A role for the thromboxane receptor in L-NAME hypertension

Helene Francois, Natalia Makanova, Philip Ruiz, Jonathan Ellison, Lan Mao, Howard A. Rockman, and Thomas M. Coffman

Divisions of 1Nephrology and 2Cardiology, Department of Medicine, Duke University and Durham Veterans Affairs Medical Centers, Durham, North Carolina; and 3Department of Pathology, University of Miami, Miami, Florida

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Francois H, Makanova N, Ruiz P, Ellison J, Mao L, Rockman HA, Coffman TM. A role for the thromboxane receptor in L-NAME hypertension. Am J Physiol Renal Physiol 295: F1096–F1102, 2008—Actions of the lipid mediator thromboxane (Tx) A2 acting through the TP receptor contribute to the pathogenesis of cardiovascular disease. To further explore the role of TxA2 in hypertension, we examined the consequences of deficiency of the TP receptor on the course of hypertension associated with endothelial dysfunction and salt sensitivity. To this end, the nitric oxide synthase inhibitor N\textsuperscript{\textast}\text{nito} L-arginine methyl ester (l-NAME) was administered to TP-deficient (Tp\textsuperscript{--/--}) and wild-type (Tp\textsuperscript{+/+}) control mice in drinking water for 21 wk along with a high-salt (HS; 6% NaCl) diet. Administration of l-NAME increased urinary excretion of TXB\textsubscript{2} to a similar extent in both Tp\textsuperscript{+/+} and Tp\textsuperscript{--/--} animals. l-NAME also caused significant and sustained elevations in blood pressure that reached a maximum between weeks 3 and 6. However, the severity of hypertension was attenuated in the Tp\textsuperscript{--/--} mice throughout the study period (P < 0.001). At the end of the study, the wild-type mice developed significant cardiac hypertrophy (23.6 ± 2% increase in heart-to-body weight ratio). The severity of cardiac hypertrophy was attenuated in the TP-deficient group (11.1 ± 2.6%; P < 0.05). In contrast, kidney hypertrophy was exaggerated in the Tp\textsuperscript{--/--} mice compared with controls (37.1 ± 5.4 vs. 12.3 ± 2.3%; P < 0.01). Moreover, the severity of glomerulosclerosis, tubule vacuolization, and interstitial chronic inflammation was also enhanced in the Tp\textsuperscript{--/--} group (P < 0.01). Thus, in l-NAME hypertension, TP receptors contribute to elevated blood pressure and cardiac hypertrophy. In this model, TP receptors also provided unexpected protection against kidney injury.

MATERIALS AND METHODS

Animal Model

TP receptor-deficient (Tp\textsuperscript{--/--}) mice were generated as previously described (37). The Tp mutation was backcrossed onto the C57BL/6 inbred genetic background for more than 12 generations using mice that were purchased from the Jackson Laboratory (Bar Harbor, ME). Aged matched male C57BL/6 Tp\textsuperscript{--/--} and wild-type (Tp\textsuperscript{+/+}) littermates were used for experiments. Animals were bred and maintained in the animal facility of the Durham VA Medical Center. The experimental procedures were approved by the Animal Care and Use Committees of the Durham VA and Duke University Medical Centers.

l-NAME Hypertension

To induce chronic hypertension, l-NAME (Sigma Chemicals, St. Louis, MO) was administered to mice in drinking water (50 mg·kg\textsuperscript{-1}·day\textsuperscript{-1} from week 1 to week 17 and then 100 mg·kg\textsuperscript{-1}·day\textsuperscript{-1} from week 17 until week 21). To maximize the severity of hypertension, animals were simultaneously administered a high-salt (HS; 6% wt/wt NaCl) chow (Harlan Teklad).

Physiological Studies

Systolic blood pressure measurements in conscious mice. Systolic blood pressures were measured in conscious mice using a computerized tail-cuff system (Hatters Instruments, Cary, NC) (12). After 2 wk of daily training, blood pressures were recorded at baseline for 2 wk and then 5 days each week for 20 wk. For each animal, the daily blood pressures were averaged to produce a single weekly measurement.

Transcardiac occlusion in conscious mice. After 20 wk of l-NAME+HS treatment, transthoracic echocardiography was performed in conscious mice as previously described (12). The following parameters were measured: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), and the fractional shortening (FS) was calculated as (LVEDD – LVESD)/LVEDD. The operator who performed and measured the echocardiograms was masked to the genotype of the experimental groups. All

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measurements were made manually and the average of three beats was recorded for each parameter.

