Increased Pressor Sensitivity to Chronic Nitric Oxide Deficiency in Hyperthyroid Rats

Isabel Rodríguez-Gómez, Juan Sainz, Rosemary Wangensteen, Juan Manuel Moreno, Juan Duarte, Antonio Osuna, Félix Vargas

Abstract—We studied the effects of a possible interaction between partial nitric oxide deficiency and thyroid hormone excess on the long-term control of blood pressure (BP) and morphological and renal variables and examined the role of the renin-angiotensin system in the increased BP of this interaction. Eight groups (n=8 each) of male Wistar rats were used: a control group; 3 groups that were treated with thyroxine (50 µg/d), Nω-nitro-L-arginine methyl ester (L-NAME; subpressor dose, 1.5 mg · kg⁻¹ · d⁻¹), or thyroxine plus L-NAME; and another 4 similarly treated groups that received losartan (20 mg · kg⁻¹ · d⁻¹) in their drinking fluid. All treatments were maintained for 3 weeks. The time course of tail systolic BP was recorded once a week. At the end of the experimental period, we measured mean arterial pressure in conscious rats and assessed the morphological, metabolic, plasma, and renal variables. Thyroxine produced a mild BP increase from the second week of treatment and an increase in plasma angiotensin II and plasma nitrates/nitrites by the end of the study. Simultaneous administration of thyroxine and a subpressor dose of L-NAME produced a marked BP increase that reached significance from the first week of treatment. Losartan produced normotension in thyroxine-treated rats and attenuated the BP elevation in thyroxine+L-NAME–treated rats. Hyperthyroid rats showed relative renal and ventricular hypertrophy, absence of absolute left ventricular hypertrophy, and proteinuria. These alterations were not changed by losartan. We conclude that an impaired nitric oxide system might have a counterregulatory homeostatic role against the prohypertensive effects of thyroid hormone and that the renin-angiotensin system plays an important role in thyroxine+L-NAME hypertension. (Hypertension. 2003;42:220-225.)

Key Words: blood pressure ■ hyperthyrophy, cardiac ■ losartan ■ nitric oxide ■ hyperthyroidism

The hyperthyroid state is an endocrine disorder associated with important changes in hemodynamic, renal, and cardiac function.²⁻⁳ Hyperthyroidism manifests a hyperdynamic circulation, with increased cardiac output, increased heart rate, and decreased peripheral resistance.²⁻⁴ These characteristic cardiovascular manifestations of hyperthyroidism have been reproduced in rats by thyroid hormone treatment.¹⁻³ Animal studies have reported a dose- and time-related increase in arterial pressure⁶,⁷ and have shown that the hyperthyroid state affects cardiac and renal weight and reduces renal sodium excretion.²⁻⁵ It is well known that nitric oxide (NO) plays a major role in the regulation of vascular tone,⁷ renal sodium excretion,⁸,⁹ and therefore, of arterial blood pressure (BP).¹⁰ Both acute and chronic administration of NO synthase (NOS) inhibitors increase systemic arterial BP.¹¹,¹²

Hyperthyroidism in rats increases the responsiveness of resistance vessels to the endothelium-dependent vasodilator acetylcholine.¹³ Fernández et al¹⁴ demonstrated that hyperthyroidism leads to a significant and reversible enhancement in rat liver NOS activity. More recently, our group reported¹⁵ that NOS activity is upregulated in tissues primarily related to BP control in hyperthyroid rats. Our finding suggested that increased NO production might contribute to the hyperdynamic circulation in hyperthyroidism and might have a protective homeostatic effect on the increased BP that accompanies this endocrine disease.

Hyperthyroidism is accompanied by hyperactivity of the renin-angiotensin system (RAS).¹⁶⁻¹⁸ Thus, plasma renin activity and aldosterone are directly related to plasma levels of thyroid hormones.¹⁶,¹⁷ Moreover, previous studies from our laboratory have demonstrated that short-term RAS blockade markedly decreases arterial pressure and improves renal hemodynamics and excretion in hypertensive hyperthyroid rats¹⁹ and that long-term administration of captopril prevents thyroxine (T₄)-induced hypertension.¹⁸ These results indicate that the RAS plays an important role in the increased BP and renal alterations of hyperthyroidism.

