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REVIEW

Is phosphatidylglycerol essential for terrestrial life?

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Abstract Lipids are of increasing importance in understanding biological systems. Lipids carrying an anionic charge are noted in particular for their electrostatic interactions with both proteins and divalent cations. However, the biological, analytical, chemical and biophysical data of such species are rarely considered together, limiting our ability to assess the true role of such lipids in vivo. In this review, evidence from a range of studies about the lipid phosphatidylglycerol is considered. This evidence supports the conclusions that this lipid is ubiquitous in living systems and generally of low abundance but probably fundamental for terrestrial life. Possible reasons for this are discussed and further questions posed.

Keywords Lipid · Phosphatidylglycerol · Membrane · Anionic · Signal

Introduction

The structure of phosphatidylglycerol (PG) was formally determined from lipid isolates of the single-cell photosynthetic organism *Scenedesmus* in the late 1950s [1]. Within a decade of its discovery, PG was found in higher plants [2, 3], Gram negative bacteria [4, 5] and mammals [6, 7]. The principal steps of the biosynthesis were elucidated in the Kennedy laboratory [8], and a laboratory synthesis was completed [9] at around the same time. Lipid derivatives of PG produced in vivo were discovered about ten years after structural determination of the original [10, 11]. The discovery of PG in the archaeon *Haloferax volcanii* in the 1970s indicated that it is a constituent of all three domains of terrestrial life, a fact that hints that it may be ubiquitous and perform one or more fundamental biological functions.

Recent lipid profiling has shown that PG has a relatively low abundance with respect to phosphatidylethanolamine (PE) in prokaryotes and either PE or phosphatidylcholine (PC) in eukaryotes [12, 13, 14]. This suggests that its structural contribution is minimal or controlled tightly. Its molecular structure (Fig. 1) is analogous to phosphatidylinositol (PI, which comprises an inosityl moiety instead of the glyceryl one in PG), which may be the reason that the two sometimes have similar activity [15] and transport [16, 17], and why they are sometimes bracketed together [18–20].

PG's head group comprises a second glyceryl moiety on the phosphate (Fig. 1), which attracts hydration and thus has a larger effective head group diameter than phosphatidic acid (PA). This means that PG is both a cylindrical (type 0) lipid under model and physiological conditions [21] and possesses an anionic charge. The latter directs its relationship with cations [21–25]. PA, the progenitor of lipids in several species [26] is regarded as a cone-shaped (type II) lipid [27–29]. The molecular structure of PG also bears a similarity to that of cardiolipin (CL); CL can be described as one equivalent of glycerol with a phosphatidate moiety on either primary hydroxyl. Since its discovery, biochemical research into PG has been dominated by its roles in the surfactant of lung tissue, chloroplast membranes and in both bacterial and mammalian systems.

Lung surfactant

PG is the second largest lipid constituent of lung surfactant (LS) in almost all mammals [19–32]. The concentration of PG

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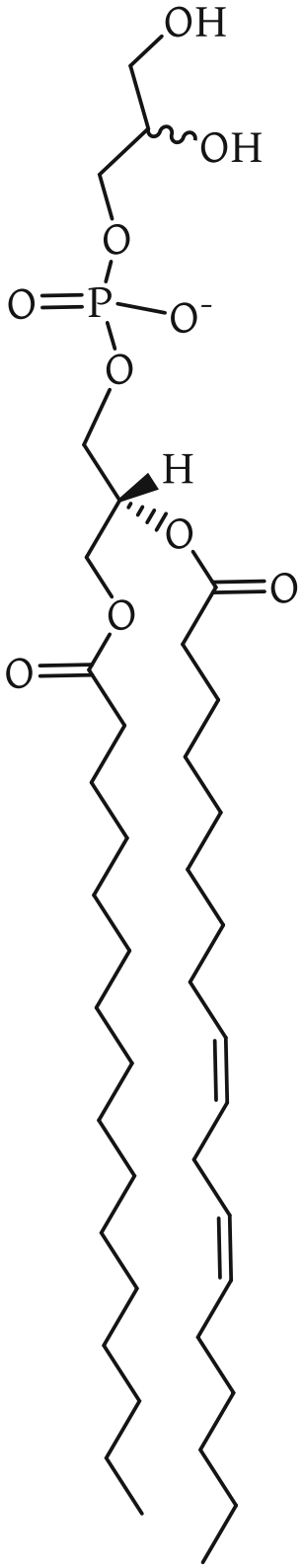

Fig. 1 The molecular structure of phosphatidylglycerol

in LS is around 10 %, which is considerably higher than the concentration of PG in the membranes of mammalian cells [12, 33–35] and of lung cells in particular [36]. Studies of ozone-based damage have shown that PG has a fluidising effect on LS [37].

