

## Original Research

# Candesartan cilexetil protects cavernous tissue in spontaneously hypertensive rats

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In previous experiments, our group demonstrated morphological changes in erectile tissue from male spontaneously hypertensive rats (SHR). The present study was performed to determine whether an angiotensin II receptor blocker could protect cavernous tissue (CT) from these structural alterations in SHR. Male SHR and Wistar-Kyoto (WKY) rats were studied during 4 months. Rats were divided into three groups: SHR ( $n = 10$ ), SHR with candesartan cilexetil ( $n = 10$ ) and WKY rats ( $n = 10$ ). Candesartan cilexetil 7.5 mg/kg/day was administered orally throughout the study. CT was processed for pathology studies. The amount of (1) cavernous smooth muscle (CSM), (2) vascular smooth muscle (VSM), (3) collagen type III, and the rat endothelial cell antibody (RECA-1)/tunica media ratio in cavernous arteries were evaluated. SHR with candesartan cilexetil showed a lower blood pressure, a lower percentage of CSM, smaller VSM area, with a higher RECA-1/media ratio, and a lower percentage of collagen type III, when compared to untreated SHR. In addition, SHR showed a positive correlation between systolic blood pressure (SBP) and CSM amount ( $r = 0.91$ ;  $P < 0.01$ ), and SBP and the percentage of collagen type III ( $r = 0.88$ ;  $P < 0.01$ ); these correlations were not observed either in SHR treated with candesartan cilexetil or in WKY rats. We conclude that candesartan cilexetil provides a significant protective role against morphologic changes in vessels as well as in cavernous spaces of the erectile tissue, caused by high blood pressure, in SHR.

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## Introduction

Impotence or male erectile dysfunction (ED), the persistent inability to achieve or maintain an erection for satisfactory sexual performance, is a widespread and troublesome condition among middle-aged men, and it is partly vascular in origin.<sup>1</sup> Data from the Massachusetts Male Aging Study (MMAS) show that the annual incidence of ED in men between 40 and 70 y old is 26 per 1000 men.<sup>2</sup> Both cigarette smoking and high levels of high-density-lipoprotein cholesterol are recognized to be

associated with vascular impotence.<sup>3,4</sup> Moreover, ED is increased in prevalence in hypertensive patients, and it is highly associated with cardiovascular disease.<sup>5–9</sup> The discussion whether in hypertensive patients, high blood pressure itself or the antihypertensive therapy constitutes a cause of ED has always been a controversial point. Antihypertensive drugs are most commonly associated with ED.<sup>10</sup> However, arterial hypertension seems to produce substantial anatomic changes through the vascular tree, including cavernous vessels. In previous experiments, our group demonstrated morphological changes in erectile tissue from male spontaneously hypertensive rats (SHR).<sup>11</sup> These alterations were characterized by proliferation in cavernous smooth muscle (CSM) and vascular smooth muscle (VSM) along with cavernous tissue (CT) fibrosis. Furthermore, these findings were highly correlated with the arterial hypertension level. Additionally, recent data from DOCA-salt and stroke-prone-spontaneously hypertensive rats have demonstrated a decreased erectile response associated with hypertension.<sup>12</sup>

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In the last few years, therapeutic intervention against the renin–angiotensin–aldosterone system (RAAS), by both angiotensin I converting enzyme (ACE) inhibitors and more recently through angiotensin II type 1 (AT1) receptor antagonist, has been increasing in acceptance as a useful antihypertensive therapy worldwide. Candesartan cilexetil, a potent, highly selective AT1 receptor antagonist with insurmountable binding properties and slow off-rate from the receptor, has demonstrated to be effective and well tolerated when used in moderate or severe hypertension.<sup>13</sup> Therefore, the purpose of the present study was to evaluate the possible beneficial effects of candesartan cilexetil on CT in a recognized rat model of arterial hypertension.

## Methods

All the experiments were approved by the Hospital Alemán ethic committee and the teaching and research committee, and according to the NIH guide for the care and use of laboratory animals. Inbred male spontaneous hypertensive rats (12 weeks old) (SHR) ( $n=20$ ) and normotensive Wistar-Kyoto (WKY) rats ( $n=10$ ) (Laboratory of Experimental Medicine, Hospital Alemán-Charles River Laboratories, Wilmington, MA, USA) were housed in individual cages at room temperature  $21 \pm 2^\circ\text{C}$  and a 12 h light/darkness cycle (0700–1900). Rats were divided into three groups: G1 SHR ( $n=10$ ), G2 SHR with candesartan cilexetil ( $n=10$ ) and G3 WKY rats ( $n=10$ ). During 4 months, candesartan cilexetil 7.5 mg/kg/day was administered continuously in drinking water to G2, whereas rats from G1 and G3 received regular water. All the animals were allowed to drink regular tap water and were fed standard rat chow with normal salt content ‘*ad libitum*’, throughout the experiment. In order to achieve the adequate doses of candesartan cilexetil ingested by each animal, every day the rats were weighed, the drinking consumption was recorded, and then doses were adjusted to the right proportion.