Although plasma renin activity shows a heterogeneous pattern in NO inhibition hypertension,¹¹ there is considerable evidence of the important role of the RAS in this type of hypertension. The participation of the RAS is supported by data showing that RAS blockade prevents or attenuates the development of Nω-nitro-L-arginine methyl ester (L-NAME)
hypertension. In fact, a functional balance exists between angiotensin II (Ang II) and NO in normal conditions. With this background, the present study was designed to evaluate whether NO has homeostatic protective effects on BP and other variables in the hyperthyroid state. Moreover, given the importance of the RAS in the hypertension induced by both long-term administration of T4 and long-term blockade of NO, we also determined the effects of long-term RAS blockade on the hypertension induced by the simultaneous administration of subpressor doses of T4 and L-NAME.

**Methods**

**Animals**

Sixty-four male Wistar rats born and raised in the experimental animal service of the University of Granada were used. All experiments were performed according to European Union guidelines for the ethical care of animals. Rats initially weighing 150 to 175 g were randomly assigned to 1 of 2 experiments and were further assigned to 4 groups. In the first experiment, the groups were as follows: control, L-NAME, T4, and T4/L11001 L-NAME. In the second experiment, groups similar to those in experiment 1 were treated with losartan: control/L11001 losartan, L-NAME/L11001 losartan, T4/L11001 losartan, and L-NAME/T4/L11001 losartan. Each experimental group comprised 8 animals. All rats had free access to food and tap water, except where stated. Losartan (200 mg/L; 20 mg · kg−1 · d−1) was given in the drinking water and L-NAME (1.5 mg · kg−1 · d−1) by gavage. The concentration of losartan in the drinking fluid was adjusted every 2 days according to the fluid intake of the animals to ensure that a similar dose was administered to both T4-treated and control groups. Hyperthyroidism was induced by injecting T4 (Merck), 50 μg/d SC, dissolved in 0.5 N NaOH isotonic saline. This dose was previously used and does not produce marked arterial hypertension.

**Experimental Protocol**

The treatments were administered for 3 weeks. Body weight and tail systolic blood pressure (SBP) were measured once a week. Tail SBP was measured by tail-cuff plethysmography in unanesthetized rats. When the experimental period was completed, all rats were housed in metabolic cages with free access to food and their respective drinking fluids, and treatments were continued for 4 days (2 days for adaptation and 2 experimental days) to measure food and fluid intake and to collect urine samples. Twenty-four-hour urine volume, proteinuria, creatinine, and total excretion of sodium and potassium were measured. The means of the values obtained for each intake or urinary variable during the 2 experimental days were used for statistical analyses between groups.

After completion of the metabolic study, the rats were anesthetized with ethyl ether. A polyethylene catheter (PE-50) containing 100 U heparin in isotonic, sterile, NaCl solution was inserted into the femoral artery for intra-arterial BP and heart rate measurement in conscious rats and for extraction of blood samples. The catheter was tunneled subcutaneously, brought out through the skin at the dorsal side of the neck, and protected with a silver spring. Twenty-four hours after implantation of the femoral catheter, intra-arterial BP was measured with a TRA-021 transducer connected to a 2-channel recorder (Letigraph 2000, Letica SA). After 30 minutes of stabilization, values from the last 5 minutes recorded were averaged and used for comparisons between groups. Subsequently, blood samples taken with the femoral catheter were used to determine total protein, electrolytes, creatinine, Ang II, and nitrate and nitrite (NOx) concentrations. Blood samples were taken as follows: the first 1.5 mL drawn was used for Ang II determination, the next 3 mL was used for measurement of the remaining biochemical variables, and finally the rats were exsanguinated. Subsequently, the kidneys and ventricles were removed and weighed. The heart was divided into right ventricle and left ventricle plus septum.

**Analytical Procedures**

Proteinuria was measured by the method of Bradford. Plasma and urinary electrolytes and creatinine were measured in an autoanalyzer.
(Beckman CX4, USA). Plasma Ang II levels were measured in methanol-extracted samples with a radioimmunoassay kit (Eurodiaagnostica) purchased from Izasa SA. Plasma NOx concentration was measured by using nitrate reductase and the Griess reaction.24

Statistical Analysis
The evolution of SBP with time was compared with the use of a nested design, with groups and days as fixed factors and rat as a random factor. When the overall difference was significant, the Bonferroni method with an appropriate error was used. Comparisons of each variable at the end of the experiments were done by performing a 1-way ANOVA. When the overall ANOVA was significant, we then performed pairwise comparisons with the Bonferroni and Newmann-Keuls methods.

