Enalapril Attenuates Oxidative Stress in Diabetic Rats

Elena M.V. de Cavanagh, Felipe Inserra, Jorge Toblli, Inés Stella, César G. Fraga, León Ferder

Abstract—Oxidative stress is involved in both the pathogenesis and complications of diabetes. ACE inhibitors can slow the progression of cardiac and renal impairments related to diabetes. The effect of enalapril treatment on oxidative stress and tissue injury was studied in hearts, kidneys, and livers from streptozotocin-induced diabetic rats. Twenty-four rats were divided into the following groups: streptozotocin (65 mg/kg, single intraperitoneal dose), streptozotocin+enalapril (20 mg enalapril/L drinking water), and control (intraperitoneal saline). Seven months after streptozotocin injection, organs were studied by light microscopy and collagen III immunolabeling. Tissue lesions and collagen labeling were graded by a semiquantitative score (0 to 4). Total glutathione content, glutathione redox status (reduced/oxidized glutathione), antioxidant enzyme activities, protein-associated sulfhydryls, thiobarbituric acid–reactive substances, and fluorescent chromolipids were determined in tissue homogenates. Glycemia was higher in both the streptozotocin and streptozotocin+enalapril groups relative to the control group. In the streptozotocin group, creatinine clearance and body weight were lower, and systolic blood pressure and urinary albumin excretion were higher than in the streptozotocin+enalapril and control groups. Heart, kidney, and liver lesion/labeling scores were significantly higher in the streptozotocin group compared with the streptozotocin+enalapril and control groups. Kidney and liver total glutathione was lower in the streptozotocin group relative to the control group (P<0.05). Enalapril treatment significantly attenuated the reduction of total glutathione. In the heart, kidney, and liver, both glutathione and proteins were relatively more oxidized in the streptozotocin group relative to the control group (P<0.05). Protein and glutathione oxidation were attenuated in the streptozotocin+enalapril group in the 3 tissues studied (P<0.05). Enalapril treatment attenuated the oxidation of lipids in the heart and kidney (P<0.05). Tissue fibrosis scores were inversely correlated with (1) both total glutathione and reduced/oxidized glutathione in heart, kidney, and liver and (2) glutathione reductase activity in the kidney. These results suggest that in streptozotocin-induced diabetic rats, the protective action of enalapril might be mediated, at least in part, by its effect on tissue oxidant/antioxidant status. (Hypertension. 2001;38:1130-1136.)

Key Words: diabetes mellitus — oxidative stress — angiotensin II — angiotensin-converting enzyme inhibitors — enalapril — diabetic nephropathy

Experimental and clinical evidence indicates that oxidative stress is involved in both the pathogenesis and the complications of diabetes mellitus.1,2 Oxidative stress has been implicated in the destruction of pancreatic β-cells3 and could largely contribute to the oxidant tissue damage associated with chronic hyperglycemia.4 A number of reports have shown that antioxidants can attenuate the complications of diabetes in patients5 and in experimental models.3,6 ACE inhibitors have been shown to attenuate the progression of cardiac7,8 and renal9,10 impairments related to diabetes and to reduce the risk of death in diabetic patients.7 The beneficial actions of ACE inhibitors seem to be independent of their effect on blood pressure,7,9,10 but it is not fully understood how they provide such protection. Some studies have focused on their in vitro antioxidant properties,11 and others have shown that chronic treatment with ACE inhibitors can increase the endogenous antioxidant defenses in healthy animals12-14 and in patients with end-stage renal disease under hemodialysis therapy.15 Other studies have pointed to the possible protective antioxidant action of ACE inhibitors in the blood16 and kidneys17 of streptozotocin (STZ)-induced diabetic rats. In the present study, we investigated the effect of prolonged enalapril treatment on diabetes-related lesions and oxidant damage in the hearts, kidneys, and livers of STZ-diabetic rats.

Methods

Animals and Biochemical Determinations
The experiments were approved by the Ethics Committee of the Institute of Cardiovascular Research (Buenos Aires, Argentina) and followed the recommendations of the US National Institutes of Health, Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1985).

