Differential Suppression of Pressure-Overload Cardiac and Aortic Hypertrophy in Rats by Angiotensin-Converting Enzyme Inhibitors

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ABSTRACT—Role of tissue angiotensin-converting enzyme (ACE) in the development of pressure-overload cardiovascular hypertrophy was examined in rats by comparing the inhibitory effect of trandolapril (high efficiency on tissue ACE) with that of enalapril (low efficiency) at equally antihypertensive doses. Rats with abdominal aorta banded or sham-operated were orally treated with trandolapril (0.5 mg/kg per day), enalapril (20 mg/kg per day) or vehicle for 8 weeks after the surgical maneuvers. In vehicle-treated rats, the banding raised the intra-aortic systolic pressure by 58%, diastolic pressure by 31%, maximum velocity of pressure rise by 65%, left ventricular (LV) weight by 41%, LV hydroxyproline concentration by 56%, aortic mass by 46%, LV ACE activity by 45%, and aortic ACE activity by 265%. Although both drugs equally reduced the aortic systolic pressure to approx. 70% and diastolic pressure to approx. 80% that of banded rats receiving vehicle, trandolapril partially prevented the LV hypertrophy, whereas enalapril yielded non-significant suppression. Trandolapril completely prevented the LV increments in hydroxyproline and ACE activity, whereas enalapril partially inhibited the LV hydroxyproline increase with little inhibition of LV ACE activity. In contrast, both inhibitors almost completely prevented the aortic hypertrophy, with the ACE activity of the aorta being potently inhibited. These results suggest that tissue ACE is the principal factor for pressure-induced aortic hypertrophy and an important yet non-essential factor for LV hypertrophy.

Keywords: Aortic banding, Trandolapril, Enalapril, Collagen, Organ difference

High blood pressure is a major stress to which compensatory hypertrophy occurs in cardiac (1) and arterial walls (2). In this sense, cardiovascular hypertrophy is regarded as a result of physiologically adaptive mechanisms. However, many lines of clinical evidence have shown that the left ventricular hypertrophy (LVH) imparts a substantial risk of morbidity and mortality from cardiovascular diseases including heart failure, myocardial infarction and cardiac arrhythmia (1, 3). For example, incidence of other cardiovascular diseases are increased several fold if cardiac hypertrophy is present (4–6). Cardiac hypertrophy itself is a morbid state resulting from over-adaptation of the heart to pressure load and is recognized as a direct cause of cardiac death (7). Hypertrophy of a large artery is also a risk of cardiovascular diseases such as arteriosclerosis, atherosclerosis and aortic aneurysm (2, 8, 9). Despite such importance in an epidemiological sense, pathophysiological mechanisms underlying the development of cardiovascular hypertrophy have so far been incompletely understood. Therefore, to improve the long-term prognosis of cardiovascular diseases, investigations should be performed with the aim of elucidating the pathophysiological basis of cardiovascular hypertrophy.

It is known that antihypertensive agents of several different classes such as \( \alpha_1 \) - and \( \beta \)-adrenoceptor blockers, thiazide diuretics and calcium antagonists are capable of reducing LVH, presumably in part by reducing pressure load. Interestingly, angiotensin-converting enzyme (ACE) inhibitors are suggested to be more effective in regressing LVH (10–12) and hypertensive vascular hypertrophy (13, 14) than other classes of antihypertensive agents with equal hypotensive effects. The reason for such a class-difference is not fully understood, but presumably it is because the tissue ACE that is upregulated by hypertensive stress in the heart (15) and large vessels (16–18) may aggravate cardiovascular hypertrophy by producing angiotensin II which has potent growth-promoting activity (19–21). However, it is not clear how and to what extent the tissue ACE participates in hyper-
tensive cardiac and aortic hypertrophy. To address this question, we established rat models with their left ventricle (LV) and upper aorta exposed to pressure overload by narrowing the abdominal aorta and used them to test our hypothesis that the tissue ACE may be a critical factor to promote cardiovascular hypertrophy by quantitatively determining the pressure load-induced upregulation of cardiac and aortic ACE and also by estimating the effects of tissue ACE inhibition on cardiovascular hypertrophy.

