Chemical Diversity of Lipids

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Lipids represent some of the most complex biological molecules and their diversity is crucial for their cellular functions. The wide range of chemical and physical properties of different lipids determines a variety of roles for these compounds in biological processes. According to their structures, lipids can be divided into two main groups: the non-polar lipids (acylglycerols, sterols, non-esterified (free) fatty acids, hydrocarbons, alcohols, wax and steryl esters) and polar lipids (phosphoglycerides, glycosylglycerides and sphingolipids). Triacylglycerols act as energy stores and metabolic fuels. Polar lipids and sterols are important structural components of cell membranes where they may have many diverse functions. Arranged as bilayers, they establish permeability barriers for cells and organelles and provide a microenvironment for membrane-associated proteins as well as directly participating in metabolism and a multitude of membrane fusion events [1]. Waxes as surface coverings are integral to water balance and also protect organisms from noxious environmental conditions. In addition to a structural role, lipids serve as important intermediates in cell signaling pathways (e.g. sphingolipids, inositol lipids, phosphatidic acid, lysophospholipids, oxidative products) and play a role in mediating cellular responses to the environment [2]. In this chapter we will summarize our knowledge on structural diversity of lipids providing information on the various lipid classes and also fatty acids and lipid mediators that occur naturally.

1.Glycerolipids

1.1. Acylglycerols (glycerides)

The basic structure of glycerolipids is a glycerol (propane-1,2,3-triol) backbone to which are esterified the hydrophobic acyl groups (fatty acids). Monoacylglycerols and diacylglycerols are fatty acid mono- and diesters of glycerol, respectively. These partial glycerides are important intermediates in metabolism. Triacylglycerols are fatty acid triesters of glycerol. They are accumulated as storage products. Triacylglycerols are the major compounds of most natural fats and oils.

1.2. Glycerol ethers

Alkyl ethers and alk-1-enyl ethers (or plasmalogens) are two general types of glycerol ethers. Mono- and dialkyl ethers have been reported to occur naturally. Examples include batyl alcohol (*sn*-1-*O*-octadecylglycerol) and chimyl alcohol (*sn*-3-*O*-tetramethylhexadecylglycerol) as monoalkyl ethers, and diphytanylglycerol (*sn*-2,3-di-*O*-teramethylhexadecylglycerol) as a dialkyl ether. Although trialkyl ethers have not yet been found in Nature, they have been synthesized with various combinations of saturated and unsaturated chains. In addition, mono- and diacyl derivatives of alkyl ethers are reported from some natural sources.

Similarly to alkyl forms, the mono- and dialk-1-enyl ethers of glycerol have been identified in natural samples. Acylated (mono- and diacyl derivatives) alk-1-enyl ethers (or neutral plasmalogens) have been also reported [2].

1.3. Glycerophospholipids

The structure of glycerophospholipids is characterized by a 1,2-diacyl-3-phospho-sn-glycerol, or phosphatidyl moiety, and a variable headgroup linked to the phosphate. Major phosphoglycerides found in Nature are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidylinositol (PI) and diphosphatidylglycerol (DPG) (or cardiolipin). The simplest phosphoglyceride, phosphatidic acid is a minor compound in most tissues.

Phosphatidylcholine, the trivial name “lecithin”, is a neutral or zwitterionic phospholipid (Fig. 1). It is the most abundant phospholipid in animal tissues and the main component of non-chloroplast membranes in plants amounting to about 50% of the total lipids. In bacterial membranes, PC is found in small quantities. PC is a useful bilayer component, having a cylindrical shape and a net neutral charge [1].

Phosphatidylethanolamine (trivial name “cephalin”) also has a net neutral charge (Fig. 1). PE is widespread and usually the second most abundant phospholipid in animal and plant membranes. It is also the main lipid component of microbial membranes. In animal tissues, phosphatidylethanolamine may exist in diacyl, alkylacyl and alkenylacyl forms. Moreover, animal phosphatidylethanolamine usually contains higher levels of arachidonic and docosahexaenoic acids in comparison to the other zwitterionic phospholipid, phosphatidylcholine. The partly methylated derivatives of PE (phosphatidyl-*N*-monomethyl-ethanolamine, phosphatidyl-*N*-dimethyl-ethanolamine) are found in small amounts in many organisms. These derivatives are metabolic intermediates in the conversion of phosphatidylethanolamine into phosphatidylcholine. In some tissues, *N*-acylated derivatives of PE may be present in significant amounts. These compounds are involved into the endocannabinoid signalling system through release of N-acetylethanolamines following phospholipase D action [3].

Phosphatidylglycerol is negatively charged (Fig. 1). It is the major phosphoglyceride in photosynthetic tissues and many bacteria. In plants, phosphatidylglycerol is the only phospholipid present in significant quantities in the thylakoid membranes where it can comprise 10% of the total lipids with a high proportion (up to 70%) in the outer monolayer. An unusual fatty acid, Δ3-*trans*-hexadecenoic acid (16:1(3t)), is found in eukaryotic photosynthetic organisms, specially esterifying the *sn*-2 position of PG [4]. It is interesting to note that both the *trans*-configuration of a double bond and its Δ3 position are very unusual for naturally-occurring fatty acids. PG-16:1(3t) is thought to play an essential role in photosynthetic membranes [5].

Although phosphatidylglycerol is only a minor phospholipid in animal tissues (1-2% of total phospholipids), it can be the second abundant phospholipid in lung surfactant at up to 11% of the total [6].

For bacteria, phosphatidylglycerol is present in almost all types. In *Escherichia coli*, for example, phosphatidylglycerol accounts for 20% of its membrane lipids. The diacyl form of PG is more common in many bacteria, but some may contain the alkylacyl- and alkenylacyl derivatives as predominant forms. A number of prokaryotic species, including *Salmonella typhimurium* and *Escherichia coli*, and parasitic protozoa, such as *Trichomonas vaginalis* and *T. foetus*, have been found to contain acylphosphatidylglycerol (1,2-diacyl-*sn*-glycero-3-phospho-(3’-acyl)-1’-*sn*-glycerol) in appreciable amounts [7]. For example, *Corynebacterium amycolatum* contained about 30% of this lipid with oleate as a dominant fatty acid on the head group of glycerol [8]. A fully acylated phosphatidylglycerol (*bis*-phosphatidic acid or phosphatidyldiacylglycerol) and its plasmalogen analogues have been also identified in a marine bacterium MB 45. In some bacteria, an amino acid (lysine, ornithine, arginine, or alanine) may be attached to the 3’-hydroxyl of the base glycerol to form an *O*-aminoacylphosphatidylglycerol. Two other unusual derivatives of phosphatidylglycerol have been isolated from the primitive organisms, the Haloarchaea. They were identified as phosphatidylglycerol sulfate and phosphatidylglycerol phosphate methyl ester.

