INTRODUCTION

Lysophosphatidic acid (LPA), a bioactive lyso-type lipid mediator, acts through G protein-coupled receptors (GPCRs) LPA1-6 (Choi and Chun, 2013). Three Edg subfamily GPCR members (LPA 1-3), and three non-Edg (purinergic) GPCRs (LPA4-6) have been reported (Choi and Chun, 2013; Yanagida et al., 2013). Similar lyso-type phospholipids, such as lysophosphatidylserine (LPS), lysophosphatidylethanolamine (LPE), lysophosphatidylglycerol (LPG), and lysophosphatidylcholine (LPC) have also been reported to act through putative GPCRs. However, few studies have been conducted on putative GPCRs (Park et al., 2005; Park et al., 2006; Park et al., 2007; Jo et al., 2008; Lee et al., 2008; Makide et al., 2009). Recently, GPR34, GPR174, and P2Y10 were reported to be GPCRs for 2-acyl LPS (Inoue et al., 2012; Kitamura et al., 2012; Makide and Aoki, 2013). However, it is controversial whether GPR34 acts as an LPS receptor in mice (Sugo et al., 2006; Iwashita et al., 2009; Liebscher et al., 2011; Kitamura et al., 2012; Ritscher et al., 2012).

LPE, a lyso-type phospholipid, has been detected in human serum at concentrations of about several hundreds of ng/ml (Misra, 1965; Makide et al., 2009). In 2007, the intracellular Ca²⁺ ([Ca²⁺]i) enhancing actions of LPE was supposed to be mediated through GPCRs, but not through GPCRs for LPA, in SK-OV3 and OVCAR-3 ovarian cancer cells (Park et al., 2007). In a previous study, we found that LPE-induced Ca²⁺ response and cell proliferation in MDA-MB-231 breast cancer cells, whereas LPE had less or no significant effect. However, LPE modulations of MAPKs (ERK1/2, JNK and p38 MAPK) was not different to those by LPA in the cells. These data support the involvement of LPA1 in LPE-induced Ca²⁺ response and cell proliferation in breast MDA-MB-231 breast cancer cells but unknown GPCRs (not LPA1) in LPE-induced responses in SK-OV3 cells. Furthermore, although LPE and LPA utilized LPA1, LPA utilized more signaling cascades than LPE, resulting in stronger responses by LPA in proliferation and migration than LPE in MDA-MB-231 cells.

Key Words: Lysophosphatidylethanolamine, LPA1, Lysophosphatidic acid, GPCR, Breast, Receptor
of an LPA, antagonist. In addition, we tested the effect of LPE and LPA on cell migration and MAPK activities.

MATERIALS AND METHODS

Materials

1-oleoyl-2-hydroxy-sn-glycero-3-phosphoethanolamine (18:1 LPE), 1-stearoyl-2-hydroxy-sn-glycero-3-phosphoethanolamine (18:0 LPE), 1-oleoyl-2-hydroxy-sn-glycero-3-phosphoethanolamine (ether-linked 18:0 LPE), 1-palmitoyl-2-hydroxy-sn-glycerol-3-phosphoethanolamine (16:0 LPE), 1-myristoyl-2-hydroxy-sn-glycerol-3-phosphoethanolamine (14:0 LPE), and 1-oleoyl-2-hydroxy-sn-glycerol-3-phosphate (sodium salt) were purchased from Avanti Polar Lipids (Alabaster, AL, USA). AM-095 was obtained from Sigma-Aldrich (St. Louis, MO). Fura 2-AM was purchased from Chemscence (New Jersey, USA), and WST from Daeil lab service (Seoul, Korea).

Cell culture

The human MDA-MB-231 breast cancer cell line was obtained from the American Type Culture Collection (ATCC, Manassas, VA). Cells were cultured at 37°C in a 5% CO₂ humidified incubator, and maintained in high glucose DMEM, containing 10% (v/v) heat-inactivated fetal bovine serum, 100 units/ml penicillin, 50 µg/ml streptomycin, 2 mM glutamine, and 1 mM sodium pyruvate. The SK-OV3 human ovarian cancer cell line was maintained as recommended by the supplier (Park et al., 2013).