To analyze the role of local tissue ACE in cardiovascular hypertrophy, the present study employed trandolapril for its high efficiency in tissue ACE inhibition, while enalapril was used as a reference drug because it would induce much less effective and much less persistent inhibition on tissue ACE than trandolapril with equal hypotensive effect (22). Taking advantage of the obvious difference in efficiency between these 2 agents and by using the agents at their doses that induce an equal reduction of pressure overload, we intended to distinguish the antihypertrophic effect due to ACE inhibition from that due to pressure load reduction. This would enable us to estimate the net role of tissue ACE in pressure-overload cardiovascular hypertrophy.

MATERIALS AND METHODS

Aortic banding

Male Wistar rats (SLC, Shizuoka), 8-week-old and weighing 230 to 260 g, were randomly allocated into 6 groups. Groups 1, 2 and 3 underwent coarctation of the abdominal aorta (banded groups, n=6 each). Under pentobarbital anesthesia (40 mg/kg b.w., i.p.), the abdominal aorta was constricted at 3 sites in the area from immediately above the right renal artery down to the superior mesenteric artery with 3/0 silk suture by ligation of the aorta together with a stainless steel wire (0.8 mm φ), which was pulled out thereafter. Groups 4, 5 and 6 (n=5 each) were sham-operated groups in which the aorta was only exposed but no narrowing was made. The present study was conducted in line with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society and by the Committee of Shimane Medical University.

Administration of ACE inhibitors

The doses of trandolapril (0.5 mg/kg per day) and enalapril (20 mg/kg per day) that exerted equal reduction of intra-thoracic aorta pressure in the abdominal aorta-banded rats upon repeated dosing for 2 weeks were determined in a pilot study using a separate set of rats. Drug treatment by gavage (once daily) began on day after the above mentioned surgery and lasted for 8 weeks. Groups 1 and 4 received the vehicle (0.25% carboxymethyl-cellulose-Na [CMC-Na] solution containing 1% dimethyl sulfoxide [DMSO]). Groups 2 and 5 received enalapril and groups 3 and 6 were given trandolapril. Both of the ACE inhibitors were prepared as stock solutions in neat DMSO, which was diluted with CMC-Na solution to appropriate concentrations immediately before the daily dosing.

Hemodynamic measurements and tissue preparation

At 24 hr after the final dosing of 8-week repetitive treatment, rats were anesthetized with pentobarbital (40 mg/kg, i.p.) and a polyethylene catheter was inserted into the right common carotid artery of each rat so that tip of the catheter was placed immediately above the aortic valve. Through this catheter, which was connected to a pressure transducer (DX-312; Nihon Kohden, Tokyo), intra-aortic systolic blood pressure (SBP) and diastolic blood pressure (DBP), maximum velocity of pressure rise (Ao dp/dtmax), and heart rate (HR) were measured by use of an pressure amplifier (AP-621G, Nihon Kohden), a differential operator unit (EQ-601G, Nihon Kohden), and a HR counter (AT-621G, Nihon Kohden), respectively.

Immediately after these measurements were accomplished, rats were sacrificed by an intra-arterial injection of 1 M KCl (1.5 ml) and then the heart and the upper aorta including the aortic arch and thoracic aorta (down to the diaphragm) were excised. Wet weights were measured for the LV and the upper aorta. Length of the upper aorta was also measured to calculate its weight per unit length. A cross-section of LV with 1-mm thickness was taken from the mid portion and fixed in neutral buffered formalin. After fixation for 24 hr, the slices were photographed, and the cross-sectional area of LV wall was measured by a 2-dimensional image analyzer (Nikon Cozmozone 1SA, version 2; Nikon, Tokyo). The slices then were embedded in paraffin to make 5-μm-thick sections, which were stained with hematoxylin-eosin and Azan for morphometric analysis.