Food and water intake, and urinary sodium excretion. To determine whether the TP mutation affected food and water intake, urinary volume, or sodium excretion, wild-type and TP-deficient mice were housed in metabolic cages where input and outputs could be carefully monitored. Food and water intake were determined daily. Urine volume was measured in tared containers. Urine sodium concentration was measured with a flame photometer.

Contribution of AT1 angiotensin receptor activation to blood pressure elevation in l-NAME hypertension. In a separate experiment, groups of Tp+/+ (n = 13) and Tp−/− (n = 11) mice were treated with l-NAME and HS diet. After 5 wk, the specific AT1 receptor blocker losartan (20 mg·kg−1·day−1) was administered in the drinking water for an additional 14 days. Blood pressures were measured throughout the 8 wk by tail-cuff manometry.

Measurements of urinary excretion of albumin, TxB2, and 8-isoprostane. To collect urine specimens, mice were individually housed in specially designed metabolic cages that accommodate individual mice (12). Twenty-four-hour urines were collected before and 3, 6, and 20 wk after the l-NAME was initiated. Urine was clarified by 15 min of centrifugation (14,000 rpm) and then stored at −80°C. Albumin concentrations were determined by ELISA (Albuwell, Exocell) (12). Concentrations of thromboxane B2 (TxB2) were measured using an ELISA assay in fresh urine samples (Cayman Chemical, Ann Arbor, MD) (12). For measurement of 8-isoprostanes, urine was collected and stored in the presence of 0.005% BHT at −80°C. Concentrations of 8-isoprostane were measured by ELISA (Cayman Chemical). Urinary creatinine concentration was determined using the alkaline picrate method (The Creatinine Companion, Exocell) (12). Results are expressed as urinary albumin/creatinine (A/C), TxB2/creatinine (TxB2/C), and 8-isop/C ratios.

Creatinine clearance. To estimate glomerular filtration rate (GFR), we measured 24-h creatinine clearance in groups of wild-type (n = 7) and TP-deficient mice (n = 7) after 14 wk of l-NAME and HS diet. Urine samples were collected over 24 h in metabolic cages as above. Plasma creatinine was measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) (35). Because of excellent correlation between urinary creatinine concentrations measured by LC-MS/MS and Jaffe’s reaction (35), concentrations of creatinine in urine were measured by alkaline picric acid method using a kit (Exocell, Philadelphia, PA). Creatinine clearance in microliters per minute was calculated as: urine creatinine (µg/µl) × urine volume (µl/day)/plasma creatinine (µg/µl) × 1,440 min/day.

Analysis of tissue pathology. After 21 wk of study, mice were euthanized and their organs and left kidneys were excised and immediately weighed. Heart-to-body weight ratio (H/B) and left kidney-to-body weight ratios were determined in four groups of mice: the wild-type and TP-deficient mice treated with l-NAME and HS diet constituting the main experimental groups, and two additional groups of age-matched wild-type and TP-deficient mice fed a normal diet without l-NAME. To provide an indication of the effect of the l-NAME and HS diet, the data are presented as percent difference between control and l-NAME + HS groups for each genotype.

Tissues were then fixed in 10% formalin and embedded in paraffin. Four-micrometer-thick sections were prepared and stained with hematoxylin and eosin or Masson’s trichrome to quantify extracellular matrix deposition. A pathologist (PR) who was masked to the experimental groups analyzed the slides and graded the extent and severity of the pathological lesions.

