Simple and Complex Lipids: Their Occurrence, Chemistry, and Biochemistry

W. W. Christie
The Hannah Research Institute, Ayr, Scotland KA6 5HL

Reviewing the literature published during 1984 and 1985
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1 Introduction

As in the previous review in this series,[1] the term 'lipid' is restricted to long-chain fatty acids, their derivatives, and compounds that are related structurally and functionally to these. The origin of the term 'lipid', rather than the older terms 'lipoid', 'lipin', or 'lipide', has been discussed.[2] The occurrence, chemical synthesis, and analysis of such compounds are reviewed in this paper, as are mechanistic (as opposed to regulatory) aspects of their biochemistry. Fatty acids and triacylglycerols form the subject of a separate review, as do the physical properties of lipids in relation to the structure and function of membranes, so these topics are not discussed here. The properties of glycolipids are reviewed, but the treatment is extensive only where the aliphatic parts of the molecule are of particular interest. Literature coverage is for the years 1984 and 1985.

2 Simple Lipids

2.1 Monoacylglycerols

3-Acyl-*sn*-glycerols that contain saturated fatty acids in which there are 10 to 24 carbon atoms were synthesized chemically *via* isopropylidene intermediates for studies of the polymorphism of their crystalline forms.[3] A monoacylglycerol that contained a spin-labelled fatty acid, *i.e.* 12-(*N*-oxyldimethyloxazolidinyl)stearic acid, was synthesized by allowing the acid to react with glycidol in aqueous sodium chloride solution;[4] such compounds are of value in studies of the microenvironments within biological membranes. In comparable work, 1-acylglycerols were synthesized by the reaction of a fatty acid and glycidol, in the presence of tributylamine as the catalyst.[5]

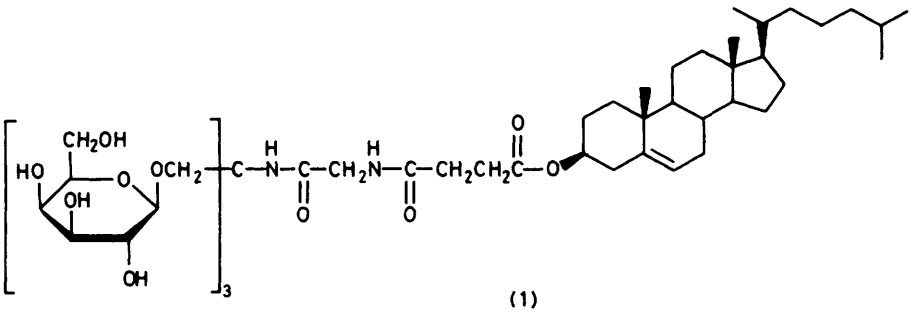
A monoacylglycerol that contains a sesquiterpenoic acid rather than a fatty acid has been isolated from the marine nudibranch *Archidoris montereyensis*, and its structure was elucidated by spectroscopy and from *X*-ray diffraction studies.[6]

The stereochemical course of the biosynthesis of triacylglycerols, *via* the monoacylglycerol pathway, in intestinal cells has been studied; 71% of the products were found to be synthesized *via* a 1,2-diacyl-*sn*-glycerol intermediate and the remainder *via* the 2,3-*sn*-isomer.[7] In contrast, structural studies appeared to indicate that the monoacylglycerol pathway does not function to a significant extent in the synthesis of the triacylglycerols of milk.[8]

2.2 Diacylglycerols

Diacylglycerols have been prepared by chemical synthesis by acylation of glycidol with fatty acid anhydrides followed by reaction with a quaternary ammonium salt.[5] 1-(Saturated acyl)-2-(unsaturated acyl)glycerols were also synthesized *via* glycidol intermediates, and by using a laevulinoyl moiety as a protecting group, since this could be removed (by reaction with hydrazine hydrate) without affecting the unsaturated fatty acids.[9]

A diacylglycerol may have appeared initially to be an unlikely candidate to act as a secondary messenger in cells, stimulating the phosphorylation of proteins, but an overwhelming body of evidence has now been amassed to confirm that this is indeed the case; the topic has been reviewed,[10] and it is also considered below in terms of the metabolism of polyphosphoinositides (Section 5). In particular, diacylglycerols modulate the action of the calcium ion–phospholipid-stimulated protein kinase C in cells in a similar manner to potent tumour promoters, such as phorbol esters. It was shown that analogues of diacylglycerols, such as dialkylglycerols and alkyl(acyl)glycerols, are not effective activators, but that 2-butyryl-1-palmitoyl-*sn*-glycerol is as potent as 1,2-dioleoyl-*sn*-glycerol.[11] Diacylglycerols that contain short-chain fatty acids (4 to 10 carbon atoms) were found to be particularly effective, probably because they are able to cross the plasma membrane into the cell. For example, 2-acetyl-1-oleoyl-*sn*-glycerol[12] and 1,2-dioctanoyl-*sn*-glycerol[13,14] were found to have a marked effect on the receptor for epidermal growth factor. Saturated diacylglycerols also function as regulators of protein kinase C in human platelets.[15] On the other hand, 2-acetyl-1-oleoyl-*sn*-glycerol inhibits the differentiation of Friend erythroleukaemic cells,[16] but fails to mimic the cell-differentiating effects of phorbol esters in human leukaemia (HL-60) cells,[17] although 2-acetyl-1-*O*-hexadecyl-*sn*-glycerol has the expected effect.[18] Among other observations, 2-acetyl-1-oleoyl-*sn*-glycerol was found to stimulate the formation of 1-phosphatidylinositol 4-phosphate in human platelets,[19] to



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stimulate the generation of superoxide[20] and to activate NADPH peroxidase[21] in human neutrophils, and to inhibit the activation of phospholipase C by angiotensin in smooth muscle cells.[22]

2.3 Simple Glyceryl Ethers

rac-1-*O*-Dodecylglycerol was found to be a powerful antibacterial agent, especially to Gram-positive bacteria such as *Streptococcus faecium*, because it stimulates autolytic activity and inhibits growth.[23] 1-Alkyl-2-acetyl-*sn*-glycerols [which are precursors of platelet-activating factor (PAF) (see Section 3.3)], though somewhat less potent than PAF as antihypertensive agents, produced responses of appreciably longer duration, with potentially fewer side-effects, *in vivo*; negative responses were obtained for a variety of analogues with similar structures.[24] Although the mechanism of the action of these compounds is not known, it is possible that they function in the tissue simply as precursors of platelet-activating factor.

A sulphydryl analogue of diacylglycerol, *viz.* 1,2-dioleoyl-3-thioglycerol, was synthesized and used in studies of transmembrane movements by exploiting its reactivity with 5,5′-dithiobis-(2-nitrobenzoic acid), which is a non-penetrating and colorimetric sulphydryl reagent.[25]

2.4 Sterol Esters and Related Compounds

The marine dinoflagellate *Gonyaulax polygramma* was found to contain a wide range of different sterols, many of which are esterified with fatty acids.[26] Similarly, a fresh-water dinoflagellate, *Peridinium lomnickii*, contains sterol esters of fatty acids; conclusive evidence for the existence of phytyl esters of sterols in an organism of this type was also obtained for the first time.[27] The major polar lipid in the hoof of the horse was shown to be cholesterol sulphate; it could be an important factor in determining the high degree of cohesiveness that is observed in this keratinized tissue.[28] An unusual acidic glycolipid was isolated from lipid extracts of human liver, and its structure was determined as 3-*O*-β-D-glucopyranuronosylcholesterol by high-resolution n.m.r. spectroscopy and mass spectrometry.[29] Long-chain (C_{16} to C_{29}) fatty acid esters of the triterpenoids 3α-hydroxylup-20(29)-ene-23,28-dioic acid and oleanolic acid have been isolated from the bark of *Schefflera octophylla*.[30]

A procedure for the synthesis of ω-[^{125}I]iodoundecyl cholesterol ether that utilized a hydroboration–iodination sequence has been described;[31] no carrier was required, so the product had a high specific activity.

A water-soluble derivative of cholesterol, the *N*-[4-(cholest-5-en-3β-yloxy)succinyl]glycine *N*-{tris[(β-D-galactopyranosyloxy)methyl]methyl}amide (1), has been prepared by chemical synthesis.[32] When added (as an aqueous micellar solution) to a dispersion of phospholipid vesicles, it rapidly associated with them and led to a seven-fold increase in the uptake of the liposome constituents by the liver; this effect is possibly mediated *via* galactose-specific recognition sites on the cells.[33] The compound also associated rapidly with low-density[34] and high-density[35] lipoproteins, greatly facilitating their catabolism by the liver.

