RESEARCH HIGHLIGHT

G protein-coupled receptors for lysophosphatidylethanolamine

Soo-Jin Park, Dong-Soon Im

Molecular Inflammation Research Center for Aging Intervention (MRCA) and College of Pharmacy, Pusan National University, Busan 609-735, Republic of Korea

Correspondence: Dong-Soon Im
E-mail: imds@pusan.ac.kr
Received: September 01, 2015
Published online: October 16, 2015

Lysophospholipids like lysophosphatidic acid (LPA) and sphingosine 1-phosphate have been intensively studied over the last several decades, and these studies have resulted in the identification of their G protein-coupled receptors (GPCR) and in the discoveries of new drugs targeting GPCRs. However, lysophosphatidylethanolamine (LPE) has not attracted much research attention. Recently, we found several interesting points regarding the action and signaling of LPE, that is, its cell-type dependence, structure specificity, and unique signaling. In particular, LPE signaling through LPA_1 receptor (type 1 lysophosphatidic acid receptor) was found to be cell type dependent, and LPEs with different chain lengths induced different responses in different cells without LPA_1 involvement. Here, we review recent findings and propose possible action modes of LPE GPCRs in different cells.

Keywords: lysophosphatidylethanolamine; lysophosphatidic acid; LPA_1; GPCR

To cite this article: Soo-Jin Park, *et al*. G protein-coupled receptors for lysophosphatidylethanolamine. Receptor Clin Invest 2015; 2: e999. doi: 10.14800/rci.999.

GPCRs for lysophospholipids

G protein-coupled receptors (GPCRs) are the largest superfamily of receptors for intercellular signaling in man [1]. Lysophospholipids, such as, lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), are deacylated lyso-type forms of phospholipids [2, 3]. LPA and S1P act as intercellular lipid mediators by activating their GPCRs, that is, $LPA_{1\text{-}6}$ or $S1P_{1\text{-}5}$ [1, 4, 5]. Signal transduction research on the GPCRs has resulted in the development of GPCR agonists and antagonists [6]. New drugs targeting GPCRs, such as, FTY-720 (Gilenya) and AM-095 have been developed or are in the process of development [7, 8]. However, other lyso-type lipids have received little research attention.

Lysophosphatidylethanolamine

Lysophosphatidylethanolamine (LPE) like other lysophospholipids, is produced by PLA_2 from phosphatidylethanolamine [9, 10], and is present in human serum at concentrations of several hundred ng/ml [11]. Initial studies on the actions of LPE conducted in the 1990s focused mainly on plants. LPE accelerates fruit color development production and retards the senescence of flowers, leaves, and harvested fruits [12-14]. In the housefly, LPE showed antifungal and antibacterial activities, [15] and in 2006, LPE was discovered to be a neurotrophic activator in cultured PC-12 mammalian cells [16]. Furthermore, LPE was found to cause reversible skeletal neuromuscular paralysis in the presence of snake neurotoxins [17]. However, the roles played by LPE on different cell types and the identities of its receptors have not been well studied.

GPCRs for LPE

Recently, it was proposed that GPCRs are involved in the actions of LPE. In 2007, LPE was reported to induce $[Ca^{2+}]_i$ increases, chemotactic migration, and cellular invasion by