At baseline and at the end of the study, samples were obtained for biochemical determinations. At the end of the experiment, all the rats were killed (pentobarbital 40 mg/kg body weight, injected intraperitoneally). The penises were rapidly excised and harvested for light microscopy (LM) and immunohistochemistry studies.

### *Blood pressure measurement*

At baseline and at the end of the experiment, systolic blood pressure (SBP) was measured by tail cuff plethysmography. Measurements were obtained with the rats restrained in a plastic chamber without

anesthesia. A pneumatic pulse transducer positioned on the ventral surface of the tail distal to the occlusion cuff detected the return of the pulse following a slow deflation of the cuff. Cuff pressure was determined by a pneumatic pulse transducer, using a programmed electro-sphygmomanometer PE-300 (Narco Bio-Systems, Austin, TX, USA), and pulses were recorded on a Physiograph MK-IIIIS (Narco Bio-Systems, Austin, TX, USA). A minimum of three such determinations were taken at each session, and the SBP registered was the average of the three readings.

### *Biochemical procedures*

After a 14-h fasting rat blood samples were collected from the tail vein in capillary tubes at baseline, and at the end of the experiment from the inferior cava vein before the rats were killed. Plasma glucose levels were measured by the glucose oxidase method with an automatic analyzer (Hitachi 911, Tokyo, Japan). Aliquots of sera were assayed for creatinine using the enzymatic UV method (Randox Laboratories Ltd, Cruclin, N Ireland). Serum cholesterol, triglycerides and electrolytes were assessed according to standard methods.

### *Tissue processing and examination*

Penises were removed, cut longitudinally and fixed in phosphate-buffered 10% formaldehyde (pH 7.2). The tissue samples were embedded in paraffin. Sections (3  $\mu\text{m}$ ) were cut and stained with hematoxylin–eosin (H&E), periodic acid-Schiff reagent (PAS) and Masson’s trichrome.

### *Immunolabelling and light microscopy*

Immunolabelling of specimens was carried out by a modified avidin–biotin–peroxidase complex technique using the Vectastain ABC kit (Universal Elite, Vector Laboratories, CA, USA). Following deparaffinization and rehydration, the sections were washed in phosphate-buffered saline (PBS) for 5 min. Quenching of endogenous peroxidase activity was achieved by incubating the sections for 30 min in 1% hydrogen peroxide in methanol. After washing them in PBS (pH 7.2) for 20 min, they were incubated with blocking serum for 20 min. Thereafter, the sections were incubated with the primary antibody, and rinsed in PBS and incubated with biotinylated universal antibody for 30 min. After washing them in PBS, they were incubated for 40 min with Vectastain Elite ABC reagent (Vector

Laboratories, CA, USA), and exposed for 5 min to 0.1% diaminobenzidine (Polyscience, Warrington, PA, USA) and 0.2% hydrogen peroxide in 50 mM Tris buffer, pH 8.  $\alpha$ -Smooth muscle actin ( $\alpha$ -SMA) and collagen type III were quantified using anti-mouse  $\alpha$ -SMA (Sigma Chemical Co., St Louis, MO, USA) monoclonal antibodies and anti-collagen type III (Biogen, San Román, CA, USA) monoclonal antibodies, at 1:100 dilution. In order to evaluate the endothelium in CT, a mouse monoclonal anti-rat endothelial cell IgG antibody (RECA-1) (Abcam Ltd., Cambridge, UK), which reacts with rat endothelial cell antigen, at 1:200 dilution, was used.

Control sections where the primary antibody was omitted were performed in each experimental group.

### Morphological analysis

Histological sections were studied in each animal by an image analyzer Image-Pro Plus ver. 3 for windows (Media Cybernetics, LP, Silver Spring, MD, USA). Morphological analyses were performed on 10 microscopic fields per section, examined at a magnification of  $\times 100$ , with the observer blind to the animal group, and the data were averaged. We evaluated the amount of (a) CSM, expressed as a percentage of positive  $\alpha$ -SMA immunostaining in cavernous space (CS), (b) VSM, expressed as positive  $\alpha$ -SMA immunostaining in the vascular wall from penis arteries, and (c) collagen type III in CT expressed as a percentage. In order to assess the relationship between endothelial area and tunica media in arteries from CT, the RECA-1/media ratio was evaluated.

### Statistical method

Values were expressed as mean  $\pm$  s.d. All statistical analyses were performed using absolute values and processed through GraphPad Prism, version 2.0 (GraphPad Software, Inc., San Diego, CA, USA).

