PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent activation of p42/44 MAPK and EGFR transactivation

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Mendez, Mariela, and Margot C. LaPointe. PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent activation of p42/44 MAPK and EGFR transactivation. Am J Physiol Heart Circ Physiol 288: H2111–H2117, 2005. First published December 30, 2004; doi:10.1152/ajpheart.00838.2004.—Upon induction of cyclooxygenase-2 (COX-2), neonatal ventricular myocytes (VMs) mainly synthesize prostaglandin E2 (PGE2). The biological effects of PGE2 are mediated through four different G protein-coupled receptor (GPCR) subtypes (EP1–4). We have previously shown that PGE2 stimulates cAMP production and induces hypertrophy of VMs. Because the EP4 receptor is coupled to adenylate cyclase and increases in cAMP, we hypothesized that PGE2 induces hypertrophic growth of cardiac myocytes through a signaling cascade that involves EP4-cAMP and activation of protein kinase A (PKA). To test this, we used primary cultures of VMs and measured [3H]leucine incorporation into total protein. An EP4 antagonist was able to partially block PGE2 induction of protein synthesis and prevent PGE2-dependent increases in cell surface area and activity of the atrial natriuretic factor promoter, which are two other indicators of hypertrophic growth. Surprisingly, a PKA inhibitor had no effect. In other cell types, G protein-coupled receptor activation has been shown to transactivate the epidermal growth factor receptor (EGFR) and result in p42/44 mitogen-activated protein kinase (MAPK) activation and cell growth. Immunoprecipitation of myocyte lysates demonstrated that the EGFR was rapidly phosphorylated by PGE2 in VMs, and the EP4 antagonist blocked this. In addition, the selective EGFR inhibitor AG-1478 completely blocked PGE2-induced protein synthesis. We also found that PGE2 rapidly phosphorylated p42/44 MAPK, which was inhibited by the EP4 antagonist and by AG-1478. Finally, the p42/44 MAPK inhibitor PD-98059 (25 μmol/l) blocked PGE2-induced protein synthesis. Altogether, we believe these are the first data to suggest that PGE2 induces protein synthesis in cardiac myocytes in part through activation of the EP4 receptor and subsequent activation of p42/44 MAPK. Activation of p42/44 MAPK is independent of the common cAMP-PKA pathway and involves EP4-dependent transactivation of EGFR.

prostaglandin E2; epidermal growth factor receptor; cyclooxygenase; G protein; ventricular myocyte; mitogen-activated protein kinase

CARDIAC HYPERTROPHY IS AN ADAPATIVE RESPONSE OF THE HEART TO SEVERAL CARDIOVASCULAR DISEASES. Vasoactive molecules such as ANG II, endothelin-1, and phenylephrine are known mediators of cardiomyocyte hypertrophy. In vitro and in vivo studies have demonstrated that cardiac hypertrophy occurs along with induction of the hypertrophic program including reexpression of fetal genes (e.g., atrial natriuretic peptide (ANP), β-myosin heavy chain, and skeletal muscle α-actin), activation of immediate early genes (e.g., c-fos, c-jun, and erg-1), and increased protein synthesis and morphological changes (e.g., cell size and sarcomeric structures; Refs. 31, 48, 54).

Cyclooxygenase-2 (COX-2) products have gained special interest as promoters of cell growth aside from their role in inflammation (3, 33, 51). In vivo studies (24) have shown that in the heart, COX-2 inhibition reduces hypertrophy and fibrosis in a mouse model of myocardial infarction. We have previously reported (33) that in an inflammatory setting, neonatal ventricular myocytes (VMs) preferentially produce prostaglandin E2 (PGE2) over other prostaglandins, and addition of PGE2 promotes their growth. In other cells, PGE2 has been implicated in tumor growth and mitogenesis (3, 23, 32, 51), and HEK-293 cells that overexpress both COX-2 and PGE2 synthase grow faster than normal cells (34). The biological effects of PGE2 are mediated via four different G protein-coupled receptor (GPCR) subtypes (EP1–4). EP1 activation results in Ca2+ mobilization, and the EP3 receptor is coupled to a Gxi protein that leads to decreased cAMP levels. Both EP2 and EP3 are coupled to Gαs, and their activation results in increased cAMP levels (37). There is evidence that EP subtypes are involved in cell growth. The EP1 receptor subtype has been implicated in growth of keratinocytes (56), primary cultures of hepatocytes (22), and breast cancer cells (19). However, our previous findings (33) demonstrate that EP3 is more likely than EP1 to be involved in PGE2-induced protein synthesis in cardiac myocytes. In agreement with this, in vitro (46, 47, 51) and in vivo (35) reports have implicated the EP4 receptor as a mediator of cell growth.