Statistical analysis. Data are expressed as means ± SE. Statistical significance was assessed using one- and two-way ANOVA, paired or unpaired Student’s t-test for parametric variables, and Mann-Whitney U-test for nonparametric variables.
after initiation of L-NAME and HS diet, systolic blood pressures increased in the $T_\text{p}^{+/+}$ mice from 118 ± 1 to 138 ± 2 mmHg ($P < 0.001$). During the same period, blood pressures in the TP-deficient mice increased by a similar magnitude, from 118 ± 2 to 137 ± 2 mmHg ($P < 0.001$). However, as shown in Fig. 2, the blood pressures in the two groups began to diverge after week 2. In the wild-type group, pressures continued to increase and reached a maximum between 3 and 6 wk. By contrast, the severity of hypertension was significantly blunted in the TP-deficient animals and blood pressures remained consistently lower in the $T_\text{p}^{--}$ compared with wild-type mice throughout the study period ($P < 0.001$ by ANOVA). Because the levels of blood pressure appeared to be falling in both groups at week 16, the L-NAME dose was increased from 50 to 100 mg·kg$^{-1}$·day$^{-1}$. This led to a modest but significant increase in systolic blood pressure in both wild-type (from 145 ± 3 to 151 ± 3 mmHg; $P < 0.01$) and $T_\text{p}^{--}$ mice (from 137 ± 3 to 144 ± 3 mmHg; $P < 0.01$). However, the difference in blood pressure between the two experimental groups was maintained throughout the remainder of the experiment. Thus, the absence of TP receptors significantly attenuated the extent of L-NAME hypertension.

**Food and Water Intake, Urine Sodium Excretion, and Kidney Function**

To examine whether the $T_\text{p}$ mutation might affect food intake, drinking, or urinary sodium excretion, additional groups of wild-type ($n = 10$) and TP-deficient mice ($n = 10$) were given either normal (0.4% NaCl) diet or L-NAME + HS diets while their blood pressures were measured. After 3 wk, they were placed in metabolic cages where food and water intake were monitored and urine was collected. As shown in Table 1, compared with the normal diet, water intake and urine volume were significantly increased in mice of both genotypes after 3 wk of L-NAME + HS treatment. However, there were no significant differences in body weight, food and water intake, or urine volume between genotypes before or after 3-wk L-NAME+HS treatment.

To assess the consequences of the absence of the TP receptor on kidney function, we measured creatinine clearance as an estimate of GFR in groups of TP-deficient and wild-type mice after 14 wk of L-NAME and the HS diet. The average creatinine clearance in the wild-type mice treated with L-NAME and HS (460 ± 101 μl/min) was within the GFR range for conscious normal mice reported previously by others (32). Creatinine clearances of the TP-deficient mice receiving L-NAME and HS (454 ± 58 μl/min) were not significantly different from the wild-type group. Plasma creatinine concentrations were also similar between the groups (0.085 ± 0.007 mg/dl in the $T_\text{p}^{+/+}$ group vs. 0.096 ± 0.009 mg/dl in the $T_\text{p}^{--}$ group). Thus, GFR is well preserved in mice treated for more than 3 mo with L-NAME and HS diet. Moreover, the attenuated hypertension seen in the TP-deficient mice cannot be explained by differences in renal function.

**Evaluation of Cardiac Hypertrophy and Function During L-NAME Hypertension**

To determine whether the TP receptor might influence cardiac responses in L-NAME hypertension, we performed trans-thoracic echocardiographies in conscious mice to assess their cardiac systolic function. After 20 wk of L-NAME treatment, FS was measured as an index of cardiac systolic function in both $T_\text{p}^{+/+}$ and $T_\text{p}^{--}$ mice. FS was in the normal range in both wild-type (0.646 ± 0.028) and TP-deficient (0.65 ± 0.039) mice, and there was no difference in FS between the groups. Cardiac dimensions were also similar between the groups. For example, LVESD were 3.0 ± 0.1 and 3.2 ± 0.1 mm in the $T_\text{p}^{+/+}$ and $T_\text{p}^{--}$ mice, respectively ($P = NS$). Accordingly, the difference in blood pressures between the two groups observed during the chronic L-NAME treatment cannot be explained by differences in cardiac systolic function.

All of the animals survived the entire study period and at the end of 21 wk of L-NAME administration, we assessed the extent of cardiac hypertrophy. As shown in Fig. 3, we observed significant cardiac hypertrophy in wild-type animals compared with untreated, nonhypertensive controls with a 23.6 ± 4.8% increase in the H/B weight ratio compared with untreated animals ($P < 0.01$). The $T_\text{p}^{--}$ animals treated with L-NAME also developed modest cardiac hypertrophy (11.1 ± 2.6% increase in H/B wt ratio compared with untreated $T_\text{p}^{--}$ mice). However, compared with the wild-type group treated with L-NAME, the extent of cardiac hypertrophy was significantly attenuated in the L-NAME-treated $T_\text{p}^{--}$ mice ($P < 0.05$).