For parameters with Gaussian distribution, comparisons among groups were carried out using ANOVA; for those parameters like histological data with non-Gaussian distribution, comparisons were performed by the Kruskal–Wallis test (nonparametric ANOVA) and Dunn's multiple comparison test. A value of  $P < 0.05$  was considered to be significant. To evaluate the relationship between (1) SBP and the amount of CSM, and (2) SBP and the percentage of collagen type III in CT, the Spearman rank correlation was performed.

## Results

At baseline, there were no significant differences between SHR and WKY rats regarding metabolic parameters. However, SHR groups (G1 and G2) presented lower body weight and higher blood pressure than WKY rats, as illustrated in Table 1, panel a.

As expected, at the end of the experiment, while rats from G1 (SHR) showed a marked elevation of SBP relative to WKY rats (G3), those from G2 (SHR with candesartan cilexetil) presented blood pressure records considerably close to the control WKY rats (Table 1, panel b). Additionally, serum creatinine was also significantly higher in G1 (SHR) in comparison with the other groups, which presented similar

**Table 1** Parameters evaluated at baseline and after 4-month treatment in all groups

Mean $\pm$ s.d.	G1 SHR (n = 10)	G2 SHR + candesartan cilexetil (n = 10)	G3 WKY (n = 10)	P
<i>(a) At baseline</i>				
Body weight (g)	214.5 $\pm$ 7.5	212.5 $\pm$ 7.3	229.3 $\pm$ 4.1*	<0.01
Systolic blood pressure (mmHg)	150.4 $\pm$ 4.5	151.8 $\pm$ 4.4	120.2 $\pm$ 1.3*	<0.01
Serum creatinine ( $\mu$ mol/l)	54.8 $\pm$ 4.4	53.9 $\pm$ 2.6	52.1 $\pm$ 1.7	NS
Serum glucose (mmol/l)	5.9 $\pm$ 0.5	6.0 $\pm$ 0.5	5.7 $\pm$ 0.4	NS
Serum cholesterol (mmol/l)	0.9 $\pm$ 0.10	0.8 $\pm$ 0.06	0.9 $\pm$ 0.08	NS
Serum triglycerides (mmol/l)	0.4 $\pm$ 0.03	0.4 $\pm$ 0.02	0.4 $\pm$ 0.02	NS
[Na] <sub>s</sub> (mmol/l)	144.4 $\pm$ 1.7	143.5 $\pm$ 2.1	143.4 $\pm$ 2.3	NS
[K] <sub>s</sub> (mmol/l)	4.9 $\pm$ 0.3	5.0 $\pm$ 0.3	4.9 $\pm$ 0.4	NS
<i>(b) After 4-month treatment</i>				
Body weight (g)	275.7 $\pm$ 5.8	268.8 $\pm$ 7.3	311.7 $\pm$ 5.2*	<0.01
Systolic blood pressure (mmHg)	194.6 $\pm$ 3.6	130.7 $\pm$ 4.0**	123.7 $\pm$ 2.1	<0.01
Serum creatinine ( $\mu$ mol/l)	62.7 $\pm$ 2.6	55.6 $\pm$ 2.6***	54.8 $\pm$ 1.7	<0.01
Serum glucose (mmol/l)	6.1 $\pm$ 0.4	5.8 $\pm$ 0.4	5.9 $\pm$ 0.3	NS
Serum cholesterol (mmol/l)	0.9 $\pm$ 0.10	0.9 $\pm$ 0.04	0.9 $\pm$ 0.09	NS
Serum triglycerides (mmol/l)	0.4 $\pm$ 0.04	0.5 $\pm$ 0.03	0.4 $\pm$ 0.03	NS
[Na] <sub>s</sub> (mmol/l)	143.8 $\pm$ 2.5	143.1 $\pm$ 1.6	142.8 $\pm$ 2.3	NS
[K] <sub>s</sub> (mmol/l)	5.1 $\pm$ 0.3	5.3 $\pm$ 0.1	5.0 $\pm$ 0.2	NS

[ ]<sub>s</sub> = serum concentration; NS = nonsignificant. \*vs G1 and G2  $P < 0.01$ , \*\*vs G1 and G3  $P < 0.01$ , \*\*\*vs G1  $P < 0.01$ .

values with respect to each other (Table 1, panel b). On the other hand, at the same time, no significant changes in serum glucose, cholesterol and triglycerides, as well as serum sodium and potassium were observed between the groups (Table 1, panel b).

Microscopic examination of the CT revealed that while rats from G1 (SHR) presented a significantly increased amount of  $\alpha$ -SMA in arteries and in the CS, with respect to control WKY rats (G3), SHR treated with candesartan cilexetil (G2) showed significantly lower values, which were also similar to the WKY rats group (Table 2 and Figures 1 and 2). Moreover, the extracellular matrix expansion and the amount of collagen type III in CT were also significantly higher in rats from G1 (SHR) when compared to WKY rats, whereas SHR treated with candesartan cilexetil presented a smaller extracellular matrix with less percentage of collagen type III, as shown in Table 2 and Figures 3 and 4.

