Cardiac and renal antioxidant enzymes and effects of tempol in hyperthyroid rats

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Moreno, Juan Manuel, Isabel Rodríguez Gómez, Rosemary Wangensteen, Antonio Osuna, Pablo Bueno, and Félix Vargas. Cardiac and renal antioxidant enzymes and effects of tempol in hyperthyroid rats. Am J Physiol Endocrinol Metab 289: E776–E783, 2005.—This study evaluated the activity of cardiac and renal antioxidant enzymes [superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR)] and whether chronic treatment with tempol, a cell membrane-permeable SOD mimetic, ameliorates the hypertension of hyperthyroidism. Two experiments were performed. In experiment I, the following four groups of male Wistar rats were used: control group and three groups that received thyroxine (T4) at 10, 50, or 75 μg·rat−1·day−1. In experiment II, tempol was orally administered (18 mg·kg−1·day−1) to control and T4-treated (75 μg·rat−1·day−1) rats. All treatments were maintained for 6 wk. Body weight, tail systolic blood pressure (BP), and heart rate were measured one time a week, and direct BP and morphological, metabolic, plasma, and renal variables were measured at the end of the experiment. Enzymatic activities were measured in renal cortex and medulla and right and left ventricles. In renal cortex, SOD activity was decreased in the T4-75 group, and there was a dose-related increase in CAT activity and decrease in GPX and GR activities in T4-treated groups. Activity of all antioxidant enzymes was reduced in left ventricle in T4-50 and T4-75 groups and in right ventricle in the T4-75 group. Tempol reduced BP, plasma malondialdehyde, and total urinary excretion of F2 isoprostanes in hypertensive hyperthyroid rats but not in controls. Tempol did not improve cardiac hypertrophy, proteinuria, or creatinine clearance in hyperthyroid rats. In conclusion, the results obtained indicate that the activity of SOD, GPX, and GR in renal and cardiac tissues is decreased in hyperthyroidism and that antioxidant treatment with tempol ameliorates T4-induced hypertension.

hypertension, tempol, antioxidant enzymes, oxidative stress.

THE HYPERTHYROID STATE is accompanied by important alterations in hemodynamic, renal, and cardiac function (4, 15, 16). In rats, thyroxine (T4) produces hypertension (8, 15, 33), cardiac and renal hypertrophy, and proteinuria and reduces renal sodium excretion (4, 8, 33).

There is considerable evidence that oxidative stress from superoxide and other reactive oxygen species (ROS) contributes to the development of cardiovascular diseases, diabetes, and renal insufficiency (11, 35). Several studies have implicated oxidative stress in the pathogenesis of arterial hypertension (23, 25) in rats. Moreover, tempol (4-hydroxy-2,2,6,6-tetramethyl piperidinooxy), a stable metal-independent and cell membrane-permeable low-molecular-weight superoxide dismutase (SOD) mimetic (19), has been shown to decrease blood pressure (BP) in hypertensive rats (23, 25).

ROS play an important role in the pathogenesis of renal diseases, producing vascular, glomerular, tubular, and interstitial injury (35). Moreover, it was recently demonstrated that ROS also participates in renal hemodynamics and sodium excretion (36). Hyperthyroid rats show a reduced ability to excrete sodium after isotonic or hypertonic saline loading (33) and exhibit a blunted pressure natriuresis relationship (8). The latter was markedly improved by ANG II inhibitors (8), which were recently shown to have antioxidant properties (6). Hence, renal sodium-handling abnormalities in hyperthyroid rats may be related to the enzymes that regulate renal oxidative stress in this disease.

The hyperthyroid state in mammals is associated with an increased basal metabolism, known as thyroid calorigenesis. Hyperthyroidism in rats increases the activity of the hepatic enzymes that participate in the oxidoreduction process, increasing the generation of ROS (9, 12), and decreases the activity of hepatic SOD, catalase (CAT), and glutathione (GSH; see Refs. 9 and 12). This imbalance between prooxidant and antioxidant factors produces hepatic oxidative stress (32, 34). However, few studies have addressed the role of oxidative stress in the development of the cardiovascular (2, 10) and renal (20, 34) abnormalities of hyperthyroidism.

