Review

Hepatic secretion of lysophosphatidylcholine: A novel transport system for polyunsaturated fatty acids and choline

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Introduction

Since 1985 it has become clear that perfused liver[1] and cultured hepatocytes[2] can produce lysophosphatidylcholine that is secreted into the perfusion, or incubation medium. In the case of perfused livers, this production is about twice as high as the secretion of phosphatidylcholine,[1] whereas in the hepatocyte system it is about seven times higher.[2] Consequently, the liver has the capacity to produce relatively large amounts of lysophosphatidylcholine. Lysophosphatidylcholine is bound to albumin in the blood and it is often the second most prevalent phospholipid in plasma.[3] Its concentration remains relatively high even in patients suffering from a deficiency of lecithin:cholesterol acyltransferase (LCAT).[4] These combined observations indicate that the production of lysophosphatidylcholine by the liver provides a source for this lipid in the blood, in addition to that produced in the circulation by LCAT.

Analysis of the composition of lysophosphatidylcholine that is secreted from perfused liver[1] and hepatocytes[5,6] indicates that a major portion of the fatty acids are polyunsaturated. It has therefore been proposed that the secretion of lysophosphatidylcholine by the liver can provide a novel system for the transport of both polyunsaturated fatty acids and choline to other organs.[6,7]

In contrast to what has been stated for rat hepatocytes, no significant production of lysophosphatidylcholine could be detected in the culture medium of ovine hepatocytes.[6] If this proves to be a general finding for ruminant animals, the secretion of lysophosphatidylcholine from the liver may be restricted to non-ruminants.

This article reviews the characteristics of lysophosphatidylcholine secretion, its regulation, and some possible implications for the metabolism of polyunsaturated fatty acids and choline.

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Evidence that lysophosphatidylcholine is secreted by viable hepatocytes

In determining the physiological significance for the secretion of lysophosphatidylcholine it is important to be certain that this lipid is produced by viable cells, and that it is not the result of a non-specific degradation of phosphatidylcholine in the incubation medium. Evidence to this effect has been provided.

One possibility was that the albumin that is used in hepatocyte cultures may have contained lipases, phospholipases, or LCAT activity. This albumin was therefore heated to 60° C for 30 min and this did not cause any significant decrease in lysophosphatidylcholine production.[8] It was also possible that an extracellular phospholipase might have produced the lysophosphatidylcholine. For example, hepatic lipase might have acted in this way by exhibiting phospholipase A_1 activity.[9] This lipase can be secreted by hepatocytes[10] and by HepG2 cells.[11] The hepatocytes used in incubations were therefore washed with heparin to remove hepatic lipase.[5,6] This treatment did not alter the rate of production of lysophosphatidylcholine in the medium, confirming that hepatic lipase is unlikely to be involved in the production of this lipid.

In further experiments the continued incubation of the medium that contained ^{3}H-labeled lipids in the absence of hepatocytes did not change the ratio of labeled lysophosphatidylcholine, or phosphatidylcholine.[5] Sekas et al.[1] also observed no increase in lysophosphatidylcholine concentration in the medium used to perfuse rat livers when this was incubated in isolation, or if the perfusion was continued after removal of the liver. Furthermore, incubation of phosphatidyl[^{3}H]choline in the incubation medium obtained from hepatocytes resulted in a conversion of less than 1% of the phosphatidylcholine into lysophosphatidyl-

choline.[6] These results therefore exclude the participation of LCAT activity in the production of lysophosphatidylcholine from phosphatidylcholine in the incubation medium. In addition, the predominantly unsaturated nature of the lysophosphatidylcholine that is produced by the hepatocytes in cultures, or by liver in perfusion experiments (*Table 1*) excludes a significant participation of LCAT.

The intactness and viability of hepatocytes used to study the production of lysophosphatidylcholine was checked by measuring the loss of lactate dehydrogenase, a cytosolic enzyme, from the cells. During a 24-hour incubation less than 5% of the total lactate dehydrogenase was lost from the hepatocytes, which indicates that the cells remained intact and viable.[6] Furthermore, the lysophosphatidylcholine that was secreted was between 4- and 12-fold higher than the production of phosphatidylcholine.[2,6–8] The secretion of lysophosphatidylcholine can also be dissociated from that of phosphatidylcholine and very low density lipoprotein (VLDL) through the effects of colchicine,[2] dexamethasone plus insulin,[2] glucagon, and cAMP,[12] albumin,[8] fatty acids,[7] verapamil, EGTA, and chlorpromazine.[8] These combined results therefore indicate that lysophosphatidylcholine is not produced by the breakdown of phosphatidylcholine that has been previously secreted.

