WHAT LIPIDS DO

Their Biological Functions

For many years, lipids were considered to be intractable and uninteresting oily materials with two main functions – to serve as a source of energy and as the building blocks of membranes. They were certainly not considered to be appropriate candidates for such important molecular tasks as intracellular signalling or local hormonal regulation. In 1929, George and Mildred Burr demonstrated that linoleic acid was an essential dietary constituent, but it was many years before the importance of this finding was recognized by biochemists in general. With the discovery by Bergström, Samuelsson and others in 1964 that the essential fatty acid arachidonate was the biosynthetic precursor of the prostaglandins with their effects on inflammation and other disease states, the scientific world in general began to realize that lipids were much more interesting than they had previously thought.

Hanahan and colleagues achieved a major milestone in 1979 with the discovery of the first biologically active phospholipid, platelet-activating factor. At about the same time, there arose an awareness of the distinctive functions of phosphatidylinositol and its metabolites. Since then, virtually every individual lipid class has been found to have some unique biological role that is distinct from its function as a source of energy or as a simple construction unit of a membrane.

All multi-cellular organisms, use chemical messengers to send information between organelles and to other cells and as relatively small hydrophobic molecules, lipids are excellent candidates for signalling purposes. The fatty acid constituents have well-defined structural features, such as *cis*-double bonds in particular positions, which can carry information by binding selectively to specific receptors. In esterified form, they can infiltrate membranes or be translocated across them to carry signals to other cells. During transport, they are usually bound to proteins so their effective solution concentrations are very low, and they are can be considered to be inactive until they reach the site of action and encounter the appropriate receptor.

Storage lipids, such as triacylglycerols, in their cellular context are inert, and indeed esterification with fatty acids may be a method of de-activating steroidal hormones, for example, until they are actually required. In contrast, polar lipids have hydrophilic sites that can bind via hydrogen bonding to membrane proteins and influence their activities. Glycolipids carry complex carbohydrate moieties that have a part to play in the immune system, for example. Lipids have been implicated in a number of human disease states, including cancer and cardiovascular disease, sometimes in a detrimental and sometimes in a beneficial manner. In short, every scientist should now be aware that lipids are just as fascinating as all the other groups of organic compound that make up living systems.

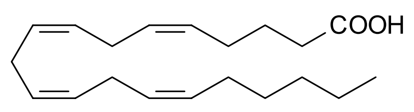
In this web document, the main biological functions of some key lipids are briefly summarized to give a general overview, but further information is available here on those pages dealing with specific lipid classes.

Fatty Acids

Fatty acids are one of the defining constituents of lipids and are in large part responsible for the distinctive physical and metabolic properties of the latter. However, they are also important in non-esterified form, i.e. as **free (unesterified) fatty acids**. They are released from **triacylglycerols** during fasting to provide a source of energy and of structural components for cells (see below), where they are of course of vital importance. However, it has become evident that there are a number of more dynamic functions of fatty acids, which are attracting great interest. It has long been known that linoleic and linolenic acids are **essential fatty acids**, in that they cannot be synthesised by animals and must come from plants via the diet. They are precursors of arachidonic, eicosapentaenoic and docosahexaenoic acids, which are vital components of all membrane lipids. However, we cannot even now claim to fully understand the reasons for the unique requirements for these fatty acids.

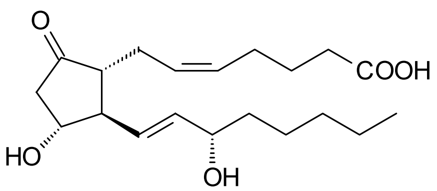
Dietary fatty acids of short and medium chain-length are not usually esterified but are oxidized rapidly in tissues as a source of 'fuel' to support all the events necessary to keep organisms functioning. Longer-chain fatty acids are usually esterified first to triacylglycerols or structural lipids in tissues. Although all lipids are in a state of dynamic flux, membrane lipids are conserved in content and composition in essence, except under conditions of extreme stress. Triacylglycerols are the primary storage form of long-chain fatty acids for energy purposes, and free acids can be mobilized quickly when required for transport in an appropriate form to the heart, liver and other tissues where they can be oxidized.