Extraction and quantification of hydroxyproline from the LV

Hydroxyproline concentration in the LV was quantified for the index of fibrous degeneration. The LV tissue was added with 30 volumes (v/v) of 6 M HCl and hydrolyzed at 110°C for 22 hr in a sealed glass tube. Each hydrolyzed sample was dried, neutralized with NaOH, dried in vacuo overnight, and then dissolved in 0.02 M HCl. Assay of hydroxyproline was performed by an amino acid analyzer (Model 853; Hitachi, Tokyo) on the basis of absorbance at 440 nm. Total amino acid concentration of the same samples was determined by the ninhydrin reaction and converted to the total protein weight, to which the relative amount of hydroxyproline was calculated.
Ex vivo measurement of ACE activity of LV and aorta

From the excised and weighed LV and aorta, tissue ACE was extracted as previously described (16) along with the potentially remaining drugs within the tissues. Tissues were minced and homogenized with 5 volumes (v/w) of medium consisting of 20 mM Tris-HCl (pH 8.3), 5 mM Mg acetate, 30 mM KCl, 0.25 M sucrose, and 0.5% (v/v) Nonidet P-40, a non-ionic detergent to solubilize the membrane-bound ACE and lipophilic drugs as well. The homogenate was centrifuged (20,000 × g for 20 min) at 4°C to obtain the supernatant into which tissue ACE and residual drugs, if any, were extracted. A 50-μl aliquot of the supernatants was incubated with 5 mM hippuryl-His-Leu substrate (Peptide Institute, Mino, Osaka) at 37°C for 30 min in the buffer containing 300 mM NaCl and 100 mM KH₂PO₄ (pH 8.3). The reaction was stopped with 750 μl of 3% metaphosphoric acid (Nacalai Tesque, Kyoto), and denatured protein was removed by centrifugation (3000 rpm, 10 min). An aliquot of the supernatant was analyzed for its content of hippuric acid with a reverse-phase HPLC (LC-10AD; Shimadzu, Kyoto) equipped with a Puresil C18 column (4.6 mm i.d. × 150 mm; Waters, Milford, MA, USA) on the basis of absorbance at 228 nm. The column was eluted with a 1:1 mixture of 10 mM KH₂PO₄ (pH 3.0) and methanol at a flow rate of 0.7 ml/min with the column temperature maintained at 40°C. The blank for each sample was set by adding 5 mM EDTA-Na₂. The hippuric acid-liberating activity that was inhibited by EDTA-Na₂ was defined as net ACE activity. One unit of ACE activity was the amount of the enzyme that produced 1 μmol/min of hippuric acid at the above-described conditions. Protein concentration of the tissue extracts was determined with bichinchoninic acid (BCA Protein Assay Reagent; Pierce, Rockford, IL, USA) according to the method by Smith et al. (25) using bovine serum albumin as a standard.

Chemicals

Enalapril maleate (Sigma Chemicals, St. Louis, MO, USA), CMC-Na (Maruishi Pharmaceuticals, Osaka), DMSO (Nacalai Tesque) and pentobarbital sodium (Dainabot, Osaka) were purchased from the respective manufacturers. Trandolapril was provided by Roussel-UCLAF, Romainville, France.

Statistical analyses

The results are presented as the mean±S.E.M. Statistical analysis was performed by Student's t test when a single treatment group was compared with a control group. Multiple comparison was made by ANOVA and post-hoc Bonferroni/Dunn's test. A difference was considered significant when P<0.05.

RESULTS

Systemic condition

After random allocation, there was no significant difference in body weight among the 6 groups. The body weight after 8-week treatment did not differ among the 3 different treatment groups within the subclass either banded (372±18 g for [banded + vehicle], 357±22 g for [banded + enalapril], and 393±10 g for [banded + trandolapril] group) or sham-operated (411±7 g for [sham + vehicle], 386±5 g for [sham + enalapril], and 386±9 g for [sham + trandolapril] group). There was no significant difference in wet weights of the lung or the liver (Table 1) among the 6 groups. Neither symptoms nor organ abnormalities indicating congestive heart failure (dyspnea, edema, ascites, etc.) was evident in any of the animals at the end of the experimental period.

