows the percentage of individual FA for oils rich in PUFA (ref.[22]).

Polyunsaturated FA of the n-6 family are activators of PPAR (γ > α). Their metabolic effects include affecting cytokine production[65], increased cholesterol synthesis, increased activity of LDL-receptors resulting from increased mRNA for LDL-receptors, increased activity of cholesterol 7α-hydroxylase (Cyp 7A1) and decreased conversion of VLDL to LDL (ref.[66]). Supplementation with n-6 PUFA leads to decreased total, LDL- and HDL-cholesterol and increased sensitivity of LDL particles to lipoperoxidation. This effect is a result of the "up-regulation" of LDL-receptors and the activity of Cyp 7A1. As ligands of PPAR-γ, n-6 PUFA increase insulin

Table 4. Average percentage of individual fatty acids in oils rich in polyunsaturated fatty acids.

Fatty acid	Sunflower seed	Safflower seed	Pumpkin seed	Sesame seed	Corn	Soya bean	Walnut	Flaxseed (linseed)	Wheat germ	Hemp seed	Evening primrose	Borage seed
12:0	–	–	–	–	–	–	–	–	–	–	–	–
14:0	–	–	–	–	–	–	–	–	–	–	–	–
16:0	7.0	7.0	9.0	9.0	11.0	11.0	7.0	5.0	16.0	6.0	6.0	10.3
18:0	5.0	2.0		4.0	2.0	4.0	2.0	4.0	0.5	2.0	2.0	3.6
18:1n-9	19.0	13.0	33.5	42.0	28.0	22.5	22.2	21.0	14.6	12.0	7.3	16.0
18:2n-6	68.0	78.0	50.5	45.0	58.0	50.0	52.0	16.0	55.0	58.0	74.0	37.0
18:3n-6	–	–	–	–	–	–	–	–	–	2.0	9.0	23.3
18:3n-3	1.0		7.0		1.0	7.0	10.0	53.0	6.9	20.0	–	–
20:0	–	–	–	–	–	–	–	–	–	–	–	–
SFA	12.0	9.0	9.0	13.0	13.0	15.0	9.0	9.0	16.5	8.0	8.0	13.9
MFA	19.0	13.0	33.5	42.0	28.0	22.5	22.2	21.0	14.6	12.0	7.3	16.0
PUFA n-6	68.0	78.0	50.5	45.0	58.0	50.0	52.0	16.0	55.0	60.0	83.0	60.3
PUFA n-3	1.0	–	7.0	–	1.0	7.0	10.0	53.0	6.9	20.0	–	–
TOTAL	100	100	100	100	100	94.5	93.2	99.0	93.0	100	98.3	90.2

SFA, saturated fatty acids; MFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

Source: U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference[22]

Note: Percentages may not add up too 100% due to some FA traces not listed; where % FA varied average values were used.

sensitivity, change the distribution of fat and the size of adipocytes[67,68]. Importantly, AA is a major precursor of eicosanoids which are potent signalling molecules both inside and outside the cell[69].

Conjugated fatty acids

As mentioned above, most PUFA are characterized by pentadiene configuration (i.e. methylene interruption) of the double bonds, with the exception of conjugated FA. Most abundant FA with a conjugated system of double bonds are isomers of LA (conjugated linoleic acid; CLA). These FA appear in red meat and dairy products; cows grazing pasture have a several times higher content of CLA in meat and milk fat than cows fed typical dairy diets. There are 28 possible isomers of CLA, which differ in the position (e.g. 7 and 9, 8 and 10, 9 and 11, 10 and 12, 11 and 13 – counting form the carboxyl group) and configuration (*cis* or *trans*) of double bonds. The type most commonly found in meat and dairy products is rumenic acid (18:2Δ9*c*,11*t*). Also, the isomer 18:2Δ10*t*,12*c* has important metabolic effects[70]. Compared to previous generations, the current human population consumes less CLA in their diet preferring white to read meat and very low fat dairy products. Thus, CLA, containing equal amounts of 18:2Δ9*c*,11*t* and 18:2Δ10*t*,12*c* isomers, is frequently used as special dietary supplement.