Activation of Gαs-coupled receptors has been described (63, 64) to mediate hypertrophic growth of cardiac myocytes through cAMP and downstream activation of mitogen-activated protein kinases (MAPKs). cAMP mediates growth-promoting signals by activation of protein kinase A (PKA) in other cell types (52, 61). However, activation of MAPKs occurs by two additional mechanisms that include 1) direct effects of cAMP (independent of PKA activation; Refs. 20, 28, 42); and 2) GPCR transactivation of epidermal growth factor receptors (EGFRs; Refs. 12, 41, 59). Thus in the present study, we examined the signaling cascade responsible for PGE2 induction of protein synthesis in cardiac myocytes. In contrast to what we hypothesized originally, we found that PGE2-induced protein synthesis in cardiac myocytes involves phosphorylation of p42/44 MAPK by a mechanism independent of cAMP and PKA activation that involves EP4-mediated EGFR transactivation.

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METHODS

Cell culture. Primary cultures of neonatal VMs were derived from digestion of 1- to 2-day-old neonatal Sprague-Dawley rat hearts (Charles River; Kalamazoo, MI) as described previously (25). After 40 h in culture with DMEM plus 10% fetal bovine serum (GIBCO), the medium was changed to serum-free medium supplemented with glutamine, insulin, selenium, and transferrin for 24 h. Cells were incubated with the different treatments for 48 h for \(^{3}H\)leucine incorporation studies and for 5 min for p42/44 MAPK and EGFR phosphorylation. In the protocols where different antagonists were used, cells were pretreated for 1 h before the addition of PGE\(_2\). This protocol was approved by the Henry Ford Hospital Institutional Animal Care and Use Committee.

Protein isolation, EGFR immunoprecipitation, and Western blot. Protein was isolated from cardiac myocytes using lysis buffer as described previously (26) that was supplemented with protease inhibitors (10 \(\mu\)g/ml leupeptin, 10 \(\mu\)g/ml aprotonin, 1 mM PMSF, 1 mM sodium vanadate, 10 mM sodium fluoride, and 20 mM glycercophosphate). For immunoprecipitation experiments, 300 \(\mu\)g of total protein was resuspended in lysis buffer that contained protease inhibitors and was incubated overnight at 4\(^\circ\)C with 10 \(\mu\)g of EGFR antibody (Santa Cruz) and 100 \(\mu\)g of protein A agarose beads. Immunoprecipitates were washed four times with lysis buffer and one time with 10 mM Tris-\(HCl\) (pH 7.6). Beads were resuspended in 30 \(\mu\)l of Western loading buffer and boiled for 5 min. Samples were rapidly centrifuged, and supernatants were electrophoresed in a 7.5% acrylamide gel and transferred onto a polyvinylidene difluoride membrane. Membranes were incubated with anti-phosphotyrosine antibody (1:2,000 dilution) in 5% milk solution prepared in Tris-buffered saline with 0.1% Tween (TBST) for 1.5 h and then washed. The appropriate secondary antibody linked to horseradish peroxidase (1:1,000 dilution) was used for chemiluminescent detection with enhanced chemiluminescence Western blot reagents (Amersham Pharmacia Biotech). The signal was detected by exposure to Fuji RX film and quantified by laser densitometry.