Polyunsaturated fatty acids are important as constituents of the phospholipids, where they appear to confer distinctive properties to the membranes, in particular by decreasing their rigidity. The presence of saturated and monoenoic acids ensure that there is a correct balance between rigidity and flexibility. Indeed, saturated and 2-hydroxy fatty acids in sphingolipids appear to give additional rigidity and hydrogen-bonding stability to the sub-domains of membranes termed '**rafts**'.



arachidonic acid

The essential fatty acids, linoleic and linolenic acids and their longer-chain polyunsaturated metabolites, such as arachidonic acid, can be found in most lipid classes, but they are also the precursors of many different types of **eicosanoids**, including the **hydroxyeicosatetraenes**, **prostanoids** (prostaglandins, thromboxanes and prostacyclins), **leukotrienes** (and lipoxins) and **resolvins**, not to forget the **isoprostanes**, which are formed by non-enzymic means. It is surely no coincidence that plant hormones, such as the **jasmonates**, are also derived from the essential fatty acids. While, they are usually treated separately in biochemical textbooks, it should not be forgotten that these compounds are in fact fatty acids. Some of them are occasionally found esterified to phospholipids (and glycosyldiacylglycerols in plants), although their short half-lives may preclude long-term storage in this form. The eicosanoids are highly potent at nanomolar concentrations in the regulation of innumerable biological activities, especially in relation to inflammatory responses, pain and fever.



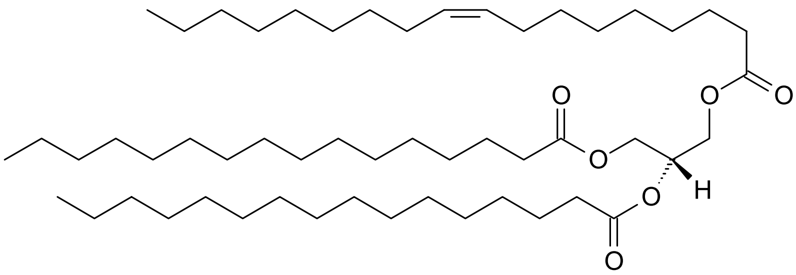
prostaglandin (PGE_2)

Fatty acids are also the biosynthetic precursors of many insect pheromones and secondary metabolites in plants.

Unesterified fatty acids can act as second messengers required for the translation of external signals, as they are produced rapidly as a consequence of the binding of specific agonists to plasma membrane receptors. Within cells, fatty acids can act to amplify or otherwise modify signals to influence the activities of such enzymes as protein kinases, phospholipases, and many more. They are involved in regulating gene expression, mainly targeting genes that encode proteins with roles in fatty acid transport or metabolism via effects on transcription factors, i.e. peroxisome proliferator-activated receptors (PPARs) in the nuclei of cells. Such effects can be highly specific to particular fatty acids. Thus, unesterified arachidonic acid may have some biological importance *per se* as part of the mechanism by which apoptosis (programmed cell death) is regulated.

Tri-, Di- and Monoacylglycerols

Virtually all the natural fats and oils of commerce consist of triacylglycerols, but here we are concerned with their biological functions. As discussed briefly above **triacylglycerols** are the storage lipid in animal and plant cells, where they occur as discrete droplets surrounded by a protective monolayer of phospholipids and hydrophobic proteins. Fatty acids are released when required by hydrolysis reactions catalysed by lipases under the influence of hormones, though a high proportion is usually re-esterified to biochemically inert triacylglycerols for extracellular transport. One specialized form of adipose tissue, brown fat, is highly vascularized and rich in mitochondria, which oxidize fat so rapidly that heat is generated. This appears to be especially important in young animals and in those recovering from hibernation. Triacylglycerols are the main lipid component in the only material designed by nature entirely as a food, i.e. milk, though triacylglycerols in seeds could perhaps be considered similarly as 'food' for the developing plant embryo until it is capable of photosynthesis.



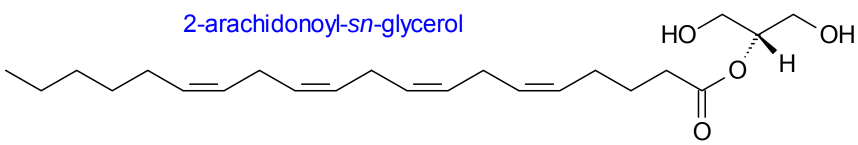
1,2-dihexadecanoyl-3-(9*Z*-octadecenyl)-*sn*-glycerol (a triacylglycerol)

However, triacylglycerol depots have other functions. Subcutaneous depots serve as insulation against cold in many terrestrial animals, as is obvious in the pig, which is surrounded by a layer of fat, and it is especially true for marine mammals. In the latter and in fish, the lipid depots are less dense than water and so aid buoyancy with the result that less energy is expended in swimming. More surprisingly, perhaps, triacylglycerols together with the structurally related glyceryl ether diesters and wax esters are the main components of the sonar lens used in echolocation by dolphins and some whales.