Hemodynamics

In the [banded + vehicle] group, SBP was increased by 74 mmHg and DBP by 29 mmHg compared with those of the [sham + vehicle] group (Fig. 1: A and B). The increase in SBP due to aorta banding was significantly suppressed by long-term treatments with trandolapril and enalapril,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lung (mg/100 g b.w.)</th>
<th>Liver (mg/100 g b.w.)</th>
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<tr>
<td></td>
<td>Sham (n=5)</td>
<td>Band (n=6)</td>
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<tr>
<td>Vehicle</td>
<td>392.8±39.3</td>
<td>407.2±23.7</td>
</tr>
<tr>
<td>Enalapril</td>
<td>395.8±27.0</td>
<td>410.3±50.3</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>362.3±19.9</td>
<td>407.4±24.7</td>
</tr>
</tbody>
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Sham: sham-operated group, Band: aortic banding group. Each group was treated with vehicle, enalapril or trandolapril for 8 weeks. Data are shown as the mean±S.E.M.
although neither drug was able to prevent the SBP rise completely to the level of the [sham + vehicle] group. In contrast, both drugs reduced the DBP to a level that was insignificantly different from that of the [sham + vehicle] group. No significant difference was detected in the SBP or DBP between the [banded + enalapril] and [banded + trandolapril] groups, confirming that the doses used in the current study were equidepressor as was designed. The Ao dp/dt\textsubscript{max}, an index of pressure overload onto the LV and upper aorta, was evidently increased by 837 mmHg/sec in the [banded + vehicle] group (Fig. 1C).

Both enalapril and trandolapril lowered this increase to the same extent, although both agents failed to reverse this index completely to the normal level. Neither coarctation nor drug treatments resulted in significant alterations in the HR at the end of the experimental period (Table 2).

**Morphological changes and collagen accumulation in the LV**

In comparison with the [sham + vehicle] group (Fig. 2A), the [banded + vehicle] group (Fig. 2B) showed myo-

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**Fig. 1.** Effects of abdominal aortic banding on systolic (A) and diastolic (B) blood pressure and the maximum velocity of intra-aortic pressure rise (Ao dp/dt\textsubscript{max}) (C), which were directly measured via an intra-aortic catheter, and the influence thereon of enalapril and trandolapril treatments. [ ]: 8 weeks after sham-operation (n = 5 each), [ ]: 8 weeks after aortic banding (n = 6 each). Data are shown as the mean ± S.E.M. *P < 0.05, **P < 0.01 vs sham-operated group. #P < 0.05 and ##P < 0.01 vs [banded + vehicle] group.
Table 2. Heart rate after 8 weeks of treatment (bpm)

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Enalapril</th>
<th>Trandolapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>376±11 (n=5)</td>
<td>377±5 (n=5)</td>
<td>392±16 (n=5)</td>
</tr>
<tr>
<td>Band</td>
<td>378±10 (n=6)</td>
<td>360±21 (n=6)</td>
<td>363±18 (n=6)</td>
</tr>
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</table>

Sham: sham-operated group, Band: aortic banding group. Each group was treated with vehicle, enalapril or trandolapril for 8 weeks. Data are shown as the mean±S.E.M.

cardial hypertrophy and marked accumulation of collagen in the interstitium. Both enalapril (Fig. 2C) and trandolapril (Fig. 2D) decreased the myocardial hypertrophy and fibrous degeneration of the LV, although trandolapril exerted a more marked effect.

