Effects of isoprostane on tubuloglomerular feedback: roles of TP receptors, NOS, and salt intake

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Welch, William J. Effects of isoprostane on tubuloglomerular feedback: roles of TP receptors, NOS, and salt intake. Am J Physiol Renal Physiol 288: F757–F762, 2005. First published December 21, 2004; doi:10.1152/ajprenal.00269.2004.—A thromboxane prostanoid receptor (TP-R) agonist U-46,619 enhances tubuloglomerular feedback (TGF). Glomerular expression of TP-R and enhancement of TGF by U-46,619 increase with salt intake. We investigated the hypothesis that 8-isoprostaglandin F₂α (8-Iso) activates TGF via TP-R. The maximal TGF response in rats was assessed from the fall in proximal stop flow pressure (PSF; an index of glomerular capillary pressure) during loop of Henle (LH) microperfusion of artificial tubular fluid (ATF) at 40 nl/min. Microperfusion of 8-Iso (10⁻⁴ M) into the efferent arteriole (EA) enhanced TGF responses by 20 ± 3% (P < 0.01). TGF response to 8-Iso was independent of dietary salt [ΔTGF%, low salt (LS): 21 ± 5%; normal salt (NS): 17 ± 4%; high salt (HS): 29 ± 8%; not significant (ns)], unlike the salt-dependent effect of U-46,619 (ΔTGF%, LS: 41 ± 5%; NS: 52 ± 4%; HS: 112 ± 21%). Ifetroban, the TP-R antagonist, abolished TGF responses to 8-Iso and U-46,619 at all levels of salt intake. During luminal perfusion of N-monomethyl-L-arginine (L-NMA), the effect of 8-Iso on TGF was enhanced in NS and HS but not in LS (LS: 22 ± 6 vs. LS + l-NMA: 28 ± 6%, ns; NS: 18 ± 4 vs. NS + l-NMA: 40 ± 4, P < 0.01; HS: 27 ± 3 vs. HS + l-NMA: 65 ± 6, P < 0.01). However, U-46,619 did not further increase TGF after l-NMA in all salt groups (LS: 43 ± 7 vs. LS + l-NMA: 51 ± 6, ns; NS: 52 ± 7 vs. NS + l-NMA: 48 ± 8, ns; HS: 114 ± 21 vs. HS + l-NMA: 74 ± 22, ns). In conclusion, activation of TP receptors by U-46,619 and 8-IsopGF₂α enhances TGF. In addition, the effect of U-46,619 was salt dependent, whereas the effect of 8-IsopGF₂α was salt independent. However, stimulation of NO by 8-isoprostanes masks its salt-sensitive effect on TGF.

8-Isoprostaglandin F₂α, oxygen radicals; oxidative stress; tubuloglomerular feedback response; thromboxane A₂; nitric oxide synthase; ifetroban

THROMBOXANE A₂ (TxA₂) prostanoid receptors (TP-R) have been localized to the renal vasculature and glomeruli, cortical collecting ducts, thick ascending limb of the loop of Henle, and sites in the medulla, papilla, and transitional epithelium of the renal pelvis (3, 22). The renal circulation is especially sensitive and responsive to the vasoconstrictor effects of infused TP receptor mimetics. This has been attributed to engagement of renal vasoconstriction mediated by the tubuloglomerular feedback (TGF) process (28, 29).

TGF is initiated by a furosemide-sensitive reabsorption of Na⁺-Cl⁻-K⁺ across the luminal membrane of macula densa cells. This signal leads to release of mediators, that include adenosine, which constrict the adjacent afferent arteriolar vascular smooth muscle cells, thereby increasing the afferent arteriolar resistance and decreasing the glomerular capillary pressure and the single-nephron glomerular filtration rate (SNGFR). Microperfusion of the TP-R mimetic U-46,619 into the juxtaglomerular apparatus (JGA) enhances TGF, which is mediated by TP-R as it is blocked by specific TP-R antagonists, SQ-29,584 or ifetroban (29). Increasing dietary salt intake enhances the abundance of the mRNA for TP-R in glomeruli microdissected from the kidney (34) and enhances in parallel the potentiation of TGF by microperfused U-46,619 (26).