In addition, rats from G1 (SHR) showed a lower RECA-1/media ratio in cavernous arteries when compared to the other groups (Table 2). Nevertheless, animals that received candesartan cilexetil (G2) presented the highest RECA-1/media ratio, which suggests some benefit in the endothelium preservation (Table 2).

Finally, rats from G1 (SHR) showed a highly significant positive correlation between (1) SBP and the percentage of  $\alpha$ -SMA in CS ( $P < 0.01$ ), and (2) SBP and the percentage of collagen type III ( $P < 0.01$ ). On the other hand, these correlations were not observed either in SHR treated with candesartan cilexetil or in WKY rats, as shown in Figure 5a and b.

## Discussion

In the present study, despite the fact that CT was processed under variable pressure, which could be a

limitation for interpreting our results, SHR showed a VSM hypertrophy pattern of the penile arteries as well as an increase of the smooth muscle layer in the CS. In addition, these animals presented a reduced endothelial surface in cavernous arteries along with an increase in extracellular matrix with a higher amount of collagen type III, which were indeed very different from those shown by normotensive WKY control rats. Moreover, these findings had a high significant correlation with blood pressure levels. In contrast, SHR treated with candesartan cilexetil showed a significant protection on CT. The beneficial effect of candesartan cilexetil was characterized by a substantial reduction in CSM layer in the CS, as well as in VSM. Additionally, there was an improvement in the endothelium/media ratio in arterial vessels, through the erectile tissue. Furthermore, extracellular matrix and the amount of collagen type III were also reduced in the CT in these animals.

Disarrangement in the blood flow supply to the erectile tissue is thought to be the most frequent organic cause of ED. Vascular occlusive disease, especially of the hypogastric-cavernous bed, can decrease the perfusion pressure and arterial flow to the CS, increasing the time to maximal erection and decreasing the rigidity of the erect penis.<sup>14,15</sup> Additionally, in an established chronic animal model of vasculogenic ED, the hemodynamic contribution of reduced arterial inflow and perfusion pressure to ED has been clearly demonstrated.<sup>16-18</sup> Common risk factors for arterial insufficiency from atherosclerosis include arterial hypertension, cigarette smoking, hyperlipidemia and diabetes mellitus. This correlates clinically with arteriographic findings of diffuse, bilateral stenosis of internal pudendal, common penile and cavernous arteries in men with impotence.<sup>19</sup>

A major mechanism responsible for ED is an increase in the tone and/or contractility of smooth

**Table 2** Morphological analysis of cavernous tissue, at the end of the experiment

Mean $\pm$ s.d.	G1 SHR (n = 10)	G2 SHR + candesartan cilexetil (n = 10)	G3 WKY (n = 10)
Positive $\alpha$ -SMA immunostaining in cavernous space (%)	11.7 $\pm$ 2.2 <sup>a</sup>	2.6 $\pm$ 0.9 <sup>b</sup>	3.7 $\pm$ 0.9
Area with positive $\alpha$ -SMA immunostaining in vascular wall ( $\mu\text{m}^2$ )	14 038.8 $\pm$ 1097 <sup>a</sup>	9186.3 $\pm$ 1215 <sup>b</sup>	9860.8 $\pm$ 1036
RECA-1 <sup>c</sup> /media ratio <sup>d</sup>	1.6 $\pm$ 0.1 <sup>a</sup>	4.8 $\pm$ 0.2 <sup>e</sup>	2.2 $\pm$ 0.1
Collagen type III in cavernous tissue <sup>f</sup> (%)	11.2 $\pm$ 1.3 <sup>a</sup>	5.1 $\pm$ 0.7 <sup>b</sup>	6.3 $\pm$ 0.5

$\alpha$ -SMA =  $\alpha$ -smooth muscle actin; RECA-1 = rat endothelial cell antibody.

<sup>a</sup>vs G3  $P < 0.01$ .