***sn*-1,2-Diacylglycerols** are formed as intermediates in the biosynthesis of triacyl-*sn*-glycerols and via the action of a diacylglycerol kinase of phospholipids. In addition, they function as second messengers in many cellular processes, modulating vital biochemical mechanisms by activating members of the protein kinase C family of enzymes. They are formed together with the important inositol phosphates by the action of the enzyme phospholipase C on **phosphatidylinositol and polyphosphoinositides** mainly. Their influence is believed to extend to the pathophysiology of cancer and other disease states.

2-Monoacylglycerols are produced when triacylglycerols are digested in the intestines of animals, but they are re-esterified before they are transported elsewhere in the body. In general, monoacylglycerols are minor components of tissues, which are never permitted to accumulate because their strong detergent properties would have a disruptive effect on membranes.

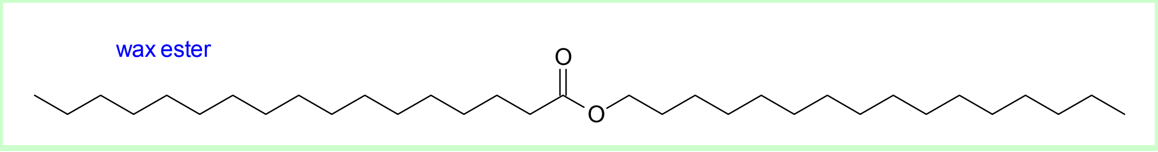
2-arachidonoyl-*sn*-glycerol



2-Arachidonoylglycerol, a further product of phosphatidylinositol catabolism, is important in animal tissues as an endogenous ligand for cannabinoid receptors and as a mediator of the inflammatory response.

Waxes

Waxes form a thin layer over all the green tissue of plants that is both a chemical and a physical barrier. This layer serves many purposes, for example to limit the diffusion of water and solutes, while permitting a controlled release of volatiles that may deter pests or attract pollinating insects. It provides protection from disease and insects, and helps the plants resist drought. Waxes also have a waterproofing and protective role for insects.

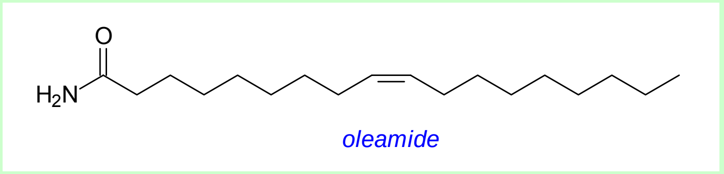


Waxes can have a storage function, as in marine organisms and for example in the seeds of the jojoba plant. Bees use wax to produce the rigid structures of honeycombs. The uropygial glands of birds secrete waxes, which they use to provide water-proofing for feathers.

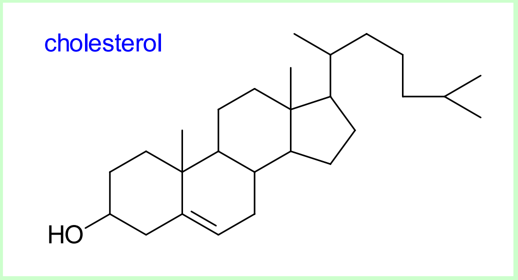
Some Other Simple Lipids

Before a fatty acid can be metabolized in tissues, it must usually be activated by conversion to a **Coenzyme A ester** or acyl-CoA, with the fatty acid group linked to the terminal thiol moiety. The thiol ester is a highly energetic bond that permits a facile transfer of the acyl group to receptor molecules. **Acyl-carnitines** assist the transport and metabolism of fatty acids in and out of mitochondria, where they are oxidized for energy production. In so doing, carnitine maintains a balance between free and esterified coenzyme A in cells.

Long-chain ***N*-acylethanolamines** are ubiquitous trace constituents of animal and human cells with important pharmacological properties. Anandamide or *N*-arachidonoylethanolamine has attracted special interest, because of its marked biological activities, exerting its effects through binding to and activating specific cannabinoid receptors. Like 2-arachidonoylglycerol, discussed above, it is an endogenous cannabinoid or 'endocannabinoid'. In contrast, oleoylethanolamide is an endogenous regulator of food intake, and could have some potential as an anti-obesity drug, while palmitoylethanolamide has separate signalling functions. The simple 'oleamide' molecule or *cis*-9,10-octadecenamide, isolated from the cerebrospinal fluid of sleep-deprived cats, has been identified as the signalling molecule responsible for causing sleep.



Cholesterol is a ubiquitous component of all animal tissues, where much of it is located in the membranes. It occurs in the free form and esterified to long-chain fatty acids (cholesterol esters) in animal tissues, including the plasma lipoproteins. It is generally believed that the main function of cholesterol is to modulate the fluidity of membranes by interacting with their complex lipid components, specifically the phospholipids such as phosphatidylcholine and sphingomyelin, increasing the degree of order by promoting a 'liquid-ordered phase'.



