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Phosphatidic acid: Mono- and poly-unsaturated forms regulate distinct stages of neuroendocrine exocytosis

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ABSTRACT

Lipids have emerged as important actors in an ever-growing number of key functions in cell biology over the last few years. Among them, glycerophospholipids are major constituents of cellular membranes. Because of their amphiphilic nature, phospholipids form lipid bilayers that are particularly useful to isolate cellular content from the extracellular medium, but also to define intracellular compartments. Interestingly, phospholipids come in different flavors based on their fatty acyl chain composition. Indeed, lipidomic analyses have revealed the presence in cellular membranes of up to 50 different species of an individual class of phospholipid, opening the possibility of multiple functions for a single class of phospholipid. In this review we will focus on phosphatidic acid (PA), the simplest phospholipid, that plays both structural and signaling functions. Among the numerous roles that have been attributed to PA, a key regulatory role in secretion has been proposed in different cell models. We review here the evidences that support the idea that mono- and poly-unsaturated PA control distinct steps in hormone secretion from neuroendocrine cells.

1. Introduction

Lipids found in eukaryotic membranes can be divided in three major classes including glycerophospholipids, sphingolipids, and sterols. Sophisticated techniques led to the identification of more than 30,000 different lipids suggesting that these molecules support many biological processes in addition to the well-known energy provider and compartment delimitation roles. Although their synthesis pathway, subcellular distribution as well as mechanisms by which they move from one compartment to another are getting better

Abbreviations: ADR, Acyldihydroxyacetone-phosphate reductase; CDP, Cytidyl phosphatidate; CDS, CDP-diacylglycerol synthase; CgA, Chromogranine A; CL, Cardiolipin; DAG, Diacylglycerol; DGK, Diacylglycerol kinase; DHAP, Dihydroxyacetone phosphate; DHAP AT, DHAP acyltransferase; FIPI, 5-Fluoro-2-indolyl des-chlorohalopemide; G3P, Glycerol 3-phosphate; GPAT, G3P acyltransferase; LPA, Lysophosphatidic acid; LPAAT, Lysophosphatidic acid-acyltransferases; PA, Phosphatidic acid; PABD, PA-binding domain; PAP, Phosphatidic acid phosphohydrolase; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PG, Phosphatidylglycerol; PI, Phosphoinositides; PLA, Phospholipase A; PLD, Phospholipase D; PS, Phosphatidylserine; TG, Triglycerides.

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understood everyday (Yang et al., 2018), there is still a gap in the comprehension of the precise function of many of them.

The acyl chain diversity in glycerophospholipids has been studied for decades, but our understanding of its contribution to cell function has remained elusive for many years, largely because of technical and conceptual limitations. Phospholipids are divided in families based on the chemical nature of their headgroup. By order of quantities found in eucaryotic membranes, the main families of phospholipids are phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphoinositides (PI) and phosphatidic acid (PA). They can exist both as monoacyl- or diacyl-glycerophospholipid forms. Variety in acyl chain in position *sn*-1 and *sn*-2 further extends the diversity of phospholipids. These chains are divided in three classes: saturated, mono- and poly-unsaturated. Based on the location of the poly-unsaturation, the later class has been further divided in subclasses of which the omega-3 (ω 3, e.g. docosahexaenoic acid, C22:6) and the omega-6 (ω 6, e.g. arachidonic acid, C20:4) are the most popular.

The acyl chain profile of a biological membrane often presents predominant combination that can be specific to some organisms, cells, and even organelles. For instance, while the endoplasmic reticulum is particularly enriched in mono-unsaturated lipids, poly-unsaturated lipids are more abundant in secretory vesicles and saturated lipids are more present in the plasma membrane (Bigay and Antonny, 2012). In mammals, the acyl chain pairings of PI are frequently composed of stearic acid (C18:0) and arachidonic acid (C20:4), while other phospholipids present a wide variety of acyl chains of diverse length and saturation. Little is known regarding the mechanisms and functions behind the phospholipid fatty acyl chain composition (Barneda et al., 2019).