Assay for p42/44 MAPK and immunoblotting. Before VMs were treated, the cells were washed every 15 min for 1 h with serum-free medium to decrease basal p42/44 MAPK phosphorylation levels. When the EP\(_4\) antagonist AG-1478 (AG) or H-89 was used, the washing medium was supplemented with the antagonist to result in 1 h of pretreatment. Cells were then treated in serum-free medium for 5 min at 37\(^\circ\)C, and the reaction was stopped with ice-cold lysis buffer supplemented with the above-mentioned inhibitors. Protein from each sample (15–20 \(\mu\)g) was electrophoresed in 7.5% acrylamide gel and transferred to polyvinylidene difluoride membranes, which were developed with a selective primary antibody (1:2,000 dilution) against phosphorylated p42/44 MAPK (Cell Signaling). As a control for protein loading, the same membranes were stripped and reblotted with phospho- and total p42/44 MAPK antibodies (Cell Signaling). Developed membranes were incubated with the different treatments for 48 h for \(^{3}H\)leucine incorporation by PGE\(_2\) (1 \(\mu\)mol/l) to prevent induction of \(^{3}H\)leucine incorporation by PGE\(_2\) (1 \(\mu\)mol/l) as a measure of protein synthesis. We found that treatment with the EP\(_4\) antagonist for 48 h blunted PGE\(_2\) induction of protein synthesis by 44% (control, 1; PGE\(_2\), 1.9 ± 0.1-fold; PGE\(_2\) with EP\(_4\) antagonist, 1.5 ± 0.2-fold; Fig. 1A).

RESULTS

PGE\(_2\) increases protein synthesis in myocytes via EP\(_4\) receptors. We have previously reported that PGE\(_2\) induces protein synthesis in VMs (33). We tested the ability of the EP\(_4\) antagonist L-161982 (10 \(\mu\)mol/l) to prevent induction of \(^{3}H\)leucine incorporation by PGE\(_2\) (1 \(\mu\)mol/l) as a measure of protein synthesis. We found that treatment with the EP\(_4\) antagonist for 48 h blunted PGE\(_2\) induction of protein synthesis by 44% (control, 1; PGE\(_2\), 1.9 ± 0.1-fold; PGE\(_2\) with EP\(_4\) antagonist, 1.5 ± 0.2-fold; Fig. 1A).

In addition to increased protein synthesis, cardiac hypertrophy is characterized by reexpression of fetal genes such as ANP and increased cell size (31, 58). To test the effect of PGE\(_2\) on ANP gene transcription, the human ANP promoter coupled to a luciferase reporter gene (−2593 hANPLuc) was transiently transfected into VMs, and cells were treated with PGE\(_2\) for 24 h. We found that PGE\(_2\) stimulated hANP promoter activity, and this could be blocked by selective inhibition of the EP\(_4\) receptor subtype (control, 1; PGE\(_2\), 1.9 ± 0.4-fold; PGE\(_2\) with EP\(_4\) antagonist, 0.6 ± 0.1-fold; Fig. 1B).
pared with the control, which was significantly decreased by pretreatment with the EP4 antagonist (Fig. 1C).

**PGE2 induces protein synthesis independently of PKA and adenylate cyclase activation.** Because the EP4 receptor is coupled to a Gs protein that leads to cAMP generation (7, 37, 43), we tested whether PKA mediates PGE2-induced protein synthesis. The PKA inhibitor H-89 (1 μmol/l) had no effect on PGE2 induction of protein synthesis (data not shown). In addition, neither activation of adenylate cyclase with forskolin (50 μmol/l) nor inhibition of adenylate cyclase with SQ-22536 (10 μmol/l) had any effect on PGE2-induced protein synthesis (data not shown).

**PGE2-induced protein synthesis involves EP4-dependent activation of p42/44 MAPK but not p38 MAPK.** We further investigated which other signaling molecules could mediate the induction of protein synthesis. We first tested whether the PGE2 signaling cascade involves p42/44 MAPK activation. Using Western blot analysis, we found that PGE2 caused rapid phosphorylation of p42/44 MAPK (control, 1; PGE2, 3.2 ± 0.5-fold; n = 10; P < 0.01), which was inhibited by 69% by the EP4 antagonist (n = 6; Fig. 2).

To study the involvement of p42/44 MAPK activation as a downstream mediator of PGE2-induced protein synthesis, we tested whether the selective p42/44 MAPK inhibitor PD (25 μM) could prevent PGE2-induced [3H]leucine incorporation. PD completely blocked the effect of PGE2 (Fig. 3); however, inhibition of p38 MAPK with SB (10 μM) had no effect (control, 1; PGE2, 1.6 ± 0.2-fold; PGE2 with PD, 1.6 ± 0.2-fold; n = 3).