Results
BP and Heart Rate
The Figure shows tail SBP, final mean arterial pressure, and heart rate in the groups from both experiments. Experiment 1 showed that T4 administration produces a mild increase in BP by the second week of treatment when compared with control rats. L-NAME administration to normal rats at the dose used in this experiment did not modify the time-course evolution of BP, as expected. However, simultaneous administration of T4 and a subpressor dose of L-NAME produced a marked increase in BP, which reached significance by the first week of treatment. Heart rate was significantly increased in both T4-treated groups. In experiment 2, T4 + losartan–treated rats showed an SBP evolution similar to that of control rats; the T4 + L-NAME + losartan group showed a mild elevation in BP, which was significant from the second week of treatment when compared controls but highly attenuated in comparison with the T4 + L-NAME group. Both T4-treated groups in experiment 2 also showed an increased heart rate. Tail SBP values were confirmed by mean arterial pressure measurements at the end of the experimental period, which were directly recorded in conscious animals in both experiments.

Morphological Variables
Both T4-treated groups in experiment 1 showed a tendency to reduced body weight compared with the control groups, although these differences did not reach significance. Relative ventricular and renal weights were significantly increased in both T4-treated groups in comparison with their control counterparts. The ratio of left ventricular to right ventricular weights, considered as an index for absolute left ventricular hypertrophy, was similar in all 4 groups of experiment 1 and 2. Losartan treatment had no significant effect on any morphological variable in either control or hyperthyroid rats (Table 1).

Plasma, Metabolic, and Urinary Variables
Plasma Ang II and plasma NOx levels were significantly increased in the T4 group. The L-NAME group showed an increase in BP, which reached significance by the first week of treatment when compared controls but highly attenuated in comparison with the T4 + L-NAME group. Both T4-treated groups in experiment 2 also showed an increased heart rate. Tail SBP values were confirmed by mean arterial pressure measurements at the end of the experimental period, which were directly recorded in conscious animals in both experiments.

<table>
<thead>
<tr>
<th>Groups</th>
<th>FBW, g</th>
<th>KW/BW, mg/g</th>
<th>VW/BW, mg/g</th>
<th>LWW/RW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>352±14</td>
<td>2.38±0.02</td>
<td>2.11±0.09</td>
<td>3.71±0.18</td>
</tr>
<tr>
<td>T4</td>
<td>316±9</td>
<td>3.13±0.11*</td>
<td>2.89±0.09*</td>
<td>3.26±0.16</td>
</tr>
<tr>
<td>L-NAME</td>
<td>355±13</td>
<td>2.31±0.05</td>
<td>2.01±0.05</td>
<td>4.24±0.27</td>
</tr>
<tr>
<td>T4+L-NAME</td>
<td>330±7</td>
<td>3.13±0.09*</td>
<td>2.88±0.12*</td>
<td>3.77±0.12</td>
</tr>
<tr>
<td>Losartan</td>
<td>347±7</td>
<td>2.48±0.07</td>
<td>2.03±0.15</td>
<td>3.55±0.20</td>
</tr>
<tr>
<td>T4+losartan</td>
<td>313±7</td>
<td>3.05±0.06*</td>
<td>2.78±0.06*</td>
<td>3.73±0.15</td>
</tr>
<tr>
<td>L-NAME+losartan</td>
<td>338±19</td>
<td>2.37±0.11</td>
<td>2.00±0.05</td>
<td>3.88±0.18</td>
</tr>
<tr>
<td>T4+L-NAME+losartan</td>
<td>314±13</td>
<td>3.25±0.07*</td>
<td>2.73±0.11*</td>
<td>3.52±0.18</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. FBW indicates final body weight; KW/BW, kidney weight/body weight ratio; VW/BW, ventricular weight/body weight ratio; and LWW/RW, left ventricular weight/right ventricular weight ratio.

