Peroxisome Proliferator-activated Receptor δ Activation Promotes Cell Survival following Hypertonic Stress*

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COX2-selective non-steroidal anti-inflammatory drugs (NSAIDs) cause selective apoptosis of renal medullary interstitial cells (RMIC) in vivo and reduce their ability to tolerate hypertonic stress in vitro. To determine the mechanism by which COX2 activity promotes RMIC viability, we examined the capacity of COX2-derived prostanooids to promote RMIC survival. Although RMICs synthesize prostaglandin E2 (PGE2) > PGI2 > PGF2α > TxA2, only PGI2 enhanced RMIC viability following hypertonic stress. RMICs do not express the prostacyclin receptor, but they do express the prostacyclin responsive nuclear transcription factor peroxisome proliferator-activated receptor δ (PPARδ). Hypertonic stress increased PGI2 synthesis 330% above base line and also activated a PPARδ specific reporter (delta response element (DRE)) by 90% above base line. Conversely DRE activity was only inhibited by the COX2-selective inhibitor SC236 but not by a COX1-selective NSAID (SC560). Overexpression of PPARδ using an adenovirus not only drove DRE activity but also prevented RMIC death due to COX2 inhibition. These studies are consistent with a model whereby hypertonicity activates COX2-derived prostaglandin production, which promotes RMIC viability through PPARδ. Inhibition of PPARδ activity may contribute to the renal papillary necrosis associated with analgesic and/or NSAID use.

Cells residing in the renal medulla are uniquely subjected to recurrent hypertonic stress with ambient tonicity rapidly shifting between 300 and 3000 mosmol. Renal medullary interstitial cells (RMICs) are a distinct cell type, physically spanning the gap between the vasa recta and medullary tubules. These cells are distinguished by the presence of abundant lipid droplets comprised of long chain unsaturated fatty acids including arachidonate (1) and have also recently been found to be the major site of renal COX2 expression (2). COX2 is an important factor promoting survival of RMICs following hypertonic stress (3, 4). COX2-selective inhibitors cause RMICs to die when exposed to otherwise non-lethal hypertonic stress (4). These results may account for the finding that RMICs are an early site of injury caused by COX-inhibiting analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (5, 6).

The downstream mechanisms through which COX2 activity promotes RMIC survival remain uncharacterized. COX2 mediates the conversion of arachidonate to major bioactive prostanooids: PGE2, PGD2, PGF2α, PGI2, and TxA2. These compounds exert a variety of cellular effects via a family of G-protein-coupled receptors that not only exhibit ligand selectivity but also differential signaling (7, 8). For example, PGI2 selectively activates a Gs-coupled cAMP-stimulating IP receptor, whereas TxA2 activates a Gi-coupled thromboxane receptor (TP receptor) (7). PGE2 interacts with at least four receptor subtypes designated EP1, EP2, EP3, and EP4 that couple through Gαi, Gαs, Gαq, and Gαl, respectively (7, 8). Other studies have suggested that biological effects of prostanooids could be mediated via nuclear receptors including the peroxisome proliferator-activated receptors α, δ(β), and γ. The goal of the present studies was to identify the COX2-derived products and their downstream targets promoting cell survival following hypertonic stress.

MATERIALS AND METHODS

Cell Culture—Rabbit medullary interstitial cells were cultured as described previously. Briefly, female New Zealand White rabbits were anesthetized (44 mg/kg ketamine and 10 mg/kg xylazine, intramuscularly). The left kidney was removed, and the medulla was dissected and minced with a razor blade under sterile conditions in 5 ml of sterile RPMI 1640 plus 10% (v/v) fetal bovine serum (HyClone, Logan, UT). This homogenate was injected subcutaneously in the abdominal wall using a 14-gauge needle. Twenty days postsurgery, subcutaneous nodules appeared. The rabbits were re-anesthetized and sacrificed by decapitation, and the nodules were removed under sterile conditions. Nodules were minced into 1-mm fragments and explanted in 75-cm² tissue culture plates. Cells were cultured in RPMI 1640 tissue culture medium supplemented with 10% (v/v) fetal bovine serum and streptomycin and penicillin. Cultures were incubated at 37 °C in 5% CO2. Tissue culture medium was changed every 48–72 h. Cells were studied in their third to fourth passages. These cells exhibit characteristic abundant oil red O positive lipid droplets, which typifies type I RMICs (9).