This study was designed to determine whether hyperthyroidism is associated with dysregulation of the main antioxidant enzymes, i.e., SOD, CAT, glutathione peroxidase (GPX), and glutathione reductase (GR), in kidney (cortex and medulla) and heart (left and right ventricles), the main target organs of hyperthyroidism. A further aim was to test whether the chronic administration of tempol ameliorates BP and other variables in this endocrine disease.

METHODS

Animals

Forty-eight 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 345 ± 32.247 g were randomly assigned to one of the two experiments and divided into the corresponding groups. Experiment I explored the effects of increasing doses of T4 on antioxidant enzymes and oxidative stress status in these animals, using a control group and groups treated with T4 at 10, 50, or 75 μg·rat−1·day−1. Experiment II studied the effects of the
antioxidant tempol on the alterations induced by hyperthyroidism, using groups treated with tempol or T4 (75 μg·rat\(^{-1}\)·day\(^{-1}\)) plus tempol. Each experimental group comprised eight animals. All rats had free access to food and tap water, except where stated. Tempol (180 mg/l; \(\sim\)18 mg·kg\(^{-1}\)·day\(^{-1}\)) was given in the drinking water. Hyperthyroidism was induced by injecting subcutaneously the dose of T\(_4\) (Merck) dissolved in 0.5 N NaOH isotonic saline. All treatments were started at the same time and were maintained for 6 wk. The experimental protocol was the same for both experiments, except that enzymatic activities were only measured in experiment I groups.

Experimental Protocol

Body weight, tail systolic BP (SBP), and heart rate (HR) were determined weekly during the course of the experiment. SBP was measured by tail-cuff plethysmography in unanesthetized rats (LE 5001-Pressure Meter; Leticia, Barcelona, Spain). At least seven determinations were made at every session, and the mean of the lowest three values within a range of 5 mmHg was used to obtain the SBP level.

After the time course study, all animals were housed in metabolic cages (Panlab, Barcelona, Spain) with free access to food and their respective drinking fluids. After 2 days of adaptation, the food and water intake and urine values were gathered during two consecutive days. The values obtained on each experimental day were averaged for statistical purposes. The urinary variables measured were diuresis, natriuresis, kaliuresis, creatinine, proteinuria, and isoprostanes.

After the metabolic study was completed, the femoral artery was cannulated with a polyethylene catheter (PE-50) that was tunneled subcutaneously and exteriorized at the dorsum of the neck. After a 24-h recovery period, direct BP and HR were recorded continuously for 60 min with a sampling frequency of 400/s (McLab; AD Instruments, Hastings, UK). The values obtained during each of the last 30 min were averaged to obtain the mean BP value. Blood samples from the femoral catheter were taken to determine plasma urea, creatinine, total protein, malondialdehyde (MDA), and electrolytes. Finally, the rats were killed by exsanguination. At the end of the treatment period, the kidneys and heart were weighed, and the heart was divided into right ventricle and left ventricle plus septum for the study of morphological variables. Samples from renal cortex and medulla and both ventricles were immediately harvested, cleaned, snap-frozen in liquid nitrogen, and stored at \(-70^\circ\)C until their processing for the measurement of enzymatic activities.

Enzymatic Determinations

Preparation of the tissue homogenate. Homogenates (25% wt/vol) of kidney (cortex and medulla) and heart (left and right ventricle) of each animal were prepared in a solution containing 50 mM potassium phosphate buffer (pH 7.4), 1 mM EDTA, and 1 mM dithiothreitol using a Polytron homogenizer (Omni International; Warrenton, VA). Tissue homogenates were centrifuged at 3,000 rpm for 10 min at 4°C to discard cellular debris. The supernatant was precipitated with a mixture consisted of 50 mM potassium phosphate buffer (pH 7.6), 2 mM EDTA, 1 mM reduced GSH, 1 mM NaN\(_3\), 0.2 mM β-NADPH, and 1 U/ml GR. The activity was calculated using the molar extinction coefficient for NADPH of 6.22 μmol\(^{-1}\)·cm\(^{-1}\) at 340 nm.

GPX Activity

GPX activity was measured spectrophotometrically (6a). The assay mixture consisted of 50 mM potassium phosphate buffer (pH 7.6), 2 mM EDTA, 1 mM reduced GSH, 1 mM NaN\(_3\), 0.2 mM β-NADPH, and 1 U/ml GR. The activity was calculated using the molar extinction coefficient for NADPH of 6.22 μmol\(^{-1}\)·cm\(^{-1}\) at 340 nm.