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Twenty-four 2-month-old male Sprague-Dawley rats (Laboratory of Experimental Medicine, Hospital Alemán, Buenos Aires, Argentina) weighing 200 to 230 g were maintained at 21 ± 2°C and with 12-hour light/darkness cycles (7:00 AM to 7:00 PM). The animals were divided into 3 groups that received a single intraperitoneal injection of the following: (1) saline solution (control group), (2) STZ at 65 mg/kg body weight (STZ group), and (3) STZ at 65 mg/kg body weight and enalapril at 20 mg/L of drinking water (STZ+E group). Enalapril treatment was started 30 days before STZ injection and lasted 8 months. The animals had free access to standard rat chow (Cargill) and drinking water and did not receive insulin. Systolic blood pressure (SBP) was evaluated by tail plethysmography with use of an electrophysymomanometer (PE-300, Narco Bio-Systems). At the end of the study, a 24-hour urine sample was collected for creatinine (Randox Laboratories Ltd) and determination of urinary albumin excretion (Bind a RId, Nanorid Products, The Binding Site Ltd). After a 14-hour fast, the animals were anesthetized with 40 mg pentobarbital/kg body weight IP. Blood samples were drawn from the abdominal aorta. The organs were perfused through the abdominal aorta with saline solution. All reagents were from Sigma Chemical Co.

Morphological Analysis
Tissues were fixed in phosphate-buffered 10% (vol/vol) formaldehyde, pH 7.2, and embedded in paraffin. Sections (5 μm) were stained with hematoxylin-eosin and Masson’s trichrome. Liver fatty changes were evaluated with oil red O. Ten microscopic fields per section were analyzed by using a Nikon E400 light microscope (Nikon Instrument Group), with the observer blind to the study group. Histological lesions (fibrosis and fatty changes) and collagen III (COL III) labeling were evaluated as follows: absent, 0; mild, 1; moderate, 2; severe, 3; and very severe, 4.

COL III Immunohistochemistry
COL III was revealed with anti–COL III monoclonal antibody (Biogen), by using a Vectastain ABC kit (Universal Elite, Vector Laboratories).

GSH+GSSG and GSSG
Total glutathione (GSH+GSSG) and oxidized glutathione (GSSG) were determined as previously described.14 Antioxidant Enzyme Activities, TBARS, and Fluorescent Chromolipids
Tissue homogenates were used for the determination of total superoxide dismutase (CuZn-SOD+Mn-SOD),13 Mn-SOD,13 and glutathione reductase (GSSG-Rd)14 activities and also for the determination of thiobarbituric acid–reactive substances (TBARS)15 and fluorescent chromolipids contents.19

Protein-SH
Tissues were homogenized with 4 vol of 300 mmol/L HClO4, 5 mmol/L EDTA, and 0.06% (wt/vol) 2,2′-bipyridine and centrifuged at 10,000g for 10 minutes. The pellets were used to determine protein-associated sulphydryl (protein-SH) groups by using 5,5′-dithio-bis(2-nitrobenzoic acid).20

Statistical Methods
Values are mean ± SD. Nonparametric Kruskal-Wallis statistics (Statview 5.0, SAS Institute Inc) were used to establish the significance of between-group differences. Spearman correlation coefficients (ρ values) were used to assess the relationships between variables. A value of ρ < 0.05 was considered significant.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results
All the rats included in the STZ and STZ+E groups had developed signs of diabetes (hyperglycemia, glycosuria, and increased drinking water consumption). Biological parameters determined at the end of the study (7 months after STZ injection, 8-month enalapril treatment) are shown in Table 1. In the STZ group, body weight was significantly lower, 25% and 16%, compared with that in the control and STZ+E groups, respectively. In the STZ group, SBP was significantly higher, 18% and 12%, than that in the control and STZ+E groups, respectively. Blood glucose was significantly higher in the STZ and STZ+E groups (303% and 313%, respectively) relative to that in the control group. In the STZ group, creatinine clearance was significantly lower, 35% and 31%, compared with that in the control and STZ+E groups, respectively. Urinary albumin excretion was significantly higher (885%) in the STZ group relative to the control group and was lower in the STZ+E group but higher (204%) than control values. Plasma potassium concentration was similar in the 3 groups studied.