Fatty acid composition of the secreted lysophosphatidylcholine

Phosphatidylcholine that is secreted by perfused livers contains about 62% of unsaturated fatty acids giving an unsaturated-to-saturated ratio of 1.6.[1] The most prevalent unsaturated fatty acid was 20:4 followed by 18:2 (*Table 1*). This composition contrasted with that found in the serum,[1] in which there was about twice the quantity of 18:2 than 20:4.

The work of Baisted et al.[5] with isolated rat hepatocytes showed a relatively similar composition of the secreted lysoPC. After an incubation of 10 minutes, about 24% of the total fatty acid was 20:4 and 15% was in the form of 18:2 (*Table 1*). The unsaturated-to-saturated ratio of the lysophosphatidylcholine in this work was about 1.9. The results from Baisted et al.[5] and Sekas et al.[1] were both obtained using livers from male rats.

Graham et al.[6] compared the secretion of lysophosphatidylcholine by hepatocytes prepared from both male and female rats that were obtained from the same litters and fed on the same batch of diet. The lysophosphatidylcholine produced by cells from male rats was again predominantly unsaturated: 20:4 constituted about 34% of the fatty acids and 18:2 about 15% (*Table 1*). The calculated saturated fatty acid-to-unsaturated ratio was 2.95. By contrast, in female rats, about 26% of the fatty acid was 20:4 and only about 5% was 18:2. The saturated fatty acid to unsaturated ratio was 2.3. These results demonstrate a sexual dimorphism in the secretion of lysophosphatidylcholine.[6]

Sex differences are also observed in the composition of hepatic phosphatidylcholine from which the lysophosphatidylcholine is probably derived. Phosphatidylcholine from the hepatocytes of female rats contains an increased proportion of 18:0 and 20:4 compared with males,[6,13–15] and this difference is maintained after culturing hepatocytes for about 24 hours.[6] It is possible that the increased proportion of 18:0 and 20:4 in phosphatidylcholine from female hepatocytes may result from a larger contribution from the methylation of phosphatidylethanolamine (*Figure 1*) to total phosphatidylcholine synthesis.[13,14,16–18] Livers from female rats also have a high capacity to convert 16:0 to 18:0 compared with those of males.[19] The sexual dimorphism in the phospholipid composition appears to result from the effects of estrogens on metabolism,[14,18] which may be mediated through the patterns of growth hormone secretion.[15,20,21] In mature male rats, growth hormone is secreted in a pulsatile fashion, but in females pulses are of smaller magnitude, and the mean concentration of growth hormones is higher.[22,23] These differences in growth hormone secretion have also been implicated in the sexually dimorphic differences of hepatic steroid metabolism,[24] in the expression of isoforms of cytochrome P-450,[25,26] and in the higher rates of VLDL secretion in females.[27] Similar effects of estrogens acting through growth hormone are therefore likely to be responsible for the differences in the fatty acid composition of the lysophosphatidylcholine that is secreted.

The lower proportion of 20:4 in the lysophosphatidylcholine secreted from the hepatocytes of female rats occurred despite a relatively high proportion of this

Table 1 Fatty acid composition of lysophosphatidylcholine secreted by perfused liver or cultured hepatocytes

Fatty acid* (Mol %)	Male rats			Female rats
	Perfused liver[1]	Hepatocytes[5]	Hepatocytes[6]	Hepatocytes[6]
16:0	15.9	19.8	10.8	5.4
16:1	0.5	4.3	n.d.	n.d.
18:0	21.4	15.1	14.5	24.2
18:1	8.8	12.1	19.2	22.9
18:2	17.0	15.3	14.7	5.1
20:4	25.7	23.6	30.0	26.4
22:6	5.3	8.3	5.8	13.3

*The relative fatty acid compositions are taken from references 1, 5, and 6 as indicated.
n.d. = not detected.