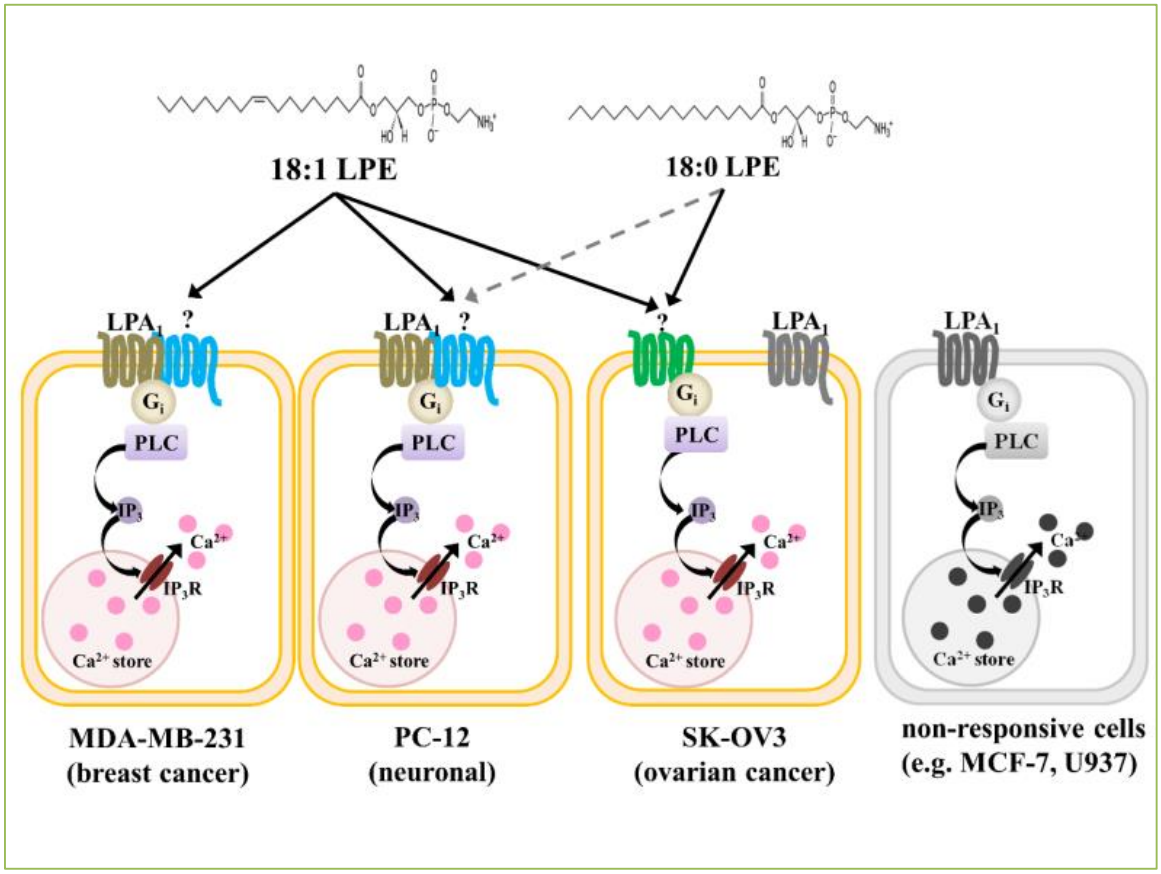

Figure 1. Possible action modes of LPE GPCRs in different cells. LPE activates LPA_1 to increase $[Ca^{2+}]_i$ in MDA-MB-231 cells and PC-12 cells. An unknown GPCR expressed in MDA-MB-231 cells and PC-12 cells might act as a co-receptor for LPE, but not expressed in LPE non-responsive cells. In SK-OV3 cells, LPEs might utilize another hitherto undiscovered GPCR to increase $[Ca^{2+}]_i$ levels.

SK-OV3 and OVCAR-3 human ovarian cancer cells[18]. Although the actions of LPE were found to be mediated through GPCRs, the involvements of LPA specific GPCRs were excluded [18]. We reported the effects of LPE in MDA-MB-231 human breast cancer cells and PC-12 neuronal cells [1, 3, 19], and unlike that reported in ovarian cancer cells, we found LPA_1 was involved in LPE signaling [1, 3, 19]. In this review, we compare LPE receptors in calcium signaling, structure-activity relationship, receptor desensitization, and involvement of LPA GPCR.

Comparison of LPE actions

Calcium signaling

Park *et al*. showed LPE-induced $[Ca^{2+}]_i$ in two human ovarian cancer cells, SK-OV3 and OVCAR-3, but not in A431, HCT-116, HeLa, MCF-7, and U937 cells [18]. In 2013, we demonstrated that LPE induced $[Ca^{2+}]_i$ in MDA-MB-231 human breast cancer cells, but not in MCF-7, SK-BR3, and T47D breast cancer cells [20], and confirmed the same effect in PC-12 neuronal cells [21]. Thus, the effects of LPE on $[Ca^{2+}]_i$ response have been confirmed in three specific cell types, that is, SK-OV3 ovarian cancer, MDA-MB-231 breast cancer, and PC-12 neuronal cells.

LPE structure

Structure-activity relationships of LPE on $[Ca^{2+}]_i$ increases in MDA-MB-231 breast cancer, PC-12 neuronal cells, and SK-OV3 ovarian cancer were studied using structurally different LPEs, that is, oleoyl LPE (18:1 LPE), stearoyl LPE (18:0 LPE), octadecanyl LPE (ether-linked 18:0 LPE), palmitoyl LPE (16:0 LPE), and myristoyl LPE (14:0 LPE) [20, 21]. 18:1 LPE and 14:0 LPE elicited $[Ca^{2+}]_i$ responses, whereas 16:0 LPE did not, in all three cell types [20, 21]. Similarly, 18:1 LPE and ether- or ester-linked 18:0 LPE were found to induce $[Ca^{2+}]_i$ in SK-OV3 and PC-12 cells [20, 21]. However, ether- or ester-linked 18:0 LPE were not active in MDA-MB-231 cells [20]. These findings indicate SK-OV3 cells and PC-12 cells have similar structural preference for LPE responses, but that MDA-MB-231 cells differ [20, 21].

