Biochem. J. (1988) 251, 1–9 (Printed in Great Britain)

REVIEW ARTICLE

The biological role of dolichol

Tadeusz CHOJNACKI* and Gustav DALLNER†

*Institute of Biochemistry and Biophysics, Polish Academy of Sciences, 02-532 Warsaw, Poland, †Department of Biochemistry, University of Stockholm, S-106 91 Stockholm, and †Department of Pathology, Karolinska Institutet, S-141 86 Huddinge, Sweden

INTRODUCTION

Phospholipids are present in eukaryotic cells primarily in membrane-bound form, whereas neutral lipids are found in large amounts in luminal compartments of organelles or in the cytoplasm as micelles or associated with apoproteins. On the other hand, dolichol is more widely distributed within the cell and in different tissues and organs. Dolichol was first identified in 1960 by Pennock, Hemming & Morton [1], and it was established by Behrens & Leloir in 1970 [2] that its phosphorylated derivative is an obligatory intermediate in the synthesis of certain types of glycoproteins. Of all lipids, this compound has thus been studied for the shortest period of time and, despite detailed investigations in many laboratories in recent years, our knowledge about the biosynthesis, distribution and function of dolichol is still fragmentary.

STRUCTURE OF DOLICHOL

Dolichol is a polyisoprenoid substance and, consequently, is among the largest lipids in the cell (Fig. 1). This polyunsaturated compound has an α-saturated isoprene residue, which may either be in the form of a free alcohol, phosphorylated or esterified with a fatty acid [3–6].

In animal cells the distribution of the various polyisoprenoids shows a distinct pattern (Table 1). The α-unsaturated form (polyprenol) occurs in small amounts ($\sim 1\%$ of the total) under normal conditions [7–10]. When dolichol synthesis is disturbed, such as in human liver cancer cells, the amount of this unsaturated lipid may increase considerably to 10–30% of the total (I. Eggens *et al.*, unpublished work).

The amounts of polyprenyl phosphate and pyrophosphate are also very low. The latter compound, with different isoprene lengths, should be present in tissues as intermediates in dolichol biosynthesis, but the distribution of these derivatives has not yet been studied. Short polyisoprenes with less than 15 residues are not present in animal cells, and those with 11 residues have been found only in pig liver (1%) [7]. A family of longer dolichols with 15–23 isoprene residues is present, in contrast with ubiquinone, which has only one major form in each individual species (nine isoprene residues in rat; ten in human).

The pattern of dolichols is species-specific, and only moderate differences in this pattern for membranes, cells and organs are observed. The major derivatives in rat are those with 18 and 19 residues, whereas in Man the major derivatives contain 19 and 20 residues [11,12]. This distribution pattern is changed only under pathological conditions, such as after treatment of rats with phthalate esters [13] or in human liver cancer [14].

All dolichols so far investigated are in the *S*-form, and probably only the *trans-trans*-poly*cis* compound is present in biological membranes, again in contrast with ubiquinone, which is in the all-*trans* form [15–17]. Depending on the tissue or membrane, a smaller or larger portion of the total dolichol is esterified with a fatty acid [18]. A large portion of the dolichyl (mono)-phosphate is in the free form and, depending on the physiological conditions, a smaller part is glycosylated with a monosaccharide [12,19]. Dolichyl pyrophosphate is present in small amounts and mostly bound to core oligosaccharides.

DISTRIBUTION

The idea that polyisoprenoid compounds are present in the cell in minute amounts originates from early studies on tissues of experimental animals before the development of h.p.l.c. Investigation of human organs with h.p.l.c., however, reveals that these lipids are present in considerable amounts, particularly in endocrine tissues (Table 2) [12,20]. Only a smaller portion (2–8%) of the total dolichol is phosphorylated in humans.

The subcellular distribution of polyisoprenoid compounds is broad, and they can be considered as general membrane components (Table 3) [14,21,22]. The mitochondrial inner membrane has a very limited total amount of dolichol ($\sim$ 0.1 g/mg of protein), and low

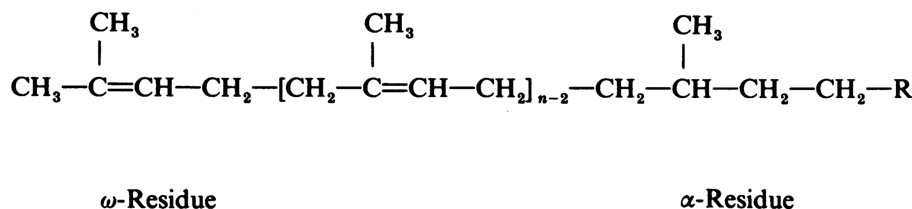


Fig. 1. Structure of dolichol

R is a hydroxy group, monophosphate, pyrophosphate or fatty acid.

Table 1. Occurrence of polyprenols in animal cells

Compound	Form, associated group	Amount (% of total)
Polyprenol	16–22 Isoprenes	1 % (liver, pituitary gland, hen oviduct)
Polyprenyl phosphate and pyrophosphate	16–22 Isoprenes	Less than 1 %
Dolichol, short	15 Isoprenes	1 %
Dolichol, long	16–23 Isoprenes	80–98 %
S-Dolichol	–	All biological dolichol
R-Dolichol	–	Only synthetic
trans-trans-poly*cis*-dolichol		All dolichol
Dolichyl ester	$C_{16:0}$, $C_{17:0}$, $C_{18:0}$, $C_{18:1}$, $C_{20:4}$ and $C_{22:6}$ fatty acids	10–60 % of neutral dolichol
Dolichyl phosphate	Free + monosaccharide attached	2–20 %
Dolichyl pyrophosphate	Free + oligosaccharide attached	Small amounts

amounts are also found in mitochondrial outer membranes, microsomes and nuclei (~ 0.3 μg/mg of protein). Easily measurable amounts are recovered in the peroxisomes, whereas in plasma membranes, Golgi vesicles and lysosomes the concentration is high (e.g. 4.5 μg/mg of protein in the latter). Dolichyl phosphate is present in microsomes and lysosomes, which contain the same level of this lipid (~ 0.2 g/mg of protein).

