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MINI REVIEW

Phosphatidylcholine's functions beyond that of a membrane brick

Samuel Furse and Anton I. P. M. de Kroon

*Membrane Biochemistry and Biophysics, University of Utrecht, Utrecht, The Netherlands***Abstract**

Since its discovery in the 19th century, phosphatidylcholine (PC) has been regarded primarily as a structural lipid. However, more recent evidence, much of it in the last five years, strongly suggests that PC has other roles. Here, we explore some of that new evidence and consider the possibility that the ultimate role of phosphatidylcholine may not be predictable.

Keywords

Lipid isoforms, lipid signalling, phosphatidylcholine

History

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Phosphatidylcholine (PC), was one of the first biological amphiphiles to be discovered (Gobley, 1874). The discovery of PC was facilitated by a combination of it readily dissolving in chloroform and its high abundance. In the first half of the 20th century it became clear that PC formed a large and important part of membranes. This led to a considerable research effort to elucidate its biophysical properties (Chapman et al., 1977; Elias et al., 1976; Salsbury et al., 1970). This research came at the same time as the advent of the fluid mosaic model of membrane structure (Singer & Nicolson, 1971, 1972), leading to a widespread view that this lipid was a cellular building block, analogous to the fired clay bricks used to build houses.

This view began to change when it was discovered that PC is a storage lipid for arachidonoyl residues (Bills & Silver, 1975; Kramer & Deykin, 1983; Ziboh & Lord, 1979). These observations were striking because they suggested for the first time that PC has a role in processes that are not exclusively physical. In this case, certain fatty acids in PCs are used in prostaglandin pathways behind responses (Bills & Silver, 1975; Ziboh & Lord, 1979). Here, we review several recent advances have expanded on the notion that PC is not just a kind of cellular brick.

A recently-discovered example of this is the relationship between PCs and Peroxisome Proliferator-Activated Receptors (PPARs). PPARs are nuclear receptor proteins that have regulatory roles in gene expression and are becoming increasingly popular as drug targets. Chakravarthy et al. (2009) have discovered that a common isoform (molecular species) of PC, 1-palmitoyl-2-oleoyl-*sn*-

glycerol-3-phosphocholine (16:0/18:1 PC, POPC), serves as the endogenous ligand for the nuclear receptor PPAR α in hepatocytes. PPAR α is a transcription factor regulating the expression of many genes that govern lipid metabolism (Kersten, 2014).

The gene expression that arises from activating PPAR α is reduced when either the fatty acid synthase (FAS) or the PC biosynthetic enzyme CEPT1, both required for the presence of POPC, is inactivated. Furthermore, established PPAR α agonists were found to compete with POPC for binding. The interaction of POPC with the other PPARs was much weaker (PPAR δ) or even absent (PPAR γ). Injection of POPC into the hepatic portal vein of live subjects (mice) over several days was followed by an increase in PPAR α -dependent gene expression and decreased hepatic steatosis (Chakravarthy et al., 2009). These results are surprising because they imply that what appears to be a rather ordinary isoform of PC, well known as a structural lipid, is able to influence gene expression in mammals with narrow specificity. The observation of POPC as a signalling molecule is supported by its relatively low abundance in the liver.

The specificity of this system becomes even more striking in the light of a study of another PPAR. The nuclear hepatocyte receptor PPAR δ was found to control a lipogenic pathway in the liver that regulates fatty acid uptake and β -oxidation by muscle. Liu et al., identified 1-stearoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (18:0/18:1 PC, SOPC) as the serum lipid regulated by diurnal hepatic PPAR δ activity (Liu et al., 2013). SOPC but not POPC therefore effects a reduction in postprandial (after-eating) levels of triglycerides and increases fatty acid use through PPAR α receptors in muscle cells.

Taken together, these signalling functions of POPC and SOPC show not only that at least two molecular species of PC are involved in related but distinct aspects of the metabolism

Correspondence: Dr Samuel Furse, PhD, Membrane Biochemistry and Biophysics, University of Utrecht, Kruytgebouw, Padualaan 8, Utrecht 3584 CH, The Netherlands. Tel: +31 (0) 30 253 3345. Fax +31 (0) 30 253 3969. E-mail: s.r.furse@uu.nl, samuel@samuelfurse.com

of fats, but also suggest that the proteins involved, *i.e.* liver PPAR α and an upstream effector of muscle PPAR α (or possibly muscle PPAR α itself), are sufficiently specific that they can distinguish between isoforms of PC as similar as SOPC and POPC.

Recent research into the human Liver Receptor Homologue 1 (LRH-1), responsible for regulating bile acid biosynthesis, revealed yet another example of a specific PC molecular species serving as agonist. The activation of LRH-1 of di-lauroyl PC (di-C12:0 PC, DLPC) was about twice that of di-caproyl PC (di-C10:0 PC) and four times of di-myristoyl PC (di-C14:0 PC). Dipalmitoyl PC (di-C16:0 PC, DPPC) did not activate the receptor at all (Lee et al., 2011). The greatest activity was induced by di-undecanoyl PC (di-C11:0 PC, DUPC), however the agonist for this receptor *in vivo* is expected to be DLPC. DLPC and DUPC did not activate PPAR α . Mass spectrometry showed displacement of *Escherichia coli* lipids by DLPC in the heterologously (in *E. coli*) expressed lipid binding domain of LRH-1, but not by DPPC. Tests *in vivo* (murine), showed that administered DLPC affected the expression of LRH-1 target genes and lowered hepatic triglycerides and serum glucose. DLPC treatment of insulin-resistant mice decreased hepatic steatosis and improved glucose homeostasis. This was supported by the observation that both the anti-diabetes and lipotropic effects are lost in liver-specific *Lrh-1* knockouts. This work made a clear case for an LRH-1-dependent phosphatidylcholine signalling pathway that regulates bile acid metabolism and glucose homeostasis.