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### Table 1. Body weight, intake, urine volume, and urinary sodium excretion $T_\text{p}^{+/+}$ and $T_\text{p}^{--}$ mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$T_\text{p}^{+/+}$</th>
<th>$T_\text{p}^{--}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>25.3 ± 0.5</td>
<td>24.9 ± 0.4</td>
</tr>
<tr>
<td>Food intake, g/day</td>
<td>1.78 ± 0.16</td>
<td>1.83 ± 0.20</td>
</tr>
<tr>
<td>Water intake, ml/day</td>
<td>3.10 ± 0.27</td>
<td>3.40 ± 0.26</td>
</tr>
<tr>
<td>Urine volume, ml/day</td>
<td>5.15 ± 0.51</td>
<td>5.44 ± 0.30</td>
</tr>
<tr>
<td>$U_{\text{Na}V}$, μmol/day</td>
<td>3.88 ± 0.388</td>
<td>3.39 ± 0.198</td>
</tr>
</tbody>
</table>

Values are means ± SE. NS, normal-salt (0.4% NaCl) diet; HS+L-NAME, high-salt (6% NaCl) diet. *$P < 0.05$ vs. NS; †$P < 0.01$ vs. NS; ‡$P < 0.001$ vs. NS.
response was attenuated in the compared with the untreated sure increasing from 127 creatinine in the TP-deficient animals (albumin excretion was 44.4 min/mg creatinine) and P t treatment (P < 0.01). However, AT1 receptor blockade had no effect on blood pressures in the basal state. Several studies showed that blockers or genetic deficiency of TP receptors do not affect blood pressure in the basal state, several studies showed that block-

Kidney Injury in l-NAME Hypertension

As one assessment of functional alterations in the kidney, we measured albumin excretion in 24-h urine samples collected from wild-type and TP-deficient mice throughout the study period. At baseline, the levels of albumin excretion were normal and very similar in the wild-type (40.3 ± 7.2 µg albumin/mg creatinine) and Tp-/- mice (41.8 ± 8.5 µg albumin/mg creatinine; P = NS). Despite the development of hypertension in both groups across the 21-wk study, albumin excretion did not increase significantly with time. At week 20, albumin excretion was 44.4 ± 6.8 µg albumin/mg creatinine in the wild-type group compared with 43 ± 6.3 µg albumin/mg creatinine in the TP-deficient animals (P = NS).

As shown in Fig. 3 and as previously reported in this model (33, 40), wild-type mice developed significant left kidney hypertrophy after receiving l-NAME for 21 wk exhibiting a 11% increase in left kidney-to-body weight ratio from 6.0 ± 0.2 to 6.7 ± 0.2 compared with untreated wild-type mice (mg/g; P < 0.05). The extent of renal hypertrophy was significantly exaggerated in the TP-deficient mice which experienced a 57% increase in left kidney-to-body weight ratio compared with the untreated Tp-/- animals from 5.5 ± 0.1 to 7.5 ± 0.3 (mg/g, P < 0.001). Furthermore, between the two groups receiving l-NAME, the LK/B ratio was significantly greater in the Tp-/- animals (7.5 ± 0.3 mg/g) compared with the Tp+/- group (6.7 ± 0.2 mg/g; P < 0.05).

Despite the absence of albuminuria, the Tp+/- mice treated with l-NAME developed significant renal structural abnormalities including glomerulosclerosis, tubule vacuolization, chronic interstitial inflammation, and fibrointimal vasculitis (see Fig. 5). A similar array of pathological abnormalities was observed in the l-NAME-treated Tp-/- mice. However, the extent of these abnormalities was more severe in the TP-deficient mice compared with the wild-type controls as reflected by significantly higher pathological scores for glomerulosclerosis (2.6 ± 0.2 vs. 1.9 ± 0.3; P < 0.01), tubular vacuolization (2.4 ± 0.4 vs. 1 ± 0.3; P < 0.001), and chronic interstitial inflammation (0.9 ± 0.3 vs. 0.4 ± 0.3; P < 0.001).

DISCUSSION

A number of TP receptor actions have physiological consequences that are relevant to regulation of blood pressure. For example, TP receptors are highly expressed in vascular smooth muscle cells, where they are linked to Gq-dependent signaling pathways (5, 10). Activation of TP receptors causes intense vasoconstriction in a number of vascular beds, including the kidney (17). Along with its actions to modulate peripheral vascular resistance, TxA2 also may influence renal epithelial functions impacting sodium homeostasis and thereby affecting blood pressure control. In the kidney, TP receptors are expressed in the ascending limb of the loop of Henle, distal convoluted tubules, and collecting ducts (1, 36) where they may influence sodium reabsorption.