There is considerable evidence that an absence of PG in the LS of foetal humans is an indicator of respiratory distress syndrome (RDS) [38], suggesting PG has a crucial role in lung function from the outset. Studies of normal foetal lung development have shown that PG appears in amniotic fluid during the last weeks of pregnancy and increases in concentration in the fortnight before birth in particular [39]. The concentration of PG in LS can be increased by the administration of cortisol [40]. PG itself can be used as a treatment for RDS partly because it prevents alveolar epithelial apoptosis and profibrotic stimulation [41]. However, it can be isomerised to by alveolar macrophages [42]. There is also evidence that PG suppresses proliferation of respiratory viral infection [43, 44, 45]. Taken together, these data suggest that PG has one or more unique properties that are essential to lung function.

Several studies have attempted to explore the role of PG in LS. A key part of this was to determine its concentration and origin. This has not always been clear; some measurements proved misleading because PG from bacteria in the vagina had contaminated the samples of amniotic fluid [46, 47]. Profiling of the fatty acid residues (FARs) of the PG offers a possible solution to this; FAs containing cyclopropyl or *c*-11 olefins indicate *Escherichia coli*, rather than any mammalian cell, as the source [48]. Accurate measurement of the FAR profile of the PG in the LS of children and adults with other respiratory conditions may be important in itself. Cystic fibrosis sufferers have considerably more 18:0 and less 16:0 in their PG than asthmatics do [49], implying that the PG in the LS of cystic fibrosis patients is less fluid than that of asthmatics. This trend is echoed in mice with CF, in which there are fewer docosahexaenoic in favour of arachidonic FARs compared to healthy controls [50].

The lower concentration of PG in the LS of babies with RDS appears to be separate from other metabolic disorders, such as diabetes mellitus [39, 51, 52] and pre-eclampsia [52]. These observations are remarkable because the majority of diabetic mothers produce babies with elevated amounts of LS [52], and there are significant changes in both triglyceride and lipid metabolism from at least as early as 16 weeks in pre-eclamptic pregnancies [53–57].

Recent evidence indicates that the general biophysical effect of PG in LS is connected to its negative charge [58], with relatively little effect on polymorphism [59, 60]. This is consistent with the expectation that PG adopts a type 0 spontaneous curvature under physiological conditions [21]. At lower temperatures, mixtures of PC and PG appear to be more ordered than the equivalent isoforms of PC alone [60], but bilayers comprising PC and PG are more permeable to potassium ions than those containing only PC [61]. The presence of negative charge also changes the bilayer's relationship with divalent cations [25, 62]; the presence of Mg^{++} and Ca^{++} ions raises the energetic cost of chain melting (becoming fluid)

[61], in contrast to hydrated unsaturated PC systems that typically melt well below body temperature. Cholesterol is less miscible in PG-containing membranes [63], and adding PG to PC-cholesterol systems can induce phase separation [58]. Presumably, the stiffening effect of cholesterol is therefore modulated by PG and restricted to areas that contain less of it. This may contribute to the observation of a fluidising effect of the presence of PG in model systems of LS [37].

This loose body of evidence underscores the need for a precise characterisation of PG's biochemical and biophysical roles in LS. Studies of the role of LS in normal lungs may offer the most straightforward answer, including the study of healthy lung systems where alternatives to PG are the norm, such as that of rhesus monkeys that comprise PI instead of PG [64].

Mammalian cells

In healthy mammalian systems, PG has been shown to activate RNA synthesis [65] and a nucleus PKC [66] but inhibit platelet activating factor [67] and PC transfer [68]. However, PG is also produced in response to viral infection and can be used by the virus to prepare its own membrane [69–71]. PLC activity on PG is compromised in Neumann-Pick disease [72], and reduced levels of PG in platelets (*e.g.*, those lacking iPLAγ) leads to longer bleeding times but is a protection against pulmonary thromboembolism [73]. Taken together, these data suggest that PG has several roles in shaping both important lipid-protein and lipid-lipid interactions. This strongly suggests a need for control to prevent PG having unfocussed or undesired effects.