Isoprostanes are formed predominantly by nonenzymic oxygen radical [O₂⁻'] conversion of arachidonate (5). The isoprostane 8-Isoprostaglandin F₂α (8-Iso-PGF₂α) increases coronary vasoconstriction (35) and systemic constriction, which is mediated via TP-R (2). Infusion of TP-R agonists into the renal artery constricts the afferent arteriole (11) and direct renal perfusion of 8-Iso-PGF₂α reduced SNGFR by activation of TP-R (21). These vasoconstrictor effects of 8-Iso-PGF₂α are similar to the effects of the thromboxane mimetic U-46,619 (10, 28, 29, 33). Therefore, we tested the hypothesis that isoprostanes activate TGF via TP receptors. This was assessed by microperfusion of 8-Iso-PGF₂α, via the efferent arteriole into the peritubular capillaries and interstitium surrounding the test nephron. We studied its acute effects on TGF, the response to blockade with ifetroban, and the effects of dietary salt intake.

In addition, we tested the role of nitric oxide (NO) on the TP-R activation of TGF. Macula densa cells express the neuronal (n) or type I isoform of NO synthase (NOS) that is activated during a TGF response. NO blunts the vasoconstrictive TGF response as evidenced by enhanced responses during NOS inhibition.

METHODS

Animal Preparation

Studies were undertaken in male Sprague-Dawley rats weighing 210–265 g obtained from Harlan-Sprague-Dawley (Madison, WI) and maintained on a standard rat chow (Purina Rat Chow, St. Louis, MO) with a sodium content of 0.3 g/100 g. All studies were approved by the Georgetown University Animal Care and Use Committee. Rats were allowed free access to food and water until the day of the study. Some groups were fed an artificial casein-based diet (Teklad, Madison, WI) with a high-salt (HS; 6 g/100 g of NaCl) or a low-salt (LS; 0.03 g/100 g of NaCl) content. This LS diet is sufficient for normal growth over 10 days. The diets were fed for 6–8 days before testing.

The renal hemodynamics, excretory function, and TGF characteristics.

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of rats fed these diets as well as the effects of U-46,619 in enhancing TGF have been described in detail previously (26).

In brief, rats were anesthetized with thiobarbital (Inactin, 100 mg/kg ip; Research Biochemicals, Natick, MA). A catheter was placed in the jugular vein for fluid infusion and in a femoral artery for recording of mean arterial pressure (MAP) from the electrically damped output of a pressure transducer. A tracheostomy tube was inserted, and the animals were allowed to breathe spontaneously. The left kidney was exposed by a flank incision, cleaned of connective tissue, and stabilized in a Lucite cup. This kidney was bathed in 0.154 M NaCl solution maintained at 37°C. After completion of surgery, rats were infused with a 0.154 M NaCl solution and 1% albumin at 1.5 ml/h to maintain euvolesma. Micropuncture studies were begun after a 30- to 45-min stabilization period.

For orthograde microperfusion of the loop of Henle (LH), a micropipette (8-µm OD) containing artificial tubular fluid (ATF) stained with FD&C no. 2 dye was inserted into a late proximal tubule. Injections of the colored ATF identified the nephron and the direction of flow. An immobile bone wax block was inserted into the micropuncture site via a micropipette (10–15 µm) connected to a hydraulic drive (Trent Wells, La Jolla, CA) to halt tubular fluid flow. A perfusion micropipette (6–8 µm) containing ATF with test compounds or vehicle was inserted into the late proximal tubule downstream from the wax block and connected to a nanoliter microperfusion pump (WPI, Sarasota, FL). A pressure micropipette (1–2 µm) was inserted into the proximal tubule upstream from the wax block to measure proximal stop-flow pressure (PSF). The pressure was recorded by a servo-null micropressure recorder (Instruments for Physiology and Medicine, La Jolla, CA). Changes in PSF are an index of glomerular capillary hydraulic pressure.