Measurement of [Ca²⁺]i concentrations

Cells were trypsin-digested, allowed to sediment, resuspended in Hepes-buffered medium (HB), consisting of 20 mM Hepes (pH 7.4), 103 mM NaCl, 4.8 mM KCl, 1.2 mM KH2PO4, 1.2 mM MgSO4, 0.5 mM CaCl2, 25 mM NaHCO3, 15 mM glucose, and 0.1% bovine serum albumin (fatty acid free), and then incubated for 40 min with 5 µM of fura 2-AM. [Ca²⁺] levels were estimated by measuring changes in fura 2 fluorescence using an emission wavelength of 510 nm and excitation wavelengths of 340 nm and 380 nm every 0.1 sec using a F4500 fluorescence spectrophotometer (Hitachi, Japan). The ratios of fluorescence intensities (λ340/λ380) at these two wavelengths were used as a surrogate of [Ca²⁺], as previously described (Chang et al., 2006; Ahn et al., 2012).

Cell proliferation

MDA-MB-231 cells (5×10⁵ per well) were seeded into 96-well plates and incubated in serum-deprived medium overnight. LPEs and LPA were dissolved in 0.1% BSA at appropriate concentrations and administered to medium for 24 h. Cell proliferation assays were carried out using the Enhanced Cell Viability Assay Kit EZ-CyTox WST protocol (Daeil Lab Service, Seoul, Korea), and fluorences were measured using a microplate reader at 450 nm.

Cell migration

Cell migration was monitored using the in vitro wound-healing assay. Briefly, MDA-MB-231 cells (2×10⁵ per well) were seeded into 6-well plates with DMEM media containing 0.5% FBS and allowed to adhere overnight. A linear scratch was made across the cell monolayer using the sharp end of a 1000-µl sterile pipette tip. Medium and non-adherent cells were removed, and cells were washed twice with PBS, and new medium containing LPE or LPA was added. Cells were permitted to migrate into wound area for 24 h. Wound closure was observed under a microscope.

Reverse transcriptase-PCR

After treatment with LPE or LPA for 5 h, first strand cDNA was synthesized using total RNA isolated using Trizol reagent (Invitrogen, USA). Synthesized cDNA products and specific primers were used for PCR with Promega Go-Taq DNA polymerase (Madison, WI, USA). The primers used to amplify 400, 294, 181, 173, and 396 bps fragments of MMPs and β-actin were as follows: MMP-2 (sense 5'-CAG GCT CTT CTC TTT TCA CAA C-3', antisense 5'-AAG CCA CGG CTT GGT TTT CCT C-3'), MMP-3 (sense 5'-CTC ACA GAC CTG ACT CCG TT-3', antisense 5'-CAC GCC TGA AGG AAG AGA TG-3'), MMP-7 (sense 5'-TAC AGT GGG AAC AGG CTC AGG-3', antisense 5'-GGC ACT CCA CAT CTG GGC T-3'), MMP-9 (sense 5'-TGG GCT ACG TTA CCT ATG ACA T-3', antisense 5'-GCC CAG CCC ACC TTC ACT CCT C-3'), and β-actin (sense 5'-CAC ACC ACC TTC TAC AAT GAG CTG-3', antisense 5'-GAG GAG CAA TGA TCT TGA TCT TAA T-3'). PCR was performed over 30 amplification cycles (denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and elongation at 72°C for 30 s) in an Eppendorf MasteCyler gradient unit (Hamburg, Germany). Aliquots of the PCR products (7 µl) so obtained were electrophoresed in 1.2% agarose gels and stained with ethidium bromide.