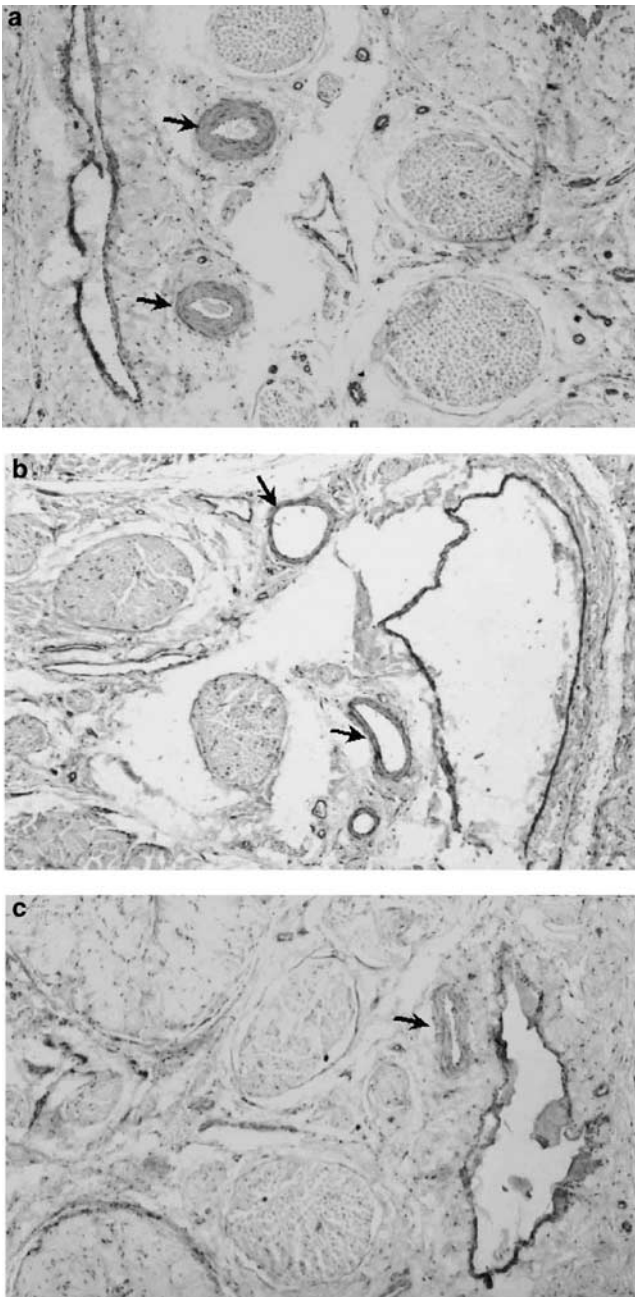
<sup>b</sup>vs G1  $P < 0.01$ .

<sup>c</sup>Area with positive immunostaining for RECA-1 in arteries from cavernous tissue, expressed in  $\mu\text{m}^2$ .

<sup>d</sup>Area corresponding to tunica media in arteries from cavernous tissue, expressed in  $\mu\text{m}^2$ .

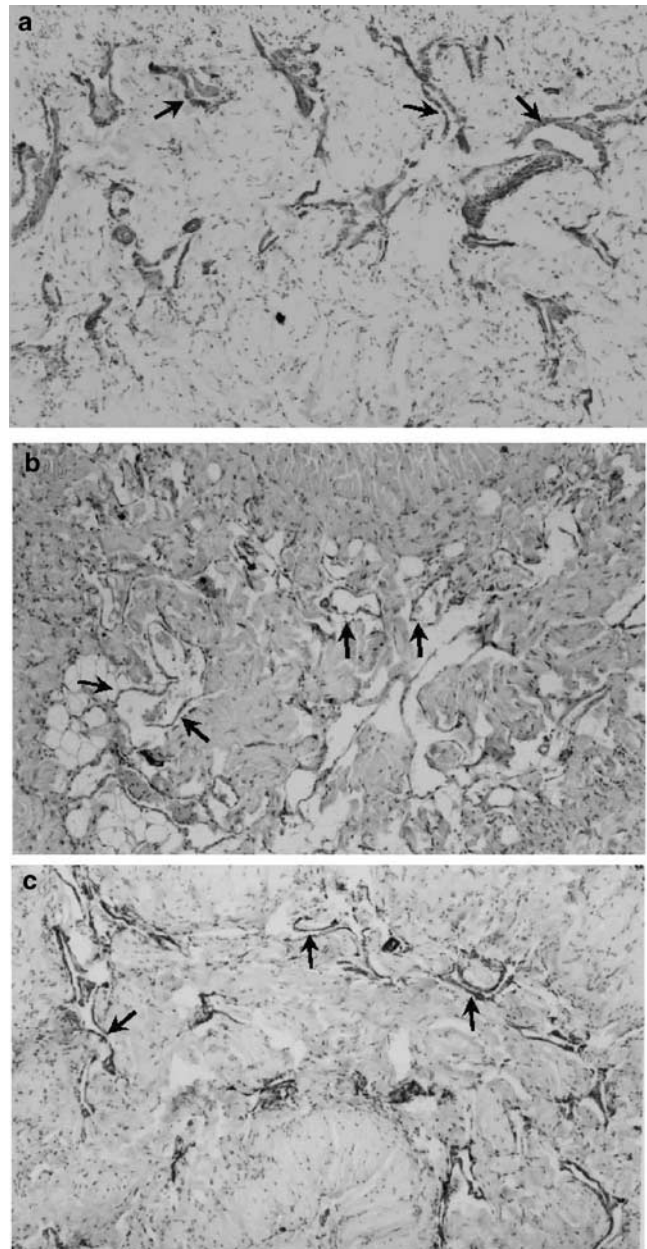
<sup>e</sup>vs G1 and G3  $P < 0.01$ .