Prostaglandin Measurement—PG production by cultured RMICs was quantitated utilizing gas chromatography/negative ion chemical ionization mass spectrometry assays as described previously (10). Cultured RMICs were treated with phorbol ester (10 nM) for 6 h, culture medium was replaced with fresh medium, and 2 h later culture medium was collected for prostanooid determination.

Immunoblotting—PPARα immunoblots were performed on whole cell lysates from cultured RMICs. Protein concentration was determined using bicinechoninic acid protein assay (Sigma). Twenty micrograms of protein extract was loaded in each lane of a 10% SDS-PAGE mini-gel and run at 120 V. Protein was transferred to a nitrocellulose membrane at 22 V overnight at 4 °C. The membrane was washed three times with...
TBST (50 mM Tris, pH 7.5, 150 mM NaCl, 0.05% Tween 20) and then incubated in blocking buffer (150 mM NaCl, 50 mM Tris, 0.05% Tween 20, and 5% Carnation nonfat dry milk, pH 7.5) for 1 h at room temperature. The membrane was then incubated with an anti-human PPARδ antibody (1:300, sc7197, Santa Cruz Biotechnology Inc., Santa Cruz, CA) in blocking buffer overnight at 4 °C. Following washing (×3), the membrane was incubated with a horseradish peroxidase-conjugated secondary antibody (1:20,000, Jackson Immuno-Research Lab) for 1 h at room temperature followed by three 15-min washings. Antibody labeling was visualized by the addition of chemiluminescence reagent (Renaissance, PerkinElmer Life Sciences), and the membrane was exposed to Kodak XAR-5 film.

RT-PCR Detection of IP Receptor Expression—Total RNA was extracted from cultured RMICs or rabbit aorta using Trizol reagent (Invitrogen). RT was performed on 1 μg of total RNA (PerkinElmer Life Sciences). A pair of degenerate primers was designed according to human and rat IP receptor sequences: TCTGTTGCTTMCCTCGCAT (forward) and GGAAGACAGCCTTKCGGAAA (reverse). A 398-bp PCR product was amplified from rabbit aorta RNA under the following conditions: 95 °C for 5 min; 35 cycles of 95 °C for 45 s, 58 °C for 45 s, and 72 °C for 45 s; 72 °C for 7 min; 4 °C. A 700-bp rabbit rabbit aldolase cDNA was amplified from the same sample used as RNA loading control.

Ad-PPARδ and Ad-GL—Adenoviral vectors encoding a human PPARδ (Ad-PPARδ) or PPARγ (Ad-GL) were a gift of Dr. Kenneth Kinzler (11). GFP adenovirus was made as previously described (4). A full-length green fluorescent protein cDNA (Green Lantern or GL, Invitrogen) was subcloned into pACCMV. The pACCMV shuttle plasmid contains the cytomegalovirus immediate early enhancer and promoter and the SV40 polyadenylation sequence. The resulting shuttle plasmids were co-transfected into HEK 293 cells along with the pJM17 vector by SuperFect (Qiagen). Ad-PPARδ was generated by a homologous recombination event, resulting in plaque formation in the HEK 293 cells. The resulting infectious adenovirus was plaque-purified. For infection of RMICs, 200 μl of virus (multiplicity of infection, 100) was added to each culture dish. After a 2-h incubation, the virus was removed and fresh Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum was added. Experiments were carried out 48–72 h after infection.

RESULTS

Prostanoids Produced in Cultured RMICs—To identify potential prostanoid(s) responsible for the survival-promoting effect of COX2 in RMICs, the profile of prostanoids synthesized by these cells was examined by gas chromatography/mass spectrometry. As shown in Fig. 1, PGE2 constitutes a major component of prostanoids produced by cultured RMICs (43.4 ng/ml/h), followed by 6-keto PGI2, a metabolite of PGI2 (3.1 ng/ml/h), TXB2 (1.4 ng/ml/h), PGF2α (1.3 ng/ml/h), and PGD2 (0.04 ng/ml/h).