Some control of PG's activity can be achieved through its abundance and FAR profile. The abundance of PG is around 0·2 % in human plasma [12] and appears almost negligible in HeLa [33, 74]. Furthermore, PG's isoform profile is relatively saturated with respect to other lipids. Only around 64 % of FARs are polyunsaturated in mammalian PG, as compared to 87 % (PC), 89 % (PE) or 84 % (PI) [12]. This may be related to its role in proliferation and differentiation.

Polyunsaturated FARs inhibit the proliferation of keratinocytes, where less unsaturated isoforms of PG, such as palmitoyl-oleoyl-PG and dioleoyl-PG, accelerate it [75]. This trend is followed by extracts of PG from natural sources. PG from Hen's eggs [76] (44 % 18:0/16:0) accelerates proliferation, but this is inhibited by PG from *Glycine max* [75] (72 % 18:2/18:3). However, the polyunsaturated isoforms of PG appear to promote differentiation at the expense of proliferation [75, 76]. This evidence supports the conclusion that DNA synthesis is inhibited by the PG produced by PLD2 [76].

The correlation between the number of unsaturated bonds and activity as a signal also has a physical dimension. The level of unsaturation of PG isoforms correlates with the fluidity profile of the lipid. Polyunsaturated PGs are the most fluid, followed by monounsaturated isoforms and lastly saturated as the least most fluid. So, the synthesis of a PG isoform that will stimulate proliferation will also tend to reduce the fluidity of the membrane. However, the precise effect of modulations in the relatively modest PG fraction in mammalian systems are unclear at present.

Plants

PG is typically more concentrated in plant systems than in animals, forming 1·5–4·5 % of the lipid fraction in subcellular plant bilayers such as the PM [77–80]. Much of the PG in plants is made in chloroplasts and thus is of prokaryotic origin [81]. The bulk of PG synthesis occurs during the early part of the light portion of the synchronous cycle, leading to the suggestion that chloroplast membrane lipids are synthesised in a sequential manner [82].

PG is required for embryo development [83], photosynthesis [84] and thylakoid membrane development [85]. These roles are reflected in the subcellular and tissue distribution of PG. The abundance of PG in the PMs of both freshwater coenocytic *Hydrodictyon africanum* and light-grown *Hordeum vulgare* is considerably lower than in whole cells [78, 79, 86]. Molecular profiling of of *H. vulgare* tissue suggest PG's abundance in the PM is also higher than non-photosynthetic tissue such as root [79].

The synthesis of PG is temperature-dependent [87], which may be important in its role in adaptation to changes in temperature. Plants adapted to low temperatures possess a very different isoform profile of PG to those adapted for warmer climes [88]. The PG isolates from sweet potato (optimum growth temperature ~20–25 °C [89, 90]) undergoes the phase transition from gel to fluid lamellar (melts) at about 40 °C (5 mM Mg^{++}) where that from spinach (optimum growth temperature ~5 °C [91]) melts at 20 °C [88]. This is the result of an inversion in the FAR profile amongst PG isoforms. Sweet potato has around 44 % 16:0 and 5 % 18:3, where spinach has 14 % 16:0 and 40 % 18:3. Results acquired from *Oryza sativa* are consistent with this [92], as are the adaptation to lower temperatures by tomato plants [93]. These data indicate that there is a survival role for the FARs in the PG fraction in plants.

A FAR that appears in PG isoforms in similar amounts in both spinach (39 %) and sweet potato (34 %) [88], and that is rarely found in mammals, is *trans*-16:1, also known as *trans*-Δ3-hexadecenoic acid. PG molecules containing this FAR have a particular role in cementing thylakoids during granum formation [94]. This may be the basis for the role of PG containing *trans*-Δ3-hexadecenoic acid in light reactions of photosynthesis [95].

However, the physical behaviour of lipids with *trans*-Δ3-hexadecenoyl residues is distinct form palmitoleoyl (*cis*-16:1). The *trans*-olefin geometry generates a weaker fluidising effect

than the *cis*-isomer, as demonstrated by melting temperatures that are closer to that of isoforms with saturated FARs of the same chain length [96, 97]. There is evidence that this applies to PG in particular [98]. The presence of a fatty acid with behaviour intermediate between saturated and unsaturated equivalents can therefore be interpreted as a control mechanism for tuning the biophysical properties of the PG fraction. The accumulation of this FAR is a marker for organ maturation as PG molecules containing *trans*-Δ3-hexadecenoic acid increase in concentration by a factor of 20 between the youngest (basal) and oldest (distal) leaf sections [99]. This is broadly consistent with different biophysical requirements of growing and matured plant organs.

