Cyclooxygenase-2 inhibition normalizes arterial blood pressure in CYP1A1-REN2 transgenic rats with inducible ANG II-dependent malignant hypertension


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Opay, Allison L., Cynthia R. Mouton, John J. Mullins, and Kenneth D. Mitchell. Cyclooxygenase-2 inhibition normalizes arterial blood pressure in CYP1A1-REN2 transgenic rats with inducible ANG II-dependent malignant hypertension. Am J Physiol Renal Physiol 291:F612–F618, 2006—The present study was performed to determine the effects of cyclooxygenase (COX)-1 and COX-2 inhibition on blood pressure and renal hemodynamics in transgenic rats with inducible malignant hypertension [strain name: TGR(Cyp1a1Ren2)]. Male Cyp1a1-Ren2 rats (n = 7) were fed a normal diet containing the aryl hydrocarbon, indole-3-carbinol (I3C; 0.3%), for 6–9 days to induce malignant hypertension. Mean arterial pressure (MAP) and renal hemodynamics were measured in pentobarbital sodium-anesthetized Cyp1a1-Ren2 rats during control conditions, following administration of the COX-2 inhibitor nimesulide (3 mg/kg iv), and following administration of the nonspecific COX inhibitor meclofenamate (5 mg/kg iv). Rats induced with I3C had higher MAP than noninduced rats (n = 7; 188 ± 6 vs. 136 ± 4 mmHg, P < 0.01). There was no difference in renal plasma flow (RPF) or glomerular filtration rate (GFR) between induced and noninduced rats. Nimesulide elicited a larger decrease in MAP in hypertensive rats (to 115 ± 4 mmHg, P < 0.05) and RPF (2.79 ± 0.14 ml/min·100 g−1·min−1, P < 0.05) in hypertensive rats but did not alter GFR or RPF in normotensive rats. Meclofenamate further decreased MAP in hypertensive rats (to 115 ± 10 mmHg, P < 0.05) but did not decrease MAP in normotensive rats. Meclofenamate did not alter GFR or RPF in either group. These findings demonstrate that COX-1- and COX-2-derived prostanoids play an important role in the regulation of renal hemodynamics and blood pressure in normotensive states (6, 11, 16, 40, 52). However, the role of COX-1 and COX-2 metabolites in hypertensive states remains uncertain.

ANG II is a potent vasoconstrictor that plays a significant role in the development of various forms of hypertension. It has generally been thought that cyclooxygenase-derived prostanoids play an important vasodilatory role in the vasculature to help counteract the effects of ANG II-induced vasoconstriction. However, several studies have demonstrated conflicting results regarding the relationship between ANG II and COX-derived prostanoids. ANG II has been shown to increase levels of prostacyclin and prostaglandin E2 in blood plasma (53, 58) as well as to stimulate the release of vasoconstrictor prostanoids such as thromboxane A2 (27, 28, 43, 53). However, uncertainty remains regarding the renal influence of COX-derived prostanoids in ANG II-dependent forms of hypertension, in particular, ANG II-dependent malignant hypertension.

Malignant hypertension is a severe form of hypertension characterized by rapidly increasing blood pressure, pressure diuresis and natriuresis, severe renal vasoconstriction and ischemia, activation of the renin-angiotensin system, microangiopathy, hemolytic anemia, and development of retinopathy (25, 60, 61). The vascular lesions of malignant hypertension in the kidney consist of myointimal proliferation and fibrinoid necrosis (25, 60, 61). Given the importance of the activation of the renin-angiotensin system to the development of malignant hypertension, and in light of evidence that ANG II stimulates the release of vasoconstrictor prostanoids, one could predict that ANG II-mediated enhancement of vasoconstrictor prostanoids contributes to the elevated arterial blood pressure and renal dysfunction in malignant hypertension.