Diphosphatidylglycerol (trivial name cardiolipin) has a unique dimeric structure with four acyl groups and two negative charges (Fig. 1). It is common in bacteria, and it can be found in the inner mitochondrial membranes of eukaryotes, i.e. those membranes which generate an electrochemical potential for substrate transport and ATP synthesis. Its metabolism and function in mitochondria has been reviewed [9].

Phosphatidylserine also has a net negative charge. It is a widespread but minor lipid in eukaryotes, accounting usually for less than 10% of the total phospholipids. Its greatest concentration has been noted for myelin from brain tissue. Phosphatidylserine is concentrated in the inner monolayer of the plasma membrane and other cellular membranes (Fig.1). Its flippase-mediated appearance on the exoplasmic face is an early indication of programmed cell death, apoptosis [1].

Phosphatidylinositol is another widespread and minor lipid with a negative charge. It is an important lipid, both as a membrane constituent and, in various phosphorylated forms as key molecules in signalling processes in eukaryotes (Fig.1). The phosphatidylinositol phosphates are found with phosphates attached at any position of the inositol ring. However, PI-4-phosphate, PI-4,5-*bis* phosphate and their 3-phosphates are the most important.

1.4. The acyl structure diversity

Monoacyl derivatives of phosphoglycerides, lyso-derivatives, are present in small amounts in most tissues, but their occurrence in large levels indicates usually the lipid degradations before or during lipid extraction. Only cereal grains contain lysophosphatidylcholine and lysophosphatidylethanolamine as the major phospholipids. Moreover, lysophospholipids, especially lysophosphatidic acid, are important signalling molecules [10].

Plasmalogens are a class of phospholipids that are present in many organisms, but are rare in plants [11]. Plasmalogens are monoacyl monoalk-1-enyl ether forms of phospholipids. In addition to an ether bond, plasmalogens contain a double bond in cis-(*Z*) configuration adjacent to the ether oxygen atom. In chemical nomenclature, this linkage is known as a vinyl-ether linkage. The most common head groups of plasmalogens are choline, ethanolamine and serine. The *sn*-1 position in plasmalogens usually contain saturated and monoenoic fatty acids, e.g. C16:0, C18:0 and C18:1), whereas omega-3 and omega-6 PUFAs are the major fatty acids that enrich the *sn*-2 position of these lipids.

Although plasmalogens are constitutions of all mammalian tissues, they are especially abundant in brain, heart, lung, skeletal muscle, mammalian spermatozoa, kidney as well as inflammatory cells. In human brain, plasmalogen PE species accounted for about 60% of PE; 26% of plasmalogen form of PC has been found in human heart [11]. Human plasma phospholipids have been reported to contain about 5% plasmalogens [12].

Plasmalogens are structural components of membranes being a reservoir for signaling molecules and/or antioxidative agents; also, they play an important role in shaping the biophysical properties of the cell membranes. Plasmalogens are important in modulating the stability of lipid rafts. Recent studies indicate the special role of plasmalogens in vesicle fission and fusion processes in addition to their role in free radical scavenging [12]. The amount of plasmalogens is diminished in several neurological diseases, and their reduced levels are also a normal process of aging [12, 13, 14].

Platelet-activating factor or 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine is an ether analogue of phosphatidylcholine. This biologically active lipid has been found to affect aggregation of platelets and also to induce a hypertensive response at very low concentrations. More recent work has revealed its role as a mediator of inflammation and of other physiological effects on many different types of cells [15].

Archaebacteria contain large amounts of unique lipids, based on 2,3-dialkyl-*sn*-glycerol backbones, of the opposite stereochemical configuration of that found in the two other primary kingdoms, eubacteria and eukaryotes [10]. As a further diversity, they may have a number of polar head groups, existing as both phospho- and glycolipids as well as their sulfated forms [1, 16].

1.5. Glycosylglycerides

Glycosylglycerides are characterized by a 1,2-diacyl-*sn*-glycerol moiety with a mono- or oligosaccharide attached at the *sn*-3 position of the glycerol backbone. In photosynthetic bacteria, cyanobacteria, algae and higher plants, glycosylglycerides (glycolipids) are located predominantly in photosynthetic membranes. The major plastid lipids, galactosylglycerides, are neutral lipids. They contain one or two galactose molecules linked to the *sn*-3 position of the glycerol corresponding to 1,2-diacyl-3-O-(*β*-D-galactopyranosyl)-*sn*-glycerol (or monogalactosyldiacylglycerol, MGDG) and 1,2-diacyl-3-O-(*α*-D-galactopyranosyl-(1-6)-O-*β*-D-galactopyranosyl-*sn*-glycerol (or digalactosyldiacylglycerol, DGDG) (Fig. 2). MGDG and DGDG are present at 40-55% and 15-35% of the total lipids in thylakoid membranes, respectively. A characteristic feature of these lipids is a very high content of polyunsaturated fatty acids [17].

In addition to these main galactolipids, tri- and tetragalactosyldiacylglycerols as well as other homologues with a large number of different sugar combination (e.g., mannose, glucose, rhamnose) have been reported for bacteria, algae and higher plants [18,19]. For example, in Eubacteria, glycosyldiacylglycerols with one to three glycosyl units linked to *sn*-1,2-diacylglycerol were most common, but others with up to five glycosyl units have been also found. Mono- and diglucosyldiacylglycerols with the diglucoside moiety having an α-(1-2)linkage (as in kojibiose) and a galactosyldiacylglycerol have been isolated form some *Streptococcus species.* Mono- and dimannosyldiacylglycerols have been reported for *Micrococcus luteus*. In *Bacillus megaterium, N*-acetylgalactosamine has been found linked to a diacylglycerol. In glycophospholipids present in some bacteria, a glycerophosphate group is linked to a carbohydrate moiety [18].

Various gluco- and galactoglycerolipids have been also isolated in small amounts from animal tissues [20]. The galactoglycerolipids usually contain a single galactose residue which is linked through a β-glycosidic link between the C-1 of galactose and the C-3 of glycerol. The glucoglycerolipids have been reported may contain up to eight glucose residues. Moreover, alkylacyl and diacyl lipids as well as sulfated forms have been identified [20].

Another class of glycosylglycerides, which is present in appreciable amounts in both photosynthetic and in non-photosynthetic species, is the plant sulfolipid, sulfoquinovosyldiacylglycerol, or 1,2-diacyl-3-O-(6-deoxy-6-sulfo-*α*-D-glucopyranosyl)-*sn*-glycerol (SQDG) (Fig. 2). This lipid is unusual because of its sulfonic acid linkage. It consists of monoglycosyldiacylglycerol with a sulfonic acid in position 6 of monosaccharide moiety. The sulfonoglucosidic moiety (6-deoxy-6-sulfono-glucoside) is described as sulfoquinovosyl. The sulfonic residue carries a full negative charge at physiological pH. In the unicellular alga *Chlamydomonas reinhardtii,* an acylated derivative of this sulfolipid, 2'-O-acyl-sulfoquinovosyldiacylglycerol has been found. Sulfoquinovosylmonogalactosylglycerol has been isolated from the marine red alga, *Gracilaria verrucosa* (for review on algal lipids, see [19]).