The origin of conjugated FA is similar as that of *trans* FA. However, their biological effect is mostly positive[71,72]. Conjugated FA are shown to have both *in vitro* and *in vivo* antioxidant properties (probably due to the production of FA with furan structures) and anticarcinogenic effects. Paradoxically, an anti-cancer effect of beef products was found in a study which included fried meat[73,74]. The isomer 18:2Δ10*t*,12*c* inhibited fat accumulation *in vivo*, while the isomer 18:2Δ9*c*,11*t* improved parameters of lipid metabolism affecting expression of SREBP-1c and liver X receptor α (ref.[75,76]). However, conflicting results have been obtained from animal and human studies[77]. Further studies focusing on the effects of different CLA isomers would help to resolve some of these issues.

FATTY ACIDS: THE MAIN CONSTITUTIONAL COMPONENT OF LIPID CLASSES

Simple lipids are esters of fatty acids with alcohols – cholesterol, glycerol and sphingosine. With respect to the main component we differentiate the following individual lipid classes[78]:

- fatty alcohol – wax esters
- cholesterol – cholesteryl esters
- glycerol – triacylglycerols, diacylglycerols, monoacylglycerols
- alkenylglycerol – ether lipids, glycerylether diesters
- phosphoglycerol – glycerophospholipids
- glycerylhexoside – glyceroglycolipids
- sphingosine – ceramides
- phosphosphingosine – sphingophospholipids
- glycosphingosine – glycosphingolipids

The structural formulae of these lipids are shown in (Fig. 5). The pathophysiological role of fatty acids is derived from that of individual lipids.

Lipids circulate in the bloodstream assembled along with proteins into large, soluble structures termed lipoproteins. Circulating lipids (in the form of lipoproteins) consist of cholesteryl esters (CE; 60-70% of total cholesterol) and TAG situated in the non-polar core of lipoproteins, and phospholipids (mainly phosphatidylcholine and sphingomyelin) and free cholesterol in the polar envelope. Non-esterified fatty acids (NEFA; product of lipolysis and source for lipid synthesis) are bound to plasma albumin[79].

Cholesteryl esters represent the transport and storage form of cholesterol in the organism; at the temperature of