Evidence has been obtained that newly synthesized cholesterol and preformed cholesterol are utilized in different compartments in intestinal cells for the synthesis of cholesterol esters,[36] and in the liver for export into bile.[37]

Reviews have appeared on the subjects of cholesterol and the cell membrane,[38] adipose tissue and the metabolism of cholesterol,[39] fluorescent sterols as membrane probes,[40] and the physical properties of cholesterol esters.[41]

2.5 Wax Esters and Other Simple Lipids

A number of long-chain α,ω-diols (C_{29} to C_{34}) are present in the lipids that are secreted from bovine and human meibomian glands, and they have been isolated and characterized.[42] Shorter-chain compounds of this type had been known previously only from certain plant cutins. In meibomian lipids, these compounds are present in the form of esters with fatty acids, in conjunction with other wax ester constituents, and they have been isolated by chromatographic means and identified.[43] Their biosynthesis was the subject of a separate study.[44] The diesters from the uropygial gland of chickens have been isolated and the configurations of acetonide derivatives of the long-chain diols, which exist both in the *threo* and *erythro* forms, were determined by n.m.r. spectroscopy.[45] Dolichyl esters of fatty acids are well-known constituents of animal tissues, but a hitherto unidentified constituent of bovine thyroid has been shown to be dolichyl dolichoate.[46] The dolichyl fatty-acid esters of the oviduct of the mature hen were isolated and characterized, and the enzymes that are involved in their hydrolysis in the tissue were studied.[47] Although the function of such compounds is still not known, it was decided that they are probably not present in the tissue simply as a store of dolichol for the production of dolichyl phosphate. In a study of the esterification of retinol by fatty acids in rat liver cells, it was concluded that the enzymes that are responsible are not the same as those that are involved in the synthesis of cholesterol esters.[48] Similarly, the lipase that is responsible for the hydrolysis of retinol esters is not identical to the cholesterol ester hydrolase or the triacylglycerol hydrolase, although it tends to be co-purified with these enzymes.[49] In particular, it was observed that the activity of the retinol ester hydrolase was inhibited much more strongly by ether analogues of cholesterol esters than were the activities of the other hydrolases.[50] An enzyme that is capable of catalysing the formation of ethyl esters from fatty acids and ethanol was isolated from rabbit myocardium and its properties were investigated; neither ATP nor coenzyme A was required for its action.[51,52]

The surface lipids of the pupae of the tobacco hornworm (*Manduca sexta*) were found to contain wax esters consisting of novel long-chain (C_{26} to C_{28}) oxo-alcohols, in addition to oxo-aldehydes and primary alcohols, which were esterified to acetoacetic, hydroxybutyric, and acetic acids.[53,54] While the C_{26} oxo-alcohol contained the oxo-group at position 11, the oxo-group was at either position 11 or position 12 in the C_{28} isomer.

The root of the tropical plant *Salmea scandens* has been found to contain isobutylamides and phenylethylamides of highly unsaturated fatty acids.[55,56]

3 Choline-containing Glycerophospholipids

3.1 Phosphatidylcholine and Analogues

A highly asymmetric arrangement of the various ether and acyl forms of phosphatidylcholine in the plasma membranes of cancer cells has been observed; the alkyl acyl form was found exclusively on the inner leaflet, while the alkenyl acyl and diacyl forms were located on the outer surface.[57] The ether phospholipid compositions of a variety of different tissues from the human, the rat, and the guinea pig have been determined by a new method, involving selective hydrolysis of the diacyl form (using phospholipase A_1) followed by acidic hydrolysis of the plasmalogens.[58] Lung surfactant from dogs was found to contain 5% of its phosphatidylcholine as the alkyl acyl form.[59] The sulphonium analogue of phosphatidylcholine, *i.e.* phosphatidylsulphocholine, has been found in further species of diatoms and algae.[60]

An improved chemical synthesis of phosphatidylcholines has been described, starting from a phosphatidic acid and choline, the latter being in the form of the tetraphenylborate salt, in the presence of 2,4,6-tri-isopropylbenzenesulphonyl chloride as a condensing agent.[61] Dimethylphosphoryl chloride may prove to be a valuable phosphorylating agent and has been applied in the synthesis of *rac*-2-*O*-hexadecyl-1-palmitoylglycero-3-phosphocholine.[62] Syntheses, by conventional means, of samples of phosphatidylcholines that contain deuterium-labelled oleic acid (in gram quantities)[63] or other fatty acids,[64] of phosphatidylcholines and of further phospholipids that contain hexacosa-5,9-dienoic acid (from marine organisms),[65] and of phosphatidylcholines that contain different methyl-branched C_7 fatty acids[66] or [9,10-$^3H_2$]octadec-9-enoic acid (in position 2)[67] have been reported. It was demonstrated that ^{31}P n.m.r. could be used to follow the time course of synthesis of phosphatidylcholines, as sharp, distinctive, and well-resolved resonances were obtained for the starting materials, the intermediates, and the products.[68] Much valuable information on the organization and dynamics of lipids in membranes has been obtained by employing phospholipids that contain fluorescent groups in the fatty acid moieties, and a number of new syntheses of such compounds have been reported.[69–72] Similarly, studies of the lateral distribution of phospholipids in membranes have been facilitated by the introduction of photochemically reactive functional groups into the fatty-acid chains, and new syntheses have been published of compounds of this type that contain anthracene[73] and azobenzene[74] moieties.

Phosphatidylcholines that are chiral at the phosphorus moiety and of known configuration were synthesized by *N*-methylation of chirally labelled 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine, and they were used to demonstrate that the configuration was retained during transphosphatidylation with phospholipase D.[75] Thiophosphatidylcholines were synthesized for studies of polymorphism in membranes.[76] In addition, a chiral thiophosphatidylcholine was used in a study of the metal-binding properties of the phospholipase A_2 of bee venom.[77] A conformationally restricted analogue of a phosphatidylcholine in which the diacylglycerol moiety was replaced by the corresponding all-*trans*-diacylcyclopentane-1,2,3-triol was prepared by total chemical synthesis.[78] In addition, a series of homologues was synthesized in which the separation of the phosphorus and nitrogen atoms was increased incrementally from two to nine methylene units. Similarly, analogues of phosphatidylcholines in which there is a methyl group at either C-1 or C-3 of the glycerol moiety were prepared in order that the effect of the increased steric bulk on the interactions with membrane components could be studied.[79]

Acylthioester analogues of phosphatidylcholines have been synthesized; studies of their reaction with the phospholipase A_2 of pig pancreas confirmed that the stereochemistry was as expected, although the rates of reaction were two orders of magnitude lower than those of the corresponding diacyl phospholipids.[80] Similarly, a dithioester analogue of 1,2-dihexanoyl-*sn*-glycero-3-phosphocholine was hydrolysed much more slowly by lipoprotein lipase (prepared from bovine milk) than was the corresponding acyloxy ester.[81] Incorporation of an alkyl group at C-2 into *rac*-1,2-diacylglycero-3-phosphocholine brought about a substantial loss of stereospecificity in relation to hydrolysis by phospholipase C and a total loss of specificity towards hydrolysis with phospholipase D.[82] Among other phosphatidylcholine-like molecules that have been prepared by total chemical synthesis were phosphinate,[83] carbamyl,[84] and ether analogues[84] and *rac*-1-chloro-1-deoxy-2-*O*-hexadecylglycero-3-phosphocholine.[85]

A procedure for preparing natural phospholipids that are labelled with the γ-emitter ^{125}I has been described which is suitable for use in biochemical and biophysical studies.[86] Hydroxy- and hydroperoxy-derivatives of phosphatidylcholine and phosphatidylethanolamine were prepared by the reaction of lipids from rat liver with singlet oxygen, with methylene blue as the photosensitizer, and the chromatographic properties of the oxidized species were investigated.[87] In addition, studies (by means of ^{31}P n.m.r.) of the aggregation of phospholipids in organic solvents demonstrated that the rate of autoxidation is dependent on the degree of aggregation.[88]

The mechanism of the regulation of biosynthesis of phosphatidylcholine has been reviewed.[89] Evidence was obtained from studies with rat platelets, *in vitro*, that the incorporation of arachidonic acid into ether phospholipids was achieved by exchange from acyl-containing phosphatidylcholine and not *via* the free acid.[90] In a comparable study, using rabbit alveolar macrophages, it was shown that isotopically labelled arachidonic acid was incorporated with greater rapidity into 3-*sn*-phosphatidylcholine than into other diacylated phospholipids, such as phosphatidylethanolamine and phosphatidylinositol, and these were in turn more rapidly labelled than were the alkyl ether or alkenyl ether forms.[91] In addition, it was shown by others that the incorporation of arachidonic acid into 1-alkyllysophosphatidylcholine could occur in the absence of coenzyme A, ATP, and magnesium ions, suggesting that at least three mechanisms are involved in the esterification of phospholipids.[92] In contrast, in *Tetrahymena thermophila*, it appeared that the differences in the relative proportions of diacyl and alkyl acyl forms of phosphatidylcholine and phosphatidylethanolamine were simply a consequence of the selectivities of the cholinephosphotransferase and the ethanolaminephosphotransferase.[93] It was demonstrated that the acyl-CoA:phospholipid acyltransferases in porcine platelets discriminated between the $(n-3)$ and $(n-6)$ families of polyunsaturated fatty acids in esterifying 1-acylglycero-3-phosphocholine, preferring those with an $(n-6)$ double-bond system.[94] On the other hand, the epithelium of the eustachian tube in rats synthesized predominantly disaturated phosphatidylcholine, like that in lung surfactant.[95]