When microsomes, Golgi vesicles and lysosomes are sonicated and the membranes isolated, their content of dolichol plus dolichyl phosphate was about the same (0.3–0.4 μg/mg of protein) (C. Edlund *et al.*, unpublished work). The remainder is released, indicating that it is located in the luminal compartments. If the localization of dolichol in the central, hydrophobic, portion of the membrane bilayer is accepted, as discussed below, it is quite understandable that the dolichol content of the membrane itself can vary only to a very limited extent.

FUNCTIONS OF DOLICHOL

Our present information about the function of dolichol originates mainly from studies on model membranes, and our assumption here is that these results can be extrapolated to biological membranes. The experiments show that dolichol and dolichol analogues exert a considerable influence on the organization and packing of phospholipids [23–28]. Polyisoprenoids appear to increase the fluidity of phospholipids in bilayers, destabilize lipid membranes, elicit formation of inverted micelles within the membrane (H_{II} phase and lipidic particles) and increase permeability. Most interesting are the findings that dolichol enhances vesicle fusion in a concentration-dependent manner and that dolichyl phosphate stimulates the fusion of rat liver microsomes and unilamellar lipid vesicles [29]. In this way dolichol in membranes may play an important role in the extensive membrane traffic between the Golgi system, the plasma membrane and the lysosomes, which is the basis for many important events in cellular life.

Dolichol appears to be associated with phosphatidylethanolamine, in contrast with cholesterol, which displays a close relationship to phosphatidylcholine. The membrane effect exerted by dolichols is increased by increasing the chain length. The effects of polyisoprenoids on membranes may also be advantageous in the process of glycosylation. The transmembrane movement of dolichyl pyrophosphate-oligosaccharides from the site of their assembly on the outer cytoplasmic surface of the endoplasmic reticulum to the inner luminal surface [30, 31] may be elicited by the destabilizing effect of the lipid intermediate.

Experimental evidence indicates that dolichol is sandwiched between the two halves of the phospholipid bilayer (Fig. 2), i.e. between the fatty acids [26,32]. The localization of cholesterol is different, since this lipid is asymmetrically located along the fatty acids.

The major segment of dolichyl phosphate molecules are arranged in a similar manner in the hydrophobic

Table 2. Dolichol distribution in human and rat organs

	Amount (μg/g wet wt.)	
Organ	Human	Rat
Adrenal	1600	49
Brain	279	40
Kidney	192	11
Liver	452	43
Pancreas	1440	30
Pituitary gland	7170	–
Spleen	114	85
Testis	1540	13
Thyroid gland	1960	–

Table 3. Dolichol content in subcellular organelles of the liver

Very low: mitochondrial inner membranes
Low: mitochondrial outer membranes, endoplasmic reticulum, nuclei
Moderate: peroxisomes
High: plasma membranes, Golgi vesicles, lysosomes

Organelle membranes:	constant amount, 0.3–0.4 μg/mg of protein
Organelle contents:	the remainder

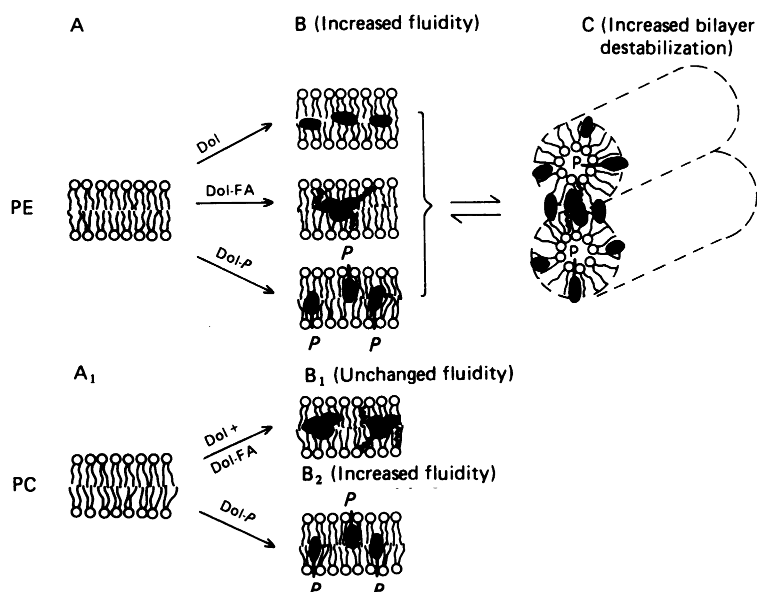


Fig. 2. Schematic representation of the suggested events after incorporation of dolichol, dolichol esters and dolichyl phosphate into phosphatidylethanolamine (PE) or phosphatidylcholine (PC) model membranes

A, phosphatidylethanolamine bilayer in liquid-crystalline state; B: upper panel, dolichol distributed homogenously in the hydrophobic domain; middle panel, dolichol esters present in clustered form in the hydrophobic domain with its phosphate group oriented perpendicular to the water interphase; dolichol, dolichol esters and dolichyl phosphate in H_{II} phase. A_1, phosphatidylcholine bilayer in liquid-crystalline state; B_1, dolichol clusters and dolichol ester clusters present in the hydrophobic domain; B_2, dolichyl phosphate distributed homogenously in the hydrophobic domain. Abbreviations: Dol, dolichol; FA, fatty acid; P, monophosphate. This Figure is taken from [24] and is reproduced with permission.

centre of the membrane, but in this case the phosphate group is located at the outer surface and the α-terminal end of the polyisoprene runs parallel with the fatty acid chains [27].

FUNCTIONS OF DOLICHYL PHOSPHATE

The function of dolichyl phosphate has been studied in detail and is well established [33,34] (Table 4). Dolichyl phosphate is an obligatory intermediate in the biosynthesis of *N*-glycosidically linked oligosaccharide chains. Dolichyl pyrophosphate bears the oligosaccharides which are enzymically and co-translationally transferred to the tripeptide Asn-Xaa-Thr (or Ser) of the growing polypeptide chain.