Among phospholipids, PA is an important intermediate metabolite in the synthesis of all membrane glycerophospholipids and is therefore playing an important structural role in living cells by contributing to membrane biogenesis. Chemically, PA consists of a glycerol backbone to which are attached, through esterification, two fatty acyl chains and a phosphate at positions *sn*-1, *sn*-2, and *sn*-3, respectively. The unique feature of PA compared to the other diacyl-glycerophospholipids is its phosphomonoester link to a small anionic phosphate headgroup (Jenkins and Frohman, 2005; Tanguy et al., 2018). The small headgroup of PA predicts that it adopts a cone-shaped structure in membranes and X-ray diffraction studies have contributed to postulate that local accumulation of PA in one leaflet of membranes modifies their topology by creating a negative curvature (Kooijman et al., 2005). This property of PA is often linked to its contribution in diverse membrane trafficking events (Ammar et al., 2013b; Tanguy et al., 2016). PA serves also as an essential signaling molecule in diverse cellular processes, through the recruitment of a broad range of cytosolic proteins to appropriate membrane locations (Kim and Wang, 2020; Tanguy et al., 2018, 2019b).

In membrane trafficking, pharmacological, molecular and genetic compelling evidences support an essential role for PA in a variety of cellular processes based on vesicle transport and fusion. For instance, PA is critical for various exocytotic events such as endocrine

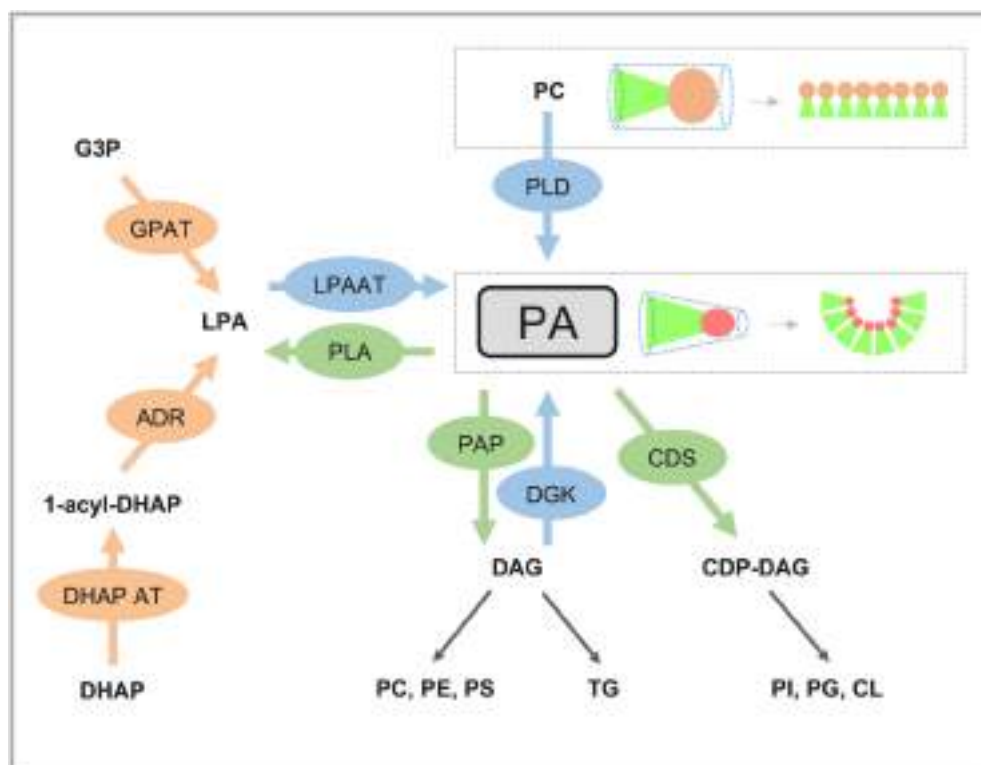


Fig. 1. The biosynthetic routes of PA, a central phospholipid.

Enzymatic pathways highlighted in orange are involved in structural PA synthesis, whereas enzymes in blue lead to the formation of signaling pools of PA. Among this last category, PLD activity transforms the cylindrical phospholipid PC into PA, a conical one, potentially inducing local negative membrane curvature. Enzymes triggering PA catabolism are shown in green.