Different molecular species of phosphatidylcholines were found to be hydrolysed at different rates in thrombin-stimulated human platelets, but the pattern is not as simple as had been thought hitherto.[96] The results indicated that the 1-acyl-2-arachidonyl species of phosphatidylcholine was not degraded by phospholipase A_2 exclusively, and that the compartmentation of species in the cell according to their metabolic origins influenced their susceptibility to hydrolysis. A neutral active phospholipase C, which hydrolysed phosphatidylcholine, and a phospholipase A_2, which was selective for plasmalogens, were identified in canine myocardium.[97] The lecithin–cholesterol acyltransferase (phosphatidylcholine–sterol acyltransferase) in human plasma is known to be capable of esterifying lysophosphatidylcholines in the presence of low-density lipoproteins; the substrate specificity of the enzyme in this reaction has now been studied.[98]

Phosphatidylcholine was shown to protect 3-hydroxybutyrate dehydrogenase against proteolysis, suggesting that the enzyme is normally immersed in the lipid bilayer *in vivo*.[99]

Neutral and ionic ether glycerolipids, especially alkyl(acyl)-glycerophosphocholines and the related alkenyl lipids, were formed from 1-*O*-alkyl- and alkenyl-glycerols by plant cell

cultures *in vitro*.[100] While the 1-*O*-alkyl-*sn*-glycerol was an excellent substrate, the 3-*O*-alkyl-*sn*-glycerol was not incorporated. The products were of value as precursors for the synthesis of platelet-activating factor (see Section 3.3). In a similar way, ether glycerolipids proved to be of great value in the study of the enzymes that are involved in the biosynthesis of phosphatidylcholine in plant tissue cultures.[101]

3.2 Lysophospholipids

It appears that oxidized phospholipids are preferred substrates for the production of lysophospholipids, especially lysophosphatidylcholines and lysophosphatidylethanolamines in hepatic lysosomes; this may be part of the mechanism for the production of such compounds during ischaemia.[102] An ATPase from radish microsomes required a lysophosphatidylcholine if it was to be able to express its activity.[103] Various *N*-alkyl- and *N*-alkenyl-carbamoyl derivatives of 2-lysophosphatidylcholine have been synthesized;[104] they have potent antimicrobial properties against protozoa and against human pathogenic and phytopathogenic fungi.

3.3 1-*O*-Alkyl-2-acetyl-*sn*-glycero-3-phosphocholines

Interest in the title compounds (more often termed 'platelet-activating factor' or 'PAF', and also occasionally abbreviated to PAF-acether, AAGPC, or AGEPC) has continued unabated. PAF has been shown to be present in the blood of normal humans and of experimental animals, but not in that from anephric patients, suggesting that the kidney plays an important part in the synthesis of the compound.[105] Additional evidence has been obtained for the presence of PAF in human amniotic fluid during labour, and in this instance the alkyl chain is composed solely of the octadecyl residue.[106] In contrast, in human neutrophils, the alkyl chain of PAF was found in one study to consist solely of a hexadecyl residue,[107] but in another study this was reportedly only 40% of the molecular species, and there were substantial amounts of 17:0, 18:0, and 18:1 isomers;[108,109] the PAF of rabbit neutrophils was also found to contain a number of different alkyl chains.[108] A new method has been developed for the determination of the structure of PAF, involving base-catalysed methanolysis at 60 °C.[110]

A total synthesis of a PAF has been reported in which 2-*O*-benzylglycerol reacted with dibutyltin to give a cyclic intermediate, which was sequentially alkylated and phosphorylated.[111] An isotopically labelled PAF was synthesized by tritiation of lyso-PAF that contained an unsaturated alkyl residue, followed by acetylation.[112] In addition, semi-synthetic preparations of PAF have been described from isotopically labelled glyceryl ethers, which were incubated with plant cell cultures; the alkyl acyl phosphatidylcholine that was formed was subsequently hydrolysed and acetylated.[113] A similar route to PAF and its ethanolamine-containing analogue made use of the fact that the natural phosphatidylethanolamine-containing fraction from bovine erythrocytes contains up to 80% as the l-*O*-alkyl form.[114] A number of analogues of PAF have been synthesized, including compounds with amide and azide linkages at position 2,[115] azido-derivatives and radioiodinated derivatives,[116] 2-(trifluoroethyl)-substituted derivatives,[117] and a phosphonate analogue.[118]

The critical micellar concentrations of PAF and several analogues were determined to show that, at normal physiological concentrations, each of these compounds is present as a monomolecular species.[119] An analysis of the proton n.m.r. spectrum of PAF in organic solvents confirmed that the preferred conformation is *gauche*.[120]

It has been claimed that rabbit platelets can synthesize PAF and a number of related phospholipids from 1-*O*-alkyl-2-acetyl-*sn*-glycerols, although this is probably not the principle biosynthetic mechanism.[121] Others have suggested that any reported synthesis of PAF in platelets might be a consequence of a small amount of contamination of the preparations with leukocytes, since synthesis of PAF could not be detected to have occurred in relatively pure preparations.[122] On the other hand, there was potentially enough of the necessary precursor in platelets to serve as a source of PAF.[123] It appears to be well established that 1-*O*-alkyl-2-arachidonyl-*sn*-glycero-3-phosphocholine is the main precursor of PAF *via* hydrolysis to lyso-PAF, thereby simultaneously releasing arachidonic acid in the free form; the lyso-PAF is subsequently acetylated. If PAF is indeed synthesized in platelets, it must be produced largely by this route.[124] Human neutrophils contain sufficient of the alkyl arachidonyl precursor to account for the amount of PAF that is synthesized; the distributions of molecular species in phosphatidylcholine and its ether-linked analogues have been determined in some detail.[125] The alkyl arachidonyl species was found to be a source of the precursor of PAF (and of free arachidonic acid) in human polymorphonuclear leukocytes.[126] In addition, evidence has been obtained that PAF is synthesized in an intracellular membrane of these cells.[127] It was shown that there is an increased synthesis of PAF in activated human eosinophils, suggesting that the compound might participate in some inflammatory and allergic reactions,[128] and it may also be involved in the processes that accompany hypoxia in the lung.[129]

The substrate specificity of the acetyl-coenzyme A acetyltransferase that is concerned in the biosynthesis of PAF by microsomes from rat spleen has been determined.[130] While lysophosphatidylcholine could serve as an acceptor for acetate, it was found that it did so at a reduced rate. Similarly, an octadecyl moiety was the preferred alkyl chain, and acetyl-coenzyme A was esterified much more rapidly than other short-chain derivatives. It appears that the activity of the acetyl-coenzyme A acetyltransferase is modulated by a phosphorylation–dephosphorylation mechanism.[131] The products of the reaction of lipoxygenase with arachidonic acid could control the rate of synthesis of PAF by enhancing the expression of phospholipase A_2,[132] and the presence of albumin might also play a part here.[133] In contrast, the C-reactive protein that occurs in plasma during acute trauma or inflammation seems to limit the effects of PAF by inhibiting the activity of phospholipase A_2, thus preventing the synthesis of PAF.[134]

In both platelets and alveolar macrophages, PAF is degraded eventually by deacetylation to 2-lyso-PAF, and it has been shown that the acetate that is released is not transferred to any other lipid product; the 2-lyso-PAF is, however, rapidly re-acylated by a mechanism that involves a direct transfer of arachidonic acid from phosphatidylcholine.[135–137] The acetylhydrolase that is responsible for the first step in the process was found in the serum of a wide range of vertebrates, but appears to be absent from avian serum.[138] When this activity was suppressed by adding a specific inhibitor *in vitro*, synthesis of PAF was observed to occur in thrombin-stimulated platelets.[139] Docosahexaenoic acid could also be transferred to 2-lyso-PAF *in vitro*.[140]