<sup>f</sup>Percentage of immunostaining positive for collagen type III on  $20 \times 10^4 \mu\text{m}^2$  of cavernous tissue.



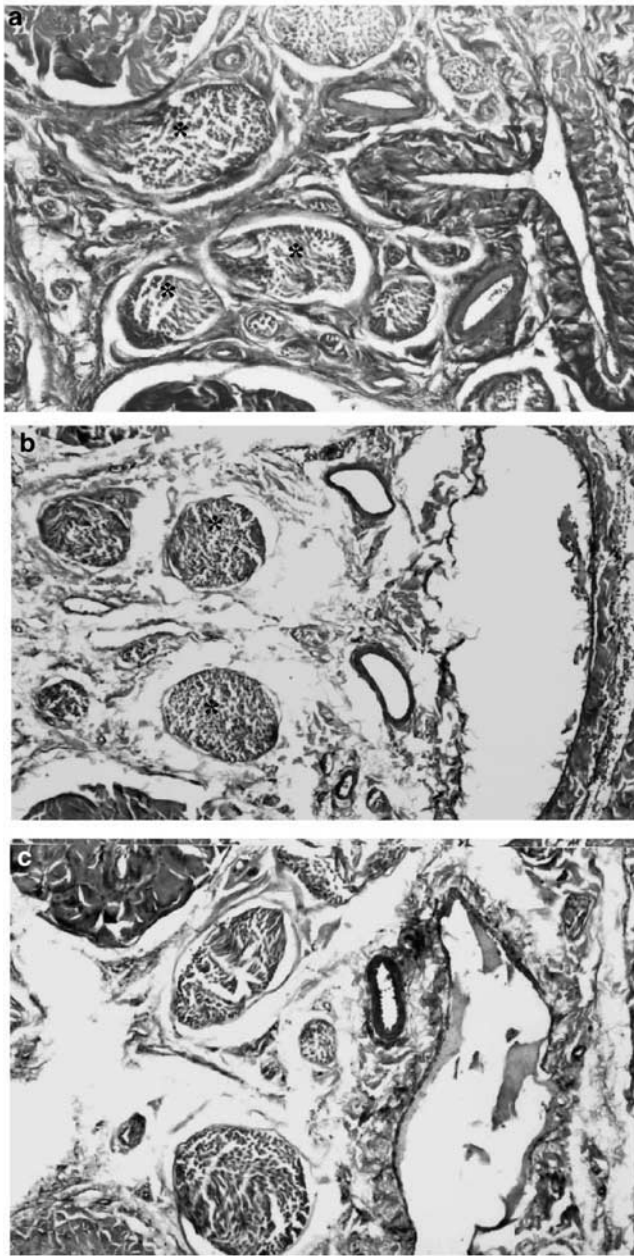
**Figure 1** Immunostaining for  $\alpha$ -SMA in vessels from CT. (a) Section from SHR showing notorious increase in  $\alpha$ -SMA in the vascular wall (arrows). (b) Section from SHR+candesartan cilexetil showing a remarkably less amount in  $\alpha$ -SMA in the vascular wall (arrows). (c) Section from WKY rat with a normal amount in  $\alpha$ -SMA in the vascular wall, as the arrow indicates (anti- $\alpha$ -SMA,  $\times 100$ ).

muscle within the corpus cavernos (cavernous smooth muscle layer in the CS) and penile arteries, which impedes the modulation of penile blood flow by physiologic regulators such as nitric oxide (NO).<sup>20</sup> Relaxation of the CSM causes increased compliance of the CS, leading to penile engorgement and erection. Therefore, any impediment to achieve this synchronized mechanism could lead to ED. A