In addition to sulfoquinovosyldiacylglycerol, the marine diatom *Nitzschia alba* has been found to contain a sulfonium analogue of phosphatidylcholine, phosphatidylsulfocholine [21]. This lipid has two methyl groups attached to the sulphur atom, and it completely substitutes for phosphatidylcholine in *Nitzschia alba*. In other marine diatoms and algae, both lipids have been found [22].

A number of lipids conjugated to taurine (ethanolaminesulfonic acid) have been reported for many organisms. So, membrane lipids of certain bacteria and algae contain taurine linked to diacylglucuronylglycerol. In a seawater bacterium *Hyphomonas jannaschiana*, which is unique because of an absence of phospholipids, a tauroglycolipid, 1,2-diacylglycerol-3-glucuronopyranosyl-sn-glycerol taurineamide was identified. An unusual glycolipid sulfate ester has been isolated from extremely halophilic bacteria [18], and a glycolipid sulfate, 2,3,6,6'-tetraacetyl-α,α-tetrahalose-2'-sulfate, from *Mycobacterium tuberculosis* [23]. For a review on the isolation, characterisation, and biochemistry of taurolipids, see [24].

In general, sulfation is a common reaction in lipid biochemistry for many reasons. It can enable solubilization of a lipid or it can convert a complex lipid to a highly anionic form for specific purposes in membranes. Sulfonolipids have the sulfur atom linked directly to a carbon atom, while in lipid sulfates the sulfur is linked to the lipid component by an oxygen atom. Sulfogalactosylglycerolipid (SGG, seminolipid) is selectively synthesized in high amounts (10 mole%) in mammalian testicular germ cells. SGG is an ordered lipid and directly involved in cell adhesion. SGG is indispensable for spermatogenesis [25].

1.6. Betaine lipids

Betaine lipids contain a betaine moiety as a polar group which is linked to the *sn*-3 position of glycerol by an ether bond. There is no phosphorus or carbohydrate group in betaine lipids. Three types of betaine lipids have been identified, 1,2-diacylglyceryl-3-*O*-4'-(*N,N,N*-trimethyl)-homoserine (DGTS), 1,2-diacylglyceryl-3-*O*-2'-(hydroxymethyl)-(*N,N,N*-trimethyl)-β-alanine (DGTA) and 1,2-diacylglyceryl-3-*O*-carboxy-(hydroxymethyl)-choline (DGCC) (Fig. 3) [26]. These betaine lipids are all zwitterionic at pH 7 since they have a positively charged trimethylammonium group and a negatively charged carboxyl group (Fig. 4). Betaine lipids are not found in higher plants, either gymnosperms or angiosperms, but are quite widely distributed in photosynthetic bacteria, algae, ferns, bryophytes, lichens, some fungi and protozoans. Based on an obvious structural similarity between betaine lipids and phosphatidylcholine and on their taxonomical distribution (namely, their reciprocal relationship in many species), it has been suggested that betaine lipids, especially DGTS, are more evolutionarily primitive lipids which, in the lower plants, play the same functions in membranes that PC does in higher plants and animals [27].

2. Diol lipids

Diol lipids have been reported only recently when techniques for their structure elucidation were developed. Small quantities of diol lipids, such as diacylpropane-1,3-diol, diesters of butane-1,3-diol and butane-1,4-diol, are found in mammalian and fish liver, mammalian adipose tissues, egg yolk, corn seed and yeast [28]. From *Actynomyces olivaceus,* mixed acyl- and alk-1-enyl derivatives of simple diols have been isolated [29]. An acylated diol phospholipid has been produced by the yeast *Lypomyces starkeyi* when grown on propane-1,2-diol [30].

3. Sphingolipids

Sphingolipids are lipids that contain sphingosine (*trans-D-erythro*-1,3-dihydroxy-2-amino-4-octadecene) or a related amino alcohol. Sphingolipids are a group of lipids with a range of diverse functions [31, 32]. It has recently become apparent, that sphingolipids are involved in many human diseases including diabetes, cancers, neurological syndromes, infections, and diseases of the cardiovascular molecules and respiratory systems [33]. Moreover, an increased interest to these molecules is determined also by an involvement of sphingolipids in the segregation/compartmentalization of membranes by self-organizing functional lipid microdomains, known as lipid rafts. Sphingolipids are found to be located exclusively in the outer (exoplasmic) leaflet of the plasma membrane bilayer. In contrast, glycerophospholipids largely prefer the inner (cytoplasmic) leaflet, and cholesterol is most likely abundant in both leaflets. The lipid raft model [34] is based on the assumption that sphingomyelin and other sphingolipids together with cholesterol are not distributed evenly in the plasma membrane, but rather assemble to specific microdomains or rafts. They act to compartmentalize and separate membrane proteins with different biochemical functions. It is believed that up to 50% of the plasma membrane may consist of such rafts, and raft formation has been shown to be crucial in modulation of signalling events in cells [35].

3.1. Sphingophospholipids and glycosphingophospholipids

Sphingomyelin (or ceramide phosphorylcholine) is the most common lipid in this class and is the phosphorylcholine ester of an *N*-acylsphingosine (or ceramide) (Fig. 4). It is a major lipid in certain membranes in animal tissues. Although it is usually lower in concentration than phosphatidylcholine, it can comprise about 50% of the lipids in certain tissues. Sphingomyelin replaces phosphatidylcholine in erythrocytes of most ruminant animals entirely. Sphingomyelin has only minor importance in plants and it seems absent from microorganisms.

In the plasma of the newborn pig and infant, 3-*O*-acyl-*D*-*erythro*-sphingomyelin has been detected. In this lipid, position 3 of the sphingosine residue was esterified by an additional fatty acid.

In addition, lyso-sphingomyelin and sphingosine phosphorylcholine have been reported to be present in tissues in small amounts. They are involved in some signaling processes in the cell in a manner similar to sphingosine-1-phosphate [36, 37]. Sphingosine-1-phosphate has been found in insects, yeasts and plants and its function as an important cellular messenger has been shown in many studies. It regulates also calcium mobilization inside the cell as well as cell growth and proliferation in response to a number of stress factors.

Ceramide phosphorylinositol, or *myo*-inositol-(1-*O*)-phosphoryl-(*O*-1)-ceramide, the sphingolipid analogue of phosphatidylinositol, which is a major component of sphingolipids in yeasts, e.g. *Saccharomyces cerivisiae*. In these organisms, two other related inositol-containing sphingophospholipids, mannosylinositolphosphorylceramide and mannosyldiinositolphosphorylceramide have been also found.

Ceramide phosphorylethanolamine, the sphingolipid analogue of phosphatidylethanolamine, reported for the first time in the housefly, *Musca domestica.* Shortly after, it was identified in the bacteria *Bacteroides ruminicola* and *B. melanogenicus* as well as in some protozoa, snails, in marine bivalves, in insects and also in chicken and rat liver [38]. In some recent studies, this lipid has been isolated from three species of oomycete plant pathogens [39] and from several species of *Sphingobacterium* [40].