and neuroendocrine exocytosis (Bader and Vitale, 2009; Vitale et al., 2001; Waselle et al., 2005), mast cell degranulation (Choi et al., 2002), endothelial cell secretion (Disse et al., 2009), acrosomal exocytosis (Lopez et al., 2012), exosome biogenesis and secretion (Ghossoub et al., 2014) and even the fast synaptic neurotransmission (Humeau et al., 2001; Schwarz et al., 2011; Raben and Barber, 2017). PA is also implicated in autophagy (Holland et al., 2016) and phagocytosis (Corrotte et al., 2006; Tanguy et al., 2019a), intracellular pathways such as tubular endosome biogenesis (Giridharan et al., 2013) and Golgi vesicle formation (Ktistakis et al., 1996), membrane wound repair (Vaughan et al., 2014) and neurite outgrowth (Ammar et al., 2013a). However, despite or perhaps due to these large implications, precise functions of PA along the secretory pathway remain unclear. The diversity of the PA biosynthetic routes together with the possible occurrence of many different PA species based on their fatty acyl chain composition open the possibility for multiple roles in a given cellular function.

2. The different sources of phosphatidic acid

In mammals, cellular PA production involves several major routes (Pokotylo et al., 2018; Zegarlińska et al., 2018; Tanguy et al., 2019b) (Fig. 1). Structural PA is synthesized through two acylation reactions: the glycerol 3-phosphate (G3P) pathway and the dihydroxyacetone phosphate (DHAP) pathway, both leading to lysoPA (LPA), a mono-acylated form of PA. LPA is subsequently transformed into PA during a second acylation step (Vance and Vance, 2004). PA generated from these *de novo* pathways is the main intermediate in the synthesis of all triacylglycerols and glycerophospholipids, as it is actively transformed by PA phosphohydrolase (PAP) into diacylglycerol (DAG) in the endoplasmic reticulum (Vance and Goldfine, 2002). PA can also be transformed by cytidyl phosphatidate (CDP)-DAG synthetase (CDS) into CDP-DAG, which fuels the synthesis of PI, phosphatidylglycerol (PG) and cardiolipin (CL). Different phospholipases A (PLA) can also deacylate PA into LPA.

Additionally, three alternative biosynthetic pathways use distinct lipid precursors to produce so-called “signaling” PA (Fig. 1). The first pathway involves phosphorylation of DAG to produce PA using ATP as a phosphate source by one of the 10 different DAG kinase (DGK). The second pathway involves acylation of LPA by specific LPA-acyltransferases (LPAAT) to generate PA (Jenkins and Frohman, 2005). Six human LPAAT isoforms have been cloned and characterized (Leung, 2001), but more proteins displaying LPAAT activities have recently been identified. For instance, the RIBEYE protein in synaptic ribbon enabling ultra-fast synaptic release possesses an LPAAT activity providing PA (Schwarz et al., 2011). The third pathway involves phospholipase D (PLD), which catalyzes the hydrolysis of the distal phosphodiester bond of PC to form PA and choline. Six isoforms of PLDs have been identified based on sequence homology, among them PLD1 and PLD2 being the best characterized isoforms. It is of note that until now no direct PLD activity *per se* has been documented for the PLD3-5 isoforms (Frohman, 2015). The complexity and diversity of PLD, DGK and LPAAT families suggest that they are involved in various specific cellular functions which are, probably, not redundant. In general, signaling PA generated from these enzymes is implicated in multiple processes such as cytoskeleton organization, cell survival, proliferation, membrane and vesicle trafficking (Nelson and Frohman, 2015). Intriguingly PC to PA conversion by PLD transforms a cylindrical phospholipid into a conical one. Since biophysical models have proposed that intermediates of the membrane fusion reaction require such cone- or inverted cone-shaped lipids, a direct role of PA as a fusogenic lipid has been proposed (Vitale, 2010). Interestingly, PLD localization to specific membranes compartments depends on key domains of the enzymes (Du et al., 2003) and probably involves deciphering the phosphoinositide landscape of intracellular membranes (Sztacho et al., 2019).