Light microscopy showed large areas of fibrosis in the hearts of rats belonging to the STZ group (Figure 1A). In the STZ group, the fibrosis score was 5 times higher than in the control group (Table 2, Figure 1A). The fibrotic changes in the heart were significantly (86%) reduced in the STZ+E group relative to the STZ group (Table 2, Figure 1B).

The kidney interstitium of the STZ group showed tubule epithelial cell atrophy, mononuclear cell infiltrates, and fibrosis (Figure 2A). In the STZ group, glomerular fibrosis was 21 times higher than that in the control group (Table 2). These interstitial and glomerular alterations were significantly attenuated in rats from the STZ+E group (86% versus STZ group; Table 2, Figure 2B). In the STZ group, liver fibrosis was 3 times higher than that in the control group (Table 2, Figure 3A). In the same group, the presence of cytoplasmic lipid deposits was confirmed by oil red O staining (Table 2). In the STZ+E group, these changes were significantly lower than those in the STZ group (73% versus STZ+E group; Table 2, Figure 3B). Significant increases in COL III immunostaining were observed in hearts and kidneys of the STZ group (3 and 5 times higher, respectively) relative to the control group (Table 2). STZ+E rats presented significantly lower COL III staining in those tissues (68% in heart and 41% in kidney versus STZ group, Table 2).

<p>| Table 1. Biological Parameters of Control and STZ-Induced Diabetic Rats With or Without Enalapril Treatment |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>STZ</th>
<th>STZ+E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>375±9</td>
<td>281±4*</td>
<td>334±6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121±1</td>
<td>143±1*</td>
<td>128±1</td>
</tr>
<tr>
<td>Glycemia, mg/dL</td>
<td>104±7</td>
<td>419±19</td>
<td>430±11†</td>
</tr>
<tr>
<td>CrCl, ml/min</td>
<td>1.24±0.02</td>
<td>0.81±0.05†</td>
<td>1.17±0.01</td>
</tr>
<tr>
<td>UAE, mg/d</td>
<td>8.20±1.30</td>
<td>80.8±8.5*</td>
<td>24.9±3.7†</td>
</tr>
<tr>
<td>Plasma K+ , mmol/L</td>
<td>5.72±0.08</td>
<td>5.77±0.06</td>
<td>5.86±0.06</td>
</tr>
</tbody>
</table>

CrCl indicates creatinine clearance; UAE, urinary albumin excretion. Values are mean ± SE of 5 to 7 animals.

*P<0.05 vs control; †P<0.05 vs STZ+E; and ‡P<0.01 vs control.
GSH+GSSG Content and GSH/GSSG

Tissue glutathione data are presented in Table 3. GSH+GSSG content in the kidneys and liver was significantly lower (37% and 81%, respectively) in the STZ group relative to the control group. In the STZ+E group, kidney GSH+GSSG levels were similar to levels in the control group. In the heart, GSH+GSSG content was similar in the control and STZ groups. In the STZ+E group, heart GSH+GSSG content was significantly higher (23%) than that in the control group. In the heart, kidney, and liver of the STZ group, glutathione redox status (GSH/GSSG) was significantly lower (88%, 83% and 81%, respectively) than that in the control group, indicating that glutathione was relatively more oxidized. In the STZ+E group, kidney and liver GSH/GSSG values were significantly higher (330% and 344%, respectively) than those values in the STZ group and similar to values in the control group. In the heart of the STZ+E group, GSH/GSSG was significantly higher (326%) than that in the STZ group but significantly lower (50%) than that in the control group.