Ceramide phosphorylglycerol is known as a membrane component in anaerobic bacteria of the genus *Bacteroides* and in the oral pathogen *Porphyromonas gingivalis* [41].

A sphingoid analogue of phosphatidic acid, ceramide-1-phosphate, has recently emerged as potent bioactive agent. Studies have defined biological functions for this lipid related to control of numerous aspects of cell physiology including cell survival and mammalian inflammatory responses [37].

The first sphingolipids identified in some plants were glycolipids with phytosphingosine and/or dehydrosphingosine backbone containing both inositol and phosphate. They have been named "phytoglycosphingolipids" and more than twenty molecular forms have been identified with glucuronic acid, glucosamine and many other carbohydrate moieties. The analysis of such compounds has been thoroughly discussed in [42, 43].

From the bacterium *Sphingobacterium spiritivorum*, ceramide phosphorylmannose was reported for the first time. Archaebacteria have been shown to contain various phosphoglycolipids [18].

Another type of glycosphingophospholipids are glycosphingolipids which are further phosphorylated, i.e. where the ceramide is linked directly to sugar moieties not via phosphate group. The earthworm, *Pheretima hilgendorfi,* has been shown to contain such lipids, namely cholinephosphoryl–6Galβ1–1Cer and cholinephosphoryl–6Galβ1–6Galβ1–1Cer. In addition, triglycosylsphingophospholipids with either a terminal mannose or galactose linked to phosphorylcholine were also present in this species. Some filamentous fungi contain glycosphingophospholipids (e.g. phosphocholine-containing glycosyl inositol phosphorylceramides) [41].

3.2. Ceramides

Ceramide is formed by attachment of a fatty acid (linked by an amide bond) to the amino group of sphingosine or other related amino alcohol. The most commonly found sphingosyl alcohols are D-erythro-sphinganine (dihydrosphingosine, sphinganine), D-erythro-sphingosine (sphingosine, 4-sphingenine), C20-dihydrosphingosine (icosasphinganine) and 4-hydroxy-D-erythro-sphinganine (phytosphingosine, 4-hydroxysphinganine).

Although ceramides are usually found at trace levels in tissues, they play important biological roles [1]. Moreover, they are synthesized as the key intermediates in the biosynthesis of complex sphingolipids.

3.3. Cerebrosides

Cerebrosides are glycosides of *N*-acyl long-chain bases (ceramides). Galactose and glucose are the monosaccharides usually found. Galactosylceramide is the principal glycosphingolipid in brain tissue [2]. In general, galactosylceramides are present in all nervous tissues, accounting for up to 2% of the dry weight of grey matter and 12% of white matter. Oligodendrocytes contain large amounts of these lipids.

Glucosylceramides are considered as characteristic compounds of plants but also found in low amounts in animal tissues, such as spleen, nervous tissues and erythrocytes. In plants, they are abundant in photosynthetic tissues [42]. From non-photosynthetic tissues, monoglycosylceramides containing a β-D-mannopyranosyl residue has been isolated.

In addition, fucosylceramide has been reported in a colon carcinoma and a xylose-containing cerebroside was identified in an avian salt gland. Glycosylceramides with mannose and glucuronic or galacturonic acids as sugar moieties have been isolated from some microorganisms. *O*-acylated (with fatty acids in various positions of the sugar moiety) glucosyl- and galactosylceramides have been also found in brain tissues in small amounts. In equine brain, a galactosylceramide with a long-chain cyclic acetal at the carbohydrate moiety, plasmalo-galactosylceramide, has been identified [44].

Galactosylceramides usually contain large amounts of 2-hydroxy fatty acids, which are linked to the sphingosine base through the amino group. In addition, odd chain fatty acids may also present. Typical fatty acids reported are behenic (C22:0), lignoceric (C24:0), nervonic (C24:1n-9), cerebronic (α-OH C24:0) and 2-hydroxynervonic (α-OH C24:1) [2].

3.4. Oligoglycosylceramides

Di- and oligoglycosphingolipids (with two or more sugar residues linked to a ceramide base) are important components of cellular membranes of most eukaryotic organisms and bacteria. Lactosylceramide is the most abundant diglycosphingolipid (or diosylceramide) which is found in most animal tissues at low levels. In kidney and pancreas, galabiosylceramide has been also found. Diosylceramides with mannose units have been reported for some primitive animal species and in plants.

Neutral oligoglycosylceramides containing three and up to over twenty sugar units in the chain are characteristic of some animal tissues. There are seven main types of these compounds based on their structural and biosynthetic relationships. In each type, glucose (Glc) is the primary sugar linked to ceramide with galactose (Gal), N-acetylglucosamine (GlcNAc), N-acetylgalactosamine (GalNAc) or mannose (Man) as additional monosaccharides [2].

In general, hundreds of different neutral oligoglycosphingolipids have been identified, and each mammalian organ has a characteristic pattern of neutral ceramides, with kidney, lung, spleen, and blood containing large amounts. In erythrocytes, for example, megaloglycolipids with up to 50 sugar groups are present, but tri- to pentaglycosylceramides are usually more abundant.

The majority of these compounds are located on the plasma membrane facing into the extracellular space. The structure of carbohydrate units may determine the function of oligoglycosphingolipids and one of most important of them involves the immune defense system [45].

In plants, two series of oligoglycosylceramides with either mannosyl or galactosyl residues are synthesized by elongation of glucosylceramide. They are located in the endoplasmic reticulum, Golgi, tonoplast and plasma membranes. Their functions in plants are not well-known [46].

3.5. Gangliosides

Gangliosides are glycosphingolipids that contain a ceramide linked to a glucosylgalactosylsialic acid (β-D-*N*-acetylneuraminic acid or sialic acid) residue via glycosidic linkages to one or more of the monosaccharide units, i.e. via the hydroxyl group on the position 2, or to another sialic acid residue. The level of these lipids is around 6% of total lipids in the brain tissues. Neuronal membranes contain 10-12% gangliosides of the total lipid content (20-25% of the outer layer). They are also present at low levels in all animal tissues but not found outside of the animal kingdom.

Gangliosides are involved into control of cell growth and differentiation as well as cell interactions [45]. They also play a key role in the immune defense systems. Many of these reactions are mediated through the location of these molecules in membrane rafts. A recent comprehensive volume [47] has covered their roles in health and disease.

3.6. Glycosphingolipid sulfates

Glycosphingolipids with a sulfate ester group attached to the sugar moiety are termed glycosphingolipid sulfates (sulfatides or sulfoglycosphingolipids). The distribution of these compounds in mammalian tissues as well as their fatty acid composition and base composition are usually similar to those of cerebrosides. 3’-Sulfo-galactosylceramide is an example of one of the more abundant glycolipid components of brain. It has been also found in many other organs, especially in kidney. In addition to these “classical” sulfatides, a whole series of sulfatides in organisms ranging from mycobacteria to mammals have now been characterized. These include sulfolactosylceramide and other sulfate esters derived from oligoglycosylceramides of the globo- and ganglio-series isolated from human kidney, and ganglioside sulphatides from echinoderms (a class of marine animals e.g. star fish, sea urchins [48].