Table 4. Involvement of dolichyl phosphate and pyrophosphate in the synthesis of *N*-glycosidically linked oligosaccharides

Abbreviations: Dol, dolichyl; *P*, phosphate; *PP*, pyrophosphate; Man, mannose; Glc, glucose; GlcNAc, *N*-acetylglycosamine.

Product	Substrate transferred from:
Dol-*P*-monosaccharide	
Dol-*P*-Man	Man from GDP-Man
Dol-*P*-Glc	Glc from UDP-Glc
Dol-*PP*-oligosaccharide	
Dol-*PP*-GlcNAc	GlcNAc*P* from UDP-GlcNAc
Dol-*PP*-GlcNAc	GlcNAc from UDP-GlcNAc
Dol-*PP*-GlcNAc$_2$-Man$_5$	Man from GDP-Man
Dol-*PP*-GlcNAc$_2$-Man$_5$-Man$_4$	Man from Dol-*P*-Man
Dol-*PP*-GlcNAc$_2$-Man$_9$-Glc$_3$	Glc from Dol-*P*-Glc

Information about the importance of polyisoprenoid structure to the glycosylation process is also available (Table 5). α-Saturation of dolichyl phosphate is a requirement for its reaction with activated nucleotide-sugars [35–37]. The isoprene length of polyisoprenes occurring in animal cells has no influence on the construction of the sugar chain: all individual dolichols react equally well with the different activated monosaccharides [37–39]. The short dolichyl phosphate species are poor sugar acceptors, but since they are absent from animal cells, this finding has no physiological importance. The centre of asymmetry at C-3 gives rise to *S* and *R* configurations [15,16,40]. The *R*-form is not glycosylated, since the naturally occurring lipid intermediates are in the *S*-form [41]. Dolichyl phosphate contains two *trans* isoprene units, whereas the remaining units are in the *cis* configuration. It is not known whether this arrangement influences glycosylation or not, but it is probably not decisive for the rate of sugar transfer [42]. Whether or not the level of dolichyl phosphate can be a rate-limiting factor in glycoprotein synthesis has been discussed intensively and the question is not yet decided. It seems reasonable to believe that the availability of this intermediate is in fact rate-limiting under certain conditions [43–46].

A particular arrangement in the membrane may be required for the optimal participation of dolichyl phosphate in glycosyltransferase reactions. An effective capacity to accept sugars may be dependent on the specific association of dolichyl phosphate with the transferase in a lipid environment consisting of, for example, a destabilized bilayer structure [47–49].

Table 5. Influence of dolichyl phosphate on glycoprotein synthesis

Parameter	Effect on glycoprotein synthesis
α-Unsaturation	Not utilized
Isoprene length (17–22)	None
S- and *R*-forms	*S*-form is preferred
Number of *cis* and *trans* residues	Probably not decisive
Amount	May be rate-limiting

The main function of dolichyl phosphate is its participation in glycoprotein synthesis and this lipid probably has no other major role in cellular processes. Only a small portion of the total cellular dolichol is phosphorylated when the total amount is large (e.g. human tissues), whereas a large part is phosphorylated when the amount of dolichol is small (e.g. rat liver microsomes). The phosphorylated form is not as widely distributed within the cell, and although the amount of dolichol may be greatly decreased or increased in various physiological and pathological conditions, the amount of dolichyl phosphate is constant or changed only to a moderate extent [50]. Obviously the glycosylation of protein is a necessary process in living organisms, both under normal and pathological conditions, which does not allow any large variations in the level of the important carrier dolichol phosphate.

BIOSYNTHESIS OF DOLICHOL

The initial steps in the biosynthesis of dolichol are identical with the initial steps in the biosynthesis of cholesterol and ubiquinone, following the pathway:

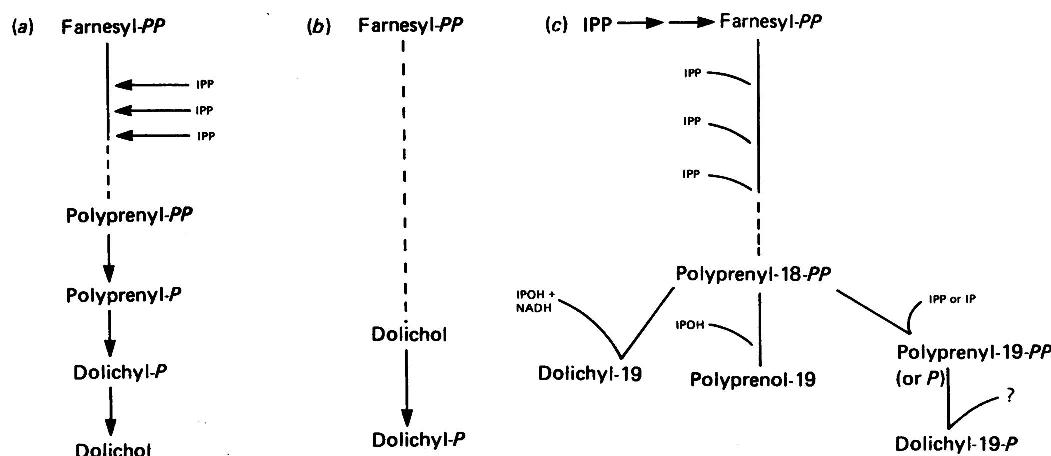
$$\text{Acetate} \rightarrow \text{mevalonate} \rightarrow \text{farnesyl polyphosphate}$$

The terminal portion of polyisoprenoid synthesis begins with the condensation reactions in which the sequential addition of *cis*-isopentenyl polyphosphate to *trans-trans*-farnesyl phosphate takes place [3,51–53]. According to the original proposal, after these condensation reactions, when the appropriate isoprenoid chain length has been attained, the α-unsaturated pyrophosphate derivative is dephosphorylated to the monophosphate, followed by α-saturation to yield dolichyl phosphate (Scheme 1*a*). Further dephosphorylation yields dolichol. An alternative hypothesis was proposed from studies on sea urchin, in which dolichol represents the end product (Scheme 1*b*); phosphorylation of this compound could be the source of dolichyl phosphate [54,55].