Carboprostacyclin (cPGI2) Increased RMIC Survival following Hypertonic Stress—NaCl was added to abruptly increase tonicity from 300 to 500, 550, or 600 mosmol. RMICs tolerated a shift of 250 mosmol or less, but when osmolality was increased to 600 mosmol, 80 ± 12% of RMICs died (Fig. 2A). The ability of exogenous PGs to promote RMIC survival following exposure to lethal hypertonic stress was examined. Pretreatment of RMICs with PGE2 or the thromboxane A2 agonist U46619 did not affect cell viability following exposure to 600 mosmol. In contrast, PGD2 and PGA2 decreased cell viability following hypertonic stress compared with vehicle-treated cells. Importantly the prostacyclin analog cPGI2 (20 μM) significantly increased RMIC survival almost 3-fold following hypertonic stress (20.0 ± 3.4% versus 55.3 ± 7.8%; n = 3; p < 0.01) (Fig. 3).
Expression of Prostacyclin Receptors in RIMCs—Potential targets of prostacyclin action on RMIC were identified by RT-PCR using primers specific for the cell surface G-protein-coupled IP receptor and nuclear transcription factor PPARδ, and by immunoblot using antibody specific for the PPARδ (13, 14). Although RT-PCR demonstrated abundant expression of IP receptor in aorta, IP receptor mRNA was absent from cultured RMICs (Fig. 4). In contrast, PPARδ mRNA and protein were detected in RMIC by RT-PCR and immunoblot. Immunoreactive protein migrated at the same speed on SDS gel as recombinant PPARδ protein transduced into RMICs via adenoviral vector (Ad-PPARδ) (Fig. 4).

Hypertonicity Increased PPARδ Activity through Increased PGI2 Release—To examine whether PPARδ is involved in RMIC survival-promoting action of COX2/PGI2 following hypertonic stress, the effect of tonicity on endogenous PPARδ activity was examined using a DRE luciferase reporter, i.e. a DRE luciferase reporter construct. Fig. 5 shows hypertonicity nearly doubled PPARδ transcriptional activity when RMICs were switched to a non-lethal hypertonicity of 550 mosmol (1.9 ± 0.09-versus 1.0 ± 0.02-fold; n = 3; p = 0.01). Hypertonicity also increased PGI2 production (Fig. 2B), and the exogenous PGI2 analog cPGI2 activated PPARδ reporter activity by 2.7-fold at a concentration of 20 μM (Fig. 5), suggesting a link between increased PGI2 production and PPARδ activation during hypertonic stress. Interestingly, the concentration at which PGI2 significantly activated PPARδ is identical to the concentration at which PGI2 prevented RMIC death in otherwise lethal hypertonic culture conditions (Fig. 3).

COX2 Not COX1 Inhibitors Block PPARδ Activity—Because COX2 is a key enzyme responsible for prostanoid production in RMICs, the effect of COX2 inhibitors on PPARδ activity was examined. The COX2-selective inhibitor SC236 dose-dependently inhibited the PPARδ reporter activity (from 1.0 ± 0.16- to 0.128 ± 0.12-fold in the presence of 20 μM SC236; n = 4; p < 0.01). In contrast, the structurally similar COX1 inhibitor SC560 significantly increased PPARδ activity by 1.3 ± 0.13-fold (n = 4, p < 0.05). The ability of COX inhibitors to inhibit PPARδ activity also correlated with their ability to induce RMIC death (Fig. 6). Importantly, RMIC death caused by the COX2 inhibitor was prevented in cells transduced with an

Fig. 3. Effects of prostaglandins on viability of cultured RMIC exposed to hypertonic stress. Cultured RMICs were treated with PGE2 (10 and 20 μM), cPGI2 (10 and 20 μM), U46619 (20 μM), PGD2 (20 μM), and PGF2 (20 μM) for 12 h, followed by hypertonic stress (600 mosmol/kg) for 48 h. Cell viability was assessed using crystal violet assay as described under “Materials and Methods.” *, p < 0.05; **, p < 0.01 versus vehicle-treated cells.

Fig. 4. Expression of PPARδ and IP receptor in cultured RMICs. A, immunoblot of PPARδ on protein extracts from cultured rabbit RMICs or RMICs transduced with human PPARδ adenovirus (Ad-PPARδ). 20 μg of protein lysate was subjected to SDS-PAGE and immunoblotted with anti-human PPARδ antibody. B, RT-PCR of IP receptor on total RNA extracted from cultured RMICs or rabbit aorta. A 700-bp rabbit glyceraldehyde-3-phosphate dehydrogenase (GAPDH) PCR product was obtained from the same sample used as RNA loading control.