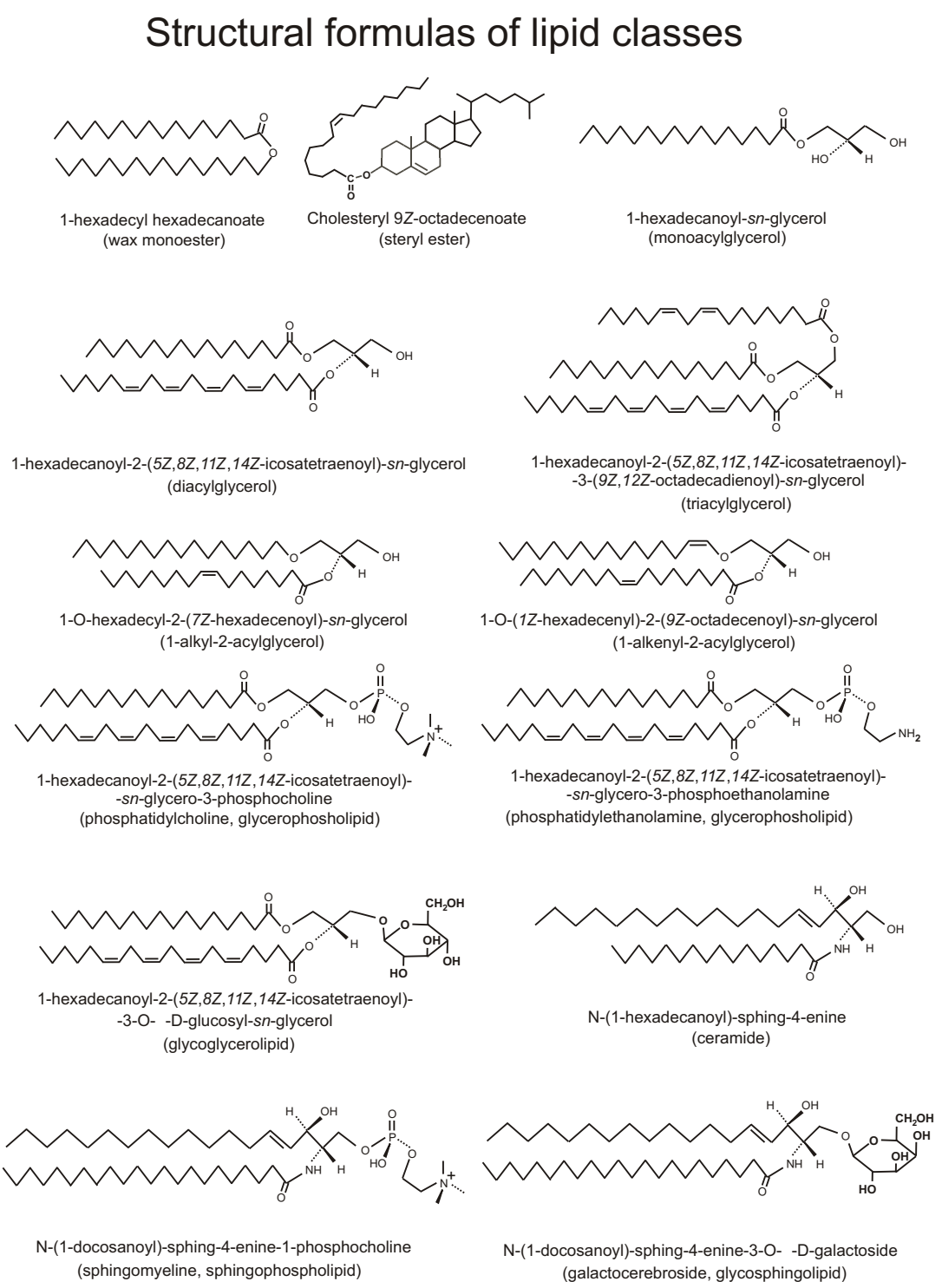

Fig. 5. Structural formulas of lipid classes.

the interior media they form liquid crystals. Cholesteryl esters in lipoproteins contain predominately linoleic acid (approx. 50%), followed by oleic (18%), palmitic (15%) and arachidonic (7%) acids[80]. Intracellularly stored cholesteryl esters contain predominately oleic and palmitoleic acids. In humans, cholesteryl esters are synthesized intravascularly through a reaction catalyzed by the enzyme lecithin:cholesterol acyltransferase (LCAT). This enzyme transfers LC PUFA from C2 carbon atom of lecithin to 3-β-OH group of cholesterol, thus forming cholesteryl ester and lysolecithin. Cholesteryl esters form a substantial part of the LDL and HDL core. Moreover they are a main component of lipid inclusion of macrophages and foam cells localized in atherosclerotic lesions.

Triacylglycerols are the main core components of VLDL and chylomicrons, as well as lipid inclusions of adipocytes. The most abundant FA in TAG is oleic acid (40%) followed by palmitic (22%) and linoleic (20%) acids[81]. A similar content of FA was also found in adipose tissue: oleic acid – 50%, palmitic acid – 22% and linoleic acid – 12%, since TAG are formed, partially, by FA re-

leased from adipose tissue which are representative of its content.

Phospholipids (PL) are along with cholesterol the main lipids of the lipoprotein envelope and represent polar (hydrophilic) lipids. Molecules of PL are freely exchanged not only between individual lipoproteins, but also between the lipoprotein envelope and plasma membranes. This process is facilitated by specific transfer proteins. The composition and content of individual PL in the lipoprotein envelope is similar for the main lipoprotein classes, with the exception of chylomicrons. The most buoyant phospholipid class is phosphatidylcholine (PC, lecithin), whose content in plasma reaches 60–70%, followed by sphingomyelin (SM, 10–20%), lysolecithin (LPC, 3–5%) and phosphatidylethanolamine (PE, 2–6%). Minor phospholipids in plasma are phosphatidylserine (PS, 1–2%) and phosphatidylinositol (PI, 1–2 %). In plasma PC the dominating FA is palmitic acid (30%), followed by linoleic (25%), stearic (14%), oleic (11%) and arachidonic (11%) acids[80]. Plasma phospholipid FA content reflects in approximation that of cell membrane phospholipids and it thus may be characterized as the "functional" lipid pool. The FA profile of the main plasma lipid classes of healthy individuals is shown in (Table 5) (ref.[82]).