Much of the interest in the biological activity of PAF has centred on its effect on the aggregation of platelets, and a thio-analogue of PAF had a less potent effect than PAF itself.[141] The kinetics of the binding of PAF to human platelets have been studied and the results appear to confirm that PAF initiates responses by processes that are receptor-mediated.[142] PAF is certainly involved in the flux of calcium in cells and with the metabolism of 1-phosphatidylinositol 4,5-bisphosphate. For example, it was suggested that the effect on the mobilization of calcium might be an indirect one,[143] and could be mediated *via* the synthesis and turnover of polyphosphoinositides.[144–146] Evidence has also been produced that uptake of calcium is related to the synthesis of phosphatidic acid, by a process that is known to be stimulated by PAF.[147] In addition, PAF could exert some of its effects by inhibiting adenylate cyclase in platelets.[148,149] Analogues of PAF which inhibit the effects of PAF on the aggregation of platelets appear to operate by preventing its synthesis either by inhibiting the action of phospholipases or by blocking receptor sites.[150,151] Among wider

physiological effects of PAF that have been reported are acetylcholine-like effects in exocrine secretory glands,[152] the stimulation of phospholipases in fibroblasts,[153] the deactivation of the esterification of cholesterol in plasma,[154] the stimulation of hormone-sensitive GTPase,[155] and the activation of macrophages.[156]

4 Phosphatidylethanolamine and Related Lipids

By means of fast-atom-bombardment (FAB) mass spectrometry, it was shown that nearly 80% of the phosphatidylethanolamine fraction of cardiac sarcoplasmic reticulum is of the plasmalogen form.[157] Plasmenylethanolamine was found in the erythrocyte membranes from dystrophic chickens, but not in those of normal birds.[158] Marked changes occur in the composition of molecular species of plasmenylethanolamine in normal human myelin during development.[159] Perhaps more surprising was a report that nearly 90% of the phosphatidylethanolamine fraction in rabbit sperm was the dialkenyl form, with the remainder being the diacyl form (none of the alkenyl acyl form was apparently present).[160] Although diether lipids are known from a number of bacterial species, this appears to be the first report of the natural occurrence of a dialkenyl ether.

A facile procedure for the synthesis of phosphatidylethanolamines that contain deuteriated fatty acids from the corresponding phosphatidylcholines by exchanging the base (catalysed by phospholipase D) has been described.[64] Similarly, in a semi-synthetic approach (as it is not easy to acylate lysoplasmenylethanolamines), lysoplasmenylcholine was prepared, acylated, and converted into a plasmenylethanolamine by phospholipase-D-catalysed exchange of the base.[161] A number of analogues of phosphatidylethanolamine have been synthesized for studies of their physical properties in membranes. For example, a fluorescent probe was introduced into the molecule to assist studies of the spontaneous transfer of lipids that occurs in bilayers.[162] Syntheses of conformationally restricted homologues of phosphatidylethanolamine and phosphatidyl-*N*,*N*-dimethylethanolamine were described in which the diacylglycerol moiety was replaced by a diacylcyclopentane-1,2,3-triol, and in which the separation between the phosphorus and the nitrogen atoms was increased incrementally from two to nine methylene units.[78] In initial attempts to prepare cyclopentano-phosphatidyl *N*-methylethanolamines, using methylamine as an amination reagent, extensive aminolysis (with formation of *N*-methylpalmitamide) occurred.[163] However, it proved to be possible to circumvent the problem by using a somewhat different method in which *N*-benzyl-*N*-methylamine was employed as the nucleophile. Syntheses of phosphatidylethanolamines that contained two palmitoyl groups and in which ^{17}O and ^{18}O were introduced chirally into the polar head-group have been reported; the absolute configuration of each product was confirmed by ^{31}P n.m.r. spectroscopy after its conversion into derivatives of defined structure.[164] Similarly, chiral 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphoethanolamines were synthesized (and characterized by ^{31}P, ^{13}C, and ^{1}H n.m.r. spectroscopy) for studies of the stereospecificity of phospholipase D.[165] A procedure has been described for linking the water-soluble drug 'methotrexate' and related compounds covalently to phosphatidylethanolamines, as a means of introducing them into lipid bilayers.[166] For studies of the recognition of model membranes by the immune system, an analogue of phosphatidylethanolamine was synthesized in which the lipid was linked to a peptide (spacer molecule), which was in turn bound at the *N*-terminus to fluorescein (the hapten molecule).[167] In a similar way, a sulphonylazide moiety was introduced into the polar head-group of phosphatidylethanolamine (to enable a photo-activable interaction with proteins),[168] an *N*-hydroxysuccinimide ester was prepared (to bind to compounds that have a free amino-group),[169] and a procedure was described for synthesizing phosphatidylethanolamine in such a manner that it was bound to AH-Sepharose™ (for use in the affinity purification of enzymes that are involved in the metabolism of phospholipids).[170]

By experiments *in vitro*, it was shown that the relatively high concentrations of molecular species of phosphatidylethanolamine that contain penta- and hexa-enoic fatty acids in Ehrlich ascites tumour cells are largely a consequence of the specificity of the ethanolaminephosphotransferase.[171] In *Escherichia coli* there appears to be a metabolic cycle in which the fatty acids at position 1 of phosphatidylethanolamine are utilized for some purpose, while the resulting 1-lysophospholipid is re-acylated by an acyl-carrier-protein-dependent acyltransferase.[172] Serine was found to be employed for the biosynthesis of the ethanolamine moiety of phosphonolipids in a species of *Paramecium*, although ethanolamine itself was the precursor in the phospholipids.[173] In the rat, phosphatidylethanolamine that had been introduced intravenously in the form of chylomicrons was removed much more rapidly from the circulation than was phosphatidylcholine; much of this metabolism took place in the liver, by a degradative rather than an exchange process.[174]

The methylation of phosphatidylethanolamine to mono- and di-*N*-methyl forms and thence to phosphatidylcholine is involved in the transduction of receptor-mediated signals within cells. In the adipocyte, too, it was shown that the phospholipid methyltransferase activity was greatly stimulated by the hormones adrenocorticotropin and insulin, suggesting an important physiological role for the pathway here.[175] In endothelial cells, thrombin induces an increase in the rate of methylation of phospholipids, followed by an influx of calcium ions and release of the von Willebrand factor.[176] A physical chemical study of the interaction of phosphatidylethanolamine and its methylated forms with calcium ions was carried out; the di-*N*-methyl form interacted most strongly, and the effect was mediated by pH.[177] The phospholipid *N*-methyltransferases from murine thymocyte microsomes have been partially purified and characterized.[178] They appeared to be located on the external side of the microsome vesicles.[179]

N-Acylphosphatidylethanolamines were identified as constituents of the lipids of the central nervous system of fish at levels of 0.1 to 0.9% of the total phospholipid; both the alkenyl acyl and diacyl forms were isolated and characterized.[180] The properties of canine myocardial phosphatidylethanolamine *N*-acyltransferase have been investigated.[181] *N*-Acylethanolamine-containing phospholipids disappear as individuals of the amoeba *Dictyostelium discoideum* aggregate; the biochemical basis of this process has been investigated.[182,183] Several *N*-acylphosphatidylethanolamines have been synthesized and tested as activators of glucocerebrosidase in various forms of Gaucher's disease; the presence of a net negative charge on the molecule is more important than the nature of the acyl group.[184]

5 Phosphatidylinositol and Polyphosphoinositides

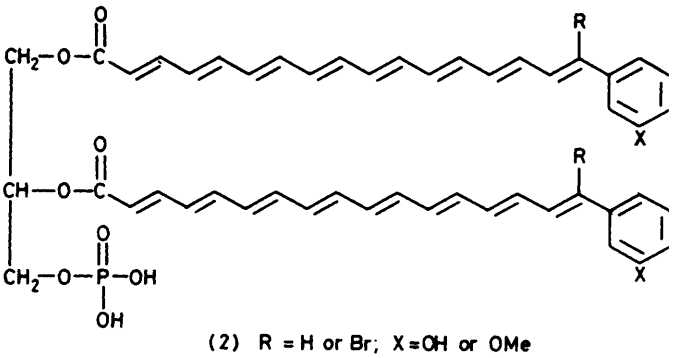
Unlike the phosphatidylinositol from animal tissues, which contains mainly stearic acid in position *sn*-1 and arachidonic acid in position *sn*-2, soybean phosphatidylinositol was found to contain palmitic, stearic, and linoleic acids in the primary position and linoleic acid in the secondary position.[185] In stimulated human neutrophils, the fatty-acid composition of the phosphatidylinositol was quite different from that of the diacylglycerols or of the phosphatidic acid; it was concluded that the phosphatidic acid was probably derived from a small pool of newly synthesized phosphatidylinositol.[186] In contrast, all of the inositol phospholipids, phosphatidic acid, and diacylglycerol were found to possess a common 1-stearoyl-2-arachidonoylglycerol backbone in thrombin-stimulated

platelets, suggesting that they are all readily interconverted.[187] Electrostatic interactions were found to be important in the transfer of phospholipids that is catalysed by a phosphatidylinositol-transfer protein from bovine brain.[188] In isolated rat glomeruli, it was found that a number of reagents which stimulate the synthesis of prostaglandins also enhance the turnover of phosphatidylinositol, although the nature of the pathway for release of arachidonic acid remains to be determined.[189] Enzymes from platelets that exert phospholipase C activities towards phosphatidylinositol[190] and lysophosphatidylinositols[191] have been characterized. A phosphatidylinositol kinase that co-purified with the receptor for epidermal growth factor has been prepared and its properties were investigated.[192] The tumour promoter phorbol myristate acetate appears to stimulate the phosphatidylinositol kinase in human platelets.[193]