A number of observations, however, indicate that the free alcohol and its phosphorylated form are not freely interconvertible, but that their biosyntheses follow two distinct pathways [10,56,57] (Scheme 1*c*). According to this scheme, in the final condensation reaction isopentenol is added instead of isopentenyl pyrophosphate and the absence of a leaving group (pyrophosphate) thus terminates the reaction. Simultaneously with this condensation, an NADH-dependent α-saturase, present in the cytoplasm, saturates the α-isoprene residue and produces dolichol. This latter enzyme is ineffective in saturating the corresponding phosphorylated derivative and the exact mechanism for the biosynthesis of dolichyl phosphate remains to be clarified.

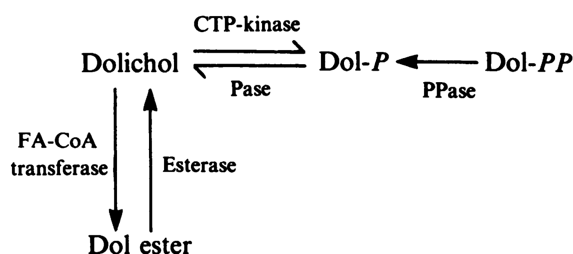
Ozonolytic fragmentation has demonstrated that a limiting amount of polyprenyl pyrophosphate is present in the cell, and this pool may be used for the completion of dolichol biosynthesis [56]. However, most of the dolichol and dolichyl phosphate required by the cell must be synthesized *de novo*. Reactions involving the terminal products are also well known (Scheme 2). After transfer of the oligosaccharide chain to the protein acceptor, the remaining dolichyl pyrophosphate is dephosphorylated in the lysosomes, where a monophosphatase is also present and can, at least *in vitro*, give the free alcohol [22,58–60].

Microsomal CTP-kinase phosphorylates dolichol *in vitro*, but the role of this enzyme *in vivo* is not clear [61,63]. This enzyme appears to have a major role in sea-urchin development [54], but its functional importance in hepatocytes is limited [64]. It is possible that this reaction does not proceed under steady-state conditions. Possibly when high rates of glycoprotein synthesis are required, such as during development, hypertrophy and regenera-



Scheme 1. Pathways suggested for dolichol synthesis

Abbreviations: -*P*, monophosphate; -*PP*, pyrophosphate; '18' and '19' refer to numbers of isoprene units; IPOH, isopentenol.



Scheme 2. Terminal reactions in the biosynthetic pathway for dolichol

Abbreviations: Dol ester, dolichyl ester; Dol-*P*, dolichyl phosphate; Dol-*PP*, dolichyl pyrophosphate; FA, fatty acid; Pase, phosphatase; PPase, pyrophosphatase.

tion or when pathological conditions such as malignant transformation disturb glycoprotein synthesis [65], the CTP-kinase may function to produce the phosphorylated compound. The esterification of dolichol with a fatty acid occurs in endoplasmic reticulum, whereas the antagonistic reaction, hydrolysis of dolichyl ester, occurs exclusively in the lysosomes [18].

SITES OF BIOSYNTHESIS

The three end-products of the mevalonate pathway have multiple sites of biosynthesis (Table 6). Dolichol is synthesized in the endoplasmic reticulum [52,66,67] and, to a certain extent, also in peroxisomes [68,69]. Ubiquinone is found not only in mitochondria, but also in other subcellular fractions, and a portion of this lipid is synthesized in the endoplasmic reticulum [70]. Cholesterol synthesis is regarded to be a microsomal process [71], but a biosynthetic system yielding this steroid is also operative in the peroxisomes [72,73]. Cholestyramine treatment increases the rate of peroxisomal cholesterol synthesis 120-fold, although affecting the microsomal rate of synthesis to only a moderate extent. Inducers also have differential effects on dolichol synthesis at these two locations. Clofibrate treatment, for example, increases the microsomal and decreases the peroxisomal rate. Most interestingly, the systems for both dolichol and cholesterol biosynthesis in peroxisomes appear to be located in the luminal compartment, in contrast with the microsomes, where both processes are associated with the membrane. Biosynthesis of these lipids at several locations may reflect their involvement in specific processes at different locations. Alternatively, synthesis at one location may provide reserve capacity to maintain a basic rate of production when the major site of synthesis is disturbed.

Table 6. Sites of biosynthesis of products from mevalonate

Product	Sites
Polyisoprenols	Endoplasmic reticulum, peroxisomes
Ubiquinone	Mitochondria, endoplasmic reticulum
Cholesterol	Endoplasmic reticulum, peroxisomes

BIOSYNTHETIC BALANCE AND TURNOVER

The central role of hydroxymethylglytaryl-CoA reductase in cholesterol biosynthesis is well established, and modulation of this enzyme plays an important role in the regulation of cholesterol production [74]. Naturally, if this enzyme is inhibited with compactin or mevinolin, dolichol synthesis is also inhibited. In spite of the fact that a common mevalonate pathway is involved in the biosynthesis of cholesterol, ubiquinone and dolichol, there is much debate over the extent to which changes in the metabolite flow in one direction influence the biosynthesis of the other two compounds [75].

The situation is complicated by the fact that incorporation studies using radioactive intermediates of the mevalonate pathway are not necessarily reliable. The mevalonate pools in different tissues are very different; in kidney, liver and lung they are (relative values) 1, 5 and 8 respectively [76]. It also appears that treatment of rats with different drugs influences the size of the mevalonate pool. Consequently, an increased incorporation of, e.g., radioactive mevalonate into a final product may represent a change in pool size rather than a change in biosynthetic rate.

It is quite clear from the results presented to date that further regulation of dolichol and dolichyl phosphate synthesis occurs in the terminal steps, i.e. at the level of the condensation reactions and probably also at the level of the saturation process [77–79]. Regulation of dolichol synthesis is expected to be the focus of intensive investigations in the near future.