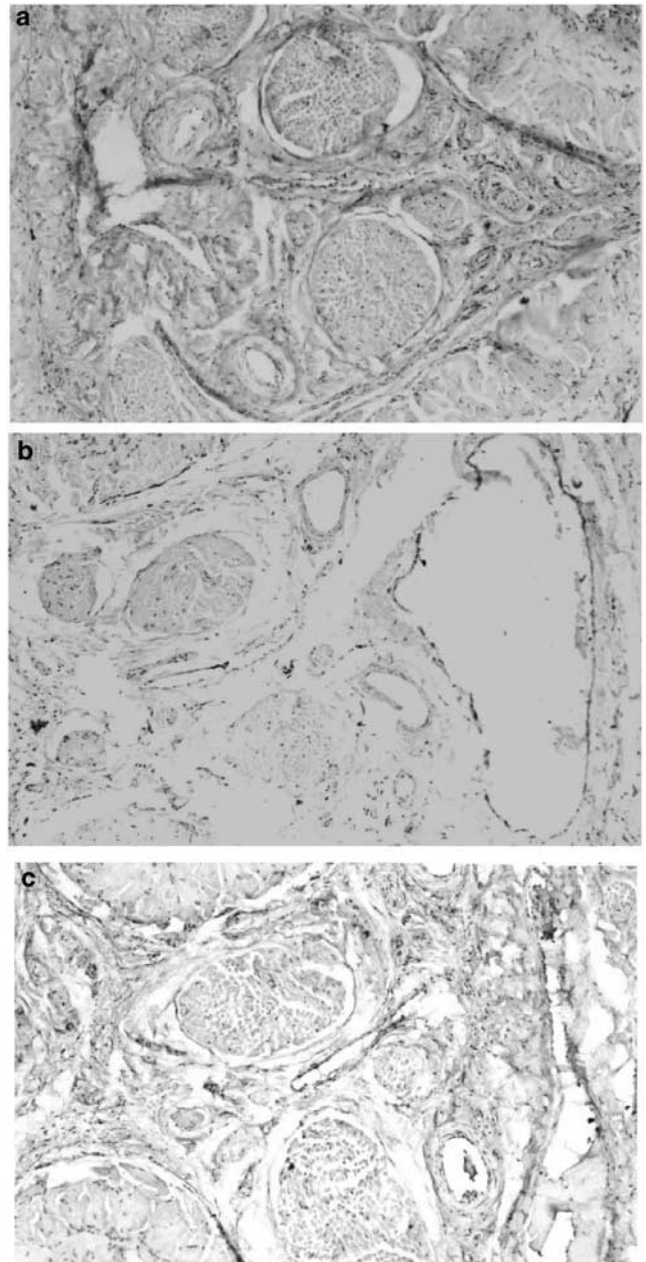
**Figure 2** Immunostaining for  $\alpha$ -SMA illustrates CSM layer in CS. (a) Section from SHR. Note an increase in the thickness of the CSM layer in CS (arrows). (b) Section from SHR+candesartan cilexetil. Arrows show a substantial reduction in the thickness of the CSM layer in CS. (c) Section from WKY rat with normal thickness of the CSM layer in CS, as the arrows indicate (anti- $\alpha$ -SMA,  $\times 100$ ).

number of studies report different changes in the CSM cells. Some of these changes are considered as the result of the aging process and others correspond to pathological modifications probably due to certain diseases or specific risk factors related to the vascular system.<sup>21-23</sup> In extracavernosal segments of the vascular bed, the tone and contractility of VSM and, then, the modulation of regional blood



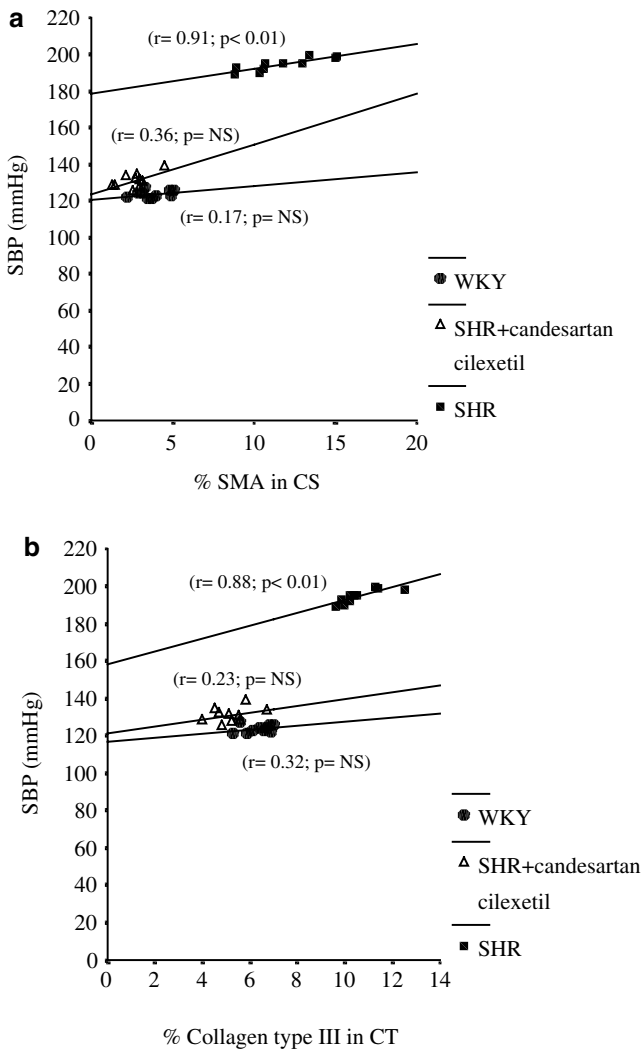
**Figure 3** Masson's trichrome staining showing extracellular matrix expansion in CT. (a) Section from SHR illustrating a substantial increase in the extracellular matrix (in blue). (b) Section from SHR + candesartan cilexetil with clear less expansion in the extracellular matrix (in blue). (c) Section from WKY rat showing a normal amount of extracellular matrix (in blue) (Masson's trichrome,  $\times 100$ ).