4. Phosphonolipids

Phosphono analogues of various phospholipids, which consist of aminoethylphosphonic acid residues, have been found in Nature [49]. The aminoethylphosphonic acid moiety may be linked through a phosphorus-carbon bond to either a ceramide or diacylglycerol backbone of phosphonolipids. Ceramide aminoethyl phosphonate (or ceramide ciliatine) was the first phosphono analogue of sphingosylphosphatides which has been identified in sea anemones (Fig. 5). Lately, it has been also detected in a number of molluscs, protozoa, bacteria and in bovine brain tissue together with its *N*-methyl derivative. In some bacterial species, phosphonolipids with a 1-hydroxy-2-aminoethane residue linked to the phosphorus moiety have been also detected. Phosphonoglycosphingolipids, e.g. 6-*O*-(aminoethylphosphono)galactosyl ceramide (Fig. 5) and its *N*-methylethane derivative, have been isolated from marine invertebrate. The role and biochemical functions of these lipids are still unknown.

The phosphono form of phosphatidylethanolamine, 1,2-diacyl-*sn*-glycerol-3-(2'-aminoethyl)phosphonate (Fig. 5), is present in several species of protozoa as well as in bovine tissues and in human aorta. Its alkylacyl and alkenylacyl forms have also been found.

From freshwater cyanobacteria *Aphanizomenon flos-aquae,* 2-acyloxyethylphosphonate (with unusual biosurfactant properties) has been isolated.

Phosphonolipids have been reviewed in invertebrates [50, 51].

5. Arsenolipids

Lipid-soluble arsenic compounds were first identified from marine organisms over 30 years ago. By now, more than 100 naturally occurring arsenolipids have been detected in a wide range of organisms, including lichens, fungi, freshwater and marine algae, invertebrates, fishes, plants and animals [52]. The level of accumulation of these lipids may vary from 1.5 to 33.8 µg/g dry weight. Some plants and hyper-accumulators contain more than 1 mmol As g^{-1} dry weight.

In some species, arsinoyl fatty acids were found as free fatty acids rather than being esterified in complex lipids, but in herring roe, mass spectrometry established that highly unsaturated fatty acids of this type were esterified in phosphatidylcholine, while in salmon roe, an analogous 30C fatty acid with eight double bonds was detected in the phosphatidylethanolamine fraction [53]. In addition, evidence has been obtained for their presence in triacylglycerols from blue whiting. Many different lipid classes, including triacylglycerols and various phospholipids, were found to contain arseno-fatty acids in the green alga *Coccomyxa* (Trebouxiophyceae, Chlorophyta) when cultivated in a medium containing arsenic [54]. A total of 39 molecular species of arsenic triacylglycerols (AsTAG), 15 arsenic phosphatidylcholines (AsPC), 8 arsenic phosphatidylethanolamines (AsPE), 6 arsenic phosphatidylinositols (AsPI), 2 arsenic phosphatidylglycerols (AsPG) and 5 unknown lipids (probably ceramides) were identified. The structures of all molecular species were confirmed by tandem MS. Dry matter of the individual strains contained different amounts of total arsenolipids, i.e. *C. elongata* CCALA 427 (0.32 mg/g), *C. onubensis* (1.48

mg/g), *C. elongata* S3 (2.13 mg/g). Possible biosynthesis of long-chain lipids with the end group $Me_2As(O)$ has also been suggested [54].

A complex arsenic-containing glycophospholipid is present in fish and other marine organisms, i.e. diacylglycerophospho-2-hydroxypropyl-5-deoxy-5-(dimethylarsinoyl)-*β*-ribofuranoside, and this has now been characterized from several species of brown algae (seaweeds) by modern mass spectrometric methods [53].

Many species of bacteria (as well as most algal species examined) seem to be capable of converting arsenic compounds into their methylated derivatives, such as trimethylarsine [55].

Structures, distribution, the possible metabolism of arsenolipids, as well as analytical techniques used for their separation, identification and quantification are thoroughly reviewed in [52].

6. Other esters

A group termed “other esters” includes a large variety of functionally diverse lipids. Wax esters are a typical example [see 56]. The term “wax” is commonly used for esters of long-chain fatty acids with long-chain primary alcohols, but sometimes it is used for the entire mixture of lipids containing waxes as a part. Ester waxes are present in both plants and animals where they form the water-repellent surface coating, e.g. skin surface of animals and the leaf cuticle. Esters of normal alcohols with mono- or multibranched fatty acids have been found in the preen glands of birds [2]. Complex waxes (where either the fatty acid or the alcohol component or both has a complex structure) have been isolated from some bacteria. Diesters of phthiocerols (33C-35C branched-chain diols) with mycocerosic acids (29C-32C branched-chain acids) are examples of these compounds which have been reported for *Mycobacterium* spp. [57].

Two types of diester waxes are characteristic of animal skin-surface lipids. In the first, a hydroxyl group of hydroxy fatty acid is esterified to a normal fatty acid whereas its carboxyl group is attached to a fatty alcohol. In the second type, waxes consist of an alkane α,β-diol in which both hydroxyls are esterified with fatty acids [58].

Ester forms are found in the commonly-occurring sterols and vitamin alcohols, such as vitamin A, the D vitamins, and vitamin E, as well as in carotenoids (flowers and green algae) and terpenoids (rose petals). Various other esters have been reported in different bacteria and yeasts where they may occur as glycoside and amino acid derivatives. For more details, see [2].

7. Fatty acids

Fatty acids are aliphatic monocarboxylic acids. Over 1000 fatty acids are known with different chain length, positions, configurations and types of unsaturation. Addition of various functional groups along the aliphatic chain brings more structural and functional diversity to this group.

7.1. Saturated fatty acids

In most natural lipids, straight- or normal-chain saturated components (even-numbered) account for up to 10-40% of the total fatty acids. Straight-chain fatty acids with 16 and 18 carbon atoms are the most common naturally-occurring compounds in animals and plants although odd- and even-numbered homologues from 2- 36 carbon atoms have been reported for natural samples [2]. In general, fatty acids do not exist as free carboxylic acids because their high affinity for many proteins. Moreover, elevated levels of free (non-esterified) fatty acids are usually artefacts as a result of cell damage which allows lipases to break down the endogenous acyl lipids. Table 2 shows the examples of the most important straight chain saturated fatty acids together with the information on their distribution.