Western blot

MDA-MB-231 cells (5×10⁵ per well) were seeded in 60-mm dishes, and incubated in DMEM medium containing 0.5% FBS overnight. After treatment with LPE, cells were trypsinized and collected by centrifugation at 1500 rpm for 3 min. After washing twice with PBS, cell pellets were dissolved and boiled in 200 µl of sample buffer containing 62.5 mM Tris-HCl (pH 6.8), 10% glycerol, 2% SDS, 5% 2-mercaptoethanol, and 0.05% bromophenol blue. Proteins (40 µg) were resolved by 8% SDS-polyacrylamide gel electrophoresis and electrophoretically transferred to nitrocellulose. Blots were incubated with specific primary antibodies recognizing the phosphorylated forms of p44/42 MAP kinase (ERK), p38 MAP kinase, or SAPK/JNK, and then with HRP-conjugated secondary antibodies (Cell Signaling Technology, Danvers, MA, USA). Signals were developed using an enhanced chemiluminescence system (Pierce Biotechnology Inc., Rockford, IL, USA).

Statistics

Results are expressed as means ± SEs for the indicated number of determinations. The significances of differences were determined by ANOVA, and statistical significance was accepted for p values of <0.05.

RESULTS

Effects of different LPEs on [Ca²⁺]i concentration in MDA-MB-231 and SK-OV3 cells

Previously, we observed LPE-induced increases of [Ca²⁺] in MDA-MB-231 breast cancer cells and SK-OV3 ovarian cancer cells (Park et al., 2007; Park et al., 2013) (Fig. 1A, B). In the present study, we applied 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). As shown in Fig. 1A, C, 18:0 LPE, ether-linked 18:0 LPE, and 16:0 LPE did not evoke a [Ca²⁺] increase in MDA-MB-231 cells, whereas 14:0 and 18:1 LPE did (Fig. 1A, C). In SK-OV3 cells, 18:0 LPE and ether-linked 18:0 LPE evoked a [Ca²⁺] increase, though less than that caused by 18:1 LPE (Fig. 1B, D). Although 16:0 LPE did not increase

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**Fig. 1.** Structure-activity relationships of LPE in [Ca²⁺] increases in MDA-MB-231 and SK-OV3 cells. Representative [Ca²⁺] traces of MDA-MB-231 cells (a breast cancer cell line) (A) and of SK-OV3 cells (an ovarian cancer cell line) (B) treated with 10 μM of LPE or LPA. Arrows indicate when LPE or LPA was added. The data shown are representative of more than four independent experiments. Efficacies of different chain-length LPE- and LPA-induced Ca²⁺ responses as compared to digitonin in MDA-MB-231 cells (C) and SK-OV3 cells (D) are shown as histograms. Results are the means ± SEs of three independent experiments.

**Fig. 2.** Effect of AM-095 on LPE-induced [Ca²⁺] increases in MDA-MB-231 and SK-OV3 cells. Representative [Ca²⁺] traces of MDA-MB-231 (A) and SK-OV3 cells (B) pretreated with AM-095 or vehicle for 5 min and then treated with 10 μM of LPE or LPA. Arrows indicate when LPE or LPA was added. The data shown are representative of more than four independent experiments. Efficacies of LPE- and LPA-induced Ca²⁺ responses as compared to digitonin in MDA-MB-231 (C) and SK-OV3 cells (D) are shown as histograms. Results are the means ± SEs of three independent experiments. Statistical significance: **p<0.01, ***p<0.001 vs. AM-095 non-treated cells.
[Ca^{2+}]_i in SK-OV3 cells, 14:0 LPE did induce (Fig. 1D). 18:1 LPE was the most potent of the LPEs tested in both cell types (Fig. 1). 18:0 LPE and ether-linked 18:0 LPE induced a [Ca^{2+}]_i increase in SK-OV3 cells only (Fig. 1). Because 18:1 LPE was the most potent LPE among tested LPEs, we used 18:1 LPE in the further study and it was stated as LPE without specification of 18:1 hereafter.