Bacteria

The turnover of PG in bacteria has been researched in detail (reviews [100–103]), and it is now regarded as an important component of virtually all bacteria [26, 104, 105]. It is typically present at a much higher abundance than in mammalian cellular membranes [106]. The distribution of PG is inhomogeneous both laterally and between the two membranes of Gram negative bacteria [107–109] (reviews [110–112]). PG has a particular role in protein folding [113] and protein binding [114, 115]. It also activates a glycerol phosphate acyl transferase [116], implying that PG is involved in a positive feedback loop that produces PA and thus all membrane lipids. PG is also required for the transport of proteins across inner membranes [117]. Fluorescence microscopy has provided considerable evidence for inhomogeneous lipid distribution in bacteria [118]. Biophysical reasons for inhomogeneous distribution are less clear. It may be a means for distributing negative charge, with the aim of regulating processes such as the assembly of the 'Z-ring' [119], that relies on negative charge in the membrane, the proteins that regulate the formation of the division plane [120] and DNA replication [121–123]. It may also be a homeostatic measure, with respect to high salt concentrations [124].

It appears that PG is synthesised during cell elongation [26, 104] and metabolised during fission steps of the cell cycle in *E. coli* [26, 108], suggesting it has one or more roles in maintaining the integrity of the cell envelope through cell proliferation. One of these may be linked to its being a cofactor in the synthesis of the cell wall [125]. This may in turn be linked to cell survival through its role in antibiotic resistance in the Gram negative bacterium *Serratia marcescens* [126].

These data suggest that there is more than one biophysical role and probably several (perhaps species-dependent) metabolic roles for PG in prokaryotes. This is not immediately obvious from the relatively small number of synthesis routes for PG in bacteria. It is produced in the manner of a bulk lipid. Control of PG's effects may also include degradation of the lipid. The major route for metabolism of PG in prokaryata is through synthesis of CL (review [127]). Furthermore, there is evidence that PG can be used to make PE in both Gram negative *E. coli* [128] and Gram positive *Bacillus megaterium* [129, 130], hinting that this is a feature common to many or even all prokaryotes.

More minor routes for metabolising PG are in producing amino acid derivatives [11, 131, 132] and producing PGs acylated with FARs [133]. It is also a source of phosphatidyl and of *sn*-glycerol-1-phosphate groups [134]. It is not clear what the physical behaviour of many of these derivatives is; however, the charge carried may be net 0 or even positive (e.g., lysyl-PG), implying that the charge of this lipid may be modulated by such elaborations. The presence of analogues of PG with different electrostatic properties raises the question of whether the PG may be being stored. The presence of such derivatives instead of PG may be expected to reduce its efficacy in processes such as assembling the Z-ring, or regulating the proteins involved the formation of the division plane. It may also be expected to inhibit DNA synthesis, therefore.

Concluding remarks

The evidence relating to PG's presence and behaviour in biological systems indicates that it probably exists in all cells but typically at a low abundance. This ubiquity in turn suggests that it has one or more fundamental roles in vivo. However, it is not yet clear precisely why PG is an essential but minor component in lung surfactant, in both viral attack and proliferation or what the limits of bacterial membranes' ability to replace PG are [26]. This is in contrast to the phase behaviour [135, 136] and conformation [137–139] of PG in model systems, which are relatively well understood.

One analysis of this lipid is to draw on the relationship between its structure and behaviour. PG is relatively unusual amongst lipids in that it is both invariably type 0 and anionic. Other major anionic lipids, PA [27–29], PI [140, 141], PI-4-*P* [142, 143] and CL [104, 144], can behave as type II lipids, and with the arguable exception of PI [77], typically do so under physiological conditions. Thus, the presence of PG confers a negative charge on a membrane without increasing stored curvature elastic stress.

In order to clarify the true extent of its influence in vivo, further work is required to dissect both the types of role (*e.g.*, signalling, biophysical) and the concentration-dependency (thresholds). This may require isosteric forms of PG, for example in which the hydroxyl groups are methylated or replaced with fluorine atoms. Furthermore, the distribution of PG in major cell types has not yet been probed fully. Such studies may reveal a low threshold-dependence of the effects of PG, or relatively fast (re-)distribution. This body of

evidence suggests that even a minor component of the lipid fraction as such can have a major contribution to cellular activity, albeit with the caveat that considerable further study is required to understand it fully.

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