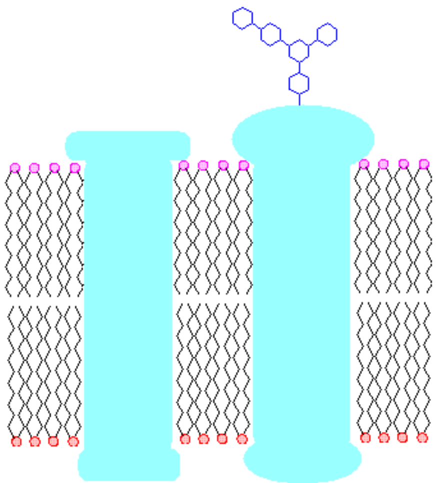
There is also considerable evidence for more intimate protein-cholesterol interactions that may regulate the activities of certain membrane proteins. It is of course the precursor of bile acids and steroidal hormones.

In plants, cholesterol tends to be a minor component only of a complex sterol fraction that includes campesterol, β-sitosterol, stigmasterol, Δ5-avenasterol and brassicasterols, while yeasts and fungi tend to contain ergosterol as their main sterol component. Plant sterols are also able to regulate membrane fluidity and permeability, and they modulate the activity of membrane-bound enzymes.

Complex Lipids in Membranes

The characteristic feature of all membrane lipids is that they contain both hydrophobic and hydrophilic constituents, i.e. they are amphiphilic. As such, they are weak surfactants and they tend to form aggregates in bilayer or hexagonal-II arrangements in aqueous media in the normal temperature ranges that prevail in living cells. However, in natural membranes, there is a mixture of lipid types, which determine that bilayer structures predominate.

Glycerophospholipids, such as phosphatidylcholine, phosphatidylethanolamine and so forth, together with the sphingolipids, such as sphingomyelin and the glycosphingolipids, and cholesterol are essential structural elements of all the biological membranes that provide the permeability barriers between cells and between organelles within cells. In the conventional model, which is illustrated here in two dimensions, polar lipids form a bilayer with the polar head groups oriented towards the aqueous phase while the hydrophobic fatty acyl moieties are arranged internally.



Proteins, such as enzymes, transport systems or signalling receptors, span the bilayer and take up a considerable proportion of the membrane surface. They interact via their basic amino acid residues with the ionic groups of polar lipids via electrostatic interactions, generating a net charge that is mainly negative or zwitterionic. In the process, their biological properties may be modified.

The distribution of lipids in each of the membrane leaflets is asymmetric with phosphatidylcholine and sphingolipids located in the outer leaflet of the plasma membrane, for example, while phosphatidylinositol (and polyphosphoinositides), phosphatidylethanolamine and phosphatidylserine occur primarily in the inner leaflet. Cholesterol occurs in roughly equal proportions in both faces, where it modulates the fluidity of membranes by its interaction with phospholipids. Further heterogeneity is imposed by specific associations of phospholipids with membrane proteins, while the sphingolipids together with cholesterol arrange themselves into distinct sub-domains or '**rafts**' (see below) with certain membrane enzymes, and they act to compartmentalize these and of course their different biochemical functions.

Each glycerophospholipid with its distinctive polar head group and characteristic fatty acid composition modifies the properties of a membrane in a unique manner and contributes to its overall properties. Thus, structural features, such as the geometry of phospholipids (e.g. 'cone shape' as opposed to 'inverted-cone shape'), determine how membranes bend and fuse.

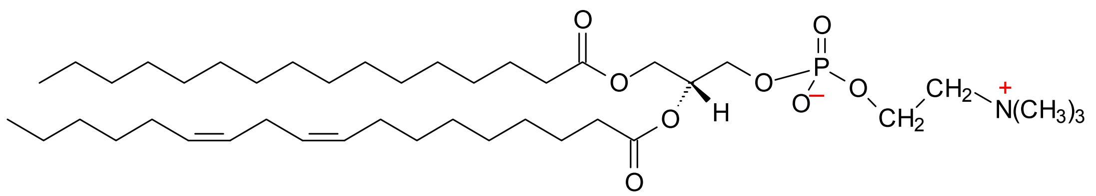
It is evident that the balance between saturated, monoenoic and polyunsaturated fatty acids is important in maintaining the optimum degree of fluidity of a given membrane. Docosahexaenoic acid, for example, adopts a more flexible and compact conformation than more saturated chains with an average length only 60% of that for oleic chains, and this in turn increases the conformational disorder of saturated chains in mixed-chain phospholipids. In bacterial membranes, branched-chain and cyclopropane fatty acids modify the fluidity in an analogous manner. When ether and plasmalogen forms of lipids are also taken into account, membranes can contain a thousand distinct molecular species of phospholipid. It is obviously impossible to quantify the relative importance of each of these to the physical and biological properties of membranes, and some general assessments only are possible.