All tissues are capable of synthesizing dolichol [76]. Thus redistribution between organs via the blood, which takes place with cholesterol, does not occur to any great extent with dolichol. High specific rates of dolichol synthesis are observed in kidney, spleen and liver. However, because of its large volume, muscles synthesize 50% of the total body dolichol. Common diets are rich in polyisoprenoid compounds, but longer dolichols are not taken up from the intestine [80]. α-Unsaturated short polyprenols in the diet do enter the liver to a limited extent and are α-saturated, esterified and phosphorylated there [81]. However, no elongation to larger dolichols seems to occur, and, therefore, this uptake seems to lack physiological significance.

Dolichol synthesized in the liver is transported to the blood in relatively small amounts [82]. Endogenously synthesized dolichol is present in the blood at the following concentrations (μg/ml): 0.03 (free alcohol); 0.1 (ester); and 0.05 (dolichyl phosphate). All the polyisoprenes in the blood are associated with the high-density-lipoprotein fraction. Dolichol is recovered in the urine in negligible amounts and dolichol found in the faeces originates both from the diet and from the bile [76,83].

The excretion of dolichol in bile is far from sufficient to account for dolichol turnover, which naturally raises questions concerning dolichol catabolism. No pathways for dolichol breakdown are known, but such pathways should exist, considering the rates of turnover of these lipids. Direct measurements *in vivo* of half-lives of dolichols in liver endoplasmic reticulum gave values between 80 and 118 h, depending on the size of the polyisoprene [84]. The half-lives of the dolichols in lysosomes are between 115 and 137 h, whereas microsomal dolichyl phosphate exhibits a half-life of 32 h.

When dolichol was injected into the bloodstream, it was taken up by the hepatocytes and thereafter appeared exclusively in the lysosomes [85]. The breakdown of the exogenous lipid is somewhat slower than that of the endogenous compound. Upon incubation of isolated hepatocytes with liposomes, dolichol was taken up by the cells and, under the conditions employed, the lipid appeared both in the microsomes and the mitochondria [86]. Thus there are differences in the catabolism of dolichol at different subcellular locations and also differences between the catabolism of dolichol and dolichyl phosphate.

DOLICHYL ESTER

Our present knowledge about dolichyl esters is limited for at least three reasons: it is difficult to extract these esters, hydrolysis before or during extraction occurs easily, and it is also difficult to separate them by h.p.l.c. [87,88]. These lipids are present in all organs, but in different amounts, and 10–60 % of the total dolichol at different locations is esterified [18] (Table 7). In rat liver 75, 62 and 44 % of the total neutral dolichol in the lysosomes, Golgi vesicles and microsomes respectively is esterified. There are considerable differences in the fatty acid compositions of the dolichol esters in different subcellular organelles.

Liver microsomes contain an enzyme which esterifies dolichol utilizing fatty-acyl-CoA as substrate. This enzyme, like the others participating in dolichol synthesis, is localized at the outer, cytoplasmic, surface of the endoplasmic reticulum. The role of bound fatty acids may be to target the lipid to different intracellular locations, as discussed below.

INTRACELLULAR TRANSPORT OF DOLICHOL

Dolichol synthesis occurs mainly in the endoplasmic reticulum, and this organelle has to supply all other membranes, with the exception of peroxisomes, with this lipid. In addition, liver dolichol is transferred to the bile and the blood. Clearly, extensive transport of dolichol in various directions occurs in the cell.

Table 7. Dolichyl esters in the rat

(*a*) *Distribution*
All organs, primarily spleen and liver.
Subcellular organelles contain 44–75 % of the total neutral dolichol.

(*b*) *Dominating fatty acid composition*
Endoplasmic reticulum: $C_{16:0}$, $C_{18:0}$, $C_{18:2}$
Mitochondria: $C_{16:0}$, $C_{18:0}$, $C_{20:4}$
Golgi vesicles: $C_{16:0}$, $C_{17:0}$
Lysosomes: $C_{16:0}$, $C_{18:0}$, $C_{18:2}$, $C_{20:4}$
Cytosol: $C_{16:0}$, $C_{18:0}$

(*c*) *Properties of the acyl-CoA:dolichol acyltransferase*
Fatty acyl-CoA species are substrates
Localized on the cytoplasmic surface of the endoplasmic reticulum

(*d*) *Functions of fatty acid moiety*
Probable signal for:
(*a*) cytoplasmic transport (complexed with other lipids and proteins)
(*b*) luminal transport to lysosomes (lipid micelles)
(*c*) luminal transport to blood (in high-density lipoprotein)

Table 8. Transport of dolichol in the liver.

Abbreviation: ER, endoplasmic reticulum

ER → cytoplasm (carrier) → organelles
ER → ER-lumen → Golgi lumen → lysosomal lumen
ER → vesicle transport to organelles
ER → Golgi lumen → blood
ER → bile → intestine

The directions of dolichol transport in the liver are listed in Table 8. It is generally accepted that phospholipids synthesized on the cytoplasmic surface on the endoplasmic reticulum become associated with protein carriers and are subsequently transported to different organelles [89,90]. Originally, it was believed that the information built into the carrier protein determine, on the one hand, the nature of the lipid carried and, on the other, the direction of movement. However, most investigations demonstrated that most of the phospholipid exchange proteins isolated are non-specific as lipid acceptors and also transfer lipids to most membranes.

Recently it was proposed that the nature and localization of fatty acids may play a role in the targeting lipids, serving as signal moieties [91] analogous to signal polypeptides [92]. In this way the movement of lipids from their site of synthesis to the final location depends not only on the carrier proteins, but also on the fatty acids present.

This principle may be also utilized in the cytoplasmic transfer of dolichyl esters. Protein–lipid complexes also containing dolichol have been isolated from liver cytoplasm, and the time course of labelling suggested that this dolichol is participating in a transfer process [93,94]. It was also found that the endoplasmic-reticulum–Golgi system contains luminal dolichols which are transferred to lysosomes only if they are esterified with a fatty acid [18]. This strongly suggests a role for the fatty acid as a signal for targeting dolichol transfer to the lysosomes. Interestingly, this transport does not seem to involve a protein carrier, since lipid particles isolated from the lysosomal contents contained phospholipid, cholesterol, ubiquinone and dolichol, but no protein (C. Edlund *et al.*, unpublished work). Dolichol may also be transferred to various intracellular compartments by vesicle transport, which is a mechanism well-known to operate in the cell.