3. Role of phosphatidic acid in neuroendocrine exocytosis

The requirement for PA in calcium-regulated exocytosis in neuroendocrine and endocrine cells is probably one of the best documented role for PA in membrane trafficking (Bader and Vitale, 2009). Early studies in bovine chromaffin cells reported the inhibitory action of butanol on exocytosis through the inhibition of PA synthesis by PLD (Caumont et al., 1998; Galas et al., 1997). These observations were supported by experiments in different cell models (Choi et al., 2002; Hughes et al., 2004; O’Luanaigh et al., 2002), but the lack of specificity of butanol has later been questioned (Su et al., 2009). Overexpression of wild type and dominant-negative PLDs provided the first direct molecular evidence supporting the involvement of PA generated by the PLD1 isoform in hormone release in neuroendocrine chromaffin cells (Vitale et al., 2001). PLD1 silencing experiments further supported the notion that PLD1 is the major source for PA synthesis during exocytosis in chromaffin cells (Zeniou-Meyer et al., 2007). Furthermore, the use of a molecular sensor for PA revealed a predominant calcium-stimulated accumulation of PA at the plasma membrane in cells undergoing exocytosis (Zeniou-Meyer et al., 2007). Additional studies highlighted a tight regulation of PLD1 activity by several upstream signaling pathways involving small GTPases and the kinase RSK2 (Béglé et al., 2009; Momboisse et al., 2009; Vitale et al., 2005, 2010; Zeniou-Meyer et al., 2008), revealing a finely tuned production of PA at granule docking sites in stimulated chromaffin cells. Finally, in line with the selective production of PA near exocytotic sites at the plasma membrane, capacitance recordings of chromaffin cells silenced for PLD1 indicated that this enzyme controls the population of fusion competent secretory granules at the plasma membrane (Zeniou-Meyer et al., 2007).

More recently, electron microscopy and morphometric analysis on mouse adrenal gland slices revealed a reduced number of secretory granules in *Pld1* knockout mice adrenal chromaffin cells (Carmon et al., 2020) and a 50% reduction of the number of secretory granules visually docked at the plasma membrane (Tanguy et al., 2020). Supporting the idea that PA might play a role in the biogenesis of dense-core secretory granules, the dual PLD1/PLD2 inhibitor 5-fluoro-2-indolyl des-chlorohalopemide (FIPI) reduced the number of secretory granules synthesized in a COS-7 cell line expressing chromogranin A (CgA), a member of the granin family playing an important role in granule biogenesis (Carmon et al., 2020). In line with these observations, a PA-binding domain (PABD) was found in the CgA sequence that effectively binds to PA in membrane models, and the overexpression of a CgA PABD-deleted form in

endocrine cells significantly reduced the number of secretory granules indicating that the “granulogenic” activity of CgA might involve its ability to bind PA (Carmon et al., 2020).

Carbon fiber amperometry recordings of individual mouse chromaffin cells revealed that *Pld1* knockout decreased by nearly 60% the frequency of amperometric events corresponding to single granule fusion, in good agreement with the apparent reduction of the number of morphologically docked granules seen in the *Pld1*^{-/-} adrenal gland (Tanguy et al., 2020). Shape analysis of individual amperometric spikes and pre-spikes, which provide information on kinetic parameters of single fusion events revealed that the kinetics of the pore dilation and the duration of the exocytotic event were affected by the absence of PLD1 (Tanguy et al., 2020). Supporting the