Fig. 5. Effect of cPGI2 and hyperosmolality on PPARδ reporter DRE-driven luciferase activity. Cultured RMICs were co-transfected with DRE-driven firefly luciferase vector and TK-driven Renilla luciferase vector. Cells were treated 12 h later with carboprostacycin (0–20 μM (A)) or NaCl (to generate hypertonicity, 500 and 550 mosmol (B)). 48 h after transfection luciferase activities were tested as described under “Materials and Methods.” DRE luciferase activity was adjusted by Renilla luciferase activity, and the -fold of increases compared with 0 μM cPGI2 or 300 mosmol was displayed. **, p < 0.01 versus 0 μM cPGI2 or 300 mosmol, n = 6.
RMICs. This lethal effect of COX2 inhibitor was blocked by
Following hypertonic stress, low concentrations of SC236 killed
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RMICs were cultured to confluence and co-transfected with DRE-driven
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RMICs were cultured to confluence and treated with the COX2 (SC236) or
COX1 (SC560) selective inhibitor. Cell viability was determined 48 h
were cultured to confluence and treated with the COX2-selective (SC236) or COX1-
selective (SC560) inhibitor for 36 h, followed by determination of lucif-
erase activity as described under “Materials and Methods.” To examine the effect of PPARδ overexpression on PPARδ reporter activity, cultured RMICs were transduced with Ad-PPARδ. 24 h later the cells were co-transfected with DRE-driven firefly luciferase vector and TK-driven Renilla luciferase vector; 12 h later the cells were exposed to COX2 inhibitor (SC236) for 36 h as in other groups. B, cell viability. RMICs were cultured to confluence and treated with the COX2 (SC236) or COX1 (SC560) selective inhibitor. Cell viability was determined 48 h later using crystal violet assay. To examine the effect of PPARδ overexpression on cell viability, cultured RMICs were transduced with Ad-PPARδ. The cells were then treated with COX1 and COX2 inhibitors for 48 h and cell viability was assessed. **, p < 0.01 versus vehicle-treated cells; ##, p < 0.01 versus 20 μM SC236-treated cells, n = 6.

adenovirus-driving PPARδ expression. PPARδ activity in these
cells was increased —5-fold from 0.128 ± 0.12- to 0.62 ± 0.11-
fold (p < 0.01), with cell viability increased from 9.6 ± 0.5 to
76.6 ± 3.8% (n = 4, p < 0.01) in the presence of 20 μM SC236 (Fig. 6).

PPARδ Activation Restores Osmotic Tolerance of COX2-inhibited RMICs—When subjected to osmotic stress, RMICs are markedly sensitized to the lethal effects of COX2 inhibition. To further characterize the role of PPARδ in promoting RMIC survival, an adenoviral vector was used to overexpress PPARδ. Following hypertonic stress, low concentrations of SC236 killed RMICs. This lethal effect of COX2 inhibitor was blocked by overexpression of PPARδ (Fig. 7).

DISCUSSION
Medullary interstitial cells are a major source of renal pros-
taglandin synthesis and play an important role in modulating
renal medullary blood flow and salt absorption (9). COX is a
key enzyme converting arachidonic acid to PGH2, which is then
converted to different bioactive prostaglandins through differ-
ent synthases (7, 15). Although COX1 is constitutively expressed in many tissues including the collecting duct, COX2 expression is generally induced by growth factors, cytokines, or osmotic stress (4, 16, 17). Accumulating evidence suggests COX2 is selectively expressed in renal medullary interstitial cells where it may play a role in promoting cell survival (2–4). The present studies demonstrate that COX2-derived prostacyclin may be a key component allowing RMIC to survive hyper-
tonic conditions present in the renal medulla.

Cultured RMICs produce several prostaglandins including PGF2α > PGJ2 > PGF2α > TxA2. However, only carbaprostacyclin, an analog of PGJ2, has the ability to increase the tolerance of RMIC to hypertonic stress that also increases prosta-
cycin synthesis. This result is consistent with early reports that show the protective effect of prostacyclin in other organ injury including the heart (18) and brain (19, 20). The bio-
activity of PGJ2 is generally via activation of a cell surface
G-protein-coupled IP receptor that activates Gs and increases
CAMP levels or via activation of a nuclear transcription factor PPARδ and downstream PPARδ-responsive gene transcription (13, 21). The present study examined the involvement of these mechanisms in PGJ2’s protective effect against hypertonic stress. Only PPARδ but not the IP receptor was detected in cultured RMICs. When RMICs were switched from isotonic conditions to a hypertonic medium, PPARδ transcriptional activity was markedly increased. Activation of PPARδ by hyper-
tonicity appears to be mediated through increased PGJ2 produ-
tion following hypertonic stress, based on the observations that hypertoncity also increased prostacyclin synthesis and exogenous cPGJ2 directly activated PPARδ specific reporter in cultured RMICs.