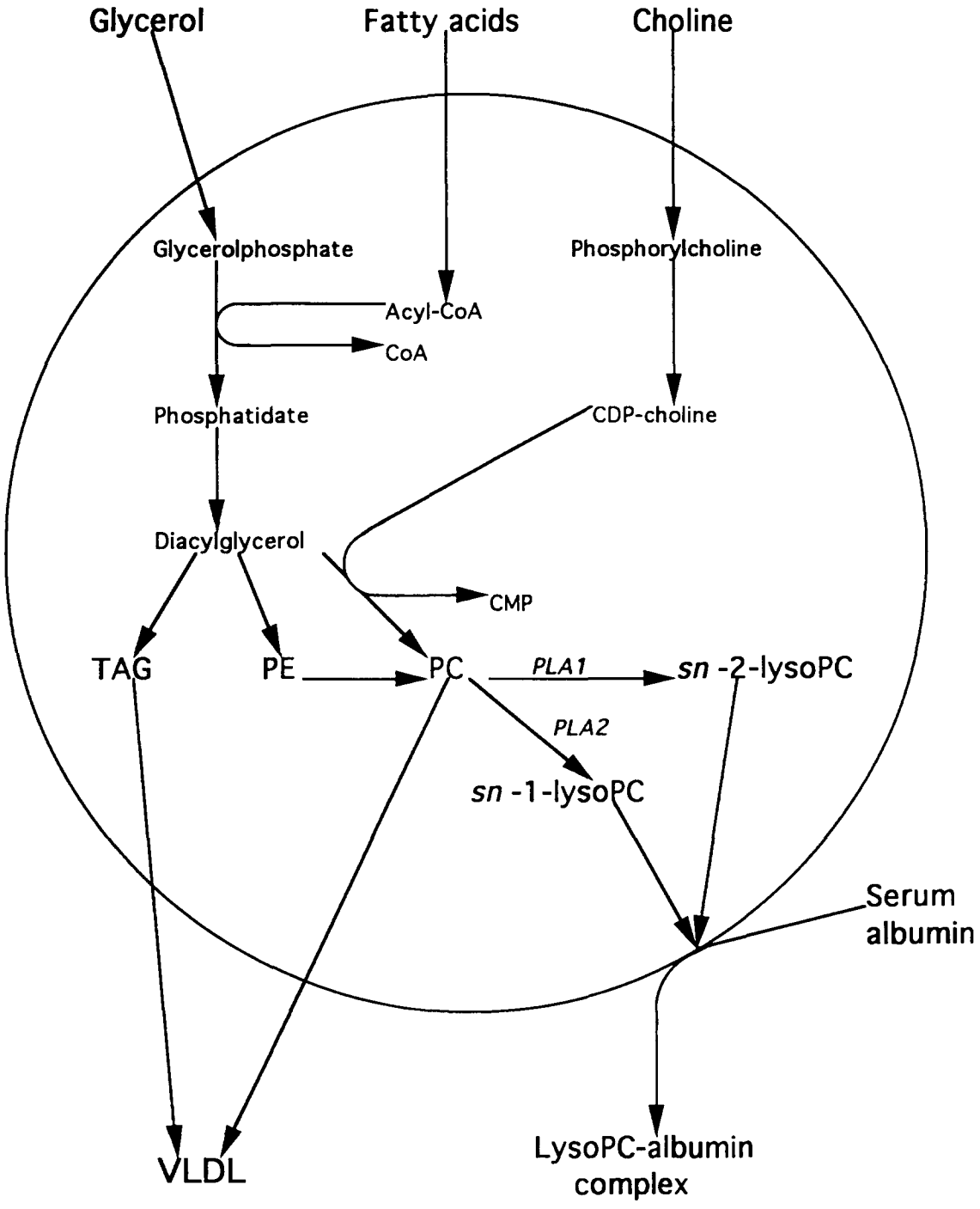

Figure 1 Schematic representation of the synthesis of triacylglycerol and phosphatidylcholine by hepatocytes, and the secretion of VLDL and lysophosphatidylcholine. The production of lysophosphatidylcholine is probably regulated by phospholipase A_1 and A_2 activities, and the secretion depends on its removal from the hepatocyte surface by an excess of circulating albumin. The following abbreviations are used: DAG, diacylglycerol; PC, phosphatidylcholine; PLA, phospholipase A; and TAG, triacylglycerol.

fatty acid in the phosphatidylcholine of the hepatocytes compared with the male rats.[6] It is therefore likely that separate pools of phosphatidylcholine are used for the production of lysophosphatidylcholine. Such a selection has also been observed in the secretion of phosphatidylcholine in VLDL.[28]

The effects of the exogenous fatty acids on the secretion of lysophosphatidylcholine by hepatocytes