GR Activity

GR activity was determined by the procedure of Carlberg and Mannervik (5) with minor modifications. The assay solution contained 50 mM potassium phosphate buffer (pH 7.6), 2 mM NADPH, and 20 mM oxidized glutathione. The reaction was initiated by the addition of H\(_2\)O\(_2\), and absorbance at 340 nm was recorded. The activity was calculated using the molar coefficient for NADPH of 6.22 μmol\(^{-1}\)·cm\(^{-1}\) and expressed in units per milligram of protein.

Statistical Analyses

Results are expressed as means ± SE. The evolution of tail SBP and HR with time was compared using a nested design. When the overall difference was significant, Bonferroni’s method with an appropriate error was used. The other variables measured at the end of the experimental period were compared with one-way ANOVA, and subsequent pairwise comparisons were performed with the Newmann-Keuls test.

RESULTS

Biological Variables

T\(_4\) administration produced dose-related increases in BP and HR (Fig. 1). Figure 2 shows the BP and HR data of control, T\(_4\) (75 μg·rat\(^{-1}\)·day\(^{-1}\)), tempol, and T\(_4\) + tempol groups. Figure 2, left, depicts the evolution of the tail BP and HR measured by plethysmography, and Fig. 2, right, shows the final mean arterial pressure and HR measured by direct recording in conscious rats. Administration of T\(_4\) at 75 μg·rat\(^{-1}\)·day\(^{-1}\) induced a time-dependent rise in tail BP that was significantly attenuated by the coadministration of tempol. Tail BP was lower in T\(_4\) + tempol rats throughout the last four measurements of the study when compared with T\(_4\)-untreated rats. Administration of tempol to normal rats did not significantly modify the BP. BP measurements from the femoral catheter in conscious rats at the end of the experiment confirmed the values obtained by the indirect method. HR measured by...
plethysmography or at the end of the study show that this variable was not significantly affected by tempol treatment in normal or T4-treated rats.

Antioxidant Enzyme Activity

Total SOD activity was significantly decreased in the renal cortex of the T4-75 group. There was a dose-related increase in CAT and decrease in GPX and GR activities in renal cortex of T4-treated groups. In renal medulla, the only difference in enzyme activities was a significantly increased CAT activity in the T4-75 group (Fig. 3). In left ventricle, significant dose-related reductions in all antioxidant enzymes were observed in the T4-50 and T4-75 groups. A similar tendency was observed in right ventricle, but significance was only reached in the T4-75 group, except for CAT activity (Fig. 4).

Morphological, Plasma, and Urinary Variables

There was a dose-related decrease in body weight gain and final body weight in the T4-treated groups (Table 1). Tempol did not significantly modify body weight in control or T4-treated rats. Absolute kidney weight was not significantly different in the experimental groups when compared with controls. An increase in relative kidney weight in T4 groups reached significance at the doses of 50 and 75 μg·rat⁻¹·day⁻¹. Absolute left ventricular weight was similar in all groups except for the T4 + tempol group, which showed an increase. Absolute right ventricular weight was significantly increased in T4-treated rats. There was an increase in relative left and right ventricular hypertrophy (left or right ventricle-to-body wt ratio) in T4 groups. The left-to-right ventricular weight ratio was decreased in all T4-treated groups. Tempol did not significantly modify relative renal or cardiac weights in control or T4-treated rats (Table 1).

There were no significant differences in plasma sodium or potassium among the groups in either experiment. Creatinine levels were significantly increased in the groups treated with 75 μg·rat⁻¹·day⁻¹. Total plasma protein was reduced in the T4-75 group. These last two variables were unaffected by...
tempol treatment. T4 administration produced significant increases in plasma MDA in T4-50 and T4-75 groups, but it was not increased in T4-treated rats. Tempol did not change MDA values in normal rats (Table 2).