Recently, a transgenic rat line [strain name TGR (Cyp1a1Ren2)] was created that allows the induction of vari-
ous degrees of ANG II-dependent hypertension (24). This transgenic rat line was generated by inserting the mouse Ren2 renin gene, fused to an 11.5-kb fragment of the cytochrome P-450 1a1 (Cyp1a1) promoter, into the genome of the Fischer 344 rat (24). Cyp1a1, which catalyzes the oxidation of a wide range of endogenous lipophilic compounds and xenobiotics (7, 14, 56), is not constitutively expressed. However, Cyp1a1 is highly inducible on exposure to various aryl hydrocarbons such as indole-3-carbonyl (I3C) (7, 14, 15, 23, 30, 45, 56). Induction of Cyp1a1 is mediated by the aryl hydrocarbon receptor, which is a basic helix-loop-helix transcription factor that binds to specific DNA elements in the Cyp1a1 promoter (7, 56). Rats transgenic for the Cyp1a1-Ren2 construct do not constitutively express the Ren2 renin gene. The Ren2 gene is expressed, primarily in the liver, only after induction of the Cyp1a1 promoter by aryl hydrocarbons such as I3C (24). Essentially, induction of the Cyp1a1 promoter by I3C is used to drive hepatic expression of the Ren2 renin gene. In this transgenic rat model, induction of the Cyp1a1 promoter by dietary administration of I3C results in a fixed level of expression of the Ren2 renin gene and in the development of ANG II-dependent hypertension (24). At a dose of 0.3% (wt/wt), dietary I3C induces malignant hypertension, characterized by loss of body weight, polyuria, polydipsia, lethargy, and piloerection. Therefore, this model allows the induction of ANG II-dependent malignant hypertension using a benign and naturally occurring dietary supplement without the need for surgical intervention, dietary salt manipulation, or the administration of steroids.

The present study was performed to determine the effects of COX-2 and COX-1 inhibition on blood pressure and renal hemodynamics during the development phase (6–9 days) of malignant hypertension, before the appearance of severe renal morphological changes that occur after more prolonged (14 days) induction of the Cyp1a1-Ren2 transgene (24).

METHODS

The experimental procedures in this study conform to National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Tulane University Health Sciences Center. All animals used in this study were bred at Tulane University School of Medicine from stock animals supplied from the University of Edinburgh (Edinburgh, UK). Experiments were performed on two groups of 9- to 12-wk-old adult male Cyp1a1-Ren2 transgenic rats (TGR). One group (n = 7) was fed a diet of normal rat food containing the aryl hydrocarbon, I3C (0.3% wt/wt; diet TD 00554, Harlan-Teklad, Madison, WI), for 6–9 days to induce malignant hypertension (35, 44). A second group (n = 7) of male Cyp1a1-Ren2 transgenic rats was fed a diet of normal rat food (diet TD 90229, Harlan-Teklad), which did not contain I3C, and served as noninduced normotensive controls. Both groups of rats had unrestricted access to food and tap water until the day of the experiment.

Acute renal clearance experiments were performed on all rats. The animals were anesthetized with pentobarbital sodium (50 mg/kg ip) and placed on a thermostatically controlled surgical table to maintain body temperature at 37°C. A tracheostomy was performed, and the rats were allowed to breathe room air enriched with 100% oxygen as described previously (34, 36, 38). The left external jugular vein was cannulated to allow intravenous infusion of solutions and additional doses of anesthetic. The rats were infusé intravenously, at a rate of 1.2 ml/h, with isotonic saline containing 6% albumin (bovine, Calbiochem, San Diego, CA) during the surgery and thereafter with isotonic saline containing 1% albumin, 7.5% polyfructosan (Inutest, Lintz, Austria), and 1.5% para-aminobenzoic acid (PAH; Merck, Whitehouse Station, NJ). The left carotid artery was cannulated to allow monitoring of systemic arterial pressure. Mean arterial pressure (MAP) was measured with a Statham pressure transducer (model P23 DC) and recorded with a computerized data-acquisition system (MP100 system; BIOPAC Systems, Santa Barbara, CA) with the AcqKnowledge software package (version 3.2.4, BIOPAC). A suprapubic incision was made, and the bladder was exposed by blunt dissection through the abdominal wall. The bladder was catheterized to allow timed collections of urine. Following the surgery, the animals were allowed to stabilize for 1 h before the initiation of the experimental protocol.