The effects of adding various fatty acids to hepatocytes on the secretion of lysophosphatidylcholine was determined by measuring the incorporation of radioactive

choline, glycerol, and the fatty acids.[7] The incorporation of glycerol and choline into lysophosphatidylcholine of the medium (*Figure 1*) was stimulated two to three fold by all unsaturated fatty acids tested (*Figure 2*). In contrast, 16:0 or 18:0 failed to stimulate secretion when the fatty acids were added separately. The addition of 1 mmol/L 18:0 with 1 mmol/L 18:2 demonstrated that the incorporation of 18:2 into lysophosphatidylcholine occurred at a rate of about four times higher than that of 18:0.[7] These results confirm the preferential use of polyunsaturated fatty acids in lysophosphatidylcholine secretion. The effects of fatty acids on lysophosphatidylcholine secretion differed from those for triacylglycerol and phosphatidylcholine because the secretions of these lipids were stimulated by the saturated fatty acids, 16:0 and 18:0.[7]

The competition between different fatty acids on the production of lysophosphatidylcholine in the incubation medium was examined further by using gas liquid chromatography to determine the fatty acid composition of the lysophosphatidylcholine.[6] The addition of 1 mmol/L 18:0 to the incubation medium produced an enrichment of about 9% in its content in secreted lysophosphatidylcholine. This was accompanied by a decrease in the percentage of 18:1 and 18:2 with no significant change in the proportion of 20:4. The saturated to unsaturated ratio of the lysophosphatidylcholine decreased from 2.95 to 1.90. Conversely, the addition of the 1 mmol/L concentrations of the unsaturated fatty acids, 18:1 or 18:2, increased the unsaturated to saturated ratio. Addition of 18:1 increased the relative content of this fatty acid in lysophosphatidylcholine by about 25%.[6] This was accompanied by a decrease in the content of 20:4. Similarly, addition of 18:2 to the incubation medium increased its relative concentration by about 19% in lysophosphatidylcholine, and it decreased that of 20:4 by about 15%.

18:1 and 18:2 also stimulated the secretion of lysophosphatidylcholine by about two fold.[7] Consequently, part of their effects were probably mediated by providing additional glycerolipid for lysophosphatidylcholine secretion rather than by competing with the 20:4. It is therefore concluded that the secretion of 20:4 in lysophosphatidylcholine is well preserved despite the addition of exogenous fatty acids to the incubation medium.

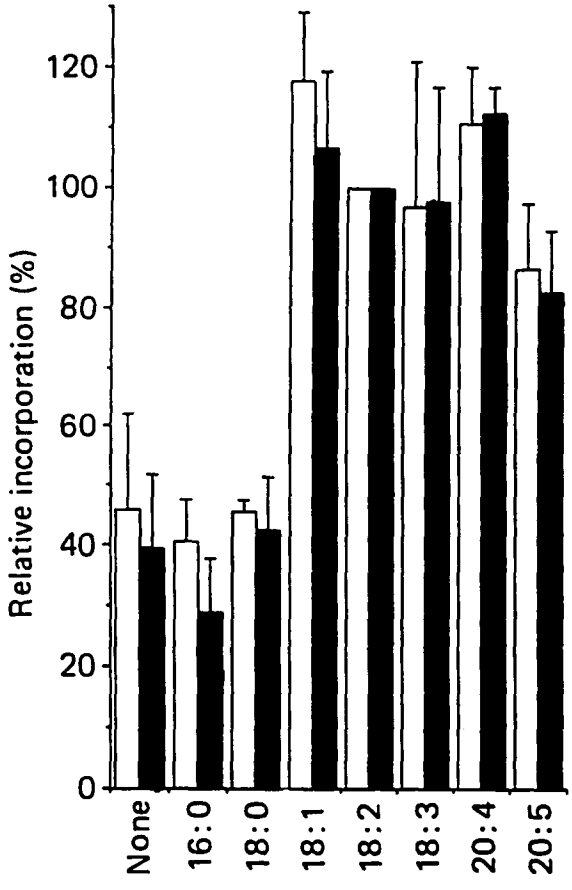

Figure 2 Effects of exogenous fatty acids on the secretion of lysophosphatidylcholine by cultured rat hepatocytes. Rat hepatocytes were incubated with 1 mmol/L [^{3}H]glycerol, 100 μmol/L [^{14}C] choline and 1 mmol/L of the fatty acids indicated. The incorporations of glycerol (□), and choline (■) are expressed relative to that obtained with 18:2. Results are means ± S.D. for three to seven independent experiments, except for glycerol incorporation with 16:0 where the mean ± range for two experiments is shown. The figure is taken from reference 7 with permission.