Measurements of TGF were made from values of PSF recorded in each nephron during zero loop perfusion and during perfusion with ATF at 40 nl/min, which produces a maximal response. TGF responses were recorded before and during microperfusion of drugs in artificial plasma (AP) into the efferent arteriole (EA) supplying the peritubular capillaries (PTC) and interstitium around the test nephron. For these studies, drugs were made up in AP, stained with green dye, and drawn up into a micropipette (10–12 µm) that was inserted into the welling point of a surface EA. Tubule sites for LH microperfusion were selected based on the peritubular anatomy identified by the perfused AP. After sufficient perfusion to identify the anatomy, TGF responses were recorded after 3–4 min at 0 flow through the EA (before) and during microperfusion via this EA micropipette at 10 nl/min. This rate of perfusion is ~10% of effenter arteriolar blood flow. In a limited series TGF measured 5 min after cessation of EA perfusion was normal, indicating the effects of 8-iso-PGF2α were reversible. In previous studies, we showed that microperfusion of AP alone at this rate does not alter TGF responses. Therefore, the effects of EA microperfusion with vehicle were not measured in these studies.

Protocols

Series 1: TGF dose-response effects of 8-Iso-PGF2α microperfused into the EA and effects of ifetroban. These studies were designed to test the hypothesis that 8-Iso-PGF2α enhances TGF responses via activation of TP-R. TGF responses were assessed by LH microperfusion of ATF in single nephrons before and during EA microperfusion of 8-Iso-PGF2α, at 10−7 to 10−3 M. Following this collection period ifetroban, the TP-R antagonist was infused intravenously as a bolus of 10 mg/kg and then at 10 mg·kg−1·h−1. After 15–30 min, the TGF response to 8-iso-PGF2α was assessed again in separate nephrons. This dose of ifetroban is fully effective in blocking the increase in MAP produced by infusion of U-46,619 (10).

Series 2: effects of dietary salt on TGF responses to 8-Iso-PGF2α and blockade by ifetroban. These experiments were designed to test the hypothesis that TGF responses to 8-Iso-PGF2α increase with salt intake in parallel with the increase in TP-R mRNA expression found previously (34). Groups of LS (n = 7), normal salt (NS; n = 6), and HS (n = 5) rats were prepared for microperfusion. The effects of EA microperfusion of 8-Iso-PGF2α (10−4 M) in AP were studied during LH microperfusion of ATF by paired observations in the same tubule. After intravenous infusion of ifetroban, measurements were repeated in separate tubules.

Series 3: effects of dietary salt on the role of macula densa-derived NO to blunt the effects of 8-iso-PGF2α on TGF. This series tested the role of macula densa NO on the effects of 8-Iso-PGF2α on TGF. These experiments were similar to series 2 with TGF responses assessed before and during EA microperfusion of 8-Iso-PGF2α. The effect of NO on TGF was also assessed by LH microperfusion of ATF + N-nitroarginine (l-NMA; 10−4 M), before and during EA delivery of 8-iso-PGF2α in separate tubules. l-NMA is a nonspecific inhibitor of NO, but we showed that when it is delivered directly into the nephron its effects are consistent with reduction of nNOS activity in the macula densa (30).

Series 4: effects of dietary salt on the role of macula densa-derived NO to blunt the effects of U-46,619 on TGF. This series tested the role of NO in offsetting the full expression of U-46,619 on TGF. This study followed the protocol in series 3 except U-46,619 (10−6 M) was perfused into the EA.

Drugs

Ifetroban (BMS-180,291) was a gift from Bristol-Myers-Squibb (Princeton, NJ). U-46,619 and 8-Iso-PGF2α were obtained from Cayman Chemicals (Ann Arbor, MI). l-NMA was obtained from Sigma (St. Louis, MO). ATF is similar to native proximal tubular fluid (in mM: 123 NaCl, 4 NaHCO3, 5 KCl, 2 CaCl2, 7 urea, and 2 MgCl2). AP is 6% albumin and (in mM) 140 Na, 120 Cl, 20 HCO3−, and 6 K+.

Statistical Methods

Values are reported as means ± SE. An ANOVA was applied to the within-group data; where appropriate, a post hoc Dunnett’s t-test was applied thereafter. Values are taken as statistically significant as P < 0.05.