The turnover of phosphatidylinositol and of the polyphosphoinositides 1-phosphatidylinositol 4-phosphate (PIP) and 1-phosphatidylinositol 4,5-bisphosphate (PIPP) is induced by a wide variety of extracellular messenger molecules, including neurotransmitters, hormones, growth factor, and platelet-activating factor amongst others, and they appear to function in the trans-membrane control of cellular functions. As diacylglycerols are among the important metabolic products, the topic is also discussed in Section 2.2, and has been reviewed.[10,194] Part of the metabolic effects of polyphosphoinositides may be mediated through binding of calcium ions, and the nature of the binding forces has been investigated.[195] The shape of erythrocytes is affected greatly by the concentrations of a number of factors (such as magnesium ions and ATP) that are of importance to the metabolism of polyphosphoinositides, the rates of biosynthesis of which were also markedly altered by altering the concentrations of those factors in four mammalian species.[196] In experiments with rabbit platelets that had been stimulated with low levels of thrombin, no decrease in the amount of PIPP was observed;[197] it was suggested that the increases in levels of phosphatidic acid that have been observed under such conditions are a consequence of synthesis *de novo* from dihydroxyacetone phosphate and glycerol 3-phosphate.

A procedure has been developed for the analysis of the individual phosphate groups in PIP and PIPP, involving first an assay of the 5-phosphate in PIPP by a 5-phosphate-specific phosphomonoesterase from erythrocyte membranes, then an assay of the 4-phosphate of PIP and of the total monoester phosphate content (4-phosphate plus 5-phosphate) of PIPP by reaction with an alkaline phosphatase from bovine intestine.[198] The specificity of the latter enzyme towards PIPP was studied independently by other workers.[199] Evidence has also been published for the presence of a specific PIPase activity in human erythrocyte membranes that did not affect PIPP or lysoPIPP.[200] In addition, the properties of the PIPP phosphodiesterase and phosphomonoesterase from rat brain[201] and the phosphodiesterase activity in mouse pancreatic minilobules[202] have been studied.

Phospholipase C activity is known to play an important part in the turnover of phosphatidylinositol, PIP, and PIPP in cells, and hormonal factors that control the activity of this enzyme are of special significance. It was concluded that in thrombin-stimulated human platelets most of the breakdown of phosphatidylinositol occurs by a direct reaction of phospholipase C on phosphatidylinositol itself rather than on PIP and PIPP.[203] On the other hand, PIP and PIPP were found to be competitive substrates to phosphatidylinositol for hydrolysis by phospholipase C, and PIPP (in particular) might be involved in the regulation of the activity of the enzyme.[204] In frog retina, the activity of the PIPP-specific phospholipase C was activated by light.[205] Cleavage of PIP and PIPP, if catalysed by a phospholipase C from ram seminal vesicles, is known to lead to the formation of cyclic phosphates; these were isolated and characterized, and some of their biological properties in platelets and in photoreceptor cells of *Limulus polyphemus* were investigated.[206]



(2) R = H or Br; X = OH or OMe

6 Phosphatidic Acid and Other Acidic Phospholipids

6.1 Phosphatidic Acid and Related Lipids

Distinctive phosphatidic acid molecules, containing esters of different xanthomonadin pigments (2) rather than fatty acids, have been isolated and characterized from among the lipids of the bacterium *Xanthomonas campestris* pv. *juglandis*.[207]

The changes in the molecular species composition of the phosphatidic acid of rat lung and liver during the perinatal stage of development have been determined.[208] Little change in the disaturated species, in particular, was found to occur in the liver during this period, but the proportion of this fraction in the lung increased nearly two-fold. Phosphatidic acid was found to be formed rapidly from diacylglycerols in isolated bovine rod outer segments, and it is not metabolized to other phospholipids.[209] Evidence was obtained from kinetic studies that in rat liver the glycerophosphate acyltransferases are distinct enzymes from those that catalyse the acylation of dihydroxyacetone phosphate;[210] the properties of the latter have been the object of a separate study.[211] A procedure has been developed for the assay of acyldihydroxyacetone phosphate and lysophosphatidate in animal tissues.[212] A phospholipase A_1 that is relatively specific for phosphatidic acid, and with properties somewhat different from those of other phospholipases and lipases, has been detected in porcine platelets.[213] With this tissue, 1-decanoyl-*sn*-glycerol 3-phosphate was found to induce the aggregation of platelets through an extracellular action, and the lyso-compound may not function as a secondary messenger.[214] Phosphonate,[215] fluorescent, and radiolabelled[216] analogues of phosphatidic acid have been prepared by chemical synthetic procedures.

Although many different phospholipids appeared to be capable of providing arachidonic acid for the production of icosanoids in rat alveolar macrophages, evidence has been obtained that lyso(bis)phosphatidic acid is a primary source.[217] The hereditary disorder Niemann–Pick disease is characterized, among other features, by an accumulation of lyso(bis)phosphatidic acid in the tissues. The fatty acids of this lipid class from several tissues were found to comprise more than 80% unsaturated components, with oleic, linoleic, and docosahexaenoic acids predominating.[218]

6.2 Phosphatidylserine

Phosphatidylserine is a ubiquitous, if minor, component of the tissues of all higher plants. It was therefore rather a surprise to find that, in eighteen different species that were examined, the fatty acid components included appreciable amounts of very-long-chain saturated acids (C_{20} to C_{26}) and related monoenoic (C_{22}, C_{23}, and C_{24}) constituents.[219] The substrate specificity of the L-serine base-exchange system in rat liver microsomes was studied and appeared to be consistent with the pattern of molecular species that has been observed *in vivo*.[220] In a related study of the incorporation of labelled serine into lipids in isolated rat hepatocytes, the results also suggested that most of the phosphatidylserine is formed by base-exchange, with only a

negligible incorporation from other putative intermediates.[221] The deacylation – re-acylation cycle appears to play a small part only. The membrane-associated phosphatidylserine synthases from the micro-organisms *Saccharomyces cerevisiae*[222] and *Bacillus licheniformis*[223] have been purified and characterized, as has the phosphatidylserine decarboxylase from *Clostridium butyricum*.[224] In baker's yeast, the phosphatidylserine decarboxylase activity was regulated in co-ordination with the enzymes in the pathway of biosynthesis of phosphatidylcholine that involves *N*-methylation.[225]

A synthetic fluorescent phosphatidylserine derivative was used to demonstrate that *N*-substituted aminophospholipids could activate a central pathway of aggregation and secretion from platelets.[226] With human erythrocytes, phosphatidylserine appears to cause agglutination through a combination of hydrophobic and ionic interactions.[227] The physical chemistry of the binding of calcium ions to phosphatidylserine has been studied.[195]

6.3 Phosphatidylglycerol and Bisphosphatidylglycerol

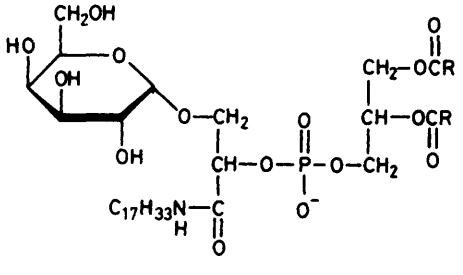
In the thylakoid membrane of several species of plant, much of the phosphatidylglycerol was found in the outer leaflet, where it comprised 66 to 77% of the total lipids; *trans*-hexadec-3-enoic acid, which is a major constituent of the fatty acids of the phosphatidylglycerol, was exclusively located in the outer leaflet.[228] From a detailed analysis of the molecular species of phosphatidylglycerol in cold-stressed *Dunaliella salina*, it was suggested that two distinct biosynthetic pathways operate.[229] Phosphatidylglycerol was found to be the biosynthetic precursor for the poly(glycerol phosphate) backbone of bifidobacterial lipoteichoic acid.[230] The movement of phosphatidylglycerol across membranes was studied by synthesizing a thio-analogue and following the process in lipid vesicle preparations by using a thiol-specific reagent.[25]

In acute alveolar injury in the dog, it was observed that the low level of phosphatidylglycerol in the surfactant was due to a relatively high rate of turnover to bisphosphatidylglycerol (cardiolipin).[231] Adriamycin has the capacity to complex bisphosphatidylglycerol, and was used as a probe to demonstrate that 57% of this lipid is located in the cytoplasmic face of the inner membrane of mitochondria.[232] By similar experiments it has been demonstrated that bisphosphatidylglycerol is the receptor for creatine phosphokinase in the membranes of mitochondria.[233]