It is very probable, even if not yet proven, that blood dolichol is synthesized in the liver and transported through the endoplasmic reticulum–Golgi system to the blood, like other lipids which are associated with apoproteins. Transfer of dolichol to the bile is an active and extensive process. The mechanism of this transfer has not yet been studied, but it has been proposed that cholesterol in the bile originates from the lysosomes [95] and is transported by a vesicular process, which may also be the case for dolichol.

EXPERIMENTAL AND HUMAN PATHOLOGY

The levels of dolichol and some of its derivatives in a number of conditions and pathological states have been investigated and considerable changes described (Table

Table 9. Alterations in dolichol and dolichyl phosphate in experimental and human pathology

Condition	Levels of:	
	Dolichol	Dolichyl phosphate
Newborn	Low	Close to adult
Aging	Increased in brain, liver and blood	No change
Regenerating liver	High	No change
Treatment with:		
Phenobarbital	Decreased in lysosomes	No change
2-Acetylaminofluorene	Increased in microsomes	No change
N-Nitrosodiethylamine	Increased in microsomes	No change
Di-(2-ethylhexyl) phthalate	Increased in lysosomes, changed pattern	Decreased in microsomes
Turpentine	Increased in lysosomes	No change
Phenylhydrazine	Decreased in spleen	Increased in spleen
Preneoplastic noduli (rat)	Increased in microsomes	Some decrease
Cirrhosis (human)	Decreased	No change
Primary liver cancer (human)	Decrease; increased α-unsaturation, changed pattern	No change
Neuronal ceroid–lipofuscinosis (human)	Increased in brain	Increased in brain
Lipofuscinosis (dog)	No change	Increased in brain
Alzheimer's disease	Increased in brain	

9) [13,50,65,96–100]. Levels of dolichol (in most cases also including dolichyl ester) increase during aging and, under a number of experimental conditions, such as treatment with inducers of the endoplasmic reticulum and peroxisomes, carcinogenesis and feeding with cholesterol and cholestyramine, both increases and decreases in the amounts of dolichol in tissues, microsomes and/or lysosomes have been described. In addition, modulations in the rate of dolichol synthesis have been observed. Various changes in dolichol amount and composition were also found in humans under conditions such as cirrhosis, liver cancer, ceroid lipofuscinosis and Alzheimer's disease [14,101–107]. In contrast with the free alcohol, the level of dolichyl phosphate shows little or no change. The different changes in the levels of dolichol and dolichyl phosphate under many conditions also support the hypothesis that those two compounds are produced by different biosynthetic pathways and regulated separately.

FINAL REMARKS

Dolichol and its derivatives are the lipids discovered most recently in eukaryotic cells and, consequently, our knowledge of their biochemistry, structural role in membranes and functions are quite limited, at least in comparison with the other lipids. The great interest and developments which have taken place in the field of glycoproteins have revealed the function of dolichyl phosphate. On the other hand, dolichol and its esterified form have not yet had the advantage of being incorporated into a field enjoying rapid discoveries and development. We are in a stage experienced by many other fields, collecting data to reach a level where reasonable conclusions can be made and hypotheses formulated.

These polyisoprenoids represent a major lipid component of human endocrine organs. They determine important properties of model, and probably also biological, membranes. They serve as inducers of membrane fusion. They are actively transported within the cell and secreted from the cell, probably with the help of their fatty acids. Modulation of their amount and structural composition may determine some of the changed membrane properties observed under experimental pathological conditions and in human diseases. In the coming years of experimentation we must find out more about their relationship to other lipids and proteins in the membrane, their possible association with enzymes, their biosynthesis and degradation and their influence on complex biochemical processes. An interesting and exciting time in this field of biochemistry will result in the confirmation or replacement of the ideas and conclusions presented in this review.

REFERENCES

1. Pennock, J. F., Hemming, F. W. & Morton, R. A. (1960) Nature (London) **186**, 470–472
2. Behrens, N. H. L. & Leloir, L. F. (1970) Proc. Natl. Acad. Sci. U.S.A. **66**, 153–159
3. Hemming, F. W. (1974) in Biochemistry of Lipids (Goodwin, T. W., ed.), vol. 4, pp. 39–97, Butterworth, London
4. Dallner, G. & Hemming, F. W. (1981) in Mitochondria and Microsomes (Lee, C. P., Schatz, G. & Dallner, G., eds), pp. 655–682, Addison-Wesley, Reading, MA
5. Hemming, F. W. (1983) in Biosynthesis of Isoprenoid Compounds (Potter, J. W. L. & Spurgeon, S. L., eds.), vol. 2, pp. 305–354, John Wiley, New York
6. Rip, J. W., Rupar, C. A., Ravi, K. & Carroll, K. K. (1985) Prog. Lipid Res. **24**, 269–309
7. Mankowski, T., Jankowski, W., Chojnacki, T. & Franke, P. (1976) Biochemistry **15**, 2125–2130
8. Radominska-Pyrek, A., Chojnacki, T. & Pyrek, J. S. (1979) Biochem. Biophys. Res. Commun. **86**, 395–401
9. Hayes, G. R. & Lucas, J. J. (1980) J. Biol. Chem. **255**, 7536–7539
10. Exström, T. J., Chojnacki, T. & Dallner, G. (1984) J. Biol. Chem. **259**, 10460–10468