The experimental protocol consisted of two 30-min control urine collections, after which the rats received a single intravenous bolus of the selective COX-2 inhibitor nimesulide (3 mg/kg iv; Sigma, St. Louis, MO). This dose of nimesulide has been previously demonstrated to elicit selective blockade of COX-2 (3, 4, 49). The rats were allowed to stabilize for 30 min, and two additional 30-min urine collections were then obtained. The animals were then given an intravenous bolus of the nonselective COX inhibitor mefenamic acid (5 mg/kg iv; Sigma). After a 30-min stabilization period, two additional 30-min urine collections were obtained. The rate of the intravenous fluid administration remained constant at 1.2 ml/h throughout the experiment. Arterial blood samples (~300 μl) were collected after the second, fourth, and sixth urine collections to allow determination of whole kidney hemodynamics and excretory function. At the end of each experiment, both kidneys were removed, decapsulated, blotted dry, and weighed.

Urine volume was determined gravimetrically. Inulin and PAH concentrations in both urine and plasma were measured by standard spectrophotometry. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were estimated from the clearance of inulin and PAH, respectively. Plasma and urine sodium and potassium concentrations were measured by flame photometry. Renal blood flow was calculated as RPF/(1−hematocrit). Renal vascular resistance (RVR) was determined from the quotient of MAP and calculated renal blood flow.

Statistical analyses were performed using one-way ANOVA, one-way repeated-measures ANOVA, and two-way ANOVA with one factor repeated followed by Tukey’s test when appropriate. Statistical significance was defined as P < 0.05. All data are expressed as means ± SE.

RESULTS

Chronic administration of 0.3% I3C in Cyp1a1-Ren2 rats (n = 7) resulted in the development of severe hypertension (188 ± 6 vs. 136 ± 4 mmHg, P < 0.01; Fig. 1). The development of hypertension was associated with a 13% reduction in body weight (from 285 ± 8 to 248 ± 8 g, P < 0.01), and rats induced with I3C exhibited reduced body weight compared with noninduced rats (248 ± 8 vs. 318 ± 10 g, P < 0.01). In addition, the hypertensive rats demonstrated severe lethargy, polyuria, piloerection, and adoption of a hunched posture, which are clinical manifestations of malignant hypertension in the rat (24, 25, 60, 61). These observations confirm that chronic dietary administration of 0.3% I3C induces malignant hypertension in Cyp1a1-Ren2 transgenic rats (24, 25, 35, 44).

MAP responses to the intravenous administration of the COX-2 inhibitor nimesulide and the nonselective COX inhibitor mefenamic acid are summarized in Fig. 1. Intravenous bolus administration of nimesulide elicited a decrease in MAP in both induced and noninduced Cyp1a1-Ren2 rats. However, the decrease in MAP was greater in hypertensive rats than in normotensive rats (188 ± 6 to 140 ± 8 vs. 136 ± 4 to 113 ±
8 mmHg, respectively, $P < 0.01$ in both cases). The intravenous administration of meclofenamate induced a further decrease in MAP in hypertensive Cyp1a1-Ren2 rats (140 to 115 mmHg, $P < 0.05$) but did not decrease MAP in normotensive rats.

Figures 2 and 3 illustrate GFR and RPF responses to intravenous administration of nimesulide and meclofenamate. As shown in Figs. 2 and 3, there was no difference in GFR or RPF between induced and noninduced Cyp1a1-Ren2 rats. However, the administration of nimesulide decreased GFR (0.9 ± 0.13 to 0.44 ± 0.05 ml·min$^{-1}$·g$^{-1}$, $P < 0.05$) and RPF (2.79 ± 0.27 to 1.35 ± 0.14 ml·min$^{-1}$·g$^{-1}$, $P < 0.05$) in hypertensive rats but did not alter GFR or RPF (1.08 ± 0.27 vs. 0.84 ± 0.06 and 3.04 ± 0.18 vs. 3.07 ± 0.36 ml·min$^{-1}$·g$^{-1}$, respectively, not significant) in normotensive rats. The administration of meclofenamate did not alter GFR or RPF in either normotensive or hypertensive rats.

As shown in Fig. 4, RVR in Cyp1a1-Ren2 rats induced with I3C was significantly higher than in the noninduced normotensive rats (34.19 ± 3.25 vs. 24.13 ± 1.40 mmHg·ml$^{-1}$·min·g, $P < 0.05$). Figure 4 also illustrates the effects of intravenous administration of nimesulide and meclofenamate on RVR in hypertensive and normotensive rats. Nimesulide increased RVR in hypertensive rats (34.19 ± 3.25 to 60.31 ± 7.45 mmHg·ml$^{-1}$·min·g, $P < 0.05$) but did not alter RVR in normotensive rats. The subsequent administration of meclofenamate had no effect on RVR in either group.