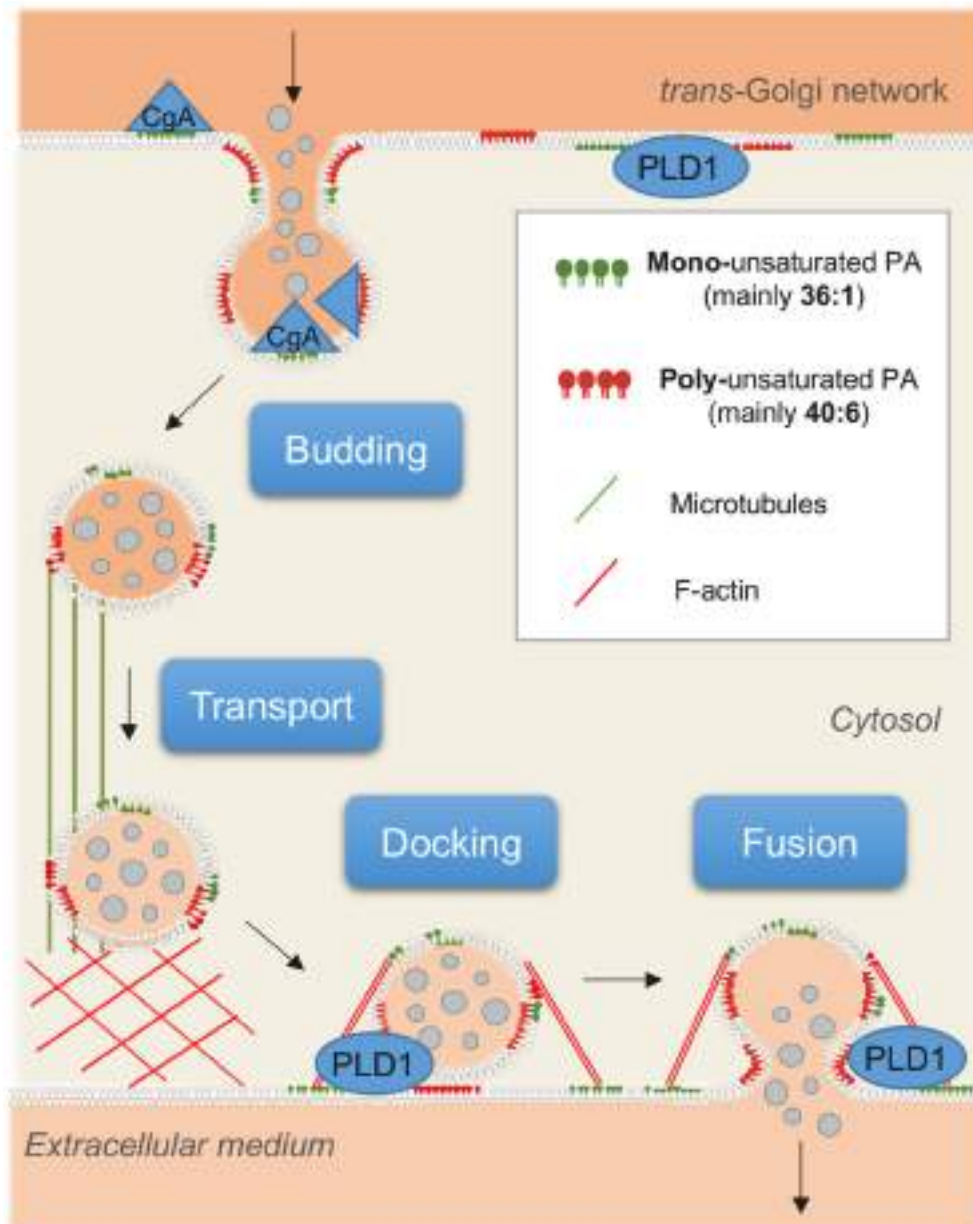


Fig. 2. Model depicting the different PA species involved in neuroendocrine secretion.

Secretory granules are formed by budding from the Golgi apparatus and then actively transported toward the plasma membrane, where they undergo regulated exocytosis to release their cargo into the extracellular medium. Among lipids involved in this journey, specific PA species can modulate different steps of the regulated secretory pathway. PLD1 contributes to the synthesis of mono- and poly-unsaturated PA species found in the *trans*-Golgi network membrane, where they may promote granule biogenesis through their interaction with CgA. Stimulation of exocytosis increases the synthesis by plasma-membrane bound PLD1 of mono-unsaturated PA that favors docking of granules to the plasma membrane and poly-unsaturated PA promoting membrane curvature and fusion pore formation. Note that PA can rapidly flip across membrane leaflets when it is not in tight interaction with specific proteins, suggesting that PA can probably distribute between the two leaflets of granule membranes.

physiological relevance of these *in vitro* observations, catecholamine levels in the blood of new-born mice were reduced by *Pld1* knockout (Tanguy et al., 2020). These observations were further substantiated by the use of FIPI and by the isoform-selective PLD1 inhibitor on bovine chromaffin cells that mimicked the effect observed by amperometry on *Pld1*^{-/-} mouse chromaffin cells (Tanguy et al., 2020). Altogether, these findings indicate that the production of PA by PLD1 controls several stages of the neuroendocrine secretory pathway including biogenesis of secretory granules, the number of secretory granules undergoing exocytosis, and also at the single granule level, the duration of the initial fusion pore and its expansion required to release neuropeptides and peptide hormones (Fig. 2). This composite role of PA led to the idea that the sequential stages underlying the secretory pathway could actually require distinct PA subspecies involved in specific functions.