7.2. Branch-chain fatty acids

Branch-chain fatty acids are usually saturated and have a methyl-group as the branch. In marine animals, unsaturated branched-chain fatty acids have been found, and branches other than methyl are present in microbial lipids. Two distinct types, which are often found in bacteria, are the *iso*-methyl branched fatty acids with the branch point on the penultimate carbon (one from the end) and *anteiso*-methyl branched fatty acids with the branch point on the *ante*-penultimate carbon atom (two from the end). Fatty acids with these structures and with 10 to more than 30 carbon atoms have been identified in some bacteria and other microorganisms. However, branch points can also be found in other positions. For example, 10-*R*-methyloctadecanoic acid (or tuberculostearic acid) (Fig. 6) is a characteristic of the tubercle bacillus and related species. A wide range of mono-methyl branched fatty acids occur in some mammalian tissues with the uropygial (preen) gland of birds as a major source. In membranes, they have a function (as an alternative to double bonds) in increasing the fluidity of the lipid bilayer [1].

7.3. Monoenoic (monounsaturated) fatty acids

Straight- or normal-chain (even-numbered) monoenoic fatty acids (with one double bond) amount to a significant proportion of the total fatty acids in most natural lipids. The double bond is usually of the *cis*- or *Z*-configuration, but some fatty acids with *trans*- or *E*-double bonds are found. For example, a major fatty acid esterified to phosphatidylglycerol in the photosynthetic membranes of higher plants and algae is *trans*-3-hexadecenoic acid. Often the *cis* bond is present at the Δ9 position.

The most common monoenes are straight-chain compounds with 16 or 18 carbon atoms. Table 3 shows examples and the occurrence of the most abundant monoenoic fatty acids.

A *cis*-bond in a fatty acid introduces a kink (a 60° bend) in the acyl chain with a restriction in motion at that point. Very long chain (C22:1 and longer) *cis*-monoenoic acids have relatively high melting points, whereas the more common 18C monoenes are usually liquid at room temperature [1, 2].

In addition to the normal ethylenic double bonds, some fatty acids possess acetylenic bonds. They have been found in rare seed oils and some moss species (See 7.10 for more details).

7.4. Methylene-interrupted polyunsaturated acids

Significant amounts of polyunsaturated fatty acids (PUFA) with methylene-interrupted (with two or more double bonds of the *cis*-configuration separated by a single methylene group) are found in all higher organisms. In higher plants, the number of double bonds are usually two or three, but in algae and other lower plants as well as in animals there can be up to six (Table 4).

The n-6 and n-3 families are two principal families of polyunsaturated fatty acids occurring in nature and are derived biosynthetically from linoleic (9-*cis*, 12-*cis*-octadecadienoic or C18:2n-6) and α-linolenic (9-*cis*, 12-*cis,* 15-*cis*-octadecatrienoic or C18:3n-3) acids, respectively (Fig. 6). Both of these fatty acids are synthesized in plants which can insert double bonds at the Δ9, Δ12 and Δ15 positions in a 18C chain but not in animals (which can insert double bonds at the Δ9, but not at Δ12 and Δ15). Therefore, these two acids are essential dietary components. In animals, further double bonds are inserted between the carboxyl group and the Δ9 position by Δ5 and Δ6 desaturase enzymes and the chain can also be extended in two carbon units at the carboxyl end of the molecules by elongase enzymes.

In animal biology, long chain metabolites of linoleate and linolenate may be even more important. The functions of arachidonic (C20:4n-6), eicosapentaenoic (C20:5n-3) and docosahexaenoic (C22:6n-3) acids make them also conditionally essential [59]. They are signaling molecules and are involved in the regulation of gene expression. These fatty acids are also precursors of eicosanoids, including prostaglandins (e.g. PGE_2 and PGE_3 series), thromboxanes, leukotrienes, and lipoxins, which have a variety of important biological properties (See section 9 for more details).

Polyunsaturated fatty acids are found in most lipid classes, but they are especially important as acyl chains of phospholipids where they contribute to the particular physical and biological functional properties of the membranes [1, 2].

7.5. Bis- and polymethylene-interrupted acids

Fatty acids with *bis*- or polymethylene- interrupted double bonds, or a mixture of methylene- and polymethylene-separated unsaturation, are found in some plants and marine organisms. From sponges and some other marine invertebrates, a wide range of such fatty acids, the demospongic acids, have been isolated. They have *bis*-methylene-interrupted *cis*-double bonds and chain lengths (both odd and even) ranging from 16 to 34 carbons. Double bonds in positions delta 5 and 9 are usual, although additional bonds may be present in position 7 and/or 9 together with methyl branching.

Bis-methylene-interrupted acids with a Δ5 *cis*-double bonds only are common in gymnosperms (conifers) with a typical example being pinolenic acid (5-*cis*,9-*cis*,12-*cis*-octadecatrienoic acid). This fatty acid has been found in a number of pine and larch species at the levels of 25 to 30% of total seed fatty acids. In angiosperms, 5-*cis*,13-*cis*-docosadienoic acid (Fig. 6) was reported in the seed oil of meadowfoam (*Limnanthes alba)* (16% of the total fatty acids). An analogue of pinolenic acid with a *trans* double bond in position 5 (5-*trans*,9-*cis*,12-*cis*-C18:3) was found to be the main fatty acid of the seed oil of *Aquilegia vulgaris* (columbine) [1, 2].

7.6. Non-methylene-interrupted fatty acids

Marine organisms, in particular invertebrates, are a major source of unique fatty acids, non-methylene-interrupted (NMI) FAs identified in various molluscs in wide ranges of concentrations (up to 20%), such as C20:2 Δ5,11, C20:2 Δ5,13, C22:2 Δ7,13 or C22:2 Δ7,15. These FAs are synthesized via unusual biosynthetic pathways. Such NMI FAs have also been identified in algae, echinoderms, sponges, and tropical rays. The most intriguing organisms are sponges containing very long-chain Δ5,9 FA. A third double bond can occur in the NMI FAs as reported in some marine organisms, such as C20:3 Δ7,13,16 or C30:3 Δ5,9,23. Lipids of invertebrates from deep-sea hydrothermal and cold-seep vents gave rise to an intense research activity including reports on unprecedented NMI polyunsaturated FA. The bivalve molluscs are able to synthesize *de novo* the NMI FAs but their precise biological interest is presently not well-known, although structural and functional roles in biological membranes have been suggested, in particular a higher resistance to oxidative processes and microbial lipases. Biosynthetic pathways of Δ5,9 FA in sponges were demonstrated up to 26C FA structures and include particular elongation and desaturation steps. Recently, much research has been conducted to investigate the biomedical potential of these unusual FAs. Thus, Δ5,9 FA displayed interesting antiplasmodial activity. The most promising FA topoisomerase I inhibitors to date seem to be the long-chain Δ5,9 FA. This inhibitory activity is probably partially responsible for the toxicity displayed by some of the Δ5,9 FA towards cancer cell lines [60, 61].