**PGE2-induced p42/44 MAPK activation and protein synthesis require transactivation of EGFR.** Because increasing evidence suggests that receptor tyrosine kinase transactivation links GPCR and MAPK activation, we questioned whether PGE2 could transactivate the EGFRs and mediate the effect of PGE2 on protein synthesis in cardiac myocytes. By immunoprecipitation of myocyte lysates, we found that stimulation with PGE2 for 5 min induced phosphorylation of EGFRs, and blockade of EP4 inhibited it (Fig. 4).

To identify the EGFR as a mediator of PGE2-induced protein synthesis, we tested the effect of the EGFR inhibitor AG on PGE2-induced [3H]leucine incorporation. We observed that 5 μmol/l AG completely blocked PGE2 induction of
protein synthesis (control, 1; PGE2, 1.5 ± 0.1-fold; PGE2 with AG, 1 ± 0.1-fold; n = 5; Fig. 5). Finally, we found that inhibition of EGFR activation with AG decreased PGE2-dependent activation of p42/44 MAPK by 64% (n = 3), which indicates that p42/44 MAPK activation is downstream from EGFR activation (Fig. 6). Consistent with our previous findings, inhibition of PKA with H-89 had no effect on PGE2-induced p42/44 MAPK activation (data not shown).

PGE2-dependent transactivation of EGFRs requires EGFR agonist ectoshedding. Transactivation of EGFRs has been described to occur by metalloproteinase-dependent ectoshedding of EGFR agonists (59). Inhibition of the metalloprotein-

Fig. 3. Effects of p42/44 MAPK inhibition on PGE2-induced protein synthesis. Effect of the p42/44 MAPK inhibitor PD-98052 (PD). Incorporation of [3H]leucine into total protein over 48 h is expressed as fold increase compared with control, which was arbitrarily set to 1. *P < 0.01 vs. control; #P < 0.01 vs. PGE2; PGE2 with PD-98052 vs. control, nonsignificant; n = 3.

Fig. 4. Effects of PGE2 on epidermal growth factor receptor (EGFR) activation. Total cell lysates were immunoprecipitated with an anti-EGFR antibody and blotted with a phospho-tyrosine antibody as described (see METHODS). A semiquantitative analysis of pooled data is shown (top). Although not shown in the graph, there were no changes in total EGFR (measured in density units). Control, 1; PGE2, 0.86 ± 0.3; PGE2 with EP4 antagonist, 0.94 ± 0.5. *P < 0.05 vs. control; #P < 0.05 vs. PGE2; n = 3. A representative blot showing PGE2-induced EGFR phosphorylation and blockade by the EP4 antagonist is shown (bottom). Band 1, control; band 2, PGE2 stimulation; and band 3, PGE2 with EP4 antagonist. Positive control was a lysate of EGF-stimulated A431 cells (Upstate).

Fig. 5. Effects of the EGFR receptor inhibitor AG-1478 (AG) on PGE2-induced protein synthesis. Incorporation of [3H]leucine into total protein over 48 h was measured and expressed as fold increase vs. control, which was arbitrarily set to 1. *P < 0.01 vs. control; #P < 0.01 vs. PGE2.

Fig. 6. Effects of EGFRs on PGE2-induced p42/44 MAPK activation. Effect of the EGFR inhibitor AG-1478 is shown (top). *P < 0.01 vs. control; n = 3. Representative Western blot is shown (bottom). In each experiment, the membranes were stripped and rebotted with an antibody against total p42/44 MAPK. *P < 0.01 vs. control; #P < 0.01 vs. PGE2.
as with GM (4 μM) prevented the PGE2-dependent growth response (control, 1; PGE2, $1.7 \pm 0.1$-fold; PGE2 with GM, $1.2 \pm 0.1$-fold; n = 9; Fig. 7).