Receptor desensitization

In three cell lines, LPA and LPE induced $[Ca^{2+}]_i$ responses. The involvements of LPA GPCRs in $[Ca^{2+}]_i$ induction by LPE were tested by homologous and heterologous desensitization. According to our results, LPE pre-treatment diminished both LPE- and LPA-induced $[Ca^{2+}]_i$ and LPA pre-treatment decreased LPE- and LPA-induced $[Ca^{2+}]_i$ increases in MDA-MB-231 and PC-12 cells [20, 21]. However, in SK-OV3 cells, LPE pre-treatment did not affect $[Ca^{2+}]_i$ induction by LPA and LPA stimulation did not inhibit LPE-induced response [18]. These results suggest that LPE acts on LPA receptors in MDA-MB-231 and PC-12 cells, but not in SK-OV3 cells [18, 20, 21].

LPA_1 involvement

To test whether LPE utilizes LPA receptors in MDA-MB-231, PC-12, and SK-OV3 cells, two structurally different antagonists of LPA_1 and LPA_3 receptors, that is, VPC32183 and Ki16425, and a specific LPA_1 antagonist, AM-095, were applied. All three antagonists completely inhibited LPE-induced $[Ca^{2+}]_i$ response in MDA-MB-231 and PC-12 cells, [19-21] but did not affect LPE-induced $[Ca^{2+}]_i$ response in SK-OV3 cells [18, 20]. The involvement of LPA_1 in $[Ca^{2+}]_i$ induction by LPE in MDA-MB-231 cells was further confirmed by LPA_1 knock-down using LPA_1 siRNA [20]. However, transfections with LPA_1 siRNA did not interfere the LPE-induced $[Ca^{2+}]_i$ response in SK-OV3 cells [20]. These results indicate the effect of LPE on $[Ca^{2+}]_i$ response is mediated through LPA_1 in MDA-MB-231 and PC-12 cells, but not in SK-OV3 cells [18-21].

Relations between LPE and GPCRs in different cell types

Several our studies on LPE and its receptors have indicated that LPE evokes $[Ca^{2+}]_i$ responses through GPCRs in some cell types, such as, SK-OV3, OVCAR-3, MDA-MB-231, and PC-12 cells [18-21]. LPA_1 involvement is cell-type specific, which is, it occurs in MDA-MB-231 and PC-12 cells but not in SK-OV3 cells. Furthermore, structure-activity relationships of LPE are similar in SK-OV3 and PC-12 cells, but differ in MDA-MB-231 cells [18-21], which suggests responses to LPE depend on cell type.

Cell type differences might be due to the presence of multiple GPCRs for LPE and/or the utilization of different combinations of GPCR heterodimers or oligomers. This suggestion is based on the observation that LPA_1 induces specific responses in MDA-MB-231 and PC-12 cells, but not in other cell types, such as, MCF-7 and T47D cells, although these other types express LPA_1 [20]. It is worth noting that LPA_1 has never been reported to be responsive to any lysophospholipid other than LPA in LPA_1-overexpressing cell systems [18]. Moreover, although SK-OV3 cells possess LPA_1 receptor, it is evident the action mechanism of LPE in these cells involves a GPCR other than LPA_1. Taken together, we propose a certain protein(s) might cooperate with LPA_1 for LPE-induced calcium signaling in MDA-MB-231 and PC-12 cells, and that this protein is not expressed in SK-OV3 cells (Fig. 1) and unknown GPCR(s) for LPE are present in SK-OV3 cells (Fig. 1).

Conflicting interests

The authors have declared that no competing interests exist.