Musille et al. (2012) built on the work by Lee et al., by exploring the structure of LRH-1 when bound to DLPC and other lipids and when unbound, using crystallographic data. This work revealed that LRH-1 undergoes conformational changes in response to binding a lipid ligand that depend on the lipid's fatty acid composition. Furthermore, DLPC's activity on LRH-1 is described as a typical agonist, in that it enhances the recruitment of co-activators and disfavours the binding of repressors. This contributes to LRH-1's importance as a therapeutic target. A salient question raised by these studies, that probably requires an inter-disciplinary approach, is the molecular mechanism by which nuclear receptor proteins bind to their particular PC ligands.

There is also evidence for at least two distinct roles for PC in insulin transduction (Ersoy et al., 2013; Sakai et al., 2014). Phosphatidylcholine transfer protein (PC-TP, also known as StARD2) with its ability to exchange PC molecules between lipid bilayers is the prototype of a PC-specific lipid-binding protein. Although this protein was first regarded as an inter-membrane lipid transporter, more recent evidence indicates that the principal role of PC-TP is as a lipid sensor. Ersoy et al. (2013) inhibited PC-TP with small molecule A1 and observed increased steady-state concentrations of Insulin Receptor Substrate 2 (IRS2). A1 is a sulfonamide (Shishova et al., 2011) that displaces PC molecules from the PC-TP binding site. IRS2 is an important effector of insulin signalling that is attenuated in diabetes. It is not clear whether the nature of the PC molecular species bound to PC-TP plays a role, however, earlier work by Kasurinen et al. (1990) showed that the affinity of PC-TP for PC increased with the number of unsaturated bonds on the *sn*-2 fatty acid.

Saturated PCs may be indirectly involved in regulating glucose homeostasis by providing substrate for the diglyceride kinase delta (DGK δ) that regulates glucose uptake in muscle cells. The expression of DGK δ is reduced in diabetes type 2, and DGK δ deficiency was shown to cause insulin resistance (Chibalin et al., 2008). DGK δ phosphorylates diglycerides (DGs) to give phosphatidic acid (PA); at present it is not clear whether an accumulation of DG or lack of PA causes the defect. Sakai et al. (2014) reported that the affected diglycerides typically contain palmitic acid (16:0) residues. This process is dependent upon PC-specific phospholipase-C (PC-PLC), as the addition of an inhibitor for this lipase, D609, significantly reduced the glucose-stimulated activity of DGK δ . This suggests that the glyceride products of PC-PLC activity are required for DGK δ activity, which is supported by the observation that PC-PLC co-immunoprecipitates with DGK δ , suggesting that the two proteins are adjacent *in vivo* ensuring that the substrate availability to DGK δ is high (Sakai et al., 2014). This is important because these palmitoyl-containing glycerides are distinct from *poly*-unsaturated isoforms of DG that typically come from other sources. The evidence for the conversion of PC into DG and thence to PA raises a question about how these changes affect the local physical behavior of the membrane. The conversion of PC to DG has been known for some time to have a physical influence on membrane systems (Riske & Döbereiner, 2003) (see Goñi et al., 2012, for review), but it is not immediately clear what the effects might be *in vivo*.

A unique isoform of PC, 1-oleoyl-2-palmitoyl-*sn*-glycerol-3-phosphocholine (OPPC) has been implicated in functional compartmentalisation of the plasma membrane of neurons (Kuge et al., 2014). The experimental evidence is largely based on a monoclonal antibody that specifically recognizes (*lyso*-)PCs with oleic acid installed at the *sn*-1 position in the neuronal plasma membrane. The data suggest that NGF-stimulated acyl chain remodelling of PC generates OPPC locally, a process catalyzed by a phospholipase A1 and an acyltransferase enriched in developing axon tips. Kuge et al. (2014) propose that OPPC attracts a subset of integral membrane proteins and thus defines a membrane compartment in the presynaptic neuronal plasma membrane.

These recent findings show that PC isoforms have pivotal roles in mammalian cells that are not directly connected to the role of PC as a major structural component of biological membranes. Such roles include gene regulation and homeostatic control of serum glucose concentration. Notably, the specificity of PC isoforms in such processes is quite clear, with receptors able to differentiate between PCs with different fatty acid residues. This invites speculation that the enzymes responsible for producing PCs are involved not only in directing the physical properties of mammalian membranes, but also some of the most fundamental metabolic activity of the organism.

This evidence that PC has a significant biological role that may be quite separate to its structural one comes at the same time as indications that inositides, lipids that were thought to be exclusively signalling lipids or their precursors in eukaryotes, can have a strong physical impact on membranes (Furse, 2015; Zhendre et al., 2011). This supports the notion that phospholipid classes have more than one role *in vivo*, and

suggests that it is not possible to predict what the ultimate role of a given phospholipid isoform will be, as there are now several examples of lipids that have a very similar structure but exhibit a considerable difference in bioactivity.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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