The effects of intravenous administration of nimesulide and meclofenamate on urine flow and urinary sodium excretion in hypertensive and normotensive Cyp1a1-Ren2 rats are summarized in Figs. 5 and 6. Initially, there was no difference in urine flow or urinary sodium excretion between induced and noninduced rats. However, as shown in Fig. 5, the administration of nimesulide decreased urine flow in both hypertensive and normotensive rats (31.22 ± 3.87 to 13.45 ± 1.57 and 19.81 ± 3.00 to 10.21 ± 2.05 μl/min, respectively, $P < 0.05$ in both conditions).
cases). The subsequent administration of meclofenamate had no effect on urine flow in either group. As shown in Fig. 6, administration of nimesulide elicited a decrease in urinary sodium excretion in both hypertensive (1.96 ± 0.37 to 0.50 ± 0.07 μmol/min, P < 0.05) and normotensive rats (1.67 ± 0.44 to 0.50 ± 0.07 μmol/min, P < 0.05). Subsequent administration of meclofenamate did not further alter urinary sodium excretion in either group.

**DISCUSSION**

The present study examined the effects of COX-1 and COX-2 inhibition on blood pressure and renal hemodynamics in Cyp1a1-Ren2 transgenic rats with inducible ANG II-dependent malignant hypertension. Malignant hypertension is a form of severe hypertension characterized by fibrinoid necrosis of arterioles and vascular damage in many tissues, including the kidney (25, 60, 61). The Cyp1a1-Ren2 transgenic line allows the induction of ANG II-dependent malignant hypertension (24). This transgenic line was generated by inserting a mouse Ren2 renin gene into the genome of the Fischer 344 rat (24). Extrarenal Ren2 renin gene expression is induced by the administration of the aryl hydrocarbon I3C, resulting in the development of ANG II-dependent malignant hypertension (24). Such induction of Ren2 renin gene expression using a benign and naturally occurring dietary supplement leads to the development of ANG II-dependent hypertension as a result of increased renin gene expression and plasma renin levels, which are not subject to normal physiological feedback control mechanisms. In the present study, induction of the Ren2 renin gene by dietary administration of 0.3% I3C for 6–9 days resulted in the development of hypertension. As described previously (35, 44), the hypertension was associated with a marked decrease in body weight, and the rats exhibited extreme lethargy, assumption of a hunched posture, and piloerection, which are clinical manifestations of malignant hypertension in the rat (25, 60, 61). Although MAP was markedly increased in hypertensive Cyp1a1-Ren2 rats, GFR and RPF in these rats were not significantly different from corresponding values observed in the noninduced normotensive Cyp1a1-Ren2 rats. This observation that both GFR and RPF were maintained in the normal range indicates that preglomerular vascular resistance is markedly elevated in Cyp1a1-Ren2 transgenic rats with malignant hypertension. The present data do not, however, allow determination of the relative contribution of the direct preglomerular vasoconstrictor actions of ANG II and the autoregulatory response to the increase in arterial blood pressure, which allows maintenance of normal renal hemodynamic function in these rats (2, 5, 9, 36, 37). Regardless of the mechanism, it is clear that Cyp1a1-Ren2 rats with malignant hypertension exhibit markedly increased RVR and that the ability of the preglomerular vasculature to prevent the transmission of the systemic hypertension to the glomerular capillaries is intact at this stage of the pathogenesis of malignant hypertension.

The COX-2 selectivity of nimesulide at the dose used in this study has been demonstrated in vitro (3, 4, 49). In general, nimesulide has been shown to be between 5- and 16-fold selective for COX-2 (19, 54, 55). In the present study, the administration of nimesulide decreased MAP, indicating that COX-2-derived vasoconstrictor metabolites play a role in the development of malignant hypertension in these rats. In contrast, previous experiments performed by Qi et al. (47) demonstrated that COX-2 inhibition enhanced and prolonged the peripheral vasoconstrictor effects of acute administration of ANG II in anesthetized mice. Although the reason for the apparent discrepancy between our findings and those of Qi et al. remains unclear, it could be due to differences in species differences or to differences in the models of ANG II-dependent hypertension used. Indeed, Qi et al. evaluated the effects of COX-2 blockade on the blood pressure responses to acute intravenous administration of hypertensive doses of ANG II in anesthetized mice, whereas in the present study, the effects of COX-2 inhibition were evaluated in rats exposed to prolonged (6–9 days) induction of Ren2 renin gene expression and thus to a prolonged period of elevated ANG II generation. In this regard, recent studies have indicated that prolonged ANG II exposure increases glomerular PGE2 production and upregulates glomerular COX-2 expression (22) and that ANG II induces expression of COX-2 in cultured vascular smooth muscle cells and in human endothelial cells (29, 42). Similarly, it has been demonstrated that chronic administration of ANG II stimulates thromboxane B2 (TxB2) synthesis as evidenced by increased