4. Specific PA species contribute to different steps in neuroendocrine cell exocytosis

In neuroendocrine cells, subcellular fractionation experiments revealed that Golgi, secretory granule and plasma membranes contained detectable levels of up to 40 different PA species (Carmon et al., 2020; Tanguy et al., 2020). Secretory granules were particularly enriched in poly-unsaturated forms of PA, especially PA 40:6 containing docosahexaenoic acid (DHA), a major ω 3 fatty acid (Tanguy et al., 2020). Stimulation of exocytosis selectively increased the plasma membrane level of PA containing long chain mono- and di-unsaturated fatty acids (PA 36:1, 38:1 and 38:2), by more than 6-fold (Tanguy et al., 2020). These peculiar PA are largely decreased in adrenal glands from *Pld1* knockout mice, suggesting that PLD1 known to be activated in stimulated cells is most likely responsible for their synthesis at the plasma membrane (Tanguy et al., 2020).

Incubation of cultured chromaffin cells with PA micelles proved to be an easy and effective approach to identify the PA species able to compensate for the lack of PLD activity at the plasma membrane of PLD1-depleted cells. Indeed, exogenous PA rapidly reached the intracellular leaflet of the plasma membrane as seen using the PA sensor Spo20p-GFP which was recruited to the cell membrane within minutes when cells were incubated with PA micelles (Tanguy et al., 2020). Incubation of chromaffin cells with a mixture of various forms of PA did not significantly affect catecholamine secretion *per se*. However, it rescued secretion from cells treated with PLD1 inhibitors (Tanguy et al., 2020). Interestingly, mono- and di-unsaturated forms of PA rescued secretion in PLD1-depleted cells, whereas poly-unsaturated PA did not (Tanguy et al., 2020). Using a combination of amperometric recordings and ultrastructural observations on plasma membrane sheets, we observed that mono- and di-unsaturated forms of PA are apparently involved in granule recruitment and/or docking thereby controlling the number of exocytotic events (Tanguy et al., 2020). In contrast, poly-unsaturated ω 3 PA seem to be specifically implicated in fusion pore dilation (Tanguy et al., 2020). At present, it is not known if secretory vesicle biogenesis requires a specific type of PA. Both PA (36:1) and PA (40:6) identified as predominant species in Golgi and secretory granule membranes interact with CgA and promote CgA-induced membrane deformation and remodeling (Carmon et al., 2020).

Based on these findings, we propose that various steps preceding dense-core granule exocytosis require distinct PA species, with mono- and di-unsaturated forms of PA being preferentially implicated in granule docking whereas poly-unsaturated ω 3 PA favors subsequent fusion pore dilation (Fig. 2).

5. Proteins interacting preferentially with specific species of PA

One possibility to explain the differential effects of mono- and poly-unsaturated PA species on exocytosis is that they recruit different effectors involved specifically in vesicle docking or fusion. Among the nearly 50 different proteins that have been shown to date to bind to PA (Pokotylo et al., 2018; Tanguy et al., 2019b; Zegarlińska et al., 2018), their ability to interact with specific forms of PA has not been extensively evaluated, but some information on these aspects are starting to emerge. Using an *in vitro* fluorescence liposome-based assay, we recently found that the PA-binding domain of Spo20p, Opi1p, and PDE4A1 proteins are partially sensitive to the fatty acyl length and saturation, displaying a clear preference for mono- and poly-unsaturated PA over saturated PA (Kassas et al., 2017). Alternatively, the catalytic domains of *Clostridium sordellii* lethal toxin and related large clostridial glucosylating toxins preferentially recognize saturated PA (Varela Chavez et al., 2015). Muscle creatine kinase specifically binds to PA containing saturated fatty acid- and mono-unsaturated fatty acid, but not to poly-unsaturated PA (Hoshino et al., 2019), whereas L-lactate dehydrogenase selectively interacts with poly-unsaturated PA (Hoshino and Sakane, 2020). Thus, PA-binding proteins seem to be able to discriminate between the diverse forms of PA, although the clues for fatty acid selectivity of the PA-binding domain remain obscure.

Another intriguing mode of interaction has been reported for the dynamin-related protein 1 as it interacts with the headgroup of PA and with the saturated fatty acids of nearby phospholipids (Adachi et al., 2016). Moreover, atomistic molecular dynamics simulations of artificial membranes made of PC and PA revealed that the fatty acyl chain composition of PA affected not only membrane fluidity, but also depth of the PA phosphate groups compared to the PC phosphate groups, which can also influence the presentation of PA for peripheral membrane proteins, affecting their accessibility for binding (Kulig et al., 2019). Finally, even though binding between PA and specific proteins are electrostatic at first, it has been predicted that these links are later solidified through hydrophobic interaction between the acyl chains of PA and apolar groups that can be found in the PA-binding domains (Kooijman and Burger, 2009; Tanguy et al., 2018). Therefore, variation in the hydrophobic amino acids composing these PA-binding domains could partially explain an interaction preference with specific PA species. It is important to note that these kinds of interactions could be exclusive to cone-shaped lipids, such as PA, because they induce lipid packing defects enabling a better and deeper penetration into cellular membranes.