Food intake in the experimental groups was as follows: control/H11005 4.45/H11006 0.31; T4-10/H11005 4.60/H11006 0.23; T4-50/H11005 5.11/H11006 0.12; T4-75/H11005 6.01/H11006 0.22; tempol/H11005 4.23/H11006 0.50; and T4/tempol/H11001 6.43/H11006 0.33 (g/100 g). This variable was significantly increased (P < 0.01 vs. controls) in both T4-75 and T4/tempol groups treated with the highest dose (75 µg·rat⁻¹·day⁻¹) of T4. Fluid intake (ml/100 g) was increased in a dose-related manner in T4-treated groups (control/H11005 5.73/H11006 0.28; T4-10/H11005 7.60/H11006 0.72; T4-50/H11005 9.30/H11006 1.24, P < 0.05 vs. controls; T4-75/H11005 16.10/H11006 1.30, P < 0.01 vs. controls), and tempol treatment did not affect fluid intake in control (tempol/H11005 5.45/H11006 0.27) or T4-treated (T4 + tempol/H11005 13.48/H11006 1.80, P < 0.01 vs. controls) rats. Urine variables and creatinine clearance values are shown in Table 3. Urine flow rate, total sodium, and total potassium excretion were higher in the T4-75 group, in consonance with the greater food and fluid intake of these rats. There was a dose-related increase in proteinuria in the T4 groups that reached significance at doses of 50 and 75 µg·rat⁻¹·day⁻¹, and creatinine clearance was significantly reduced in groups treated with 75 µg·rat⁻¹·day⁻¹. Tempol did not significantly modify any of these renal variables in control or T4-treated rats. T4 administration produced increases in urinary F2-isoprostanes, which were not increased in T4- and tempol-treated rats. Tempol did not change F2-isoprostane excretion in normal rats.

**DISCUSSION**

There is considerable evidence that hyperthyroidism courses with increased oxidative stress in humans and animals (9, 12, 20, 32, 34). The results of the present study show increases in 24-h urinary isoprostane F₂α excretion and plasma MDA levels in T₄-treated rats, in consonance with previous observations in hyperthyroid patients and rats (14, 26, 34). MDA is an index of lipid peroxidation, and isoprostane F₂α is a stable biomarker of superoxide production in vivo and in vitro (21). It was recently suggested that elevated levels of urinary isoprostane F₂α excretion could be used as an important biomarker for hyperthyroid disease (14). Superoxide radicals and nitric oxide can combine chemically to form peroxynitrite, which can oxidize arachidonic acid to form F₂-isoprostanes in a nonenzymatic manner (13). F₂-isoprostanes exert potent vasoconstrictor and antinatriuretic effects (13, 31). In the present study, long-term treatment with tempol reduced 24-h urinary excretion of isoprostane F₂α, and plasma MDA levels. Therefore, our findings indicate that chronic oral treatment with tempol reduces oxidative stress in hyperthyroid hypertensive rats, which might contribute to its beneficial effects on BP in these animals.

Oxidative stress can result from increased ROS generation and/or a depressed antioxidant system. The primary ROS produced in aerobic organisms is superoxide, which is highly reactive and a cytotoxic agent. Superoxide is converted to H₂O₂ by a group of enzymes known as SOD. H₂O₂ is in turn converted to water and molecular oxygen by either CAT or GPX. Hence, SOD, CAT, and GPX are the principal compo-
nents of the antioxidant defense system, and a deficiency in these enzymes can cause oxidative stress. The present study was designed to determine the effect of chronic treatment with increasing doses of T4, which increases BP (8, 22) and oxidative stress (9, 12, 20), on the activity of these antioxidant enzymes. T4-treated rats showed a significantly decreased SOD activity in renal cortex and left and right ventricles. These observations agree with previous reports showing reduced SOD activity in rat liver (9), cardiac muscle (2), and complete kidney (24). All these findings indicate a quantitative deficiency of intracellular SOD in hyperthyroid rats that may produce an increased renal and cardiovascular oxidative stress.

In this context, Gredilla et al. (10) reported that chronic administration of T4 for 5 wk induced oxidative damage in lipids, glutathione, and DNA in the mouse heart.

SOD is an enzyme that converts superoxide to H2O2 and oxygen, and its activity was reduced in renal cortex and ventricles of hyperthyroid rats. CAT is a heme protein located predominantly in peroxisomes and the inner mitochondrial membrane that catalyzes the conversion of H2O2 to water and molecular oxygen. A reduced CAT activity has been reported in the liver (9), heart muscle (2), and complete kidney (24) of hyperthyroid rats. Our results also show a reduced CAT activity in the left ventricle of hyperthyroid rats, but it was elevated in the renal cortex and medulla. We have no reasonable explanation for the increased CAT activity in renal tissues of hyperthyroid rats.