It is evident that these lipid compositions have evolved to provide a barrier to the diffusion of ionic solutes and other molecules into cellular compartments where they may not be required. At the same time, the membrane environment provides a stable molecular platform for essential metabolic events.

Glycerophospholipids

Phospholipids play multiple roles in cells other than by establishing permeability barriers. For example, they provide a matrix for the assembly and function of a wide variety of enzymes, they participate in the synthesis of macromolecules, and they act as molecular signals to influence metabolic events. For example, specific anionic lipids like phosphatidylinositol and its phosphorylated derivatives, which are concentrated on the cytoplasmic leaflet of membranes, exert a control on the properties of the membrane–cytosol interface and consequently on many aspects of membrane trafficking, including vacuole formation transport and fusion. Specific lipids of this kind are associated with particular organelles, where in combination with other signalling molecules they can recruit effector proteins with appropriate functions for each cellular compartment.

Phosphatidylcholine is a zwitterionic lipid and usually the most abundant phospholipid in membranes of animal and plants, constituting a high proportion of the outer leaflet of the plasma membrane. It is also an integral component of the lipoproteins in plasma. However, it may serve as a source of diacylglycerols with a signalling function, while the plasmalogen form especially may provide arachidonate for eicosanoid production. In addition, phosphatidylcholine is the biosynthetic precursor of **sphingomyelin** (see below) and many other signalling molecules and thus has an influence on innumerable metabolic pathways. Before it can function optimally, the enzyme 3-hydroxybutyrate dehydrogenase requires binding to phosphatidylcholine. **Platelet-activating factor** or 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, a closely related lipid, was the first biologically active phospholipid to be discovered. Amongst the innumerable activities that have been documented, it effects the aggregation of platelets at concentrations as low as 10^{-11} M, it is a mediator of inflammation and it is involved in the mechanism of the immune response.



1-hexadecanoyl-2-linoleoyl-*sn*-glycero-3-phosphocholine

Phosphatidylethanolamine is also a major component of membranes, especially in bacteria, with distinctive physical properties because of its small head group and hydrogen bonding capacity. In the bacterium *E. coli*, it supports active transport by the lactose permease, and other transport systems may require or be stimulated by it. In animal and plants, it acts as a 'chaperone' during the assembly of membrane proteins to guide the folding path for the proteins and to aid in the transition from the cytoplasmic to the membrane environment.

Phosphatidylinositol is an acidic or anionic phospholipid, a high proportion of which in animal membranes consists of the 1-stearoyl,2-arachidonoyl molecular species that is of considerable biological importance. It is the primary donor of 1,2-diacylglycerols with their specific signalling functions (see above), and of inositol phosphates with many different biological activities. In addition, it is the main source of arachidonic acid for the production of eicosanoids and of endogenous cannabinoids. In many microorganisms, phosphatidylinositol serves as an anchor that links a variety of proteins to the external leaflet of the plasma membrane via complex glycosyl bridges, i.e. **glycosyl-phosphatidylinositol(GPI)-anchored proteins**.

A further acidic lipid, **phosphatidylserine**, contributes substantially to non-specific electrostatic interactions in the inner leaflet of membranes. This normal distribution is disturbed during platelet activation and in the process of cellular apoptosis when the lipid is transferred from the inner to the outer leaflet of the plasma membrane and acts as a signal to other cell types. It is also an essential cofactor for the activation of many enzymes, including protein kinase C, which is a key enzyme in signal transduction.

Diphosphatidylglycerol or 'cardiolipin' is a unique acidic phospholipid with four acyl groups. In the mitochondria of cells, its primary location, many biological functions of this lipid have been identified, but the main ones involve activation of those enzymes concerned with oxidative phosphorylation. Indeed, it is integrated into their quaternary structure, where it is an essential component of the interface between the enzymes and their environment and may stabilize the active sites. In higher plants, cardiolipin is an integral constituent of the photosystem II complexes, which are also involved in oxidative processes, and where it may be required for the maintenance of structural and functional properties.

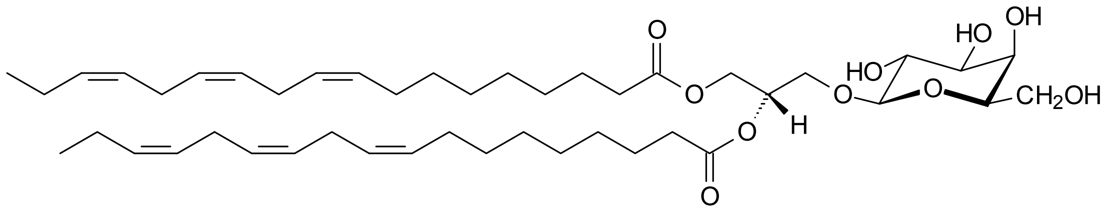
Phosphatidic acid is generally a minor component of cells, but it is a key intermediate in the biosynthesis of all other phospholipids. It is known to have signalling functions in animal cells, by specific binding to particular proteins, and it may be even more important in higher plants where it is formed rapidly in response to stresses of all kinds.