Factors affecting the secretion of lysophosphatidylcholine

Effects of albumin and α-cyclodextrin

The secretion of lysophosphatidylcholine by hepatocytes shows an almost absolute requirement for albumin in the incubation medium (*Figure 3*). For example, Graham et

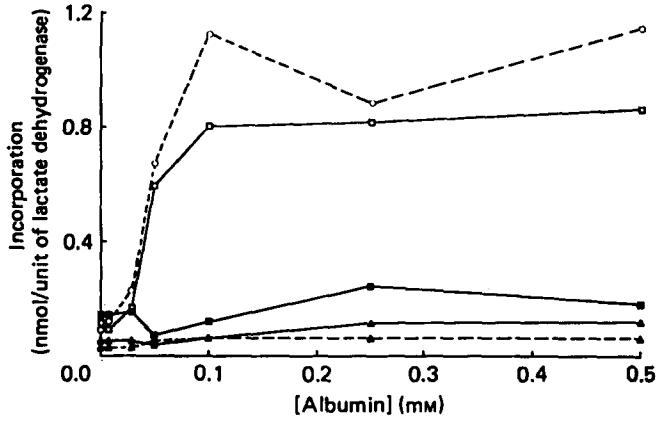

Figure 3 Effect of albumin concentration of the medium on the incorporation of glycerol and choline into glycerolipids secreted by rat hepatocytes. Rat hepatocytes were incubated with 1 mmol/L [^{3}H]glycerol and 100 μmol/L [^{14}C]choline for 8 hr in the absence of exogenous fatty acids. The incorporation of [^{3}H]glycerol into triacylglycerol (■), phosphatidylcholine (▲), and lysophosphatidylcholine (□), and that of [^{14}C] choline into phosphatidylcholine (△), and lysophosphatidylcholine (○) is shown. The results are expressed relative to the lactate dehydrogenase activities of the hepatocytes to correct for the number of viable cells. Loss of viability is accompanied by a leakage of cytosolic enzymes such as lactate dehydrogenase, whereas some non-viable cells remain attached to the culture dishes.[8] Results are reproduced from reference 8 with permission.

al.[8] demonstrated a 12- to 15-fold increase in the secretion of lysophosphatidylcholine at concentrations of albumin between 0.1–0.5 mmol/L. This means that physiological concentrations of albumin, which are in the region of 0.6 mmol/L, should sustain optimum rates of lysophosphatidylcholine release. Similarly, the work of Baisted et al.[5] demonstrated an almost absolute requirement for albumin in the incubation medium for the secretion to take place. It was therefore concluded that albumin is able to trap lysophosphatidylcholine that is produced transiently during phosphatidylcholine degradation in the hepatocytes (*Figure 1*). In the absence of albumin, lysophosphatidylcholine undergoes a reacylation cycle using acyl CoA esters[29] or is further deacylated by lysophospholipase activity.[30] The release of lysophosphatidylcholine is likely to be favored because of the additional depletion of cellular non-esterified fatty acids by albumin that would lower the concentrations of non-esterified fatty acids and acyl-CoA esters[5] that are necessary for re-esterification in the hepatocytes. Furthermore, plasma lipoproteins have the ability to bind lysophosphatidylcholine and in vivo may increase the release of lysophosphatidylcholine from the liver.[31]

These conclusions concerning the trapping of lysophosphatidylcholine in the extracellular medium are confirmed by the use of α-cyclodextrin.[5] This compound consists of six glucose residues arranged in a rigid conical conformation with a hollow interior. It is capable of forming inclusion complexes with polar hydrophobic compounds such as fatty acids.[5] α-cyclodextrin was more effective on a mass basis at releasing lysophosphatidylcholine into the medium than was albumin. However, on a molar basis, albumin was considerably more effective as an acceptor.[5]

Further experiments were performed to determine whether lysophosphatidylcholine was co-secreted with albumin from hepatocyte.[8] The experiments involved the use of cycloheximide, which produced an 88% inhibition in protein synthesis within the cells. However, the appearance of phosphatidylcholine in the medium was not significantly affected by the presence of cycloheximide (*Table 2*). This indicates that new protein synthesis is not required for lysophosphatidylcholine secretion.