Membrane lipids, which ensure fluidity and functionality, consist of PC, PE, SM and minor phospholipids (PS, PI, LPC and lysophosphatidylethanolamine-LPE). The fatty acid content in individual lipid classes influences substantially the membrane fluidity[12]. The two most abundant phospholipids in cell membranes are PC and PE, both predominately with palmitic acid and rich in PUFA. Usually PE has a higher content of PUFA. The head groups of phospholipids affect the membrane biochemical properties; some organelles may have much more PE than the cell membrane which is higher in SM. Moreover, the content of individual phospholipids in membranes and their fatty acid composition are species as well as tissue specific; liver cell membranes are high in PC, brain cell membranes are high in gangliosides, but bacterial membranes contain mostly PE.

Non-esterified FA are present in plasma under physiological conditions only in minor concentrations (0.5-1.0 mmol/l), their profile is similar to that of TAG and of adipose tissue, since they are released during TAG hydrolysis

Table 5. Fatty acid composition of cholesteryl esters, triacylglycerols, and phosphatidylcholine in plasma of healthy individuals.

Fatty acid	PC	CE	TAG
14:0	0.28 ± 0.13	0.73 ± 0.06	1.97 ± 1.00
16:0	29.10 ± 2.50	10.24 ± 1.61	25.44 ± 3.76
16:1n-7	0.56 ± 0.23	2.80 ± 1.25	3.49 ± 1.10
18:0	13.80 ± 1.33	0.82 ± 0.43	3.60 ± 1.16
18:1n-9	10.16 ± 1.78	18.33 ± 2.99	39.15 ± 4.66
18:1n-7	1.78 ± 0.45	1.25 ± 0.30	2.78 ± 0.59
18:2n-6	24.24 ± 3.22	56.08 ± 5.55	17.68 ± 4.58
18:3n-6	0.09 ± 0.06	0.81 ± 0.36	0.34 ± 0.19
18:3n-3	0.24 ± 0.10	0.66 ± 0.30	1.19 ± 0.52
20:0	0.06 ± 0.03	0.03 ± 0.03	0.07 ± 0.05
20:1n-9	0.15 ± 0.04	0.04 ± 0.05	0.45 ± 0.03
20:3n-6	2.94 ± 0.66	0.66 ± 0.18	0.31 ± 0.13
20:4n-6	10.63 ± 1.94	6.14 ± 1.94	1.25 ± 0.46
20:5n-3	0.91 ± 0.42	0.52 ± 0.39	0.23 ± 0.14
22:5n-3	0.92 ± 0.20	0.06 ± 0.07	0.34 ± 0.12
22:6n-3	3.21 ± 0.82	0.31 ± 0.17	0.55 ± 0.37
Σ SFA	43.06 ± 3.34	11.85 ± 1.98	31.24 ± 4.72
Σ MFA	12.74 ± 2.13	22.81 ± 3.74	46.14 ± 4.90
Σ n-6 PUFA	38.71 ± 2.98	63.79 ± 5.18	20.04 ± 4.85
Σ n-3 PUFA	5.27 ± 1.20	1.55 ± 0.69	2.31 ± 0.84

Σ, sum; SFA, saturated fatty acids; MFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; PC, phosphatidylcholine; CE, cholesteryl esters; TAG, triacylglycerols

Note: Fatty acid composition is expressed as a molar percentage of total fatty acids in each lipid class.

Source: Zak *et al.* (2007) (ref.[82])

in adipocytes[83]. Non-esterified FA can be oxidized, re-esterified, or metabolized (elongation and desaturation). During physical activity they are oxidized in muscles, whereas during resting periods they are oxidized in the liver and myocardium. Most NEFA are re-esterified in the liver to TAG and phospholipids. A limiting step for the mobilization of NEFA from adipose tissue to plasma is the activity of the responsible enzyme, hormone-sensitive lipase. An increased concentration of NEFA is toxic, affecting plasma membranes and resulting in arrhythmias, thrombogenesis etc. Together with increased glucose concentration, NEFA may accelerate the formation of the reactive oxygen and nitrogen substances (RONS), as well as initiation and development of endothelial dysfunction.