Effect of AM-095 on LPE-induced [Ca^{2+}]_i responses
We tested the effect of AM-095 (a specific LPA1 antagonist) to verify the involvement of endogenously expressed LPA receptors in LPE-induced [Ca^{2+}]_i response in MDA-MB-231 cells and SK-OV3 cells (Castelino et al., 2011; Swaney et al., 2011). As shown in Fig. 2, AM-095 (500 nM) completely inhibited LPA-induced [Ca^{2+}]_i responses in both cell lines and LPE-induced [Ca^{2+}]_i responses in MDA-MB-231 cells (Fig. 1). On the other hand, AM-095 (500 nM) did not affect LPE-induced [Ca^{2+}]_i responses in SK-OV3 cells (Fig. 2B, D). Therefore, LPE appeared to increase [Ca^{2+}]_i, mainly via LPA1 receptors in MDA-MB-231 cells. On the other hand, LPE appeared to increase [Ca^{2+}]_i in another manner in SK-OV3 cells.

Effects of LPE and LPA on the proliferation of MDA-MB-231 cells
In PC12 neuronal cells, LPEs from *Grifola frondosa* induced neuronal differentiation and suppressed serum-deprivation induced apoptosis via MAPK activation (Nishina et al., 2006). Therefore, in order to determine the significance of LPE-induced [Ca^{2+}]_i response, we investigated the effects of LPE and LPA on cell proliferation in MDA-MB-231 breast cancer cells. LPA induced a significant and concentration-dependently increase in cell proliferation (Fig. 3A). However, LPE did induce cell proliferation significantly but less than LPA (Fig. 3A). Structurally different LPEs and AM-095 were also applied to cell proliferation responses in both cell lines. Proliferation stimulatory effects of LPA and LPE were inhibited by treatment of AM-095, suggesting involvement of LPA1 in the proliferation stimulatory response of LPE in MDA-MB-231 cells (Fig. 3B). In SK-OV3 cells, 18:1 LPE and 14:0 LPE along with LPA significantly increased cell viability (Fig. 3C). In the presence of AM-095, LPA-induced proliferation stimulatory effect was inhibited, but not LPE-induced ones (Fig. 3C), suggesting no involvement of LPA1 in the response of LPE in SK-OV3 cells.
Effects of LPE and LPA on cell migration in MDA-MB-231 cells

In SK-OV3 human ovarian cancer cells, LPE stimulated chemotactic migration and cellular invasion (Park et al., 2007). Therefore, we investigated effects of LPE and LPA on cell migration using a wounding assay. LPA induced a significant increase in MDA-MB-231 cell migration after 24 hr (Fig. 4A, B), but LPE did not (Fig. 4A, B). In addition, we measured the expression levels of matrix metalloproteinases (MMP) by RT-PCR. LPE did not affect the gene expressions of MMPs (MMP-2, MMP-3, MMP-7, and MMP-9) (Fig. 4C), whereas LPA induced an increase in the expression of MMP-9 only (Fig. 4C).

Effects of LPE and LPA on MAPKs in MDA-MB-231 cells

We measured the activities of three modules of MAPKs, namely, ERK1/2, SAPK/JNK, and p38 MAPK, which are down-stream signaling molecules of a [Ca^{2+}] increase. Neither LPE nor LPA changed their protein levels (Fig. 5). However,
LPE and LPA induced a transient activation of ERK1/2 after 5 and 30 min of treatment (Fig. 5). Furthermore, LPE and LPA significantly inhibited SAPK/JNK activities after 5 min of treatment (Fig. 5). On the other hand, p38 MAPK was activated by LPE and LPA after 15 to 30 min of treatment (Fig. 5). Further activation of p38 MAPK was observed after 2 h in LPA-treated cells (Fig. 5B).