PPARδ is a nuclear receptor, functioning as ligand-depend-
ent sequence-specific activator of transcription (22). In the presence of ligand, PPARδ heterodimerizes with a retinoid X receptor. This heterodimer then modulates transcription by binding to a PPARδ response element or DRE in target genes. The array of specific target genes that are transcriptionally regulated by PPARδ have not yet been identified. There are several reports suggesting roles for PPARδ in adipocyte differenti-
tation, brain function, epidermal differentiation, embryo implantation, colon cancer, etc. (11, 13, 23–28). The present

![Fig. 6. Effect of selective COX2 inhibition on PPARδ reporter activity and cell viability of cultured RMICs. A, DRE activity. RMICs were cultured to confluence and co-transfected with DRE-driven firefly luciferase vector and TK-driven Renilla luciferase vector. 12 h later the cells were treated with COX2-selective (SC236) or COX1-selective (SC560) inhibitor for 36 h, followed by determination of luciferase activity as described under “Materials and Methods.” To examine the effect of PPARδ overexpression on PPARδ reporter activity, cultured RMICs were transduced with Ad-PPARδ. 24 h later the cells were co-transfected with DRE-driven firefly luciferase vector and TK-driven Renilla luciferase vector; 12 h later the cells were exposed to COX2 inhibitor (SC236) for 36 h as in other groups. B, cell viability. RMICs were cultured to confluence and treated with the COX2 (SC236) or COX1 (SC560) selective inhibitor. Cell viability was determined 48 h later using crystal violet assay. To examine the effect of PPARδ overexpression on cell viability, cultured RMICs were transduced with Ad-PPARδ. The cells were then treated with COX1 and COX2 inhibitors for 48 h and cell viability was assessed. **, p < 0.01 versus vehicle-treated cells; ##, p < 0.01 versus 20 μM SC236-treated cells, n = 6.

![Fig. 7. Effect of PPARδ overexpression on COX2 inhibitor-induced RMIC death following hypertonic stress. Cultured RMICs were transduced with GFP or PPARδ via adenoviral vector. 48 h later, RMICs were treated with COX2 inhibitor SC236 or vehicle Me2SO for 12 h followed by hypertonic stress (550 mosmol/kg). 24 h after hypertonic stress, cell viability was assessed as described under “Materials and Methods.” *, p < 0.05; **, p < 0.01.](http://www.jbc.org/)}
studies suggest that PPARδ activation is also involved in the physiological response of RMICs to environmental osmotic stress.

That COX2-mediated prostacyclin synthesis activates PPARδ in RMICs is further supported by studies showing COX-inhibiting NSAIDs blocked PPARδ reporter activity. Importantly, the inhibitory effect of NSAIDs on PPARδ activity in RMICs is limited to the COX2-selective inhibitor, while a structurally similar COX1-selective inhibitor increased PPARδ activity rather than inhibiting its activity. This is consistent with the fact that COX2 is the predominant isozyme in RMICs (3), supporting the hypothesis that the effect of NSAIDs on PPARδ is mediated through COX inhibition. Additionally, because some NSAIDs can bind to PPARs (11), it is also conceivable that the COX2 inhibitors directly prevent PPARδ activation by competing with PG12 activation of PPARδ. Importantly, the ability of COX inhibitor to block PPARδ activity correlated with its ability to kill RMICs; the COX2 selective inhibitor, which blocked PPARδ activity, killed RMICs, whereas the COX1 inhibitor, which did not inhibit PPARδ, did not kill RMICs. PPARδ overexpression prevented RMIC from COX2 inhibitor-induced cell death and was accompanied by restoration of PPARδ activity. These studies suggest that COX2-mediated PPARδ activity is a survival factor in RMICs. During hypertonic stress, the importance of COX2-derived products in maintaining RMIC survival is supported by studies that show hypertonic stress relies on PPARδ activation by prostacyclin (PG12) produced through COX2-mediated synthesis (2). 

In summary, hypertonicity can induce COX2 expression in renal medullary interstitial cells. Increased COX2 expression is associated with increased PG12 production and subsequent PPARδ activation, transcriptional activity, and increased cell survival. NSAIDs, which inhibit COX2-mediated prostacyclin release, may damage renal interstitial cells by inhibiting PPARδ activity. This could contribute to the papillotoxic effect of these drugs.

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