Lysophospholipids, i.e. with only one mole of fatty acid per mole of lipid, were long thought to be merely intermediates in the biosynthesis of phospholipids that were potentially disruptive to cells if allowed to accumulate because of their powerful detergent properties. However, **lysophosphatidic acid** has been shown to have signalling and other biological effects that are dependent on receptor mechanisms. It is produced by a wide variety of cell types and most mammalian cells express receptors for it. For example, it is involved in the activation of protein kinases, adenyl cyclase and phospholipase C, in the release of arachidonic acid, and much more. Interest was stimulated especially by a finding that lysophosphatidic acid is significantly elevated in the plasma of ovarian cancer patients compared to healthy controls, so that it may represent a useful marker for the early detection of the disease.

Other lysophospholipids including the sphingolipid analogue, sphingosine-1-phosphate (see below), exhibit a related range of activities. **Lyso-*bis*-phosphatidic acid** has a unique stereochemistry and distinctive biological functions.

Glycosyldiacylglycerols

Mono- and digalactosyldiacylglycerols, and **sulfoquinovosyldiacylglycerol** are important components of membranes of chloroplasts and related organelles, and indeed these are the most abundant lipids in all photosynthetic tissues, including those of higher plants, algae and certain bacteria. They may substitute in part for phospholipids, especially when phosphorus is limiting, although the distinctive ability of monogalactosyldiacylglycerols to form inverted micelles may be important for membrane structure and for interactions with specific proteins. The thylakoid membrane where photosynthesis occurs in plants has an asymmetric distribution of glycolipids, with much of the digalactosyldiacylglycerol on the luminal leaflet, where it may assist the movement of protons along the membrane surface to the ATPase. While many different functions have been ascribed to these lipids, it is clear that their primary importance is in their interactions with the photosynthetic apparatus.

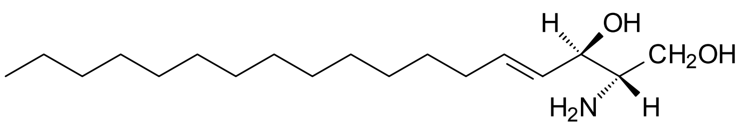


1,2-di-(9*Z*,12*Z*,15*Z*)-octadecatrienoyl-3-*O*-β-*D*-galactosyl-*sn*-glycerol

Glycosyldiacylglycerols have also been found in animal tissues, though usually in rather small amounts, and their role in mammalian membranes is poorly understood. However, **seminolipid** or 1-*O*-hexadecyl-2-*O*-hexadecanoyl-3-*O*-β-D-(3'-sulfo)-galactopyranosyl-*sn*-glycerol, which was first found in mammalian spermatozoa and testes, is known to be essential for spermatogenesis and may have a role in myelination.

Sphingolipids

Sphingolipids are distinguished by the presence of a **long-chain or sphingoid base**, such as sphingosine, to which a fatty acid is linked by an amide bond, and usually with the primary hydroxyl group linked to complex phosphoryl or carbohydrate moieties. They have an immense range of functions in tissues that are quite distinct from those of the complex glycerolipids. For example, **sphingomyelin** has structural similarities to phosphatidylcholine, but has very different physical and biological properties, while the complex oligoglycosylceramides and gangliosides have no true parallels among the glycerolipids.

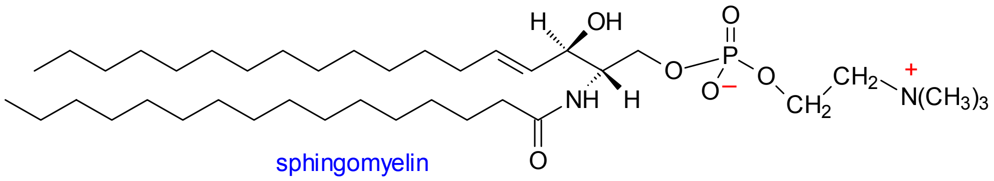


sphingosine (sphing-4-enine)

Free sphingoid bases are found trace levels only in tissues, but they are mediators of a number of cellular events. For example, they inhibit the enzyme protein kinase C, and they are inhibitors of cell growth, although they stimulate cell proliferation and DNA synthesis. Some of the structural features of the long-chain bases are only introduced after they are esterified to **ceramides**, which are also the primary precursors of the complex sphingolipids. In addition, ceramides have an important role in cellular signalling, and especially in the regulation of apoptosis, and cell differentiation, transformation and proliferation. In contrast, **sphingosine-1-phosphate** promotes cellular division (mitosis) as opposed to apoptosis, so that the balance between this lipid and ceramide, ceramide-1-phosphate and sphingosine levels in cells is critical.