**DISCUSSION**

When cardiac myocytes undergo hypertrophy, protein synthesis is elevated as are the activities of early response genes (e.g., c-myc, fos, etc.) and fetal markers (e.g., ANP, brain natriuretic peptide, myosin light chain, etc.; Refs. 31, 58). In our study, we found that PGE2 stimulation of myocyte hypertrophy involved increased protein synthesis, cell surface area, and ANP transcription, and those effects were mediated by EP4. EP4 was coupled to EGFR transactivation as well as activation of p42/44 MAPK. The fact that PGE2 has growth-promoting effects in vitro provides some explanation for in vivo studies using COX-2 inhibitors, where COX-2 inhibition after myocardial infarction improved function, decreased hypertrophy and fibrosis (24), and decreased fibroblast proliferation (49).

Prostaglandin receptors belong to the seven-transmembrane domain receptor family coupled to heterotrimeric G proteins. So far, four different PGE2 receptor subtypes have been described, which couple to different intracellular signaling cascades (37). We previously reported (33) that a selective inhibitor of the EP1 and EP2 receptor subtypes does not affect PGE2 stimulation of cardiomyocyte growth. We have extended those studies using a specific EP4 antagonist that implicates EP4 as the EP receptor subtype that mediates myocyte growth (30); this is in agreement with studies showing that the EP4 receptor mediates growth and invasiveness of colon cancer cells (35, 46, 51).

Although PGE2 results in cAMP production by myocytes (33), neither adenylate cyclase nor PKA seems to be involved in mediating the effect of PGE2. The role of cAMP in cell growth remains controversial. Its effect as a modulator of cell growth strictly depends on cell type (52). In cardiac myocytes, activation of Gαs-coupled β-adrenergic receptors by isoproterenol promotes growth (64). This effect is partially mediated through cAMP-dependent PKA phosphorylation and subsequent activation of potential growth-promoting signals such as MAPK (52, 61), activation of L-type Ca2+ channels (13, 53), and mobilization of Ca2+ (45, 53). We have previously shown that intracellular cAMP increases after myocytes are treated with PGE2 and that exogenous addition of high concentrations of cell permeable cAMP increases protein synthesis in cardiac myocytes (33). However, our results with a PKA inhibitor, an adenylate cyclase inhibitor, and an adenylate cyclase activator demonstrate that neither cAMP nor PKA is likely to mediate the hypertrophic effect of PGE2 in cardiac myocytes. We have previously shown that blockade of the EP2 subtype or activation of the prostacyclin receptor, both of which are coupled to adenylate cyclase, had no effect on PGE2-induced protein synthesis (33). Therefore, activation of different membrane-bound enzyme pools may account for the differential effects of cAMP when produced by EP4 receptor activation vs. exogenous addition or activation of other GPCRs.

It has been shown (20, 28, 42) that cAMP activates p42/44 MAPK independently of PKA through a novel pathway that involves activation of the exchange proteins directly activated by cAMP (EPACs). This does not seem to be the case in cardiac myocytes, because blocking cAMP elevation with an adenylate cyclase inhibitor had no effect on PGE2-induced protein synthesis. In addition, challenging the cells with different concentrations of the EPAC activator 8-CPT-2Me-cAMP (10–60 μmol/l) did not increase [3H]leucine incorporation (M. Mendez and M. C. LaPointe, unpublished observations).

We show here that PGE2 was able to activate the EGFR, and that EGFR inhibition blocked PGE2-induced protein synthesis. Supporting our findings, PGE, was previously reported to transactivate EGFRs in gastric epithelial cells and colon cancer cells (40). Since then, other groups have demonstrated that EGFRs mediate the effects of PGE2 on cell migration (8) and cell growth (39, 50). Activation of EGFRs has been shown to be essential for normal heart function (16). In vivo studies have implicated EGFR in cardiac hypertrophy and remodeling (17, 18, 55). Recently, EGFRs were identified as mediators of hypertrophic agents by linking stretch-mediated myocyte growth and activation of genes that serve as markers of hypertrophy such as brain natriuretic peptide (1). Thus our studies would indicate that EGFRs are involved in multiple aspects of cardiac hypertrophy and are likely to mediate the effects of COX-2 products in failing heart.

EGFRs have been shown to be activated at the plasma membrane and to be continually active even in late endosomes (14, 60), endocytosis being indispensable for EGFR-dependent downstream activation of ERK (57). In cardiac myocytes, COX-2 and the membrane-localized PGE2 synthase-1 are localized in a perinuclear compartment (33). In addition, EP subtypes are reportedly present in the nuclear membrane (4, 5). Thus it is tempting to speculate that intracellular PGE2 production acting via nuclear EP receptors maintains EGFR in an active state and thereby amplifies the signal that started at the plasma membrane.