Effects of verapamil, chlorpromazine, and EGTA

These agents interfere with Ca^{2+} metabolism. The use of these compounds appeared to be relevant because Ca^{2+} is a well-known co-factor for the action of many phospholipases. It therefore seemed likely that the production of lysophosphatidylcholine might involve such Ca^{2+}-dependent enzymes (*Figure 1*).

The Ca^{2+} channel blocker, verapamil, at 5-150 μmol/L produces a marked inhibition in the secretion of lysophosphatidylcholine (*Table 2*).[8] This concentration is similar to that which would elicit effects on secretory and excitable cells.[32,33] The results indicate that modification of Ca^{2+} fluxes through voltage-dependent channels can alter the production of lysophosphatidylcholine. Much higher concentrations of verapamil are required to decrease the secretion of phosphatidylcholine and triacylglycerol from the hepatocytes.[8] Therefore, there seems to be a fairly specific effect on lysophosphatidylcholine secretion compared to lipoprotein secretion.

Chlorpromazine is an amphiphilic amine that can displace Ca^{2+} from various intracellular binding sites, and it can inhibit glycerolipid synthesis.[34] Chlorpromazine, at concentrations between 25–250 μmol/L, inhibits the appearance of lysophosphatidylcholine in the culture medium.[8] Therefore, lysophosphatidylcholine production appears to be particularly sensitive to inhibition by chlorpromazine compared with the secretion of triacylglycerol (*Table 2*). These results again indicate a greater sensitivity for lysophosphatidylcholine production compared with lipoprotein secretion.

In these experiments,[8] there was no significant effect of 100 μmol/L chlorpromazine on the synthesis and accumulation of triacylglycerol in the cells over the 8-hr period. However, this concentration of chlorpromazine does significantly decrease the synthesis[8] and secretion of phosphatidylcholine (*Table 2*) as determined by [^{14}C]choline. By contrast, these effects are not observed with [^{3}H]18:1 (*Table 2*).[8] Similar differences are seen in the effects of 150 μmol/L verapamil on the incorporations of [^{14}C]choline and [^{3}H]18:1 into secreted phosphatidylcholine, but there is greater variability between experiments (*Table 2*). The discrepancies between the incorporation of choline and 18:2 could result partly from a contribution from the methylation of phosphatidylethanolamine to the synthesis and secretion of phosphatidylcholine.[28]

EGTA is a fairly specific Ca^{2+} chelator. This compound, when added to the incubation medium, causes a decrease in the incorporation of [^{14}C]choline into phosphatidylcholine in the hepatocytes. However, there is no significant change in the synthesis of phosphatidylcholine or triacylglycerol from [^{3}H]18:1.[8] Extracellular EDTA does inhibit the secretion of triacylglycerol and phosphatidylcholine from the hepatocytes.[8] In comparison with VLDL secretion, there is relatively little effect on the secretion of lysophosphatidylcholine (*Table 2*).[8] These responses indicate that the chelation of extracellular Ca^{2+} has relatively little effect on lysophosphatidylcholine production when compared with interference with intracellular Ca^{2+}.

These combined results indicate that part of the mechanism for lysophosphatidylcholine secretion involves a hydrolysis of phosphatidylcholine by intracellular phospholipases (*Figure 1*) that require Ca^{2+}. The participation of phospholipase that are dependent on extracellular Ca^{2+} appears unlikely. Chlorpromazine is also able to increase the pH of lysosomes, which can cause inhibition of lysosomal phospholipases. This might contribute to the observed inhibition of lysophosphatidylcholine secretion.[8]

Hormonal control of lysophosphatidylcholine production by cultured hepatocytes

Effects of glucocorticoids and insulin

Neither insulin nor the synthetic glucocorticoid, dexamethasone, significantly alter the secretion of lysophos-

Table 2 Effects of chlorpromazine, verapamil, EGTA, and cycloheximide on the incorporation of oleate and choline into glycerolipids of the incubation medium by rat hepatocytes