flow depend on a balance between angiotensin II and NO.<sup>24–26</sup> There is compelling evidence supporting that corpus cavernosum produces and secretes physiologically relevant amounts of angiotensin II and that the local renin–angiotensin system is involved in the regulation of CSM tone through angiotensin II receptor subtype 1.<sup>27,28</sup> Intracavernosal injection of angiotensin II causes contraction of



**Figure 4** Immunostaining for collagen type III in CT. (a) Section from SHR. Note an important amount in collagen type III fibers (in brown) around the vessels. (b) Section from SHR + candesartan cilexetil with evident lower amount in collagen type III fibers (in brown) around the vessels. (c) Section from WKY rat. Scanty amount in collagen type III fibers (in brown) around the vessels (anti-collagen type III,  $\times 100$ ).

CSM and terminates spontaneous erection in anesthetized dogs, while administration of an angiotensin II receptor antagonist results in smooth muscle relaxation and, therefore, erection.<sup>27</sup> Numerous studies have demonstrated that angiotensin II through AT1 receptor induces VSM cell proliferation and hypertrophy and has an essential role in extracellular matrix expansion.<sup>29–32</sup> Furthermore,



**Figure 5** Relationship between SBP and the percentage of  $\alpha$ -SMA in CS and the percentage of collagen type III in CT in all groups. (a) Correlation between SBP and the percentage of  $\alpha$ SMA in CS in all groups. Note a high and significant correlation between these two variables in untreated SHR, whereas SHR with candesartan cilexetil and WKY rats present a nonsignificant (NS) correlation. (b) Correlation between SBP and the percentage of collagen type III in CT in all groups. Untreated SHR present a significant correlation between these two variables in contrast to SHR with candesartan cilexetil and WKY rats, which show a nonsignificant (NS) correlation.

cell culture, animal models and clinical studies have supported the idea that AT1 receptor activation causes vascular superoxide release *in vitro* and *in vivo* leading to impairment of endothelium-dependent vasodilation.<sup>33,34</sup> In agreement with these findings, inhibition of AT1 receptor activation by AT1 receptor antagonist or ACE inhibitors improves endothelial dysfunction.<sup>35–37</sup> Recent studies using different strains of hypertensive rats have provided substantial information supporting the concept that drugs that interact with RAAS contribute to normalize erectile response and penile vascular structure.<sup>38,39</sup> These effects are considered independent

of the blood pressure-lowering effect since other antihypertensive drugs, for instance hydralazine, which produces a similar reduction in blood pressure without affecting the RAAS, did not result in a significant change in the penile structure.

Candesartan cilexetil as well as other angiotensin II antagonists have shown a considerable benefit controlling VSM growth and modulating extracellular protein synthesis in different tissues.<sup>40–43</sup> It is worth mentioning that many characteristics of the CSM are similar to those of VSM; therefore potential pathophysiologic projections, particularly for the use of selective angiotensin II blocking agents, have gained importance.

Since both CSM cells hypertrophy and/or hyperplasia, by producing a substantial impediment to achieve the complete compliance of the CS and, additionally, by inducing the surrounding connective tissue to express a remarkable amount of collagen type III, can considerably contribute to difficulties in normal penile tumescence, the control in both CSM growth and extracellular matrix modulation in CT plays a relevant role in this setting.

Interaction against local RAAS through AT1 receptor antagonism by candesartan cilexetil may improve penile erectile dysfunction occurring frequently in hypertensive patients by hemodynamic and nonhemodynamic mechanism of action, by at least five ways: (1) by controlling CSM growth; (2) by increasing penile blood flow through local generation of NO, and producing CSM relaxation; (3) by modulating extracellular matrix expansion in CT; (4) by improving endothelial dysfunction; and (5) by overwhelming the decrease in systemic blood pressure through improving the local blood flow.

Recent clinical experience in hypertensive patients with ED using losartan, another AT1 receptor antagonist with less affinity than candesartan for the AT1 receptor, has demonstrated some benefit with respect to satisfaction and frequency of sexual activity.<sup>44</sup>

In conclusion, despite the fact that the present experiment is limited to morphological evidence, we think that our results demonstrate that candesartan cilexetil produces a clear benefit regarding morphological abnormalities in CT caused by high blood pressure in this genetic model of arterial hypertension. At the same time, we also assume that the functional impact of these findings should be determined in future studies.

Considering the essential role of local RAAS in the regulation of erectile function, the data presented in our study provide substantial evidence supporting the potential additional value of AT1 receptor antagonism in the management of patients with hypertension. Since sexual life is one of the most important concerns in the antihypertensive therapies, the possibility of controlling high blood pressure along with erectile tissue protection rises in significance.

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