It has also been suggested that activation of the TP receptor contributes to the prohypertensive actions of ANG II. For example, infusion of ANG II increases TxA2 generation (22, 26, 30) and this enhanced production of TxA2 leads to increased renal vascular resistance (22). While TP receptor blockers or genetic deficiency of TP receptors do not affect blood pressure in the basal state, several studies showed that block-

Fig. 4. Effect of AT1 angiotensin receptor blockade on blood pressures in mice during administration of l-NAME and high-salt diet. l-NAME with high-salt diet caused a significant elevation of blood pressure in both the wild-type (■) and Tp-/- mice (▲), but the hypertensive response was attenuated in the animals lacking TP receptors. After 5 wk, losartan (20 mg·kg-1·day-1) was administered to both groups for 14 days while the l-NAME and high-salt diet were continued. Blockade of AT1 receptors reduced blood pressure in the wild-type mice, but had no effect in the Tp-/- group. After losartan treatment, there was no significant difference in blood pressures between the TP-deficient mice than in the wild-type controls. *P < 0.05 and $P < 0.01 vs. wild-type l-NAME + high salt.
ade or deletion of TP receptors attenuates ANG II-dependent hypertension (12, 19, 22, 23). For example, in a model of ANG II-dependent hypertension, we found that the absence of TP receptors was associated with reduced mortality, lower blood pressure, and less cardiac hypertrophy (12). The hyperensive actions of TP receptors were robust and easily detected in two different genetic backgrounds. Thus, several lines of evidence suggest that activation of TP receptors is a key pathway contributing to elevated blood pressure and end-organ damage in hypertension associated with high levels of circulating ANG II. However, a role for TP receptors in other forms of hypertension has not been so clearly documented.

To examine the role of TP receptors in a model of hypertension that does not depend primarily on activation of the renin-angiotensin system, we induced hypertension in mice by chronic administration of L-NAME along with a HS diet. This model was initially developed in rats where chronic inhibition of NO synthesis by L-NAME leads to hypertension accompanied by end-organ damage including nephrosclerosis (3, 33). Previous studies showed that L-NAME also causes hypertension in mice, although the severity of hypertension and kidney injury seems to be less severe in mice compared with rats (7). Because combining increased sodium intake with L-NAME treated exaggerates kidney injury in rats (13, 33, 38, 42), we administered a HS diet along with L-NAME in our studies. We reasoned that this maneuver might also cause more severe hypertension.

In our studies, a significant increase in blood pressure was observed in the wild-type group as early as 2 wk after initiation of L-NAME and the HS diet. This increase in blood pressure was sustained throughout the 21-wk study period. The development of hypertension in the wild-type animals was associated with a marked increase in urinary excretion of thromboxane and isoprostane metabolites that was apparent after 3 wk; elevated excretion of TxB2 was maintained for the duration of the study. The absence of TP receptors in the Tp−/− mice was associated with an attenuated hypertensive response to L-NAME. Hypertension was not completely prevented in TP-deficient animals as administration of L-NAME caused a significant increase in blood pressures compared with baseline. However, the extent of blood pressure elevation was reduced compared with the wild-type group and from the 3-wk time point onward blood pressures remained significantly lower in the TP-deficient animals than controls. These findings suggest that while TP activation is not the primary mechanism of blood pressure elevation with NO inhibition, it makes a significant contribution to the magnitude of hypertension. The extent of blood pressure elevation attributable to TP receptors ranged between 10 and 20 mmHg through the period of study. Based on epidemiological data, this magnitude of blood pressure increase in humans would confer significant cardiovascular risk (9). This pattern of attenuation of the hypertensive response associated with TP receptor deficiency was very similar to our observations in ANG II-dependent hypertension, suggesting that activation of TP receptors by TxA2 along with other TP agonists such as isoprostanes may be a final common pathway contributing to the pathogenesis of hypertension of diverse causes.