The conversion of H2O2 to water in mammalian cells is also accomplished by reaction with glutathione catalyzed by GPX. GPX and GR activities were reduced by T4 administration, except in renal medulla. A reduction in GPX activity has also been reported in the liver (27), heart (2), and skeletal muscle (28) of T4-treated rats. On the other hand, Sawant et al. (24) reported that chronic treatment with T4 for 5 wk induced oxidative damage in lipids, glutathione, and DNA in the mouse heart.

Table 1. Morphological variables in the experimental groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>ΔBW, g</th>
<th>FBW, g</th>
<th>KW, mg</th>
<th>KW/BW, mg/g</th>
<th>LVW, mg</th>
<th>LVW/BW, mg/g</th>
<th>RVW, mg</th>
<th>RVW/BW, mg/g</th>
<th>LVW/RVW</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>66.7 ± 9</td>
<td>397.5 ± 7.2</td>
<td>926 ± 23</td>
<td>2.33 ± 0.06</td>
<td>660 ± 22</td>
<td>1.66 ± 0.5</td>
<td>118 ± 8</td>
<td>0.27 ± 0.01</td>
<td>5.63 ± 0.42</td>
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<tr>
<td>T4, μg/kg</td>
<td></td>
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<tr>
<td>10</td>
<td>6.5 ± 3*</td>
<td>352 ± 9.5**</td>
<td>880 ± 20</td>
<td>2.52 ± 0.08</td>
<td>705 ± 18</td>
<td>2.01 ± 0.05*</td>
<td>170 ± 7†</td>
<td>0.45 ± 0.02*</td>
<td>4.04 ± 0.61*</td>
</tr>
<tr>
<td>50</td>
<td>−27.6 ± 4†</td>
<td>320 ± 10.6†</td>
<td>960 ± 18</td>
<td>2.89 ± 0.1*</td>
<td>679 ± 17</td>
<td>2.07 ± 0.07*</td>
<td>165 ± 9†</td>
<td>0.52 ± 0.02†</td>
<td>4.01 ± 0.29†</td>
</tr>
<tr>
<td>75</td>
<td>−37.4 ± 6†</td>
<td>312 ± 12.1†</td>
<td>1010 ± 35</td>
<td>3.04 ± 0.12*</td>
<td>689 ± 20</td>
<td>2.21 ± 0.07*</td>
<td>178 ± 12†</td>
<td>0.60 ± 0.04†</td>
<td>4.06 ± 0.35†</td>
</tr>
<tr>
<td>Tempol</td>
<td>74.7 ± 11</td>
<td>390.5 ± 8.5</td>
<td>916 ± 34</td>
<td>2.34 ± 0.08</td>
<td>660 ± 15</td>
<td>1.69 ± 0.03</td>
<td>121 ± 10</td>
<td>0.30 ± 0.01</td>
<td>5.43 ± 0.30</td>
</tr>
<tr>
<td>T4 + tempol</td>
<td>−35.4 ± 7†</td>
<td>333.2 ± 11.1†</td>
<td>1004 ± 27</td>
<td>3.02 ± 0.04*</td>
<td>794 ± 8*</td>
<td>2.39 ± 0.05*</td>
<td>190 ± 14†</td>
<td>0.58 ± 0.05†</td>
<td>4.07 ± 0.44*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE; n = 8 rats in each group. T4, thyroxine; ΔBW absolute change in body weight; FBW, final body weight; KW, kidney weight; KW/BW, ratio of kidney weight to body weight; LVW, left ventricular weight; LVW/BW, ratio of left ventricular weight to body weight; RVW, right ventricular weight; RVW/BW, ratio of right ventricular weight to body weight; LVW/RVW, ratio of left ventricular weight to right ventricular weight. *P < 0.05 and †P < 0.01 compared with the control group.
reported an increased GPX activity in the complete kidney of hyperthyroid rats. In general, these findings suggest that a reduction in the activity of the antioxidant enzymatic defense system (SOD, GPX, and GR) in cardiac and renal tissues of hyperthyroid rats may determine an increased oxidative stress in these organs. The reasons for these decreases are not clear and may include insufficient synthesis or increased inactivation, which would result in a low steady-state content of SOD, GPX, or GR in the tissue. Regardless of the cause, the decreased antioxidant defense may produce a reduced O2·− inactivation, as indicated by the increase in 24-h urinary isoprostane F2α excretion and plasma MDA levels in T4-treated rats.