	Relative incorporation (%) into:					
	Lysophosphatidylcholine		Phosphatidylcholine		Triacylglycerol	
Additions	Oleate	Choline	Oleate	Choline	Oleate	[Triacylglycerol] (%)
None	100 [6.23 ± 1.14(5)]	100 [3.31 ± 1.07(5)]	100 [1.23 ± 0.54(5)]	100 [0.105 ± 0.03(5)]	100 [11.71 ± 3.54(5)]	100 [5.10 ± 1.08(3)]
Chlorpromazine (100 mmol/L)	55 ± 19(4)**	28 ± 9(4)†	160 ± 136(4)	53 ± 7(4)**	75 ± 22(4)	93 ± 37(3)
Verapamil (150 mmol/L)	46 ± 24(4)*	21 ± 8(4)†	120 ± 67(4)	54 ± 34(4)	84 ± 35(4)	66 ± 5(2)
EGTA (2 mmol/L)	91 ± 12(4)	76 ± 17(4)	57 ± 34(4)	42 ± 6(4)†	64 ± 16(4)**	69 ± 25(2)
Cycloheximide (5 μg/mL)	106 ± 16(3)	110 ± 26(3)	175 ± 68(3)	92 ± 23(3)	107 ± 55(3)	94(1)

Rat hepatocytes were incubated with the compounds indicated in the presence of 0.5 mmol/L albumin, and the incorporation of [^{3}H]oleate and [^{14}C]choline into glycerolipids was measured over 8 hr. Results are means ± S.D. for the numbers of independent experiments shown in parentheses, and the values are expressed relative to the control incubation where no additions were made. This value is taken as 100%, but the absolute incorporation, in nmol of substrate incorporated/unit of lactate dehydrogenase, is also shown (in brackets) in the table. [Triacylglycerol] is expressed in nmol/unit of lactate dehydrogenase. Means ± ranges are shown where there are only two experiments. The significance of the differences in incorporation relative to the appropriate control value was calculated by using a paired *t* test, and is indicated by $*P < 0.05$; $**P < 0.02$; $\dagger P < 0.001$.
The table is taken from reference 8 with permission.

phatidylcholine.[2] This contrasts with the effects of dexamethasone, which stimulates VLDL secretion, and insulin, which inhibits this process.[2,35] However, the combination of both dexamethasone and insulin results in a significant decrease in the appearance of lysophosphatidylcholine in the incubation medium.[2] These results once again emphasize that the secretion of lysophosphatidylcholine from hepatocytes is not linked to the secretion of VLDL (*Figure 1*). This difference is further confirmed by the use of colchicine, which inhibits microtubular formation and VLDL secretion. However, this agent has no significant effect on the production of lysophosphatidylcholine.[2]

Effects of glucagon and cyclic AMP

These experiments involved measuring the incorporation of [^{3}H]glycerol and [^{14}C]choline into lysophosphatidylcholine (*Figure 1*). Incubation of the hepatocytes for up to 12 hours with glucagon and a cyclic AMP analogue significantly decreased the incorporation of choline and glycerol into lysophosphatidylcholine in the hepatocytes.[12] However, there was no significant effect on the appearance of lysophosphatidylcholine in the incubation medium. Twelve hours after adding glucagon or a cyclic AMP analogue to the medium there was an increased incorporation of glycerol and choline into the secreted lysophosphatidylcholine. This occurs when there is a greater labeling of the phosphatidylcholine in the hepatocytes.[12] The mechanism for this increased incorporation of precursors into phosphatidylcholine probably depends on the increased activity of CTP:phosphocholine cytidylyltransferase. This enzyme is rate limiting for the production of CDP choline (*Figure 1*) in the synthesis of phosphatidylcholine, and its activity is increased in the long term by glucagon and cyclic AMP.[36]

Effects of choline deficiency

The appearance of lysophosphatidylcholine in the medium was studied by using hepatocytes from choline-deficient rats.[37] These results show that even though the hepatocytes were defective in phosphatidylcholine biosynthesis, the albumin-stimulated release of lysophosphatidylcholine was similar to that obtained from hepatocytes that had been supplemented with choline. It was therefore suggested that the secretion of lysophosphatidylcholine by the liver may provide a vital supply of choline to other tissues during choline deficiency. This may be particularly important when the secretion of VLDL is suppressed.

It was also shown in these experiments that lysophosphatidylcholine from the medium was as effective as choline in restoring the secretion of VLDL in choline-deficient hepatocytes. This effect involved the reacylation of the lysophosphatidylcholine, which contributed to the phosphatidylcholine pool of the hepatocytes.[37]

Mechanism for the secretion of lysophosphatidylcholine

The exact mechanism for the secretion of lysophosphatidylcholine from hepatocytes is not firmly established. However, it probably arises mainly through the action of phospholipase A_1, which is fairly active in the liver (*Figure 1*). The breakdown of phosphatidylcholine by this enzyme would yield predominantly unsaturated lysophosphatidylcholine because the latter acids are primarily located in position 2 of glycerophospholipids after remodeling, which follows the initial synthesis. However, the presence of 25–37% of saturated fatty acids (16:0 and 18:0) in the lysophosphatidylcholine produced by the hepatocytes and perfused liver (*Table 1*) is far higher than will be expected in the *sn*-2-position

of glycerolipids.[38,39] It is therefore likely that phospholipase A_2 participates in the production of the saturated lysophosphatidylcholines that appear in the medium (*Figure 1*).