We presumed that the role of the renin-angiotensin system in hypertension associated with administration of L-NAME and a HS diet would be limited. However, we found that the losartan lowered blood pressure significantly in wild-type mice given L-NAME + HS, indicating a significant contribution of ANG II acting via the AT1 receptor. In contrast, the AT1 receptor blocker had no effect on blood pressures in the TP-deficient animals. Moreover, after treatment with losartan, the difference in blood pressure between the Tp+/- and Tp−/− mice was abrogated. These data indicate that AT1 receptor activation contributes to the severity of blood pressure elevation in L-NAME and HS feeding, consistent with previous studies (31). Furthermore, the contribution of AT1 receptors to hypertension in this setting requires TP receptors. This is similar to previous studies suggesting that a portion of the blood pressure elevation caused by ANG II is mediated via pathways involving TP receptors (12, 19, 22, 23).

The stimulus for exaggerated production of TxA2 in L-NAME hypertension and the cellular sources of thromboxane in this setting is not clear. In our previous studies in ANG II hypertension, we found that COX-1 was a major source of thromboxane generation, suggesting that a COX-1-dependent pathway, perhaps in platelets, might be involved. As elevated blood pressure is the common feature in the two models, perhaps increased pressure per se or its consequences such as shear stress may also play a role. Alternatively, the altered profile of prostanoid generation may be a direct consequence of endothelial dysfunction induced by L-NAME. For example, previous studies showed that injury can induce enhanced thromboxane production by endothelial cells in culture (6).
TP-deficient animals suggests that TP receptor pathways do not make a major contribution to free radical production in \textit{l}-NAME hypertension. Furthermore, modification of this pathway does not explain the reduced blood pressures in the TP-deficient mice. Nonetheless, because isoprostanes act as agonists at the TP receptor (2), this increase in 8-isoprostane production may contribute to the TP-dependent rise in blood pressure associated with \textit{l}-NAME and HS feeding.

Administration of \textit{l}-NAME caused significant renal hypertrophy in the wild-type mice. These animals also developed glomerulosclerosis, tubule vacuolization, and chronic interstitial inflammation. In the \textit{Tp} \textsuperscript{–/–} mice, \textit{l}-NAME-induced kidney hypertrophy was even more pronounced than in wild-type animals. The extent of \textit{l}-NAME-induced renal pathology was also accentuated in the TP-deficient mice compared with wild-type controls. This enhancement of renal structural damage in TP deficiency is particularly striking in that the severity of \textit{l}-NAME hypertension was actually attenuated in this group. Moreover, in other kidney disease models, blockade of TP receptor signaling is typically protective. For example, thromboxane antagonists reduce proteinuria and renal pathology in murine lupus nephritis (27, 34, 43) and improve renal function in cyclosporine nephrotoxicity (15, 24). The reasons for this seemingly paradoxical exaggeration of renal injury in the TP-deficient mice are not clear from our studies. Since renal hypertrophy was augmented in the TP-deficient mice, we considered the possibility that the increased renal pathology might be somehow related to this exaggerated hypertrophy response.

The effects of \textit{l}-NAME to promote renal hypertrophy have been documented previously (33, 40). While the mechanisms underlying \textit{l}-NAME-associated renal hypertrophy are not completely clear, it has been suggested that inhibition of apoptosis by \textit{l}-NAME in the kidney may contribute to this phenomenon (3, 14). In various cell systems including the kidney, prostanooids modulate programmed cell death. For example, \textit{TxA} \textsubscript{2} promotes apoptosis in thymocytes (39) and in kidney cells during pathological conditions (21), while other prostanooids such as \textit{PGE} \textsubscript{2} may protect against apoptosis (18). Thus, it is possible that the absence of TP receptors may somehow alter the balance between cell growth and apoptosis in NO deficiency.

In conclusion, chronic inhibition of NO by \textit{l}-NAME stimulates production of thromboxane. Consequent activation of TP receptors contributes to the severity of hypertension and cardiac hypertrophy. On the other hand, TP receptors attenuated the development of renal hypertrophy and pathological injury associated with \textit{l}-NAME administration. In other models of hypertension, previous studies demonstrated key contributions of TP receptors to the severity of blood pressure elevation as well as cardiac hypertrophy and fibrosis (4, 11, 12, 19, 22, 23). Taken together, these data suggest that the TP receptor is part of a final common pathway leading to increased blood pressure and end-organ injury in hypertensive diseases, independent of their primary cause.

\textbf{GRANTS}

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\textbf{REFERENCES}