6.4 Glycophospholipids

A glycerophosphosorbitol lipid, containing pigment esters, and being related in structure to the phosphatidic acid derivative (2), has been isolated and partially characterized from the bacterium *Xanthomonas campestris* pv. *juglandis*.[207] By enzymatic and chemical hydrolysis and n.m.r. spectrometric analysis of the fragments, a major phosphoglycolipid from the Gram-positive bacterium *Deinococcus radiodurans* was identified as the 2′-*O*-(1,2-diacyl-*sn*-glycero-3-phospho)-3′-*O*-(α-D-galactosyl)-*N*-D-glyceroylalkenamine (3).[234] When *E. coli* was cultured in the presence of 600 mM D-mannitol, it synthesized phosphatidylmannitol and bisphosphatidylmannitol, which are analogues of phosphatidylglycerol and bisphosphatidylglycerol respectively.[235] Such mannitol-containing phospholipids had apparently not previously been seen in Nature. The protozoan *Trypanosoma brucei* was found to contain the novel glycolipid glycosyl-1,2-di-*O*-myristyl-*sn*-glycero-3-phosphoinositol,linked by covalent bonds to the surface glycoprotein.[236]

The chemical syntheses of (diacylglycerophospho-α-D-glucosyl)glycerols,[237] (diacylglycerophospho-β-D-glucosyl)-glycerols,[238] and (diacylglycerophospho-α-D-diglucosyl)glycerol and related compounds[239] are described in a series of papers.



(3) R = alkyl

6.5 Other Phospholipids

An abnormal acidic phospholipid, phosphatidylethanol, was found in several tissues of rats that had been exposed to dietary (or injected) ethanol.[240] It may have been formed artefactually whilst the tissues were stored at low temperatures before they were analysed.[241] The final stages of a synthesis of a phosphinate phosphonate diether analogue of CDPdiacylglycerol have been published;[242] the compound is a powerful inhibitor of phosphatidylinositol synthase [CDPdiacylglycerol–inositol 3-phosphatidyltransferase] in platelets. Syntheses of phospholipids that contain photoactivatable carbene precursors in the headgroups, for crosslinking with membrane proteins,[243] and of an Acyclovir–phospholipid conjugate, as an antiviral drug,[244] have been reported.

7 Glycoglycerolipids

A partial synthesis has been reported of a spin-labelled monogalactosyldiacylglycerol, containing a 12-doxylstearoyl group;[245] the compound was used in the assay of galactolipid-transfer activity in spinach leaves. A stereospecific synthesis of long-chain 1-*O*-(β-D-maltosyl)-3-*O*-alkyl-*sn*-glycerols has been described.[246]

Sulphatoxygalactosyl(acyl)alkylglycerol, which is the major glycolipid of mammalian male germ cells, was found to bind to specific proteins in the plasma membrane.[247] Following a study of the positional distributions of fatty acids in the glycolipids of higher plants, it was concluded that much of the diacylglycerol moiety of sulphoquinovosyldiacylglycerol (and of phosphatidylglycerol) is formed biosynthetically in the chloroplasts.[248] Further experiments *in vitro* with $^{35}SO_4$ confirmed that chloroplasts are capable of autonomous synthesis of the polar headgroup.[249]

8 Sphingolipids

8.1 Ceramides, their Constituents, and Related Lipids

Free ceramide has been found as a minor constituent of the human erythrocyte membrane, and its long-chain-base and fatty-acid compositions have been determined.[250]

Sphingosine and phytosphingosine are the main long-chain bases in the glycolipids of rat foetuses, and some change in composition occur during development.[251] Convenient chemical syntheses of [1-$^2H_1$]- and [1-$^3H_1$]-sphinganine make use of natural sphinganine, prepared from bovine brain sphingomyelin, as the starting material.[252] The enzymology of serine palmitoyltransferase, which catalyses the initial committed step in the biosynthesis of sphingoid bases, has been studied.[253] In addition, results of experiments with rats suggested that the C_{18} backbone of 4*D*-hydroxysphinganine could be derived *en bloc* from sphinganine.[254]

In *Tetrahymena pyriformis*, strong evidence has been obtained that the hydroxylated fatty-acid constituents of the sphingolipids are formed by direct hydroxylation of normal fatty acids while they are linked to ceramide aminoethylphosphonate or to ceramide itself.[255,256]

The lipids of gliding bacteria of the genus *Cytophaga* are

known to contain a sulphonolipid analogue of sphingoid bases, *i.e.* capnine. It has now been demonstrated that capnine exists in the lipids of the organisms as fatty acid amide derivatives, analogous to ceramides.[257] The biosynthesis of capnine appears to occur by a condensation of palmitoyl-coenzyme A with cysteic acid.[258] On the other hand, if cysteine was added as the sole source of sulphur (with glucose) it provided the sulphur but not the carbon for the biosynthesis of capnine, suggesting that the sulphur is transferred *via* some additional carbon compound.[259]

8.2 Sphingomyelin and Similar Lipids

A simple semi-synthetic procedure for the preparation of D-*erythro*-sphingomyelins has been described in which the desired fatty acid was condensed with sphingosylphosphocholine in the presence of dicyclohexylcarbodi-imide.[260] In addition, sphingomyelins that contain fluorine-, pyrene-, and nitroxide-labelled fatty acids have been prepared by a rather similar method.[261] Sphingomyelin is known to be formed biosynthetically by transfer of the phosphocholine moiety of phosphatidylcholine to ceramide. The enzyme that is responsible has now been shown to be a transferase that has no ability to hydrolyse phosphatidylcholine.[262] The phosphatidylinositol phosphodiesterase that is activated by diacylglycerols was found to be inhibited by all choline-containing phospholipids, but especially by sphingomyelin, which may by this means have an important role in maintaining the stability of membranes.[263] In contrast, evidence has been obtained that lysosomal sphingomyelinase might be the main enzyme involved in the degradation of sphingomyelin.[264]

Various molecular species of ceramide-1-phosphoethanolamine and the phosphonolipid analogue have been isolated from the lipids of the cells of a species of *Paramecium* and characterized.[265] All contained mainly (> 90%) saturated fatty acids. Five alkali-stable lipids were obtained from the fungus *Histoplasma capsulatum*, and they appeared to consist of inositolphosphoceramides that were linked to mannose and thence to further mannose and/or galactose units.[266,267]

8.3 Neutral Glycosphingolipids and Sulpho-derivatives

The nature of the glycosphingolipids in plasma and the manner of their transport in the form of lipoprotein complexes have been reviewed.[268] Mass spectrometry and high-resolution n.m.r. spectroscopy have become the essential techniques for the determination of the structures of the carbohydrate moieties in glycosphingolipids. Two fucose-containing ceramide pentasaccharides from the plasma of blood-group O Le(a$^-$b$^-$) were isolated and the structures determined.[269] A pentaglycosylceramide, which reacted with an antibody in human serum, was characterized in rabbit erythrocytes.[270] A new blood-group-A glycolipid was found in erythrocytes,[271] and a fucosylhexaglycosylceramide was present as the H antigen in blood-group-O erythrocytes.[271,272] Similarly, the carbohydrate structures of two ceramide heptasaccharides, which reacted with the monoclonal anti-Le^a antibody, have been determined.[273] Even more of an analytical challenge was the elucidation of the structures of ceramide pentadecasaccharides in which there were up to three major branch points (in addition to a linear ceramide heptasaccharide) from rabbit erythrocytes.[274,275] Other novel glycolipids that have been isolated from mammalian tissues include a heptaglycosylceramide from kidney,[276] a series of linear poly-*N*-acetyl-lactosaminylceramides[277] and a sulphogalactosylceramide[278] from human granulocytes, a hexaglycosylceramide from rat bone marrow cells,[279] a series of mono- and bis-sulphoglycolipids from rat kidney,[280,281] and a number of distinctive fucolipids from human adenocarcinoma.[282,283] With the last, lipids with different carbohydrate moieties tended to have characteristic ceramide groups, *i.e.* containing predominantly either 2-hydroxy-C_{16} or 2-hydroxy-C_{24} fatty acids.