RESULTS

Basal data for the body weight, MAP, heart rate (HR), and TGF parameters are shown in Table 1. These data did not differ between series. Maximal TGF was consistently greater in LS-treated rats.

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<th>Table 1. BW, MAP, heart rate, and TGF</th>
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Values are means ± SE. BW, body weight; MAP, mean arterial pressure; TGF, tubuloglomerular feedback; LS, low salt; NS, normal salt; HS, high salt. *P < 0.05 compared with NS.
The effect of 8-ISO-PGF2α on TGF during graded microperfusion of the LH is shown in Fig. 1. EA microperfusion of 8-ISO-PGF2α (10⁻⁴ M) in AP enhanced TGF responses by 20 ± 5% in rats on a NS diet compared with before treatment (before: 7.8 ± 0.6 vs. 8-ISO: 9.2 ± 0.6 mmHg; n = 15; P < 0.001). 8-ISO-PGF2α reduced PSF at both 30 and 40 nl/min LH perfusion. However, during intravenous ifetroban, EA microperfusion of 8-ISO-PGF2α no longer enhanced TGF responses (Ifetroban before: 7.9 ± 0.7 vs. Ifetroban + 8-ISO: 8.3 ± 0.5 mmHg, ns). A limited dose-response (n = 4–10 tubules per dose) relationship for the maximal TGF effects of 8-ISO-PGF2α microperfused into the EA is shown in Fig. 2. It is apparent that the threshold dose for 8-ISO-PGF2α is ~1 μM and that 10⁻⁴ M is maximal. Ifetroban prevented any effect of 8-ISO-PGF2α on TGF. It is concluded that 8-ISO-PGF2α enhances TGF responses by activation of TP-R.

Basal TGF responses were dependent on dietary salt intake. TGF during LS was 9.0 ± 0.6 mmHg (n = 14), which was significantly (P < 0.01) greater than NS (7.8 ± 0.6 mmHg, n = 15) or HS (7.2 ± 0.3 mmHg, n = 15; Table 1). Maximal TGF was increased similarly by 8-ISO-PGF2α in each salt intake group (LS: +1.9 ± 0.4, P < 0.001; NS: +1.4 ± 0.3, P < 0.001; HS: +2.1 ± 0.5 mmHg, P < 0.001). Because the basal TGF responses were different in the various salt intakes, fractional comparisons were made in Fig. 3. At each level of salt intake, ifetroban prevented the effect of 8-ISO-PGF2α, similar to its effects on U-46,619-enhanced TGF (24). This shows that dietary salt intake does not determine the effects of 8-ISO-PGF2α on TGF responses and that responses to 8-ISO-PGF2α are dependent on TP-R at each level of salt intake.

During LH microperfusion of L-NMA, the effect of EA 8-ISO-PGF2α (10⁻⁴ M) was enhanced in NS and HS rats, but not in LS rats (LS 8-ISO: +19 ± 6% vs. LS L-NMA + 8-ISO: +30 ± 6%, n = 7 tubules, ns; NS 8-ISO: +17 ± 4% vs. NS + L-NMA +34 ± 4%, n = 9 tubules, P < 0.01; HS 8-ISO: +30 ± 3% vs. HS L-NMA + 8-ISO: +58 ± 6%, n = 10 tubules, P < 0.01; Fig. 4). These data suggest that 8-ISO-PGF2α enhances...
NO release within the JGA, which offsets its effects to increase TGF. This effect is absent in LS rats, which may be due to NO dysfunction associated with salt depletion (30). During NO blockade, the effect of 8-Iso-PGF2α appears to be salt dependent.

Series 4

The effect of an equipotent dose of U-46,619 (10⁻⁶ M) on TGF in various salt intakes is shown in Fig. 5. During inhibition of NO by L-NMA, the increases in TGF generated by activation of TP-R by U-46,619 were similar in LS, NS, and HS (LS U: +63 ± 6%; VS U + L-NMA: +51 ± 5%, n = 7 tubules, ns; NS U: 52 ± 5% vs. NS U + L-NMA: 46 ± 4%, n = 7 tubules, ns; HS U: 114 ± 19% vs. HS U + L-NMA: 74 ± 22%, n = 7 tubules, ns). This suggests that NO does not offset the effects of U-46,619 on TGF at any level of salt intake.