*P<0.05 vs controls.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Urinary Flow Rate, μL·100 g–1·24 h–1</th>
<th>Sodium Excretion Rate, μmol·100 g–1·24 h–1</th>
<th>Potassium Excretion Rate, μmol·100 g–1·24 h–1</th>
<th>Protein Excretion Rate, mg·100 g–1·24 h–1</th>
<th>Creatinine Clearance, ml·min–1·g–1 kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.46±0.33</td>
<td>285±26</td>
<td>452±41</td>
<td>3.01±0.33</td>
<td>1.182±0.10</td>
</tr>
<tr>
<td>T4</td>
<td>4.34±1.12*</td>
<td>352±45</td>
<td>572±68</td>
<td>8.65±0.93*</td>
<td>0.971±0.04</td>
</tr>
<tr>
<td>L-NAME</td>
<td>5.11±1.42*</td>
<td>243±9</td>
<td>582±42</td>
<td>4.40±0.61</td>
<td>1.204±0.10</td>
</tr>
<tr>
<td>T4+L-NAME</td>
<td>6.37±1.12*</td>
<td>300±47</td>
<td>633±82</td>
<td>8.82±1.56*</td>
<td>0.900±0.15</td>
</tr>
<tr>
<td>Losartan</td>
<td>4.60±0.48</td>
<td>404±43</td>
<td>666±23</td>
<td>3.35±0.29</td>
<td>0.959±0.35</td>
</tr>
<tr>
<td>T4+losartan</td>
<td>6.92±1.13*</td>
<td>565±60</td>
<td>846±93</td>
<td>8.19±0.97*</td>
<td>1.046±0.03</td>
</tr>
<tr>
<td>L-NAME+losartan</td>
<td>3.54±0.85</td>
<td>385±67</td>
<td>565±106</td>
<td>3.67±0.95</td>
<td>0.903±0.16</td>
</tr>
<tr>
<td>T4+L-NAME+losartan</td>
<td>7.47±1.27</td>
<td>387±17</td>
<td>769±58</td>
<td>8.54±1.09*</td>
<td>0.926±0.33</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. Each value is the mean of the variable on 2 consecutive days of urine collection.

*P<0.05 vs controls.
unchanged Ang II levels and reduced NOx concentrations, and the T4+L-NAME group showed a reduction in both of these variables when compared with the T4 group. All losartan-treated groups showed a marked increase in plasma Ang II levels, with no significant differences among them. Plasma NOx concentration was unaffected by losartan treatment in all groups. There were no significant differences in plasma sodium, potassium, or creatinine levels between the groups in either experiment. Total plasma proteins were significantly decreased (P<0.05) in the T4 and T4+L-NAME groups compared with controls and in the T4+L-NAME+losartan group when compared with the L-NAME–losartan group (Table 2). Metabolic studies at the end of treatment showed increased food intake (g/100 g body weight) in both T4-treated groups (T4, 11.7 ± 0.5; T4+L-NAME, 12.8 ± 1.8 (all mL/100 g body weight). Long-term treatment with losartan did not affect food or fluid intake in either control or hyperthyroid rats (data not shown).

Urine variables and creatinine clearance are summarized in Table 3. Urine volume was significantly higher in the T4-treated groups versus controls in both experiments. Total sodium and potassium excretion showed a tendency to be higher in the T4-treated animals of both experiments, although significance was not reached because of the variability of results. These data are consistent with the greater food intake of T4-treated rats. Proteinuria was significantly increased in the T4-treated groups in both experiments but was unaffected by L-NAME or losartan treatment in control and T4-treated rats. Creatinine clearance, normalized per gram of kidney weight, was not significantly affected by the T4 or L-NAME treatment. Losartan treatment did not significantly change creatinine clearance in the experimental groups.

**Discussion**

The main finding of this study is that T4-treated rats became hypertensive after partial NOS inhibition with a dose of L-NAME that did not modify BP in control rats. Various mechanisms or sets of mechanisms might participate in the increased sensitivity to partial NOS blockade in hyperthyroid rats. This study and several reports13–15 provide evidence that the hyperdynamic circulation of hyperthyroidism is accompanied by increased NO production. Anemia25 and cirrhosis of the liver26 are also associated with hyperdynamic circulation and increased NO production, and cirrhotic rats also show an increased pressor responsiveness to NO blockade.27 These observations indicate that the increased pressor responsiveness to L-NAME in hyperthyroid rats might be secondary to an augmented production of NO, which might have an important homeostatic role in these animals.