SOD and GSSG-Rd Activities

SOD and GSSG-Rd activities are shown in Table 4. CuZn-SOD activity in the heart and kidneys was significantly lower (47% and 58%, respectively) in the STZ group relative to the control group, and in the STZ+E group, enzyme activity in the heart and kidneys was slightly higher (17% and 25%, respectively) than activity in the STZ group. In the STZ group, liver CuZn-SOD activity was significantly lower, 86% and 72%, compared with that in the control and STZ+E groups, respectively. In the STZ+E group, liver CuZn-SOD activity was significantly lower (48%) than that in the control group. In the STZ and STZ+E groups, heart, kidney, and liver Mn-SOD activity was similar to the activity in the control group (control Mn-SOD activity: heart, 7.72±0.82; kidney, 7.59±0.99; and liver, 11.2±0.57). GSSG-Rd activity in the heart was similar in the 3 study groups. In the kidneys of the STZ group, GSSG-Rd activity was significantly higher, 92% and 25%, than that in the control and STZ+E groups, respectively. In the kidneys of the STZ+E group, GSSG-Rd activity was significantly higher (53%) than that in the control group. In the liver, GSSG-Rd activity was significantly lower, 28% and 20%, in the STZ and STZ+E groups, respectively, relative to activity in the control group.

Protein and Lipid Oxidation

Protein and lipid oxidation data are shown in Table 5. Protein-SH values were determined to evaluate protein oxidation. In the STZ group, protein-SH contents were significantly lower (34%, 40%, and 24% in the heart, kidney, and liver, respectively) relative to the control values.
levels in the STZ+E group were significantly higher (15%, 23%, and 17% in the heart, kidney, and liver, respectively) than those levels in the STZ group.

To evaluate lipid oxidation, TBARS and fluorescent chromolipid contents were determined. In the STZ group, heart TBARS content was significantly higher, 211% and 23%, and 17% in the heart, kidney, and liver, respectively). In the kidneys of the STZ group, the levels of fluorescent chromolipids were significantly higher than those in the control and STZ+E groups (heart, 335% and 47%, respectively; kidney, 39% and 45%, respectively). In the kidneys of the STZ+E group, fluorescent chromolipid levels were similar to those in the control group, but in the heart, they were significantly higher than levels in the control group. In the liver of the STZ group, fluorescent chromolipid content was significantly higher than that in the control group (81%) and similar to that in the STZ+E group.

Relationships Between Fibrosis and Oxidative Stress Parameters
Moderate to good negative correlations ($\rho, P<0.05$) were found between heart, kidney, or liver fibrosis scores and (1)
Kidney diabetes mellitus is a serious risk factor for the development of oxidant-mediated adaptive increases in antioxidant enzyme activities and/or direct inactivation by either oxidants or glycation.

In STZ-treated rats, enalapril treatment had an overall positive effect on the antioxidant levels in the tissues studied. In the liver, but not in the heart and kidneys, enalapril treatment prevented the STZ-related reduction of CuZn-SOD activity. In the kidneys, enalapril treatment attenuated the increase of GSSG-Rd activity, but it had no effect in the liver. Enalapril treatment hindered the STZ-related reduction of GSH+GSSG content in the kidney and liver and prevented glutathione oxidation in the 3 tissues studied. These effects of enalapril on glutathione might be relevant if demonstrated in humans, because in diabetic patients, plasma glutathione is lower and is in a more oxidized state than that in healthy control subjects. As mentioned earlier, in STZ-treated rats, enalapril protects against heart, kidney, and liver damage and concurrently attenuates oxidative stress in these tissues.

We show that enalapril treatment significantly attenuates fatty changes observed in the livers of STZ-treated rats. We have observed that ACE inhibition can also prevent liver fatty changes in rats with experimentally induced nephrotic syndrome as well as in aging (authors’ unpublished data, 2001). Moreover, the fibrotic alterations found in the perivascular and pericanalicular areas of the liver were attenuated in enalapril-treated diabetic rats. Diabetes is associated with nonalcoholic steatohepatitis, characterized by mild to moderate fatty changes in hepatic cells. However, there are no reports showing the effects of ACE inhibition on these hepatic changes.