7.7. Conjugated fatty acids

Fatty acids with two or more conjugated double bonds are found in some plants and animals. In tissues of ruminant animals (and, hence, in meat and dairy products), fatty acids with a conjugated diene system were detected as intermediates or by-products in the biohydrogenation of linoleic acid by microorganisms in the rumen. The main isomer, 9-*cis*,11-*trans*-octadecadienoic acid, may account for up to 1% of the total fatty acids of milk fat. 9-*cis*,11-*trans*-15-*cis*-octadecatrienoic acid, derived from α-linolenic acid, are present in ruminant tissues only in trace levels. This fatty acid has been shown to have a number of medical properties, especially anti-cancer and anti-atherosclerosis effects.

The only conjugated dienoic fatty acid isolated from plant sources (the seed oil of *Chilopsis linearis*) is reported to be *trans*-10,*trans*-12-octadecadienoic acid. In contrast, fatty acids with conjugated triene systems have been detected in various plant species. Tung oil is the commercial source of the most widespread fatty acid from this group, 9-*cis*,11-*trans*,13-*trans*-octadecatrienoic (α-eleostearic) acid [1, 2].

7.8. Cyclic fatty acids

Cyclic fatty acids with a carbon ring alone or at the end of the alkyl chain, occur naturally in plants, especially in certain seed oils and in microorganisms [62]. Cyclopropane fatty acids are occasionally reported from marine animals and may be synthesized by symbiotic bacteria. In addition, a variety of carbocyclic structures are formed from methylene-interrupted polyenes during food processing.

The cyclopropane fatty acid, *cis*-11,12-methylene-octadecanoic acid, was first reported for *Lactobacillus arabinosus* and given the trivial name lactobacillic acid. By now, fatty acids with a mid-chain cyclopropane group have been found in many bacterial species, including aerobic, anaerobic, Gram-negative and Gram-positive species. They may make up to 35% of the membrane lipids depending on the culture conditions.

This type of fatty acid is usually found at low levels (around 1%) in plant oils containing cyclopropene acids. Cyclopropene acids are characteristic for oils from the Malvalaceae, Sterculiaceae, Bombaceae, Tiliaceae and Sapicidaceae families with sterculic acid (9,10-methyleneoctadec-9-enoic acid) and malvalic acid (8,9-methyleneheptadec-8-enoic acid) as two major compounds. Sterculic acid is commonly more abundant (about 50% of the total fatty acids in *Sterculia foetida* oil). 2-Hydroxysterculic acid may also be present in this oil as a possible intermediate in the biosynthesis of malvalic acid (through α-oxidation of sterculic acid).

A fatty acid with terminal ring structure, 11-cyclohexylundecanoic acid, was first isolated as a minor compound of butter fat. It is produced by bacteria in the rumen and may be later digested and accumulated by the host animals. Together with homologous fatty acids, it has been also reported for many bacterial species, especially for those isolated from the extreme environments (e.g. hot springs). For example, in strains of the acidophilic and thermophilic *Bacillus acidocardarius*, 11-cyclohexylundecanoic acid and 13-cyclohexyltridecanoic acid amounted for 70 to 90% of the total fatty acids. Moreover, certain Bacillus species may also synthesize fatty acids with terminal 4C-7C rings when supplied with appropriate precursors [1, 2].

7.9. Fatty acids with oxygen-containing functional groups

A number of fatty acids and their metabolites have oxygen-containing functional groups, most commonly a hydroxyl, epoxide or furan ring [63].

Ricinoleic acid (*R*-12-hydroxy-9-*cis*-octadecenoic acid) (Fig. 6) accounts for 80 to 90% of fatty acids in castor oil (from *Ricinus communis*). It is also found in other plant species as well as in the sclerotia of the ergot fungus (*Claviceps purpurea*). Lesquerolic acid (*R*-14-hydroxy-11-*cis*-eicosenoic acid), the 20C homologue of ricinoleic acid, occurs in *Lesquerella* species (up to 70% of total fatty acids). In plants, a number of 16C and 18C mono, di and trihydroxy fatty acids are structural compounds of cutin (a polyester constituent of plant cuticle).

Recently the discovery of a seed oil with previously undescribed very-long-chain dihydroxy fatty acids has been reported [64]. The chemical structures of these FAs have been established by NMR and mass spectrometry: 7,18-$(OH)_2$-24:1Δ15 (nebraskanic acid) and 7,18-$(OH)_2$-24:2Δ15,21 (wuhanic acid). The elucidation of these structures provided insights into a novel biosynthetic pathway for the 7-OH of nebraskanic and wuhanic acids: 3-OH 20C and 5-OH 22C precursors of these 24C fatty acids occur in *Orychophragmus violaceus* seeds, and that 20C and 22C dihydroxy fatty acyl- CoAs elongation intermediates also were present in developing *O. violaceus* seeds [64].

2-Hydroxy or α-hydroxy acids have been shown to occur in sphingolipids, skin lipids, wool wax, bacterial cell wall lipids and in some seed oils. 3-Hydroxy or β-hydroxy acids are present in bacterial lipids.

Vernolic acid (or *cis*-12,13-epoxy-octadec-*cis*-9-enoic acid) (Fig. 6) was the first naturally occurring epoxy fatty acids isolated from the seed oil of *Vernonia anthelmintica*. It is also found in a number of Compositae, Malvaceae and Euphorbiaceae species in significant amounts. Other epoxy acids include coronoric acid (9,10-epoxy-12-*cis*-octadecenoic acid) which is found in some Compositae species, sunflower and other oils. A 20C homologue of vernolic acid is reported for *Alchornea cordifolia.*

The most abundant member of the family of furanoid fatty acids is a 20C furanoid acid with two methyl groups on the furan ring. Furanoid fatty acids were first detected in fish oils, but their origin from photosynthetic organisms has been proven. They are now isolated from a wide range of organisms including yeasts, algae, marine bacteria as well as plants (seeds, leaves and fruits). A particular role of these acids as scavengers of hydroxyl and hydroperoxyl radicals has been suggested [1, 2].

7.10. Acetylenic fatty acids

Fatty acids with acetylenic bonds are found in seed oils of higher plants, and they are present in the lipids of mosses, fungi and algae. They have also been detected in primitive marine animals, such as sponges, and in some insects.

Tariric (octadec-6-ynoic) acid was identified in seed oils of *Picramnia* species, where it can amount to as much as 95% of the total fatty acids; stearolic (octadec-9-ynoic) acid was detected in a seed oils of the Santalaceae and Olacaceae plants.

Complex polyacetylenic fatty acids occur in fungi, including a 9C triynoic fatty acid with a terminal triple bond from Basidiomycetes, and three phomallenic acids with an allenyldiyne structure from a *Phoma* species. Similarly, the bacterial family Actinomycetes produce mycomycin, one of the first polyacetylenic fatty acids to be characterized with two triple bonds and an allenic structure - tridecatetra-3,5,7,8-en-10,12-diynoic acid. Many similar compounds are now known. Fungi and algae may also contain complex acetylenic fatty acids with additional hydroxyl, keto and epoxyl groups or bromine atoms [65].