DISCUSSION

This study confirms previous findings that a stable TP-R agonist microperfused into the macula densa enhances TGF responses mediated by activation of TP-R. The main new findings of this study are 1) the stable isoprostane 8-Iso-PGF2α also enhances TGF responses via activation of TP-R albeit less potently than U-46,619; 2) whereas increasing dietary salt intake enhances mRNA expression for TP-R in glomeruli and kidney cortex and enhances TGF responses to U-46,619, there is no effect of dietary salt on TGF responses to 8-Iso-PGF2α; this is probably not due to activation of different receptors as the effects of 8-Iso-PGF2α are antagonized fully by ifetroban at each level of dietary salt; and 3) TGF enhancement with 8-Iso-PGF2α is blunted by macula densa-derived NO. This effect is salt dependent, as there was little effect in LS rats but increasing effects in NS and HS. Therefore, these studies demonstrate the TP-R agonist effect of 8-Iso-PGF2α in the JGA enhances TGF but also show that isoprostanes have important additional actions.

Treatment with exogenous 8-Iso PGF2α in various models shows that it is a potent vasoconstrictor in human mammary arteries (4), porcine pulmonary (14) and carotid (18) arteries, retinal microvasculature (15), and rat aorta (24), and in each study its effects were completely blocked by TP-R antagonists. Takahashi et al. (21) showed that intrarenal infusion of 8-Iso-PGF2α produced strong vasoconstriction affecting predominantly the afferent arteriole. The TP-R antagonist SQ-29,548 also blocked this action. The present study confirms these prior findings but shows a more modest response to exogenous 8-Iso-PGF2α. For example, U-46,619 microperfused into the EA at the maximal dose of 10⁻⁵ M enhanced TGF by 82 ± 7% (28), whereas the maximal effect of EA microperfusion of 8-Iso-PGF2α in this study enhanced TGF by only 21 ± 4%. Although the effect on TGF by 8-Iso-PGF2α was increased after blocking local NO, this difference in efficacy of the two agonists cannot be fully explained by the offsetting effects of NO. These effects may also be related to differences in agonist affinities or possibly to receptor subtypes. The evidence that the TGF response to 8-Iso-PGF2α is dependent on TP-R extends studies in the TP-R knockout mouse where 8-Iso-PGF2α was ineffective in altering platelet function (2).

TP-R expression in the kidney has been studied by radioligand binding, immunocytochemistry, and in situ hybridization. Glomeruli contain high-affinity binding sites for TP-R agonists (6, 33). Radioligand binding in mouse kidney shows TP-R expression in the glomeruli, vasculature, and medulla, corresponding to vasa recta. Immunocytochemical expression of TP-R using specific antibodies locates glomeruli, arterioles, and several tubule segments including proximal and distal nephron sites (3, 22). In situ hybridization techniques demonstrate binding over glomeruli, arterioles, and collecting ducts (1). Thus there is general agreement that TP-R are located in glomeruli and arterioles, but there remains uncertainty about exact sites of tubular expression and the presence of TP-R in the macula densa.

The mechanism of TP-R acting on TGF is primarily based on its role in transport signaling that regulates TGF. Transfection of cDNA for the TP-R gene into frog oocytes elicits expression of a chloride conductance (13). Microperfusion of U-46,619 into the loop of Henle of the rat enhances chloride reabsorption (29). Blockade of macula densa reabsorption of Na⁺ and Cl⁻ with luminal furosemide abolishes the effect of a low dose of U-46,619 on TGF. We concluded that TP-R engage TGF responses by enhancing the generation of the signal related to solute reabsorption at the macula densa, perhaps by enhancing basolateral chloride exit through a chloride channel. However, at high concentrations, luminal U-46,619 restores TGF responses during inhibition of macula densa reabsorption with furosemide. Therefore, we concluded that TP-R also enhances TGF via action of the afferent arteriole. This is also consistent with the distribution of TP-R to the vascular pole, and that U-46,619 constricts the isolated, perfused afferent arteriole of the rabbit by activation of TP-R (29).