Acknowledgements

This research was supported by the Basic Science Research Program of the Korean National Research Foundation (NRF) funded by the Korean Ministry of Education, Science and Technology (NRF-2011-0021158) and by a NRF (the National Research Foundation of Korea) grant funded by the Korean Government (NRF-2015-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program)

Abbreviations

GPCR: G-protein-coupled receptor; LPA: lysophosphatidic acid; LPE: lysophosphatidylethanolamine; S1P: sphingosine 1-phosphate; LPA_1: type 1 lysophosphatidic acid receptor; $[Ca^{2+}]_i$: intracellular Ca^{2+} concentration

References

1. Im DS. Intercellular Lipid Mediators and GPCR Drug Discovery. Biomol Ther (Seoul) 2013; 21:411-422.
2. Im DS. New intercellular lipid mediators and their GPCRs: an update. Prostaglandins Other Lipid Mediat 2009; 89:53-56.
3. Choi JW, Herr DR, Noguchi K, Yung YC, Lee CW, Mutoh T, *et al*. LPA receptors: subtypes and biological actions. Annu Rev Pharmacol Toxicol 2010; 50:157-186.
4. Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, *et al*. International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol Rev 2013; 65: 967-986.
5. Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH. International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. Pharmacol Rev 2010; 62: 579-587.
6. Im DS. Pharmacological tools for lysophospholipid GPCRs: development of agonists and antagonists for LPA and S1P receptors. Acta Pharmacol Sin 2010; 3:1213-1222.
7. Im DS. First-in-class antifibrotic therapy targeting type 1 lysophosphatidic acid receptor. Arch Pharm Res 2012;

35:945-948.

8. Quancard J, Bollbuck B, Janser P, Angst D, Berst F, Buehlmayer P, *et al*. A Potent and Selective S1P(1) Antagonist with Efficacy in Experimental Autoimmune Encephalomyelitis. Chem Biol 2012; 19: 1142-1151.
9. Makide K, Uwamizu A, Shinjo Y, Ishiguro J, Okutani M, Inoue A, *et al*. Novel lysophospholipid receptors: their structure and function. J Lipid Res 2014:55: 1986-1995.
10. Makide K, Kitamura H, Sato Y, Okutani M, Aoki J. Emerging lysophospholipid mediators, lysophosphatidylserine, lysophosphatidylthreonine, lysophosphatidylethanolamine and lysophosphatidylglycerol. Prostaglandins Other Lipid Mediat 2009; 89:135-139.
11. Misra UK. Isolation of lysophosphatidylethanolamine from human serum. Biochim Biophys Acta 196; 106:371-378.
12. Ryu SB, Karlsson BH, Ozgen M, Palta JP. Inhibition of phospholipase D by lysophosphatidylethanolamine, a lipid-derived senescence retardant. Proc Natl Acad Sci U S A 1997; 94:12717-12721.
13. Ozgen M, Farag KM, Ozgen S, Palta JP. Lysophosphatidylethanolamine accelerates color development and promotes shelf life of cranberries. Hort Sci 2004; 40:127-130.
14. Ozgen M, Park SH, Palta JP. Mitigation of ethylene-promoted leaf senescence by a natural lipid, lysophosphatidylethanolamine. Hort Sci 2005; 40:1166-1167.
15. Meylaers K, Clynen E, Daloze, D, DeLoof A, Schoofs L. Identification of 1-lysophosphatidylethanolamine (C(16:1)) as an antimicrobial compound in the housefly, Musca domestica. Insect Biochem Mol Biol 32004; 4:43-49.
16. Nishina A, Kimura H, Sekiguchi A, Fukumoto RH, Nakajima S, Furukawa S. Lysophosphatidylethanolamine in Grifola frondosa as a neurotrophic activator via activation of MAPK. J Lipid Res 2006; 47:1434-1443.
17. Caccin P, Rigoni M, Bisceglie A, Rossetto O, Montecucco C. Reversible skeletal neuromuscular paralysis induced by different lysophospholipids. FEBS Lett 2006; 580:6317-6321.
18. Park KS, Lee HY, Lee SY, Kim MK, Kim SD, Kim JM, *et al*. Lysophosphatidylethanolamine stimulates chemotactic migration and cellular invasion in SK-OV3 human ovarian cancer cells: involvement of pertussis toxin-sensitive G-protein coupled receptor. FEBS Lett 2007; 581:4411-4416.
19. Park SJ, Lee KP, Im DS. Action and Signaling of Lysophosphatidylethanolamine in MDA-MB-231 Breast Cancer Cells. Biomol Ther (Seoul) 2014; 22:129-135.
20. Park SJ, Lee KP, Kang S, Chung HY, Bae YS, Okajima F, *et al*. Lysophosphatidylethanolamine utilizes LPA(1) and CD97 in MDA-MB-231 breast cancer cells. Cell Signal 2013; 25:2147-2154.
21. Lee JM, Park SJ, Im DS. Lysophosphatidylethanolamine increases intracellular Ca(2+) through LPA(1) in PC-12 neuronal cells. Biochem Biophys Res Commun 2015; 461:378-382.