The SNARE protein syntaxin-1 is one of the first target candidate that comes in mind as a target protein in the secretory machinery, as it has been shown to bind to several anionic lipids including PI and PA (Lam et al., 2008). Interestingly, mutations in the polybasic site, abolishing the ability of syntaxin-1 to bind PA, resulted in a reduction of the number of amperometric spikes and increased the pre-spike foot duration in PC12 cells (Lam et al., 2008), very similarly to the amperometric traces obtained in *Pld1*^{-/-} mice chromaffin

cells or in bovine chromaffin cells with PLD1 activity pharmacologically inhibited (Tanguy et al., 2020). A similar domain enriched in positive charges that could potentially bind to anionic PA has also been recently described in vesicular SNAREs, such as VAMP-2, and reported to be required for membrane destabilization and fusion (Rathore et al., 2019). It is also worth to recall that the yeast PA binding protein Spo20p is the orthologue of the SNARE protein SNAP25. *In vitro* experiments support the idea that PA directly affects SNARE complex assembly and/or zippering (Mima and Wickner, 2009), although the function of the different PA forms has not been yet tested in this system.

The actin cytoskeleton, originally viewed as a physical barrier preventing granule recruitment, is also emerging as an active network to stabilize granule docking sites, control fusion pore lifetime and/or directly expel granule secretory content (Li et al., 2018). Several actin-binding proteins have been shown to bind to PA, including regulators of the Rho family of small GTPases, which play a key role in providing actin structures required for the late stages of exocytosis (Gasman et al., 2004; Malacombe et al., 2006; Houy et al., 2015). Spatial organization of the exocytotic sites at the plasma membrane also appears under the control of large actin structures bundled by annexin A2 (Gabel et al., 2015), a protein that binds anionic lipids including PA (Gabel et al., 2019). The next challenge will be to determine if the function of these regulators in the exocytotic machinery involves their ability to bind PA and whether they require a partnership with specific PA species.

6. Do different PA species differentially affect the fusion pore dynamics?

Fusion of two membranes requires the formation of several non-bilayer intermediates resulting in hemifusion, which is ultimately followed by membrane breakdown and formation of a pore (Chernomordik et al., 1995). For most lipids found in biological membranes, the lamellar bilayer is the most energetically favorable structure. However, cone-shaped lipids, such as PA, promote negative curvature (Kooijman et al., 2005; Monck and Fernandez, 1994) and the formation of hemifusion intermediates (Chernomordik et al., 1993, 1995). Thus, the predicted effect of a local elevation of PA due to the activation of PLD at exocytotic sites would be to promote membrane bending, particularly in the presence of calcium (Cornell and Arnold, 1996), thereby facilitating hemifusion and subsequent formation of the exocytotic fusion pore and its dilation.

The ability of PA (40:6) to specifically restore kinetics of individual amperometric events in PLD1-depleted chromaffin cells suggests that poly-unsaturated PA regulate the speed of catecholamine release and thus the dynamics of the fusion pore. Molecular modeling of different species clearly indicates that the overall geometry of glycerophospholipids is affected by fatty acyl chain composition (Hodgkin et al., 1998). It is thus likely that the ability to affect membrane topology and more specifically to modulate the fusion pore stability may be variable among the different PA species. Clearly additional experimental evidence is now required to prove or refute this possibility, but it is of interest to note that a similar model, based on lipid-induced changes in membrane curvature, has been proposed for endophilin I-mediated recycling of synaptic vesicles at the plasma membrane (Schmidt et al., 1999).