The present study demonstrates that chronic tempol administration attenuates the development of hypertension in hyperthyroid rats, in agreement with similar reports in genetic and pharmacological models of hypertension (23, 25). Similar data have been reported in other models of cerebral hypertension, where tempol reduced BP and F2-isoprostanes (23, 25).

The mechanism by which tempol reduces BP in T4-treated hypertensive rats has not been elucidated, but a leftward shift of the renal set point in hyperthyroid rats. Consistent with this observation, it was recently demonstrated that tempol lowers arterial pressure in hyperthyroid rats. Hypertensive rats have a lower BP level, indicating that antioxidant treatment produces a leftward shift of the renal set point in hyperthyroid rats. Consistent with this observation, it was recently demonstrated that tempol lowers arterial pressure in hyperthyroid rats. Hypertensive rats have a lower BP level, indicating that antioxidant treatment produces a leftward shift of the renal set point in hyperthyroid rats. Consistent with this observation, it was recently demonstrated that tempol lowers arterial pressure in hyperthyroid rats.

Another possibility is that tempol may reduce sympathetic activity. Thus the acute administration of tempol reduced BP, HR, and renal sympathetic nerve activity in hypertensive rats (29). However, the absence of HR changes in the present tempol-treated rats suggests that the effect on sympathetic function does not play a major role in the antihypertensive effect of this drug in hyperthyroidism. These data are in consonance with previous observations of our group in normotensive and N(G)-nitro-L-arginine methyl ester hypertensive rats (23).

It is well known that the hyperthyroid state is associated with cardiac hypertrophy (15). The ventricular-to-body weight ratio, a measure of relative ventricular hypertrophy, was increased in T4-treated rats. However, the left-to-right ventricular weight ratio was reduced by T4 treatment. Both ratios were unaffected by tempol treatment in the present study. These data demonstrate that ventricular hypertrophy in hyperthyroidism is not related to the BP, consistent with data previously reported by our group showing that treatments that increased or reduced BP did not modify ventricular hypertrophy in hyperthyroid rats (22). These results also indicate that cardiac hypertrophy in hyperthyroidism may be secondary to a direct trophic effect of thyroid hormones on the heart.

T4-50- and T4-75-treated groups showed increased proteinuria, and this proteinuria did not appear to be related to the BP, since it was similar in T4-75 control and T4 + tempol-treated rats in which BP was significantly reduced. These observations agree with previous reports in hyperthyroid rats (22). Although it has been reported that ROS play an important role in hypertension, the present study shows that antioxidant treatment reduces BP in hyperthyroid rats, consistent with previous observations of our group in normotensive and N(G)-nitro-L-arginine methyl ester hypertensive rats (23).
role in the pathogenesis of renal diseases, producing vascular, glomerular, tubular, and interstitial injury (35), the fact that tempol did not modify the proteinuria induced by T₄ suggests that oxidative stress does not play an essential role in this renal abnormality of hyperthyroid rats.

Creatinine clearance normalized per gram kidney weight was only significantly reduced in the T₄-75 groups. These results are in agreement with separate studies by our group using different doses of T₄ (8, 22). The present study also showed that the chronic administration of tempol does not modify glomerular filtration rate in control or hyperthyroid rats. Therefore, it is suggested that the reduced creatinine clearance of hyperthyroid rats may be secondary to factors other than oxidative stress.

In summary, the present results show that hyperthyroidism is associated with reduced antioxidant SOD, GPX, and GR activities and that tempol reduced tempol attenuates T₄-induced hypertension. It was also observed that the antihypertensive effect of tempol in T₄-treated rats is not associated with an improvement in renal abnormalities or cardiac hypertrophy.

Perspectives

Oxidative stress from superoxide and other ROS contributes to the development of cardiovascular diseases, diabetes, renal insufficiency, and arterial hypertension. This study shows that hyperthyroidism is associated with reduced cardiac and renal antioxidant defense enzyme activities and that tempol reduced BP of T₄-treated rats. However, the mechanisms underlying these observations are unknown. Recent evidence has suggested that ROS can be utilized in signal transduction events and plays an important role in the regulation of cell biology and physiology. In this regard, ROS can influence vascular reactivity, either directly or through an intermediate pathway, and participates in renal hemodynamics and sodium excretion. Therefore, further studies are required to establish which of these possible mechanisms are responsible for the increased BP and other cardiovascular and renal manifestations of hyperthyroidism.

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