A number of distinctive glycosphingolipids, including three hitherto unknown components that contain mannose, have been isolated and characterized from fresh-water[284] and sea-water[285] bivalves. The sphingoid-base and fatty-acid compositions of these lipids were also distinctive. Similarly, many different mono- to hepta-glycosylceramides were obtained from the pupae of the insect *Calliphora vicina*; the ceramide moieties were dominated by icosanoic acid and tetradecasphing-4-enine.[286,287]

During aging of human diploid foetal lung fibroblasts, the composition of the glycosphingolipids changes appreciably, and the content of ceramide monohexoside, in particular, doubles.[288] The pattern of glycosphingolipids in rat kidney was found to be dependent on age and sex, especially with respect to the ganglioside components.[289] In the neutral glycosphingolipids of the stomach of the rat, the nature of the ceramide constituents changes during development.[290] For example, the proportion of 2-hydroxylated fatty acids increases from about 55% at 22 days of gestation to over 80% in the adult, and there are also changes in the compositions of the long-chain bases. Changes in the compositions of the glycosphingolipids have been observed in the epithelial and non-epithelial compartments of the large intestine of the rat;[291] the major lipophilic constituents are phytosphingosine and 2-hydroxylated fatty acids. In the human respiratory distress syndrome, a twenty-fold increase in the concentration of glycosphingolipids, mainly lactosylceramide and paragloboside, relative to that of the phospholipids in healthy patients was found in the alveolar lavage.[292] Certain molecular species of cerebroside that have been prepared from the fungus *Schizophyllum commune* are capable of inducing its fruiting. The only difference between active and non-active species appears to be that the latter contain C_{24} fatty acids.[293] Hybrid molecules of glycosphingolipids and glycoproteins, with an amide linkage between the sphingosine and aspartic or glutamic acid residues, have been detected in the gastric epithelium of the dog.[294]

By comparison of the ^{13}C n.m.r. spectra of natural glycosphingolipids, including the Gaucher cerebroside, with those of synthetic sphingolipids of known configuration, direct evidence has been obtained for the first time for the *erythro* configuration of the sphingosine moieties.[295] *N*-Deacylated (lyso) glycosphingolipids were obtained by heating the parent compounds with anhydrous hydrazine at 150 °C for up to 25 hours.[296] Syntheses have been reported of the ceramide portion of the cerebroside which induces fruiting in *Schizophyllum commune*,[297] of the cerebroside itself,[298] of a β-D-gluco-thio-cerebroside,[299] and of an analogue of galactosylcerebroside that contained a diazomalonyl photolabel.[300]

A method for studying the biosynthesis of the carbohydrate moieties in blood-group glycosphingolipids in the solid phase, on a matrix consisting of a high-performance thin-layer-chromatography plate, has been described.[301] High concentrations of ethanol were found to inhibit the enzymatic sulphation of glycosphingolipids in the gastric mucosa.[302] In platelets, the glycoprotein thrombosporin was found to bind specifically to sulphated glycolipids.[303] The cationophore monensin induces high cellular levels of glucosyl- and lactosyl-ceramide, apparently by promoting the anabolic mono- and di-glycosylations and by inhibiting higher glycosylations.[304]

The structure of the linoleate-rich acylglucosylceramides of pig epidermis was confirmed as 1-*O*-(β-D-glucosyl)-*N*-[ω-(*O*-linoleoyl)triacontanoyl]sphingosine by n.m.r. spectroscopy.[305] Evidence was presented that this compound and related lipids have an essential function in maintaining the epidermal permeability barrier to water.[306–308] It may be an essential function for linoleic acid that is independent of its role as a precursor for arachidonic acid and prostaglandins.

8.4 Gangliosides

In erythrocytes from individuals with blood-group Cad specificity, there is a distinctive ganglioside profile, and at least one

component had not been found previously.[309] It appears to be a sialosylparagloboside with an additional *N*-acetylgalactosamine residue. A new disialoganglioside, containing a terminal *N*-acetyl-9-*O*-acetylneuraminic acid moiety, has been found in rat erythrocytes and characterized.[310] In porcine erythrocytes, ganglioside G_{D3} is a major component.[311] As mentioned above (Section 8.3), human granulocytes were found to contain hitherto unknown glycosphingolipids, and these also included novel gangliosides with a linear *N*-acetyl-lactosaminyl backbone.[277] New gangliosides that have been isolated from the nasal cartilage of the adult bovine include a component that was identified as a disialo-lacto-*N*-norhexaosylceramide; it contained mainly 16:0, 18:0, 22:0 and 24:0 fatty acids, together with sphingenine, heptadecasphingenine, and hexadecasphingenine.[312] In addition, a novel disialoganglioside was isolated from bovine adrenal medulla,[313] a pentasialoganglioside was found in embryonic chicken brain,[314] a sialosylglobotetraosylceramide was present in elevated concentrations in muscles of patients suffering from amyotropic lateral sclerosis,[315] and several distinctive gangliosides were identified in dolphin kidney.[316] Mullet roe contains a ganglioside G_{M2} that is identical to that in human brain, but with C_{18} and C_{20} phytosphingosines as the main long-chain bases and with monoenoic 2-hydroxy-compounds as the main fatty acids.[317] Gangliosides are known to be important constituents of cancer tissue, and novel branched components were found in murine leukaemia cells,[318] a ganglioside 9-*O*-acetyl-G_{D3} was a constituent of a melanoma cell line,[319] fucogangliosides were characterized from human adenocarcinoma,[320] a sialosyl-lactotetraosylceramide was an antigen in a cell lung carcinoma,[321] and a ganglioside that contains *N*-glycolylneuraminic acid was detected in a cell line that had been derived from a Marek's disease lymphoma.[322] In addition to being used in many of the papers just cited, chemical-ionization mass spectrometry,[323] fast-atom-bombardment mass spectrometry,[324] and carbon-13 n.m.r. spectroscopy[325] for the characterization of gangliosides have been the subjects of separate publications.

Modified gangliosides have been prepared in which the carboxyl group of the sialic acid residue was reduced with sodium borohydride after first preparing the methyl ester derivative (by reaction with methyl iodide in dimethyl sulphoxide).[326] The biological activity of the reduced compound appeared to be even higher than that of the native ganglioside. Lysogangliosides (deacylated) have successfully been prepared for the first time.[327] Long-chain fatty acids and acetyl groups were removed from natural gangliosides by alkaline hydrolysis, the amino-group of the sphingoid moiety was selectively protected by reaction with a hydrophobic protecting group (9-fluorenylmethoxycarbonyl), the oligosaccharide amino-groups were re-*N*-acetylated, and finally the protecting group was removed. A fluorescent derivative of a ganglioside has been prepared by oxidation of the sialic acid residue with sodium periodate and reaction of the resulting aldehyde with Lucifer Yellow.[328] A lactone derivative of ganglioside G_{M3} was prepared by a lengthy incubation with glacial acetic acid, and it was characterized by n.m.r. spectroscopy.[329] Although calcium ions were found to bind strongly to gangliosides, the complexes were rapidly dissociated by serotonin.[195]

9 Lipopolysaccharides

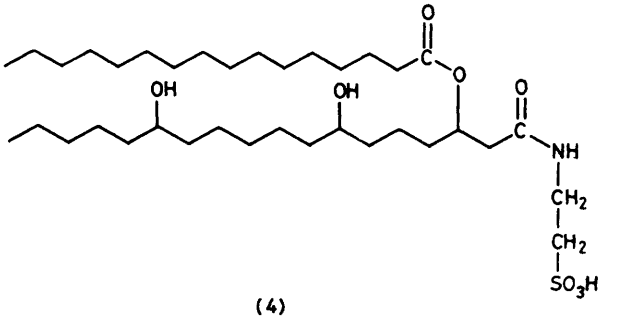
The nature and location of the amide-bound (*R*)-3-acyloxyacyl groups in Lipid A from various Gram-negative bacteria have been determined; both normal and iso-branched acyl groups with 10 to 17 carbon atoms were identified, in addition to (*S*)-2-hydroxydodecanoic acid.[330] Laser-desorption mass spectrometry was applied to dephosphorylated preparations of Lipid A from *Salmonella minnesota* to elucidate the location of the 3-hydroxytetradecanoic acid residues.[331] Hepta-, hexa-, and penta-acylmonophosphorylated Lipid A species were isolated, by high-performance liquid chromatography, from the lipopolysaccharides of the same organism, and their structures were determined by two-dimensional n.m.r. spectroscopy.[332] Eight precursors of Lipid A were isolated from a mutant of *Salmonella typhimurium*[333] and the locations of the polar substituents and of the fatty acyl groups were investigated by ^{1}H, ^{13}C, and ^{31}P n.m.r. spectroscopy.[334] A unique *N*-acylkanosamine-containing epitope was identified among the trehalose lipopolysaccharides from Mycobacteria,[335] and the nature and location of the fatty acid constituents of pyruvylated glycolipids from *Mycobacterium smegmatis* were determined.[336] Similarly, the nature of the acyl moieties that are bound to the two hydroxyl groups and the two amine residues of the D-glucosamine disaccharide phosphate backbone of the Lipid A from *Escherichia coli* was elucidated.[337]

Chemical syntheses have been reported of the Lipid A[338] and of a 1-dephospho-Lipid A from *E. coli*,[339] of a monosaccharide analogue of Lipid A,[340,341] and of glycolipids that are related structurally to the Lipid A from *Bordetella pertussis*.[342–344] In addition, the biological activities of a number of synthetic analogues of Lipid A have been investigated.[345–349]