A functional feedback balance exists between both Ang II and NO under normal conditions.22,28 However, the present data show that the administration of losartan did not alter NOx levels in T4-treated rats, which had increased plasma levels of NOx and Ang II. These data indicate that T4 simultaneously increased sensitivity to partial NOS blockade in hyperthyroid rats.29,30 This mechanism might increase peripheral resistance and therefore increase BP. Moreover, hyperthyroidism affects renal sodium handling in rats,2,5,6 reduces sodium excretion after a saline load,5 and blunts the pressure-diuresis-natriuresis response.6 These antinatriuretic effects might be aggravated by NO deficiency9,10 and contribute to producing a displacement to the right in the set point of the pressure-diuresis-natriuresis relation, as indicated by the normal sodium excretion with increased BP in the T4+L-NAME–treated group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Na, mEq/L</th>
<th>K, mEq/L</th>
<th>Creatinine, mg/dL</th>
<th>Total Protein, g/dL</th>
<th>Angiotensin II, pmol/L</th>
<th>NOx, μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>144.9 ± 0.3</td>
<td>4.14 ± 0.15</td>
<td>0.65 ± 0.02</td>
<td>6.01 ± 0.07</td>
<td>24.6 ± 3.5</td>
<td>6.30 ± 0.20</td>
</tr>
<tr>
<td>T4</td>
<td>145.1 ± 0.8</td>
<td>4.47 ± 0.07</td>
<td>0.62 ± 0.02</td>
<td>5.56 ± 0.09*</td>
<td>40.4 ± 4.6*</td>
<td>9.82 ± 0.30*</td>
</tr>
<tr>
<td>L-NAME</td>
<td>144.0 ± 0.2</td>
<td>4.42 ± 0.12</td>
<td>0.63 ± 0.01</td>
<td>5.94 ± 0.08</td>
<td>17.3 ± 3.0</td>
<td>4.50 ± 0.22*</td>
</tr>
<tr>
<td>T4+L-NAME</td>
<td>143.6 ± 0.5</td>
<td>4.84 ± 0.17</td>
<td>0.65 ± 0.02</td>
<td>5.50 ± 0.09*</td>
<td>30.3 ± 3.9*</td>
<td>5.19 ± 0.28*</td>
</tr>
<tr>
<td>Losartan</td>
<td>143.5 ± 0.8</td>
<td>4.35 ± 0.19</td>
<td>0.53 ± 0.06</td>
<td>5.46 ± 0.08</td>
<td>258 ± 10</td>
<td>6.29 ± 0.25</td>
</tr>
<tr>
<td>T4+losartan</td>
<td>144.8 ± 0.7</td>
<td>4.48 ± 0.15</td>
<td>0.56 ± 0.02</td>
<td>5.44 ± 0.09</td>
<td>290 ± 13</td>
<td>8.74 ± 0.32*</td>
</tr>
<tr>
<td>L-NAME+losartan</td>
<td>144.2 ± 1.0</td>
<td>4.90 ± 0.41</td>
<td>0.50 ± 0.01</td>
<td>5.72 ± 0.06</td>
<td>266 ± 17</td>
<td>3.79 ± 0.30*</td>
</tr>
<tr>
<td>T4+L-NAME+losartan</td>
<td>144.9 ± 0.7</td>
<td>5.23 ± 0.21</td>
<td>0.73 ± 0.09</td>
<td>5.26 ± 0.08†</td>
<td>329 ± 13</td>
<td>6.08 ± 0.30†</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM.

*P<0.05 vs control; † P<0.05 vs L-NAME or L-NAME–losartan.

**TABLE 3. Plasma Variables**
Interestingly, losartan treatment suppressed the mild pressor effect of T4 at the dose administered in our study. This observation is in line with previous findings that short- or long-term blockade of the RAS reduces BP to normal values in hypertensive hyperthyroid rats. Therefore, the present report adds new evidence of the importance of the RAS in the elevation of BP in the hyperthyroid state.