Mosses, algae and fungi contain polyunsaturated fatty acids similar to the conventional common range of (n-3) and (n-6) families, but in which the first double bond is an acetylenic bond. These include 6a,9-*cis*,12-*cis*-C18:3, 8a,11-*cis*,14-*cis*-C20:3, 6a,9-*cis*,12-*cis*,15-*cis*-C18:4 and 5a,8-*cis*,11-*cis*,14-*cis*-C20:4. These are precursors of a wide range of acetylenic oxylipins that are produced on wounding, with defensive activities against attack by fungi, bacteria and even herbivores, such as slugs.

While their primary functions are in the organisms in which they are produced, often as defence compounds, some natural acetylenic fatty acids appear to have useful pharmaceutical properties, for example as anti-cancer agents, and synthetic analogues are under development for clinical testing. They are chemically unstable and highly reactive compounds, especially in the presence of oxygen.

The structures of unusual fatty acids, including acetylenic acids, as well as their occurrence, synthesis, and biotechnological aspects, have been reviewed [66].

8. Polyacetylenes

Acetylene compounds or “polyacetylenes” (the latter term is used to describe this class of natural products, although they are not polymers and many precursors and metabolites contain only a single acetylenic bond) are a general name for a substantial class of natural products, of which all contain one or more carbon−carbon triple bond functionalities in their molecules. In this section, acetylenes are specially referred to as the cyclic and linear enyne compounds with one triple bond, whereas polyacetylenes are specially referred to as the metabolites with more than one enyne moiety. Naturally occurring polyacetylenes, although often unstable molecules, feature a wide range of structural diversity and are widespread in plants and animals. In the marine environment, they have been isolated mainly from algae and invertebrates, and have displayed a broad array of biological properties, including antifungal activity, antimicrobial activity, HIV reverse transcriptase inhibition, and cytotoxicity. In addition, important ecological roles, such as inducing metamorphosis of ascidians’ larvae, preventing fouling by barnacle larvae, and inhibiting fertilization of starfish gametes, have been ascribed to these metabolites [67]. This review provides a comprehensive overview of acetylenes/polyacetylenes isolated from marine algae and invertebrates (mainly sponges and molluscs) in the last five decades focusing on the isolation, structural characterization, and classification of more than 600 acetylenic molecules, as well as their biological relevance, thus highlighting both the structural diversity generated in this unique class of marine natural products and their potential in drug discovery.

9. Lipid mediators

Lipid signalling molecules (or lipid mediators) have assumed increasing research prominence over the last few decades. Several of the glycerolipids or sphingolipids described previously are such mediators [1, 68, 69]. Thus, glycerophospholipids such as phosphatidic acid or phosphatidylinositol (and its phosphorylated derivatives) [1] are important. Of sphingolipids, sphingosine, ceramide and their phosphorylated derivatives are notable [1, 69].

However, the main interest in lipid mediators recently has been with oxidised metabolites of polyunsaturated fatty acids (PUFAs). The first of these that was recognised were the prostaglandins [70]. The two classes of PUFAs that are essential for human health are the n-3 and n-6 families. Early experiments by the Burr's in the 1930's showed that the key dietary essential fatty acids were linoleic and alpha-linolenic acids [71] but, under certain conditions longer chain metabolites such as eicosapentaenoic (EPA) or docosahexaenoic acid (DHA) can be considered 'conditionally essential' [59].

The PUFAs can be oxidised by one of three types of enzymes---cyclooxygenase, lipoxygenase or cytochrome P450 oxidase or epoxygenase [1]. Before oxidation, the PUFA substrates are usually released from membrane phospholipids, mainly by phospholipase A2 action [72]. If the mediators produced by metabolism are 20C they are referred to as eicosanoids. If they are 22C then they are docosanoids. In general, these mediators are produced in specific tissues as a result of stimulation and rapidly catabolised to inactivate them. Thus, they are referred to as 'local hormones' in contrast to classic hormones which are produced in one tissue and then circulate in the blood to produce effects elsewhere in the body. Therefore, lipid mediators often have a short lifetime and are usually active at low concentrations.

Cyclooxygenase activity gives rise to intermediates that can be further metabolised to produce prostaglandins, prostacyclin or thromboxanes [1, 69]. These products have very different physiological effects [1, 68]. Moreover, the mediators produced from n-6 PUFA (such as arachidonic acid) are generally pro-inflammatory while those from n-3 PUFA are neutral or anti-inflammatory [1].

A second oxidation of PUFAs is by lipoxygenase. Due to their multi-functional nature, lipoxygenases can catalyse three different types of reaction (dioxygenation of lipids to give hydroperoxides; hydroperoxidation of the latter into keto lipids; formation of epoxy leukotrienes via leukotriene synthase reaction) [68]. Major products in animals are hydroperoxy-eicosatetraenes (HPETEs), hydroxyl-eicosatetraenes (HETEs) and leukotrienes [1, 68, 69].

The third oxidation is that by cytochrome P450 oxidases [1, 73, 74]. Like lipoxygenase, the cytochrome P450 oxidases can catalyse several types of reactions with major products being HETEs and epoxyeicosatrienoic acids (EETs). Catabolism yields dihydroxyeicosatrienoic acids (DHETs) [1, 68].

While the above compounds all have important physiological actions [68], more complex biosynthetic reactions have been uncovered recently [75]. These give rise to 'specialised pro-resolving mediators' (SPMs) of which protectins [1], aspirin-triggered protectins [68], resolvins [76] and maresins [77] are notable.

In contrast to animals, plants produce bioactive lipids but mainly from linoleic or alpha-linolenic acids. The 'lipoxygenase pathway' in plants begins with the production of hydroperoxide derivatives from the action of lipoxygenases [78]. After that, co-oxidation with a peroxidase can form a mixture of epoxy- and hydroxyl fatty acids. Alternatively, the hydroperoxides can be cleaved by hydroxyperoxide lyase to give an aldehyde and an oxo-unsaturated fatty acid. A third reaction is by allene oxide synthase. This forms 12-oxophytodienoic acid which is a precursor of jasmonic acid and other jasmonates. These are important effectors of growth, development and senescence [1, 78].

Recently discovered lipid mediators are fatty acid esters of hydroxy fatty acids (FAHFA). While they are found in plants as well as mammals [79], their biological actions have been studied best in mammals where they may have important roles in several important complaints such as obesity and diabetes [80].

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Cross-references

Lipid Signals; Chemistry of Glycosphingolipids; Phosphatidyl Inositides; Fatty Acid Desaturases; Lipid Domains; Lipid Mediators

Figure Legends

Figure 1

Phospholipids

Figure 2

Glycoglycerolipids

Figure 3

Betaine lipids

Figure 4

Sphingomyelin

Figure 5

Phosphonolipids

Figure 6

Fatty acid structures

Table Legends

Table 1

Classification of oligoglycolipids

Table 2

Some naturally occurring straight chain saturated fatty acids

Table 3

Some naturally occurring monoenoic fatty acids

Table 4

Some naturally occurring polyunsaturated fatty acids