TABLE 4. CuZn-SOD and GSSG-Rd Activities in Heart, Kidney, and Liver From Control and STZ-Induced Diabetic Rats With or Without Enalapril Treatment

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control</th>
<th>STZ</th>
<th>STZ+E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuZn-SOD</td>
<td>62.2±0.9</td>
<td>32.8±3.7*</td>
<td>38.3±4.0*</td>
</tr>
<tr>
<td>GSSG-Rd</td>
<td>12.8±1.3</td>
<td>12.2±1.3</td>
<td>9.33±0.48</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuZn-SOD</td>
<td>23.5±2.2</td>
<td>9.85±1.4*</td>
<td>12.3±1.4*</td>
</tr>
<tr>
<td>GSSG-Rd</td>
<td>81.6±2.2</td>
<td>156.7±2.5†</td>
<td>125.1±10.1*</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuZn-SOD</td>
<td>32.9±3.8</td>
<td>4.76±1.3†</td>
<td>17.1±2.0*</td>
</tr>
<tr>
<td>GSSG-Rd</td>
<td>28.5±1.3</td>
<td>20.6±2.8*</td>
<td>22.7±2.5*</td>
</tr>
</tbody>
</table>

Values are mean±SE of 5 to 7 animals.
*P<0.05 vs control; †P<0.0 vs STZ+E and control.

GSH+GSSG content (heart, −0.50; kidney, −0.65; and liver, −0.72) and (2) GSH/GSSG (heart, −0.54; kidney, −0.60; and liver, −0.66). In the same tissues, the negative correlations between fibrosis scores and CuZn-SOD activity were weaker than those found between fibrosis scores and either GSH+GSSG content or GSH/GSSG (heart, −0.25; kidney, −0.25; and liver, −0.41; p, P<0.05). Also, a negative correlation was observed between fibrosis scores and GSSG-Rd activities in the kidney (ρ=−0.58, P<0.05). No such relationship was found in the heart or liver.

Discussion
Diabetes mellitus is a serious risk factor for the development of renal and cardiovascular disease. It is also related to fatty changes in the liver. Diabetes-related organ damage seems to be the result of multiple mechanisms. Diabetes has been associated with increased free radical reactions and oxidant tissue damage in STZ-induced diabetic rats and also in patients. The present study shows that in rats under chronic

TABLE 5. Protein-SH, TBARS, and FC Contents in Heart, Kidney, and Liver From Control and STZ-Induced Diabetic Rats With or Without Enalapril Treatment

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control</th>
<th>STZ</th>
<th>STZ+E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein-SH, nmol GSH Eq/mg protein</td>
<td>100.1±1.3</td>
<td>66.5±2.4†</td>
<td>76.6±1.6*</td>
</tr>
<tr>
<td>TBARS, nmol MDA Eq/mg protein</td>
<td>0.52±0.03</td>
<td>1.62±0.15†</td>
<td>0.88±0.08</td>
</tr>
<tr>
<td>FC, AU/mg protein</td>
<td>43±2</td>
<td>187±9†</td>
<td>127±6*</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein-SH, nmol GSH Eq/mg protein</td>
<td>119.6±8.3</td>
<td>71.2±9.5*</td>
<td>87.4±5.3*</td>
</tr>
<tr>
<td>TBARS, nmol MDA Eq/mg protein</td>
<td>2.31±0.21</td>
<td>2.75±0.33</td>
<td>2.66±0.23</td>
</tr>
<tr>
<td>FC, AU/mg protein</td>
<td>124±7</td>
<td>173±8†</td>
<td>119±6</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein-SH, nmol GSH Eq/mg protein</td>
<td>118.3±3.7</td>
<td>90.1±1.2†</td>
<td>105.2±0.2*</td>
</tr>
<tr>
<td>TBARS, nmol MDA Eq/mg protein</td>
<td>0.67±0.08</td>
<td>0.90±0.04*</td>
<td>0.83±0.11</td>
</tr>
<tr>
<td>FC, AU/mg protein</td>
<td>192±17</td>
<td>347±39*</td>
<td>365±16*</td>
</tr>
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</table>