10 Other Complex Lipids

In a number of representative genera of methane-producing archaebacteria, the patterns of polar lipids that were obtained by two-dimensional thin-layer chromatography were investigated.[350] Different genera had distinctive lipid compositions, although species within a genus appeared to have similar compositions. In examples from the genera *Methanomicrobium*, *Methanosarcina*, and *Methanolobus*, novel core lipids were present. Degradation of the glycerol ether phospholipids of 25 methanogenic bacterial cultures with hydriodic acid gave alkyl iodides, which were converted into the alcohols and acetate esters and shown to be C_{15}, C_{20}, and C_{25} isoprenoid homologues.[351] The membrane lipid from a new, extremely thermophilic, deep-sea archaebacterium, *Methanococcus jannaschii*, which lives in hydrothermal vents, was found to contain a novel macrocyclic glycerol diether with two carbon atoms fewer than the normal bis(diphytanyl)glycerol diether.[352] Diether lipids were also found in a non-alkalophilic, non-pigmented extremely halophilic bacterium.[353]

A novel lipid, containing taurine and 3,7,13-trihydroxystearic acid (also new), was isolated from cells of *Tetrahymena pyriformis* NT-1, and was characterized as 2-[(3-hexadecanoyloxy-7,13-dihydroxyoctadecanoyl)amino]ethanesulphonic acid (4).[354] Biosynthetic studies confirmed that taurine itself was a direct precursor, while the trihydroxylated fatty acid was derived from stearic acid. Only two of twenty bacterial strains that were surveyed, *i.e. Thiobacillus* A2 and a species of *Achromobacter*, were found to contain ornithine-containing lipids; in both, a normal fatty acid was esterified to the hydroxyl group of a 3-hydroxylated fatty acid, which was in turn linked to the α-amino-group of ornithine.[355] Trehalose 6-monomycolate was identified among the lipids of *Bacterionema matruchotii*,[356] and novel mycolipenates and mycolipanolates of trehalose were found and characterized among the lipids of *Mycobacterium tuberculosis*.[357] Similarly, 6-*O*-[(C_{40-46})nocardomycoloyl]-glucose was present in the lipids of *Nocardia rhodochrous* that had grown on a glucose-supplemented medium.[358]



(4)

4-*O*-(1,2-Diacylglyceryl)-*NNN*-trimethylhomoserine, which is present in algae, has been identified as a phagostimulant for the sea hare *Aplysia juliana*.[359] A related compound, 3-*O*-(1,2-dipropionylglyceryl)-*NNN*-trimethylserine, was prepared by chemical synthesis.[360]

11 Fatty Acids that are Linked Covalently to Proteins

There appears to be increasing evidence that acylation of proteins with fatty acids post-translationally may be a general method for converting proteins which are otherwise soluble into a membrane-bound form. The linkage is often at the terminal amino-group, but it can also occur *via* a thioester bond to cysteine, as occurs in complex antigens in membranes[361] and in a number of its proteins during the development of the sea urchin *Strongylocentrotus purpuratus*.[362] Similar bonds may have been involved when bovine rhodopsin was acylated with palmitic acid;[363] the protein retained its photosensitivity. The formation of ester bonds between fatty acids and glycoproteins in gastric mucosa and submandibular glands has also been investigated.[364-367] Deacylated mucin became susceptible to proteolytic digestion. Studies with muscle cells showed that many different acylated proteins were formed, that they were not restricted to membrane locations, and that they were involved in specialized cell functions; the chain-length of the bound fatty acid also appeared to be distinctive at each site.[368] The acylation of sialoglycoproteins[369] and of acetylcholinesterase[370] by fatty acids that occurs in erythrocytes has been studied. Phospholipids have been reported to be acyl donors to membrane proteins in *Mycoplasma capricolum*.[371]

3-*O*-Fatty-acid esters of serine and threonine, in the form of the dinitrophenyl derivatives, have been synthesized chemically as an aid in the identification of components in proteolytic digesta from membrane proteins.[372]

12 Analytical Methodology

Many of the papers cited above made use of distinctive methodology for the isolation of particular components, and are not discussed further here. A two-volume work on the chromatography of lipids,[373] a monograph on lipid methodology,[374] and a guide to separation techniques for lipoproteins have appeared.[375] Shorter reviews have dealt with the analysis of lipids in general,[376] the analysis of phospholipids,[377] and either gas chromatography or high-performance liquid chromatography (h.p.l.c.), coupled with mass spectrometry, applied to the separation and identification of molecular species of lipids.[378-380]

A process of consolidation appears to have been occurring in many aspects of lipid methodology, but developments have continued apace with h.p.l.c. Because lipids (in general) lack chromophores that facilitate their spectrophotometric detection, there has been a long-felt need for a commercial 'universal' detector that could be used with solvent gradients. In the author's opinion, the transport-flame ionization detector that was developed by Privett, and which has most recently been applied to separations of triacylglycerols,[381,382] is the most sensitive and versatile yet constructed, although it is unfortunately not available commercially. An instrument that operates on the same principle has been described,[383] and is manufactured on a commercial scale, so may make an impact in the near future. One application to lipids has been published, *i.e.* in the separation of molecular species of phosphatidylglycerol and (bigalactosyl)diacylglycerol by h.p.l.c. in the reversed-phase mode.[384]

A simpler and less costly approach to the problem of detection has been provided by the 'mass detector', also known as an 'evaporative analyser' or 'light-scattering detector', in which the solvent from the h.p.l.c. column is evaporated in a stream of air while the solute passes through a light beam, causing scattering. The physical chemistry of the detection process with a commercial detector (ACS Ltd, Macclesfield, U.K.) has been investigated,[385,386] and applications to the reversed-phase separation of molecular species of triacylglycerols[387,388] and of phospholipids[389] have been described. A further elegant application was to the rapid separation of the lipid classes from animal tissues, ranging in polarity from cholesterol esters to lysophosphatidylcholine, in one step.[390] Others have demonstrated the construction and properties of a similar mass detector,[391] and have applied it to the separation of molecular species of triacylglycerols.[392] Although detectors of this type are sensitive and easy to use, the relationship between the nature and amount of the solute and the response of the detector is a complex one, so careful calibration is necessary in quantitative analyses.

Of course, h.p.l.c. in combination with mass spectrometry is an extremely powerful tool for simultaneously detecting, identifying, and quantifying lipids, although its cost is outwith the range of most analysts. Several applications to lipids have recently been described.[378-380,393-395]

Among the very large number of papers that have been published on lipid methodology in the period under review, distinctive h.p.l.c. separations were noted of phospholipid classes (including PAF),[396-403] gangliosides,[404-406] long-chain bases,[407] diastereoisomeric diacylglycerols and related compounds,[408] and molecular species of plant polar lipids,[409,410] PAF,[411] lysophospholipids,[412,413] sphingomyelin,[414] bisphosphatidylglycerol,[415] and phospholipids *via* diacylglycerol derivatives.[416,417]

13 Books and Review Articles

A number of books and review articles are discussed at the appropriate points in the above text. The author found a book on the adaptive role of lipids in biological systems by Hadley[418] to be of particular interest. In addition, comprehensive monographs have appeared on the subjects of biotechnology in the oils and fats industry,[419] oilseed technology,[420] lipids in cereal technology,[421] lipases,[422] the role of fats in food and nutrition,[423] fats in animal nutrition,[424] plant membranes,[425] the physiology of membrane fluidity,[426] intracellular lipid-binding and transfer proteins,[427] liposomes,[428,429] lipids in plants and microbes,[430] dietary fats and health,[431] and lipid metabolism in the liver.[432] The review journal *Progress in Lipid Research*[433] has contained articles on membrane structure and enzyme kinetics, 3-*sn*-phosphatidate phosphohydrolase (phosphatidate phosphatase), the phase behaviour of fats, lipid metabolism in the liver, the structures of apolipoproteins, and the oxidation of lipids and phosphonolipids. Reviews have been published in *Advances in Lipid Research*[434] on lipoprotein metabolism, leukotrienes, dietary fat and immunity, gastrointestinal digestion, the yeast membrane, the biosynthesis of carotenoids, and proteins in membranes, while *Annual Review of Physiology*[435] has included a series of articles on lung surfactant lipids. In addition, reviews have appeared on lipoproteins and apolipoproteins,[436-441] peroxidation of lipids,[442] lipid-transfer proteins,[443] thermogenesis in brown fat,[444] mammalian phospholipases,[445] insect cuticular lipids,[446] mitochondrial lipids,[447] the plasma membrane of *Acholeplasma laidlawii*,[448] the lipid composition and function of membranes,[449,450] the lipids of human milk,[451,452] and the nutrition and biochemistry of *trans*-fatty acids.[453]

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