The abundance of the mRNA for TP-R in outer cortical glomeruli or the renal cortex increases with salt intake. There is a parallel enhancement by HS of the TGF response to U-46,619. In contrast, there was no effect of salt intake on the TGF response to 8-Iso-PGF2α yet the effects of 8-Iso-PGF2α were abolished by ifetroban on all levels of salt intake. This suggests that the primary effects of 8-Iso-PGF2α on TGF are mediated by TP-R, which are modulated by a salt-dependent action. This may be by activation of macula densa NOS, as the TGF response to 8-Iso-PGF2α is enhanced by blockade of NOS and these effects of NOS inhibition were more pronounced at high levels of salt intake (30). Thus enhanced generation of NO during HS and NS may prevent the full effects of 8-Iso-PGF2α.
to enhance TGF. This is consistent with the finding that TGF responses normally are blunted by NO-derived from macula densa nNOS in nephrons of NS or HS rats, but not in those of LS rats (30). The absence of an effect of l-NMA during LS occurs despite enhanced nNOS expression. This may be due to reduced macula densa delivery and uptake of l-arginine, the substrate for NOS (31). Thus an enhancement of the generation of NO during activation of nNOS by HS and even during NS may provide an explanation for the modest effects of 8-Iso-PGF2α on TGF and the absence of an effect of dietary salt.

An alternate explanation of these results could be related to the presence of a distinct receptor for 8-Iso-PGF2α in the renal microvasculature. Fukunaga and colleagues (7, 8) suggested that isoprostanes may have distinct receptors in aortic smooth muscles and endothelial cells. They further showed that COS-7 cells transfected with TP-R had different binding affinities to 8-Iso-PGF2α and SQ-29,548, a specific TP-R antagonist (9). There is additional evidence that TP-R in platelets may be distinct from vascular receptors (17, 19). However, other studies failed to show distinct receptors in human (22) and rat (6) platelets. Subtypes of TP-R (α, β) have been described in human platelets and vascular tissue as splice variants (12) but have not been identified in rodents. The physiological importance of the TP-R isomers is not yet well understood. When both isomers were transfected into HEK cells and PGH2, the intermediate product of cyclooxygenase and TXA2 displayed full effects via the TPα isomser (23). 8-Iso-PGF2α was not tested. However, in immortalized human epithelial cells from the eye, which expressed only TPα, the agonist potency of U-46,619 was over 100-fold greater that 8-Iso-PGF2α (20). I observed a similar relationship in this study, which further suggests the differences in the action of 8-Iso-PGF2α might not be dependent on yet undiscovered rodent TP-R isomers. Finally, in this study the TP-R antagonist ifetroban completely blocked the actions of 8-Iso-PGF2α and U-46,619, data that support the effects are via a single TP-R.

The implication of these results is linked to the complex interaction of ROS and NO, especially during oxidative stress. Oxidative stress underlies many pathophysiological processes in the blood vessel wall including chronic hypertension, aging, diabetes mellitus renal insufficiency, ischemia-reperfusion injury, smoking, and dyslipidemia. Increased renal generation or excretion of isoprostanes has been found in spontaneously hypertensive rats and many models of ANG II-dependent and salt-dependent hypertension, as well as in normal subjects during smoking, human subjects with atherosclerosis, and poisoning with oxidants such as carbon tetrachloride (32). The present data show that isoprostanes may be implicated in the renal vasoconstrictive responses during oxidative stress via activation of TGF. Moreover, during oxidative stress, macula densa- and endothelium-derived NO activity is impaired and cannot therefore offset the contractile responses to the isoprostanes. This suggests that generation of isoprostanes by oxidative stress may have greater consequences on renal vasoconstriction, mediated by TGF. Exogenous 8-Iso-PGF2α increased TGF in this study, similar to that seen in models of oxidative stress (29, 32). Indeed, in the isolated, perfused afferent arteriolar preparation, TGF is increased by superoxide (16).

In conclusion, these studies demonstrate that 8-Iso-PGF2α potentiates TGF responses by activation of TP-R. However, unlike the classic TP receptor mimetic U-46,619, isoprostanes have additional, offsetting effects on TGF mediated via NO release.

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GRANTS

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