In fact, the biosynthesis and catabolism of sphingolipids involves a large number of metabolites, many of which have distinctive biological activities. In animals the relationships between these metabolites have been rationalized in terms of a 'sphingomyelin cycle', in which each of the various compounds has characteristic metabolic properties. Similar pathways occur in plants although sphingomyelin is not involved.

Sphingomyelin is by far the most abundant sphingolipid in animal tissues. In addition to serving as a source of key cellular metabolites, sphingomyelin is an important building block of membranes and like its glycerolipid analogue phosphatidylcholine tends to be most abundant in the plasma membrane of cells and especially in the outer leaflet. The sphingolipids in general contain high proportions of longer-chain saturated and monoenoic fatty acids, often accompanied by high proportions of 2-hydroxy but not polyunsaturated fatty acids.

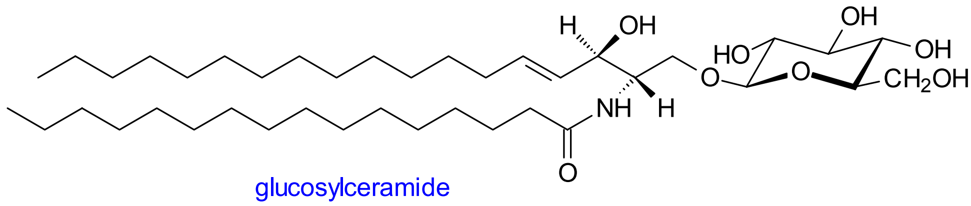


sphingomyelin

Sphingomyelin and other sphingolipids together with cholesterol are located in an intimate association in specific sub-domains or '**rafts**' (or related structures termed 'caveolae') of membranes. These are laterally segregated regions that form as a result of selective affinities between sphingolipids and membrane proteins. As sphingolipids containing long saturated acyl chains, they pack more tightly together, thus giving sphingolipids much higher melting temperatures than glycerophospholipids. This tight acyl chain packing is essential for raft lipid organization, since the differential packing facility of sphingolipids and cholesterol in comparison with glycerophospholipids leads to phase separation in the membrane, giving rise to the sphingolipid-rich regions ('liquid-ordered' phase) surrounded by glycerophospholipid-rich domains ('liquid-disordered' phase). The ordered phases are relatively resistant to attack by detergents, a property that is sometimes used to define them.

An important result of this process is that rafts contain a variety of different proteins, including glycerophosphoinositol(GPI)-anchored proteins and tyrosine receptor kinases. These provide much of the important biological properties of rafts, and are also essential to maintain their stability. Micro-domains or rafts that are enriched in sphingolipids (other than sphingomyelin), sterols and specific proteins have also been detected in the plasma membrane of plant cells.

Monoglycosylceramides or cerebrosides are common constituents of membranes of animals and plants. Galactosylceramide is the principal glycosphingolipid in brain tissue and myelin, while glucosylceramide is a major constituent of skin lipids, and is the source of the unusual complex ceramides that are found in the stratum corneum. It is also the biosynthetic precursor of the oligoglycosphingolipids. Harmful quantities of glucosylceramide accumulate in tissues of patients with Gaucher's disease, an inherited metabolic disorder. In plants, specific glucosylceramides elicit defense responses against fungal attack, and they appear to assist plants to withstand stresses brought about by cold and drought.