It is well known that the hyperthyroid state is associated with cardiac hypertrophy. The present results show that hyperthyroidism leads to an increased heart-to-body weight ratio, a measure of relative ventricular hypertrophy. In addition, treatment with T4 had no influence on the left-to-right ventricular-weight ratio, a measure of absolute left ventricular hypertrophy. Therefore, cardiac hypertrophy in hyperthyroidism affects both ventricles to a similar extent. These results agree with previous observations in T4-hypertensive rats.

Kobori et al suggested that the activated RAS, especially the cardiac RAS, of hyperthyroidism plays a role in the development of the cardiac hypertrophy of this disease. This same group reported that administration of RAS inhibitors suppressed the cardiac RAS and contributed to the regression of cardiac hypertrophy in the hyperthyroid state. In the present study, chronic Ang II type 1 receptor blockade with losartan did not significantly alter the relative ventricular hypertrophy in hyperthyroid rats, indicating that the RAS plays no role in this type of cardiac hypertrophy. These findings agree with previous observations in normotensive and hypertensive hyperthyroid rats. Unfortunately, we can find no convincing explanation that accounts for the discrepancies between our data and the observations of Kobori et al.

Although the present study was not designed to address the mechanisms by which hyperthyroidism produces cardiac hypertrophy, the data we report above indicate that cardiac hypertrophy in hyperthyroidism is unrelated to the BP or RAS. Bedotto et al reported that cardiac hypertrophy produced by thyroid hormone is independent of loading conditions and β-adrenergceptors. Taking these observations together, it could be proposed that a direct trophic effect of thyroid hormones on the heart might be responsible for cardiac hypertrophy in hyperthyroidism. In support of this proposal, studies of cultured cardiomyocytes have demonstrated that thyroid hormone directly controls gene expression and cell growth.

The present study shows that hyperthyroid rats have increased proteinuria, consistent with the presence of proteinuria in patients with Graves’ disease. This alteration might be secondary to the increased production in hyperthyroid rats of NO, a vasodilator that impairs the glomerular permeability barrier, although the fact that the proteinuria of T4-treated rats was unaffected by partial NO blockade argues against this possibility. Moreover, because proteinuria was also unrelated to BP or losartan administration, we suggest that proteinuria in the hyperthyroid state might be produced by a direct action of thyroid hormones, increasing the permeability of the glomerular barrier. In this context, Tanwani et al reported a possible association between thyrotoxic patients and a nephrotic syndrome attributable to minimal change nephropathy, a clinical entity defined by selective proteinuria that occurs in the absence of lesions in the glomerular capillary wall. The only detectable abnormalities involve the epithelial visceral cells with effacement of foot processes.

Creatinine clearance, as normalized per gram kidney weight, was similar in all experimental groups of experiment 1 and was unaffected by losartan. The normal creatinine clearance of the T4-treated rats contrasts with the reduced glomerular filtration rate previously reported by our group. These discrepancies might be a consequence of the larger dose of T4 (75 µg/d) and the longer period of treatment (6 weeks) used in the earlier studies, which produced full hypertension.

In conclusion, the present study shows that impaired NO synthesis results in increased sensitivity to the chronic pressor effect of T4, which is severely attenuated by losartan administration. These observations indicate that (1) NO contributes to the adaptive hemodynamic response to hyperthyroidism and (2) the RAS plays an important role in the hypertension induced by long-term, simultaneous administration of suppressor doses of T4 and L-NAME. In addition, our data demonstrate the presence of relative renal and ventricular hypertrophy and the absence of absolute left ventricular hypertrophy and proteinuria in hyperthyroid rats, which was unchanged by losartan.

**Perspectives**

The present study, considered alongside our recent studies on NOS activity of tissues that are primarily related to BP control in hyperthyroid rats, strongly suggests that increased NOS activity might play a protective homeostatic role in hyperthyroidism against the prohypertensive effects of thyroid hormone. An important factor in the putative antihypertensive mechanisms of NO is its antagonistic effect on the pressor actions of Ang II, because administration of losartan severely attenuated the BP increase in rats treated with T4+l-NAME. However, losartan did not normalize BP in these rats, indicating that partial NOS blockade also potentiates unknown factors that contribute to the development of this type of hypertension. Precise knowledge of the participation of different NOS isoenzymes in this adaptive hemodynamic response would allow a common pathophysiological mechanism to be established for the hyperdynamic circulation that appears, regardless of BP level, in different cardiovascular diseases.

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**References**


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