**DISCUSSION**

In the previous study, LPE-induced [Ca\(^{2+}\)] increase was found to be mediated via LPA and CD97 in MDA-MB-231 breast cancer cells (Park et al., 2013). In the present study, by applying structurally different LPEs and AM-095 (a selective LPA, antagonist), we found differences between MDA-MB-231 breast cancer cells and SK-OV3 ovarian cancer cells. In SK-OV3 cells, LPE-induced [Ca\(^{2+}\)] increases were not inhibited by AM-095, implying no involvement of LPA, which is consistent with a previous report by Park et al. (2007), who concluded no involvement of any LPA receptor in the LPE-induced response. In MDA-MB-231 breast cancer cells, LPE-induced [Ca\(^{2+}\)] increase was inhibited by AM-095, implying LPA involvement, which is consistent with our recent finding (Park et al., 2013). Therefore, our present results strongly support an idea of two previous papers about LPE action mechanisms. That is, LPE acts through GPCRs in two different ways depending on cell types: 1) using LPA, and CD97 in MDA-MB-231 cells (Park et al., 2013) and 2) using unknown GPCRs different from LPA receptors in SK-OV3 cells (Park et al., 2007). It was previously suggested that LPE-induced response in SK-OV3 ovarian cancer cells differs mechanistically from that in MDA-MB-231 cells (Park et al., 2007; Park et al., 2013). This difference is demonstrated in the present study by the synthetic LPE analogues, especially 18:0 LPE and ether-linked 18:0 LPE. Ether-linked 18:0 LPE and ester-linked 18:0 LPE produced half the response elicited by ester-linked 18:1 LPE in SK-OV3 cells, but did not produce any response in MDA-MB-231 cells. In the present study, response to LPE in SK-OV3 cells was affected by structural modifications, such as, ether linkage and chain length, but response in MDA-MB-231 cells was restricted to ester-linked 18:1 LPE. Furthermore, myristoyl LPE (14:0) induced [Ca\(^{2+}\)] increase in MDA-MB-231 cells and SK-OV3 cells, but its efficacy was less than that of 18:1 LPE and LPA in both cell lines. Myristoyl LPE-induced [Ca\(^{2+}\)] and 18:1 LPE-induced [Ca\(^{2+}\)] increases may be driven by different mechanisms, because palmitoyl LPE (16:0), which possesses a medium-size fatty acid chain (intermediate between 18:1 and 14:0 LPE) did not induce significant [Ca\(^{2+}\)] increase in either cell-line.

In PC12 neuronal cells, LPEs from *Grifola frondosa* were reported to induce neuronal differentiation and suppression of serum-deprivation-induced apoptosis via MAPK activation (Nishina et al., 2006). In the present study, the suppression of LPE-induced [Ca\(^{2+}\)] increase on cell proliferation was investigated in MDA-MB-231 cells. LPA induced a significant and concentration-dependent increase in cell proliferation in MDA-MB-231 cells, whereas LPE did less. Both responses were inhibited by AM-095, supporting involvement of LPA in the cells. However, in SK-OV3 cells LPA-induced cell proliferation was inhibited by AM-095, but LPE-induced responses were not, which again supports no involvement of LPA in SK-OV3 cells.

In SK-OV3 cells, LPE stimulates chemotactic migration and cellular invasion (Park et al., 2007). The significance of LPE-induced [Ca\(^{2+}\)] increase was investigated on cell migration using the wound- ing assay in MDA-MB-231 cells. LPA induced a significant increase in cell migration after 24 h of treatment, whereas LPE did not. LPE is less potent than LPA at increasing Ca\(^{2+}\) increasing action (Park et al., 2013), but efficacy of 10 \(\mu\)M LPE was similar to that of 10 \(\mu\)M LPA. Therefore, in order to explain the discrepancy of 10 \(\mu\)M LPE and 10 \(\mu\)M LPA-induced responses in cell proliferation and cell migration, there must be additional signaling(s) for LPA in addition to [Ca\(^{2+}\)] increase. LPE-induced [Ca\(^{2+}\)] increase was not enough to induce the same degree of proliferation and migration observed with LPA in MDA-MB-231 cells. However, LPA and LPE similarly modulated three modules of MAPKs in the cells. Therefore, it appears LPA triggers another signaling pathway in addition to the [Ca\(^{2+}\)] signaling and MAPK modulations in MDA-MB-231 cells, although further investigation of this topic is evidently required.

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