![Graph](image-url)
urinary excretion of TxB₂ in ANG II-dependent hypertension (31). Additionally, thromboxane synthesis or receptor antagonists have been shown to reduce the systemic and renal vasoconstriction produced by short-term ANG II infusions as well as to reduce blood pressure in rats receiving prolonged ANG II infusions (31). In view of this, it is possible that in the present study, the prolonged exposure to increased ANG II levels consequent to chronic induction of Ren2 renin gene expression resulted in an increase in vasoconstrictor thromboxane synthesis secondary to ANG II-induced upregulation of extrarenal COX-2 expression. In contrast, short-term administration of ANG II, such as employed by Qi et al. (47), may be of insufficient duration for such an effect to be observed. In this regard, additional studies to determine whether the development of malignant hypertension in Cyp1a1-Ren2 rats is accompanied by changes in the renal and/or peripheral vascular COX-1 and COX-2 expressions would be instructive. Whatever the mechanism, however, the present findings clearly indicate that Cyp1a1-Ren2 rats with inducible ANG II-dependent malignant hypertension exhibit pronounced reductions in arterial blood pressure following acute blockade of COX-2, indicating that vasoconstrictor prostanoids are the major type of eicosanoid generated by extrarenal COX-2 in ANG II-dependent malignant hypertension.

In the present study, administration of nimesulide decreased GFR and RPF in hypertensive Cyp1a1-Ren2 rats. Although the decreases in GFR and RPF likely occurred, in part, as a consequence of the associated reduction in MAP, the data show that COX-2-derived vasodilatory metabolites buffer the vasoconstrictor response to ANG II in the kidney and play an important role in the maintenance of RPF and GFR following induction of malignant hypertension in Cyp1a1-Ren2 rats. In normotensive Cyp1a1-Ren2 rats, the administration of nimesulide decreased MAP but had no effect on GFR or RPF. This indicates that COX-2 metabolites play a systemic regulatory hemodynamic role but have no appreciable influence on renal hemodynamics in normotensive Cyp1a1-Ren2 rats.

The nonselective COX inhibitor meclofenamate elicited a further decrease in MAP in hypertensive but not in normotensive Cyp1a1-Ren2 rats. These data suggest that COX-1 metabolites also play a role in the development of malignant hypertension in Cyp1a1-Ren2 rats but do not play a regulatory role in the maintenance of blood pressure in normotensive rats. These results are consistent with those obtained by Qi et al. (47) and suggest that COX-1-derived eicosanoids help sustain the pressor effects of ANG II. In the present study, the administration of meclofenamate did not alter GFR or RPF in either hypertensive or normotensive Cyp1a1-Ren2 rats. These data indicate that COX-1 metabolites are not substantively involved in the regulation of renal hemodynamics in either hypertensive or normotensive Cyp1a1-Ren2 rats. Nevertheless, additional studies utilizing selective COX-1 inhibitors are required to draw more definitive conclusions regarding the role of COX-1-derived prostaglandins in regulating arterial blood pressure and renal hemodynamics in Cyp1a1-Ren2 rats with ANG II-dependent malignant hypertension.