Lastly, some partial esters – monoacylglycerols (MG), diacylglycerols (DG), LPC and ceramides – are intermediate products of the synthesis or degradation of other simple as well as complex lipids. Their content in plasma is very low; some of them as second messengers (DG, inositoltriphosphate – IP_3) can regulate a wide range of cell activities. The fatty acid composition in these minor lipids reflects that of parent lipid classes.

CONCLUSION

The first part of this review on FA as biocompounds presented their classification and dietary sources, as well as the complex metabolic pathways that FA are involved in. Fatty acids in the form of phospholipids are major components of cell membranes, affecting their structure and fluidity. The degree of FA unsaturation and chain length determine the physicochemical properties of FA, and thus the functionality of cells and tissues as well as lipid mediators produced. Fatty acids can be desaturated endogenously up to the Δ9 position due to lack of certain enzymes in humans. For this reason LA and ALA must be taken from the diet and are termed essential. Further elongation and desaturation of these fatty acids results in LC PUFA, including EPA, DHA, and AA. However this process is not very efficient in humans and, thus, these FA may be termed conditionally essential. Dietary FA (in the form of TAG) are a major source of energy and determine the fatty acid composition of cell membranes and tissues. The type of fat consumed depends on the dietary sources, typically including saturated fat from animal sources and tropical plant oils (coconut, palm), and polyunsaturated fat from vegetable oils (such as olive oil for MFA; sunflower oil and soybean oil for n-6 PUFA; flaxseed oil for n-3 PUFA) and marine sources (algae and fish oils for LC n-3 PUFA). Saturated FA have been connected to adverse health effects, whereas unsaturated FA are thought to be more beneficial for human health. Specifically MFA and n-3 PUFA are characteristic for their protective role, as opposed to n-6 PUFA, with a special focus on LC n-3 PUFA (EPA, and DHA). In addition, *trans* FA have been shown to have negative effects on health, whereas conjugated FA (such as CLA) have been shown to have beneficial effects which should be further investigated. Lastly, a major role of fatty acids is being the main constitutional components of lipid classes, including TAG, PL, CE and NEFA. The second part of this review to follow will focus on the role of FA in health and disease, including the current literature on FA physiological roles and practical implications for specific conditions.

ABBREVIATIONS

AA, Arachidonic acid; AI, Atherogenic index; ALA, α-Linolenic acid; CE, Cholesteryl ester/s; CHD, Coronary heart disease; CLA, Conjugated linoleic acid; CN, Carbon number; DHA, Docosahexaenoic acid; DHGLA, Dihomo-γ-linolenic acid; DG, Diacylglycerol/s; DPA, Docosapentaenoic acid; EFA, Essential fatty acid/s; EPA, Eicosapentaenoic acid; FA, Fatty acid/s; GLA, γ-Linolenic acid; HDL, High density lipoprotein; IP_3, Inositoltriphosphate; LA, Linoleic acid; LCAT, Lecithin:cholesterol acyltransferase; LCFA, Long chain fatty acid/s; LDL, Low density lipoprotein; LPC, Lysophosphatidylcholine/Lysolecithin; LPE, Lysophosphatidylethanolamine; MCFA, Medium chain fatty acid/s; MCT, Medium chain triacyglycerol/s; MFA, Monounsaturated fatty acid/s; MG, Monoacylglycerol/s; NEFA, Non-esterified fatty acid/s; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; PL, Phospholipid/s; PPAR, Peroxisome proliferator-activated receptor/s; PS, Phosphatidylserine; PUFA, Polyunsaturated fatty acid/s; REE, Resting energy expenditure; RONS, Reactive oxygen and nitrogen species; SCFA, Short chain fatty acid/s; SFA, Saturated fatty acid/s; SM, Sphingomyelin; SREBP, Sterol response element binding protein; TAG, Triacylglycerol/s; TEI, Total energy intake; TI, Thrombogenic index; UCP, Uncoupling protein; VLCFA, Very long chain fatty acid/s; VLDL, Very low density lipoprotein.

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