11. Tavares, I. A., Coolbear, T. & Hemming, F. W. (1981) Arch. Biochem. Biophys. **207**, 427–436
12. Tollbom, Ö. & Dallner, G. (1986) Br. J. Exp. Pathol. **67**, 757–764
13. Edlund, C., Ganning, A. & Dallner, G. (1986) Chem. Biol. Interact. **57**, 255–270
14. Eggens, I., Chojnacki, T., Kenne, L. & Dallner, G. (1983) Biochim. Biophys. Acta **751**, 355–368
15. Burgos, J., Hemming, F. W., Pennock, J. F. & Morton, R. A. (1963) Biochem. J. **88**, 470–482
16. Adair, W. L. & Robertson, S. (1980) Biochem. J. **189**, 441–445
17. Chojnacki, T., Palamarczyk, G., Jankowski, W., Krajewska-Rychlik, I., Szkopinska, A. & Vogtman, T. (1984) Biochim. Biophys. Acta **793**, 187–192
18. Tollbom, Ö., Valtersson, C., Chojnacki, T. & Dallner, G. (1988) J. Biol. Chem. **263**, in the press
19. Rip, J. W., Chaudhary, N. & Carroll, K. K. (1983) J. Biol. Chem. **258**, 14926–14930
20. Rupar, C. A. & Carroll, K. K. (1978) Lipids **13**, 291–293
21. Rip, J. W., Rupar, C. A., Chaudhary, N. & Carroll, K. K. (1981) J. Biol. Chem. **256**, 1929–1934
22. Keller, R. K., Adair, W. L., Cafmeyer, N., Simion, F. A., Fleischer, B. & Fleischer, S. (1986) Arch. Biochem. Biophys. **249**, 207–214
23. Lai, C. S. & Schutzbach, J. S. (1984) FEBS Lett. **169**, 279–282
24. Valtersson, C., von Duijn, G., Verkleij, A. J., Chojnacki, T., de Kruijff, B. & Dallner, G. (1985) J. Biol. Chem. **260**, 2742–2751
25. Gruner, S. M. (1985) Proc. Natl. Acad. Sci. U.S.A. **82**, 3665–3669
26. de Ropp, J. S. & Troy, F. A. (1985) J. Biol. Chem. **260**, 15669–15674
27. van Duijn, G., Verkleij, A. J., de Kruijff, B., Valtersson, C., Dallner, G. & Chojnacki, T. (1987) Chem. Scr. **27**, 95–100
28. de Ropp, J. S., Knudsen, M. J. & Troy, F. A. (1987) Chem. Scr. **27**, 101–108
29. van Duijn, G., Valtersson, C., Chojnacki, T., Verkleij, A. J., Dallner, G. & de Kruijff, B. (1986) Biochim. Biophys. Acta **861**, 211–223
30. Hanover, J. A. & Lennarz, W. J. (1981) Arch. Biochem. Biophys. **211**, 1–19
31. Hirschberg, C. B. & Snider, M. D. (1987) Annu. Rev. Biochem. **56**, 63–87
32. McCloskey, M. A. & Troy, F. A. (1980) Biochemistry **19**, 2061–2066
33. Struck, D. K. & Lennarz, W. J. (1980) in The Biochemistry of Glycoproteins and Proteoglycans (Lennarz, W. J., ed.), pp. 35–73, Plenum Press, New York
34. Kornfeld, R. & Kornfeld, S. (1985) Annu. Rev. Biochem. **54**, 631–644
35. Mankowski, T., Sasak, W., Janczura, E. & Chojnacki, T. (1977) Arch. Biochem. Biophys. **181**, 393–401
36. Bergman, A., Mankowski, T., Chojnacki, T., de Luca, L. M., Peterson, E. & Dallner, G. (1978) Biochem. J. **172**, 123–127
37. Palamarczyk, G., Lehle, L., Mankowski, T., Chojnacki, T. & Tanner, W. (1980) Eur. J. Biochem. **105**, 517–523
38. Löw, P., Peterson, E., Mizuno, M., Takigawa, T., Chojnacki, T. & Dallner, G. (1986) Biosci. Rep. **6**, 677–683
39. Palamarczyk, G., Vogtman, T., Chojnacki, T., Bause, E., Mizuno, M. & Takigawa, K. (1987) Chem. Scr. **27**, 135–136
40. Chojnacki, T., Palamarczyk, G., Jankowski, W., Krajewska-Rychlik, I., Szkopinska, A. & Vogtman, T. (1984) Biochim. Biophys. Acta **793**, 187–192
41. Löw, P., Peterson, E., Mizuno, M., Takigawa, T., Chojnacki, T. & Dallner, G. (1985) Biochem. Biophys. Res. Commun. **130**, 460–466
42. Mankowski, T., Sasak, W. & Chojnacki, T. (1975) Biochem. Biophys. Res. Commun. **65**, 1292–1297
43. Mills, J. T. & Adamany, A. M. (1978) J. Biol. Chem. **253**, 5270–5273
44. Carson, D. D. & Lennarz, W. J. (1979) Proc. Natl. Acad. Sci. U.S.A. **76**, 5709–5713
45. Potter, J. E. R., James, M. J. & Kandutsch, A. A. (1981) J. Biol. Chem. **256**, 2371–2376
46. Mizuno, M., Takigawa, T., Kageyu, A., Nakagawa, N., Shimamura, M., Urabe, A. & Takaku, F. (1987) Chem. Scr. **27**, 11–15
47. Jensen, J. W. & Schutzbach, J. S. (1984) Biochemistry **23**, 1115–1119
48. Jensen, J. W. & Schutzbach, J. S. (1985) Eur. J. Biochem. **153**, 41–48
49. Schutzbach, J. S. & Jensen, J. W. (1987) Chem. Scr. **27**, 109–118
50. Edlund, C., Ericsson, J. & Dallner, G. (1987) Chem.–Biol. Interact. **62**, 191–208
51. Popjak, G. (1970) in Natural Substances Formed Biologically from Mevalonic Acid (Goodwin, T. W., ed.), p. 17, Academic Press, London
52. Adair, W. L. & Keller, R. K. (1982) J. Biol. Chem. **257**, 8990–8996
53. Adair, W. L., Cafmeyer, N. & Keller, R. K. (1984) J. Biol. Chem. **259**, 4441–4446
54. Rossignol, D. D., Scher, M., Waechter, C. J. & Lennarz, W. J. (1983) J. Biol. Chem. **258**, 9122–9127
55. Lennarz, W. J. (1987) Chem. Scr. **27**, 33–37
56. Ekström, T. J., Chojnacki, T. & Dallner, G. (1987) J. Biol. Chem. **262**, 4090–4097
57. Ekström, T. J., Ericsson, J. & Dallner, G. (1987) Chem. Scr. **27**, 39–47
58. Rip, J. W., Rupar, C. A., Chaudhary, N. & Carroll, K. K. (1981) J. Biol. Chem. **256**, 1929–1934
59. Appelkvist, E. L., Chojnacki, T. & Dallner, G. (1981) Biosci. Rep. **1**, 619–626
60. Burton, W. A., Scher, M. G. & Waechter, C. J. (1981) Arch. Biochem. Biophys. **208**, 409–417
61. Allen, C. M., Kalin, J. R., Sack, J. & Verizzo, D. (1978) Biochemistry **17**, 5020–5026
62. Burton, W. A., Scher, M. G. & Waechter, C. J. (1979) J. Biol. Chem. **254**, 7129–7136
63. Scher, M. G. & Waechter, C. J. (1984) J. Biol. Chem. **254**, 14580–14585
64. Åstrand, I. M., Fries, E., Chojnacki, T. & Dallner, G. (1986) Eur. J. Biochem. **155**, 447–452
65. Eggens, I., Ericsson, L. C., Chojnacki, T. & Dallner, G. (1984) Cancer Res. **44**, 799–805
66. Wong, T. K. & Lennarz, W. J. (1982) J. Biol. Chem. **257**, 6619–6624
67. Ekström, T., Eggens, I. & Dallner, G. (1982) FEBS Lett. **150**, 133–136
68. Appelkvist, E. L. (1987) Acta Chem. Scand. **B41**, 73–75
69. Appelkvist, E. L. & Dallner, G. (1987) in Peroxisomes in Biology and Medicine (Fahimi, H. D. & Sies, H., eds.), pp. 53–66, Springer-Verlag, Berlin
70. Kalén, A., Norling, B., Appelkvist, E. L. & Dallner, G. (1987) Biochem. Biophys. Acta **926**, 70–78
71. Reinhart, M. P., Billheimer, J. T., Faust, J. R. & Gaylor, J. L. (1987) J. Biol. Chem. **262**, 9649–9655
72. Appelkvist, E. L. & Dallner, G. (1987) in Pharmacology. Pharmacology and Toxicology of Peroxisomes (Proc. Int. Congr. Pharmacol. 10th) (Rand, M. J. & Raper, C., eds.), pp. 857–861, Elsevier, Amsterdam
73. Appelkvist, E. L. (1988) Biosci. Rep., in the press