It is not clear how EP4 receptors transactivate EGFRs in VMs. Several mechanisms and intracellular mediators have been described. GPCR activation by different agonists may stimulate membrane-bound metalloproteinases with subsequent release of EGFR agonists from the plasma membrane (2, 41, 59). In addition, GPCR-dependent activation of the tyrosine kinases Src and Pyk can directly activate EGFRs (21, 29). Our data showed that the metalloproteinase inhibitor GM

![Fig. 7. Involvement of metalloproteinase-dependent ectoshedding of EGFR agonist in PGE2 stimulation of protein synthesis. Effects of the metalloproteinase inhibitor GM-6001 are shown. *P < 0.01 vs. control; #P < 0.01 vs. PGE2.](http://ajpheart.physiology.org/)
completely blocked PGE$_2$-induced cell growth, which suggests that release of plasma membrane-preformed EGFR agonists is likely to mediate EGFR transactivation in our cells. At the concentration we used, the metalloproteinase inhibitor has been shown to prevent mechanical stress-induced release of heparin-binding (HB)-EGF into the culture media of neonatal cardiac myocytes (1). The EGFR agonist HB-EGF has been suggested to play an important role as a mediator of cardiac hypertrophy (2) and heart function (16). In addition, its gene expression is upregulated in a myocardial infarction model in rats (55). Although our data do not directly identify HB-EGF as the only mediator, it is likely to be part of PGE$_2$-induced hypertrophic signaling.

We demonstrated here that inhibition of EP$_4$ and EGFRs prevented PGE$_2$-induced MAPK phosphorylation by 69 and 64%, respectively. In addition, a selective p42/44 MAPK inhibitor was able to completely block PGE$_2$-induced protein synthesis, whereas a p38 inhibitor had no effect, thereby identifying ERK1/2 as a downstream mediator of PGE$_2$ and EGFRs. Because both EP$_4$ and EGFR inhibitors prevented p42/44 MAPK phosphorylation to the same extent, our data suggest that PGE$_2$-induced p42/44 MAPK activation is downstream of EP$_4$ and EGFRs. In agreement with our results, p42/44 MAPK has been implicated in GPCR-dependent regulation of cardiac hypertrophy (9). In contrast, p38 MAPK involvement in cardiac growth is more controversial. Although it has been reported to mediate the hypertrophic effects of a variety of other GPCR agonists (11, 38), recent work with genetically modified animal models suggests that p38 MAPK does not mediate cardiac hypertrophy in vivo (6, 62).

In our studies, the EP$_4$ antagonist did not completely inhibit PGE$_2$ induction of protein synthesis. However, this partial blockade does not seem to be due to incomplete antagonism of EP$_4$ receptors. We measured PGE$_2$-induced cAMP production in the absence and presence of EP$_1$ and EP$_2$ antagonists to determine the relative contribution of EP$_4$ activation to total cAMP. We found that the EP$_4$ subtype was responsible for 50% of the PGE$_2$-induced cAMP levels, and this increase was completely prevented by pretreatment of VMs with the concentration of EP$_4$ antagonist used in the present experiments (M. Mendez and M. C. LaPointe, unpublished observations). However, another explanation for the partial inhibitory effect could be chemical instability of the antagonist over a 48-h treatment period.

The partial effect of the EP$_4$ antagonist on PGE$_2$-induced p42/44 MAPK activation (~70% inhibition) might point to the participation of another EP subtype. To date, four splice variants of the EP$_3$ subtype have been described (36, 44); however, their presence in cardiac myocytes is unknown. Therefore, the possible small contribution of EP$_3$ in myocyte growth remains to be elucidated.

Together, our observations indicate that PGE$_2$ acting through EP$_4$ transactivates the EGFR, which mediates PGE$_2$ induction of myocyte growth via the p42/44 MAPK pathway. Thus in conditions where cardiac hypertrophy is accompanied by inflammation, additional targets to control the disease process might include PGE$_2$ synthesis and EP$_4$.

GRANTS
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