7. Conclusion

Lipids are now viewed as essential partners for proteins in membrane trafficking and among them the negatively charged cone-shaped PA is recognized as a key mediator in vesicle exocytosis and membrane fusion events in a variety of cell types including neurons and neuroendocrine cells. The observation that ω 3 forms of PA modulate fusion pore dynamics as seen by amperometry opens new routes of investigations. It is possible that the higher flexibility of the acyl chains of poly-unsaturated PA is particularly suited for membrane curvature, thereby reducing the energetic cost of various membrane deformation processes and facilitating fission and fusion events (Manni et al., 2018). It is tempting to propose that poly-unsaturated PA could regulate the fusion mode associated with either a large or a narrow fusion pore (Shin et al., 2018, 2020) or trigger the fusion pore dilation required for secretion of neuropeptides and peptide hormones (Ren et al., 2016). An additional challenge will be to determine if specific PA species contribute to diseases that have been associated to an alteration of PA production. These include intellectual disability diseases such as Fragile-X disease (Tabet et al., 2016) and the Coffin Lowry Syndrome (Zeniou-Meyer et al., 2008), but also neurodegenerative diseases such as Alzheimer (Oliveira et al., 2010) and Parkinson diseases where specific PA subtypes (18:1/18:1 PA) induce structural change and favor aggregation of α -synuclein, (Mizuno et al., 2017). Interestingly, a recent review also highlighted the important contribution of different DGKs isoforms and their product PA in neuronal pre- and post-synaptic functions and their potential contribution to pathologies (Barber and Raben, 2020). PA generated by PLD has also been proposed to facilitate multiple steps in cancer progression including growth, metabolism, angiogenesis, and mobility (Roth and Frohman, 2018). Although the functions of the individual PA species in these pathologies remain to be precisely established, the ability of exogenous PA to restore neuroendocrine exocytosis by provision of the adequate PA opens a route towards a better understanding of the importance of specific fatty acids in diet to improve human health.

Additional Information

The authors declare no competing financial interests.

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CRedit authorship contribution statement

Emeline Tanguy: Writing - original draft, designed the figures, Writing - review & editing. **Alexander Wolf:** Writing - original draft, designed the figures, Writing - review & editing. **Maité Montero-Hadjadje:** Writing - review & editing. **Stéphane Gasman:** Writing - review & editing. **Marie-France Bader:** Writing - original draft. **Nicolas Vitale:** Writing - original draft, designed the figures, Writing - review & editing, Funding acquisition.

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Update

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Erratum regarding missing Declaration of Competing Interest statements in previously published articles

Declaration of Competing Interest statements were not included in the published version of the following articles that appeared in previous issues of *Advances in Biological Regulation*.

The appropriate Declaration/Competing Interest statements, provided by the Authors, are included below.

1. "Roles of DGKs in neurons: Postsynaptic functions?" [*Advances in Biological Regulation*, 2019; Volume 75, 100688] 10.1016/j.jbior.2019.100688

Declaration of competing interest: The Authors have no interests to declare.

2. "Effects of the MDM-2 inhibitor Nutlin-3a on PDAC cells containing and lacking WT-TP53 on sensitivity to chemotherapy, signal transduction inhibitors and nutraceuticals" [*Advances in Biological Regulation*, 2019; Volume 72, 629] 10.1016/j.jbior.2019.03.002

Declaration of competing interest: The Authors have no interests to declare.

3. "Phosphatidic acid: Mono- and poly-unsaturated forms regulate distinct stages of neuroendocrine exocytosis" [*Advances in Biological Regulation*, 2020; Volume 79, 100772] 10.1016/j.jbior.2020.100772

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4. "Altered chondrocyte differentiation, matrix mineralization and MEK-Erk1/2 signaling in an INPPL1 catalytic knock-out mouse model of opsismodysplasia" [*Advances in Biological Regulation*, 2019; Volume 76, 100651] 10.1016/j.jbior.2019.100651

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5. "Protein-protein interaction analysis highlights the role of septins in membrane enclosed lumen and mRNA processing" [*Advances in Biological Regulation*, 2019; Volume 73, 100635] 10.1016/j.jbior.2019.100635

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6. "Thromboprophylaxis in COVID-19" Rationale and considerations" [*Advances in Biological Regulation*, 2021; Volume 81, 100819] 10.1016/j.jbior.2021.100819

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7. “Fructose-1,6-bisphosphatase: From a glucose metabolism enzyme to multifaceted regulator of a cell fate” [Advances in Biological Regulation, 2019; Volume 72, 628: 41–50] 10.1016/j.jbior.2019.03.001

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8. “Recent advances in MDS mutation landscape: Splicing and signaling” [Advances in Biological Regulation, 2019; Volume 75, 100673] 10.1016/j.jbior.2019.100673

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