Normal vascular tone depends on the interaction between vasoconstrictors (e.g., ANG II, catecholamines, thromboxane, leukotrienes, and endothelin) and vasodilators (e.g., kinins, prostaglandins, and nitric oxide). It has been reported that ANG II infusion results in increased prostaglandin and thromboxane generation (26), but the role of COX metabolites in mediating vascular responses to ANG II is complex. A variety of bioactive prostanoids can be formed from arachidonic acid, including PGE₂, PGl₂, PGF₂α, PGD₂, and thromboxane A₂. These prostanoids can have many different effects on cardiovascular and renal function by acting as either vasodilators or vasoconstrictors (47). For example, PGl₂ acts as a vasodilator, TXA₂ acts as a vasoconstrictor, and PGE₂ can act as either a vasodilator or a vasoconstrictor depending on the type of receptor with which it interacts (1, 47, 57). In the kidney, it has been shown that PGl₂ primarily acts as a vasodilator to protect the kidney from excessive vasoconstriction (46). Studies have shown that activation of EP₂ receptors mediates PGE₂-induced vasodilation in the rat kidney and that the EP₂ receptor is the major PGE₂ receptor in pregglomerular vascular smooth muscle cells (46). EP₁ and EP₄ receptors are also widely distributed throughout the body (39). A study in which an EP₁ agonist was injected into vascular smooth muscle and resulted in increased MAP suggests PGE₂ elicits a contractile response in the systemic vasculature via the EP₁ receptor (39). Contractile thromboxane receptors are also expressed on systemic blood vessels and renal microvessels, glomeruli, mesangial cells, thick ascending limbs of the loops of Henle, and collecting ducts (26). In light of this evidence, it appears that the differential distribution of vasoconstrictor and vasodilator prostanoid receptors as well as differential production of vasodilator and vasoconstrictor prostaglandins in the systemic and renal vasculature may be responsible for the opposite effects of COX-2 inhibition on the systemic and renal circulations that were observed in this study. However, further studies are required to address this issue.

Several studies have supported a role for constrictor prostanoids in the development of ANG II-dependent hypertension (33, 43). TXA₂ is the biologically active precursor of TxB₂ and produces vasoconstriction and platelet aggregation (33). It has been shown that urinary TxB₂ excretion and the release of TxB₂ from vascular and renal cortical tissues in vitro are increased in rats with severe ANG II salt hypertension and that treatment with a TXA₂ receptor blocker lowers blood pressure in ANG II salt-hypertensive rats (33). Although COX-1 is generally associated with the synthesis of thromboxane (TXA₂) (10), it has been shown that TXA₂ is also a product of the COX-2 pathway (4). In view of this, and given the evidence that ANG II upregulates expression of COX-2, it is possible that increased peripheral COX-2 production of TXA₂ contributes to the elevated arterial blood pressure in the ANG II-dependent model of hypertension used in the present study. An additional possibility is that metabolism of 20-HETE to vasoconstrictor prostanoids by COX-2 located on endothelial cells of the peripheral vasculature contributed to the elevated arterial blood pressure in the hypertensive Cyp1a1-Ren2 rats. In this regard, 20-HETE formation by Cyp4A enzymes in vascular smooth muscle cells has been shown to be stimulated by ANG II (50). In addition, 20-HETE formation and Cyp4A expression have been shown to be increased in various models of experimental hypertension (8, 50). Furthermore, it has been demonstrated that 20-HETE is metabolized by COX in endothelial cells to the vasoconstrictor prostanoids TxB₂, 20-hydroxy-PGG₂, and 20-hydroxy-PGH₂ and that endothelium-dependent vasoconstriction by 20-HETE is inhibited by the COX inhibitor diclofenac (48, 50). However, further studies are required to
determine the potential contribution of COX-2-dependent generation of vasoconstrictor prostanoids from 20-HETE to the pathogenesis of ANG II-dependent malignant hypertension in Cyp1a1-Ren2 rats.

In summary, the present findings demonstrate that COX-1 and COX-2-derived prostanoids contribute importantly to the development of malignant hypertension in Cyp1a1-Ren2 transgenic rats. The elevated arterial blood pressure in Cyp1a1-Ren2 transgenic rats with malignant hypertension is produced, at least in part, by vasoconstrictor prostanoids generated by both the COX-1 and COX-2 enzymatic pathways. These data also indicate that COX-2-derived prostanoids play a regulatory role in the maintenance of arterial blood pressure in normotensive Cyp1a1-Ren2 rats. Furthermore, COX-2-derived vasodilatory metabolites play an important role in the maintenance of RPF and GFR following induction of malignant hypertension in Cyp1a1-Ren2 rats. Such maintained renoprotective effects of COX-2-derived vasodilatory metabolites act to prevent excessive vasoconstriction and contribute to the maintenance of renal hemodynamics in Cyp1a1-Ren2 transgenic rats with malignant hypertension.

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REFERENCES


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