In the experiments that have been performed on the secretion of lyso PC, it has not been possible to investigate the position of the acyl groups on the lysophosphatidylcholine. This is because isomerization takes place during the period of the relatively long incubations that are required to obtain sufficient quantities of material to analyze. Furthermore, isomerization of the lysophosphatidylcholine occurs on the silica gel used for purification.[40] An alternative approach might be to use Nuclear magnetic resonance spectroscopy,[41] but this only gives the average composition of the 1- and 2-lysophosphatidylcholines. The analysis would not indicate whether the unsaturated fatty acid is on the 2-position as expected.

Despite these gaps in our knowledge, it is likely that phosphatidylcholine from the hepatocytes is hydrolyzed partially by Ca^{2+}-dependent phospholipases (*Figure 1*) because Ca^{2+} antagonists such as chlorpromazine and the Ca^{2+} channel blocker, verapamil, inhibit lysophosphatidylcholine production at relatively low concentrations (*Table 2*). However, addition of EDTA to the incubation medium to complex extracellular Ca^{2+} had relatively little effect on lysophosphatidylcholine production. It is also possible that verapamil and chlorpromazine might inhibit hepatic phospholipase A_1 directly, because this effect has been demonstrated using tissue from the heart.[42]

The effective removal of the lysophosphatidylcholine from the hepatocytes is dependent on an acceptor molecule in the medium. Physiologically, this would be supplied by albumin, which dramatically stimulates lysophosphatidylcholine secretion. The attachment of lysophosphatidylcholine to albumin enables it to be removed from the liver by the circulation (*Figure 1*). The mechanism can explain the occurrence of the lysophosphatidylcholine in the blood that can be seen even in the presence of LCAT deficiency.[4]

Physiological significance of hepatic lysophosphatidylcholine secretion

In rats, lipophosphatidylcholine is rapidly removed from the blood with a half-life of about 47 min.[43] Most of the labeled lysophosphatidylcholine is recovered in the liver, small intestine, skeletal muscles, lung, kidneys, and heart. The liver can therefore reuse some of the secreted lysophosphatidylcholine unless it is rapidly removed. In squirrel monkeys, one pool of lysophosphatidylcholine in the blood has a half-life of about 12 min.[44] After about 20 min about 19% of the labeled lysophosphatidylcholine that is injected into the blood of squirrel monkeys is found incorporated into the brain.[45] It has therefore been suggested that this lipid can provide a transport system for choline to the brain where it can act as the precursor for phosphatidylcholine and acetylcholine.[45,46] However, other authors have questioned whether lysophosphatidylcholine has the ability to cross the blood brain barrier.[47]

The lysophosphatidylcholine that is taken up by tissues can be rapidly reacylated from phosphatidylcholine.[43–45,48] This provides an additional mode of synthesis for phosphatidylcholine in addition to the CDP-choline pathway and the methylation of phosphatidylethanolamine. Alternatively, some of the lysophosphatidylcholine that is taken up by tissues can be degraded to water-soluble compounds including choline, phosphorylcholine, and betaine.[45]

Although lysophosphatidylcholine concentration in the blood is relatively high (0.2 mmol/L) compared with about 10 μmol/L for glycerophosphorylcholine and choline, the concentration of phosphatidylcholine is about 1–2 mmol/L.[3,49] Most of the phosphatidylcholine is present in lipoproteins whose uptake by tissues is governed by endocytosis that is receptor mediated, e.g., by the apoB/E receptor. The rapid removal of lysophosphatidylcholine from the blood does not depend on lipoprotein receptors, and therefore this lipid can provide tissues with a source of choline and unsaturated fatty acids that is independent of lipoprotein metabolism.

It is concluded that the predominantly polyunsaturated lysophosphatidylcholine that is produced by hepatocytes can be bound rapidly to albumin in the circulation and carried to other tissues. It can then be taken up and metabolized by extrahepatic tissues. The secretion of lysophosphatidylcholine from the liver could therefore provide a novel transport system for carrying choline and polyunsaturated fatty acids (primarily 20:4) to other organs.

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