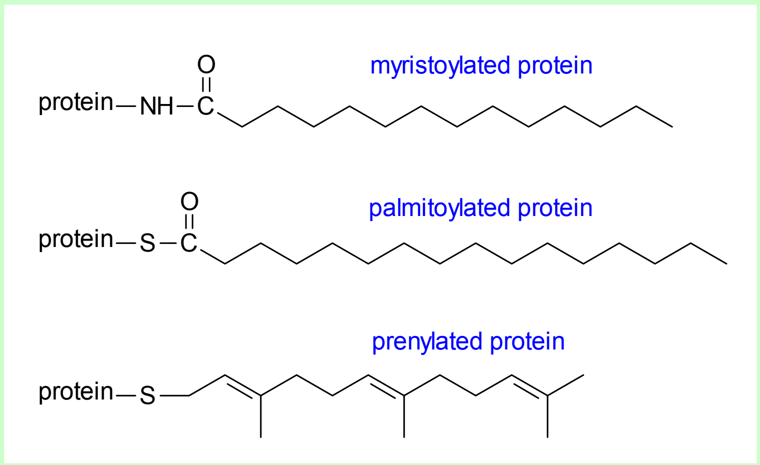
glucosylceramide

The membranes of animals and plants contain a wide range of complex **oligoglycosylceramides** (several hundred different head groups). Most of these occur on the external leaflet of the plasma membrane in rafts, where they are important components of the body's immune defense system, both as cellular immunogens and as antigens. For example, certain glycolipids are involved in the antigenicity of blood group determinants, while others bind to specific toxins or bacteria. Some function as receptors for cellular recognition, and they can be specific for particular tissues or tumours.

Glycosphingolipid sulfates are highly polar acidic molecules that are important in the transport of sodium and potassium ions and osmoregulation in animal tissues; they may also have a role in the protection of the intestinal mucosa against digestive enzymes. **Gangliosides** are complex oligoglycosylceramides containing sialic acid residues so they are also highly polar and acidic. They are cell-type specific antigens that control the growth and differentiation of cells and have an important role in the interactions between cells, especially in the immune defense systems. They are especially important for myelination in brain and other nervous tissues. In addition, gangliosides act as receptors of interferon, epidermal growth factor, nerve growth factor, insulin and many other metabolites, and in this way they regulate cell signalling. Certain gangliosides bind to specific bacterial toxins and they mediate interactions between microbes and host cells during infections.

Proteolipids and Lipoproteins

Proteins that contain covalently bound fatty acids or other lipid moieties, such as isoprenoids, cholesterol and glycosylphosphatidylinositol, are known to be widespread in nature with a variety of important functions. The term **proteolipid** is used to define such complexes, and to differentiate them from the plasma lipoproteins. Two main types of protein with a fatty acid modification have been described, i.e. those with only myristoyl and those with predominantly palmitoyl moieties, each with a distinctive type of linkage, amide or thiol ester, respectively. The prenylated lipids contain an isoprenoid group, farnesyl or geranylgeranyl, linked via a sulfur atom (thiol ether bond) to the protein. The so-called "hedgehog" proteins, which are important in cellular development, are modified by both cholesterol and *N*-palmitoyl moieties.



It is now clear that such modifications are important in determining the activities of proteins and in targeting them to specific subcellular membrane domains, including the rafts in plasma membranes. Thus, both myristoylated and palmitoylated proteins are targeted to rafts (as are the GPI-anchored proteins), but prenylated lipids are not. It noteworthy that many signalling proteins are modified by lipids with implications for the relevant events at the cell surface.

Lipoproteins are complex aggregates of lipids and proteins (not bound covalently) that render the lipids compatible with the aqueous environment of body fluids and enable their transport throughout the body of all vertebrates. Within the circulation, these aggregates are in a state of constant flux, changing in composition and physical structure as the peripheral tissues take up the various components before the remnants return to the liver. The most abundant lipid constituents are triacylglycerols, free cholesterol, cholesterol esters and phospholipids (phosphatidylcholine and sphingomyelin especially), though fat-soluble vitamins and anti-oxidants are also transported in this way. Free (unesterified) fatty acids and lysophosphatidylcholine are bound to the protein albumin by hydrophobic forces in plasma. Ideally, the lipoprotein aggregates should be described in terms of the different protein components or apoproteins (or 'apolipoproteins'), as these determine the overall structures and metabolism, and the interactions with receptor molecules in liver and peripheral tissues. However, the practical methods that have been used to segregate different lipoprotein classes have determined the nomenclature. Thus, the main groups are classified as chylomicrons (CM), very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL), based on the relative densities of the aggregates on ultracentrifugation.

Suggested Reading

The various documents dealing with individual lipid classes on this website have reading lists attached that should help our readers. In addition, the book '*Bioactive Lipids'* (edited by A. Nicolaou and G. Kokotos, Oily Press, Bridgwater, 2004) can be recommended as an invaluable single source of information. I also like -

- Dowhan, W. and Bogdanov, M. Functional roles of lipids in membranes. In: *Biochemistry of Lipids, Lipoproteins and Membranes (4th Edition)*, pp. 1-35 (edited by D.E. Vance and J.E. Vance, Elsevier Science) (2002).
- Eyster,K.M. The membrane and lipids as integral participants in signal transduction: lipid signal transduction for the non-lipid biochemist. *Adv. Physiol. Edu*., **31**, 5-16 (2007).
- Haucke, V. and Di Paolo, G. Lipids and lipid modifications in the regulation of membrane traffic. *Current Opinion in Cell Biology*, **19**, 426-435 (2007).

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