FC indicates fluorescent chromolipid; MDA, malondialdehyde; and AU, arbitrary units. Values are mean±SE.
*P<0.05 vs control; †P<0.05 vs STZ+E.
the reduction of antioxidant levels may be the result of glycation and/or direct oxidation. Because enalapril treatment did not correct hyperglycemia, it is possible to assume that the effect of ACE inhibition on the level of a particular antioxidant will depend, at least in part, on the prevalence of either glycation or oxidation as a mechanism of antioxidant inactivation in a tissue. Alternatively, the lack of a defined pattern in the response of the organ antioxidant levels to enalapril treatment might result from differences in tissue metabolism and/or penetration of this drug. This could arise from (1) the capacity of a particular tissue to transform enalapril (a prodrug) into its active form (enalaprilat) and/or (2) the existence of tissue renin-angiotensin systems with different levels of expression and/or activity of ACE. In addition, an effect of enalapril on the antioxidant defenses might have occurred in certain cell types but not in others and was not detected because the determinations were carried out in whole tissue homogenates.

Interestingly, the protective action of enalapril on protein and lipid oxidation was consistent. STZ-induced oxidant damage to proteins was revealed by the lower tissue content of protein-bound sulfhydryl groups in the heart, kidney, and liver. Lipid oxidation was demonstrated by the higher content of both TBARS and fluorescent chomolipids. The treatment with enalapril of STZ-injected animals lowered oxidant damage to proteins in the 3 tissues studied and to lipids in the heart and kidney. The apparent lack of agreement between the unpatterned effect of enalapril on tissue antioxidant defenses and the consistency of enalapril-mediated protection against protein and lipid oxidation might be improved by increasing the number of antioxidants under screening.

The dose of enalapril used in the present study does not modify normal blood pressure in healthy rats. It is well known that blood pressure tends to increase in diabetic animals and patients. In the present study, we show that SBP was higher in STZ-induced diabetic rats compared with control rats, and this rise was prevented by enalapril treatment. On the other hand, glutathione depletion causes hypertension in normal rats. In this context, and in addition to the hemodynamic effects of enalapril, the observed lower SBP in enalapril-treated diabetic rats may be mediated, at least in part, by the maintenance of GSH+GSSG content within the physiological range.

The inverse relationships observed between tissue fibrosis and antioxidant levels were more significant for both GSH+GSSG content and GSH/GSSG than for CuZn-SOD activity. Also, GSSG-Rd activity was inversely related to the capacity of enalapril to increase both GSH+GSSG content and the GSH/GSSG ratio.

In previous work, we observed the concurrence of increased antioxidant defenses and plasma and urine NO levels in enalapril-treated animals. NO was possibly derived from the potentiation of bradykinin by chronic enalapril treatment. In different systems, NO was able to either increase or decrease antioxidant defenses. In the present study, we have not evaluated NO production. However, the participation of NO as a direct or indirect modulator of the increase of antioxidant defenses associated with enalapril treatment is a subject that deserves further investigation.

Previous reports have shown that ACE inhibitors administered for a maximum of 12 weeks can attenuate oxidative stress in the kidney and blood of experimentally diabetic animals. In the present study, we have extended those observations to a longer ACE inhibitor treatment period and to the liver and heart. In addition, the negative correlations found between tissue fibrosis and antioxidant defense levels suggest that enalapril treatment might afford protection, at least in part, by increasing the endogenous antioxidant defenses. However, angiotensin II can stimulate the production of free radicals, and blood pressure can induce oxidative stress through its effect on vessel wall stretching. In this regard, it is still unclear whether in the present model of diabetes the effect of enalapril on oxidative stress parameters is related to either a direct lowering of the effects of angiotensin II or a lowering of blood pressure or both.

In conclusion, the present results confirm the beneficial effects of ACE inhibition on heart and kidney diabetes-related lesions and add a novel protective action against liver damage in STZ-induced diabetic rats. This study shows a negative correlation between tissue fibrosis and glutathione-related antioxidant defenses. We also report a multitargeted effect of enalapril against oxidative damage in the heart, kidney, and liver. The antioxidant activity of ACE inhibitors could afford a novel mechanism for the protective/prophylactic action of these compounds.

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References


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