74. Brown, M. S. & Goldstein, J. L. (1980) J. Lipid Res. **21**, 505–517
75. Keller, R. K. (1987) Trends Biochem. Sci. **12**, 443–445
76. Elmberger, P. G., Kalén, A., Appelkvist, E. L. & Dallner, G. (1987) Eur. J. Biochem. **168**, 1–11
77. Keller, R. K. (1986) J. Biol. Chem. **261**, 12053–12059
78. Keller, R. K. (1987) Chem. Scr. **27**, 63–70
79. Adair, W. L. & Cafmeyer, N. (1987) Chem. Scr. **27**, 19–23
80. Keller, R. K., Jehle, E. & Adair, W. L. (1982) J. Biol. Chem. **257**, 8985–8989
81. Chojnacki, T. & Dallner, G. (1983) J. Biol. Chem. **258**, 916–922
82. Elmberger, P. G. & Engfeldt, P. (1985) Acta Chem. Scand. **B39**, 323–325
83. Connelly, L. W. & Keller, R. K. (1984) Biosci. Rep. **4**, 771–776
84. Edlund, C., Brunk, U., Chojnacki, T. & Dallner, G. (1988) Biosci. Rep., in the press
85. Edlund, C., Chojnacki, T. & Dallner, G. (1983) Biochem. Biophys. Res. Commun **115**, 917–923
86. Edkström, T., Chojnacki, T. & Dallner, G. (1982) J. Lipid Res. **23**, 972–982
87. Adair, W. L. & Keller, R. K. (1985) Methods Enzymol. **111**, 201–218
88. Ericsson, J., Chojnacki, T. & Dallner, G. (1987) Anal. Biochem., in the press
89. Wirtz, K. W. A. (1974) Biochim. Biophys. Acta **344**, 95–117
90. Zilversmit, D. B. (1983) Methods Enzymol. **98**, 565–573
91. Valtersson, C., Filipsson, L. & Dallner, G. (1986) J. Lipid Res. **27**, 731–741
92. Walter, P., Gilmore, R. & Blobel, G. (1984) Cell (Cambridge, Mass.) **38**, 5–8
93. Appelkvist, E. L., Chojnacki, T. & Dallner, G. (1985) Acta Chem. Scand. **B39**, 72–74
94. van Dessel, G., de Wolf, M., Lagrou, A., Hilderson, H. J. & Dierick, W. (1986) Biochim. Biophys. Acta **878**, 338–345
95. Coleman, R. (1987) Biochem. J. **244**, 249–261
96. Pullarkat, R. K. & Reha, H. (1982) J. Biol. Chem. **257**, 5991–5993
97. Potter, J. E. R. & Kandutsch, A. A. (1982) Biochem. Biophys. Res. Commun. **106**, 691–696
98. Keller, R. K. & Nellis, S. W. (1986) Lipids **21**, 353–355
99. Andersson, M., Appelkvist, E. L., Kristensson, K. & Dallner, G. (1987) J. Neurochem. **49**, 685–691
100. Marino, M., Trentalance, A. & Hemming, F. W. (1987) Chem. Scr. **27**, 51–54
101. Ng Ying Kin, N. M. K., Palo, J., Haltia, M. & Wolfe, L. S. (1983) J. Neurochem. **40**, 1465–1473
102. Keller, R. K., Armstrong, D., Crum, F. C. & Koppang, N. (1984) J. Neurochem. **42**, 1040–1047
103. Wolfe, L. S., Ivy, G. O. & Witkop, C. J. (1987) Chem. Scr. **27**, 79–84
104. Pullarkat, R. K. (1987) Chem. Scr. **27**, 85–88
105. Haltia, M. (1987) Chem. Scr. **27**, 89–91
106. Eggens, I., Bäckman, L. & Valtersson, C. (1988) Br. J. Exp. Pathol., in the press
107. Eggens, I. & Ericsson, J. (1988) Cancer Res., in the press