In the vehicle-treated groups, the LV weight of the banded group showed a 41% increase compared with that of the sham group (Fig. 3A). The long-term treatment with trandolapril suppressed the cardiac hypertrophy significantly yet not completely to the normal level (Fig. 3A). Enalapril showed a tendency to reduce the cardiac hypertrophy, but the difference did not reach a significant level (Fig. 3A). Cross-sectional area of LV was also increased in the [banded+vehicle] group (24.3±1.5 mm² /100 g b.w., P<0.01) compared with that of the [sham+vehicle] group (18.1±0.5 mm²/100 g b.w.). Trandolapril inhibited the increment in the LV cross-sectional area significantly (19.3±0.6 mm²/100 g b.w., P<0.05), whereas enalapril did not (21.6±1.2 mm²/100 g b.w.).

Hydroxyproline concentration in the LV was increased in the [banded+vehicle] group compared with the [sham+vehicle] group (Fig. 3B). Such a pressure overload-induced increase in hydroxyproline concentration in the LV was completely blocked by the long-term treatment with trandolapril, but was only partially attenuated by the enalapril treatment at its equidepressor dose. Neither trandolapril nor enalapril influenced the LV hydroxyproline concentration of the sham-operated groups.

Fig. 2. Histological appearances of left ventricle (LV: coronal section of middle LV portion and Azan-stained preparation) treated with vehicle, enalapril or trandolapril for 8 weeks. A: Sham-operated group treated with vehicle. B: Aorta-banded group treated with vehicle. C: Aorta-banded group treated with enalapril. D: Aorta-banded group treated with trandolapril. Bars indicate 100 μm (original magnification × 50).
ACE activity in the LV

LV ACE activity was increased by 45% in the [banded +vehicle] group, although it was not significantly different from that of the [sham +vehicle] group (Fig. 3C). The ex vivo measurement of ACE activity of the LV tissue that was obtained 24 hr after the final drug administration revealed that enalapril was no longer effective at all in persistently inhibiting the LV ACE activity of the banded group, whereas trandolapril still completely suppressed the LV ACE activity to the level below that of the vehicle-treated heart. It was noted that trandolapril suppressed the LV ACE activity of the sham-operated rats below the basal level as well.

Morphological changes in the upper aorta

The weight per unit length of the upper aorta was significantly increased in response to pressure overload in the [banded +vehicle] group (Fig. 4A). Both enalapril and trandolapril suppressed the pressure overload-induced increase in aortic weight almost completely to the normal level. In contrast to their effects on the LV weight, preventive effects on the aortic hypertrophy were not
different between the 2 drugs.

**Tissue ACE activity in the upper aorta**

The pressure overload induced a marked increase (by 265%) in ACE activity of the upper aorta of the [banded + vehicle] group (Fig. 4B). Long-term trandolapril treatment suppressed not only the pressure stress-induced increase in aortic ACE activity but also the basal ACE activity of the sham-operated aorta. Consequently, trandolapril depressed the aortic ACE activity in both banded and sham groups to a similar level apparently below that of the [sham + vehicle] control group, although not significantly different from the normal control. In contrast to its effect on the LV ACE activity, enalapril treatment exhibited a potent suppression of the pressure overload-induced increment in aortic ACE activity, yet it was not as potent as the trandolapril treatment (Fig. 4B).

**DISCUSSION**

The current study demonstrated quantitative alterations in cardiovascular hypertrophy in association with the changes in tissue ACE activity. The pressure overload induced the hypertrophy of the LV and upper aorta, LV collagen accumulation, and upregulation of tissue ACE activity in the LV and aorta. Trandolapril was an effective tool for elucidating the role of tissue ACE in the development of cardiovascular hypertrophy because it completely reversed the increment of tissue ACE activity both in the heart and aorta. Despite this fact, trandolapril only partly suppressed the cardiac hypertrophy, whereas it completely prevented the aortic hypertrophy and cardiac collagen accumulation. These findings suggest differential roles of the upregulated tissue ACE in the development of cardiac and aortic hypertrophy and cardiac collagen synthesis.

Inter-organ difference was also detected in the increases of tissue ACE activity: the increase was only 45% of the

![Graph](image-url)

**Fig. 4.** Effects of abdominal aortic banding on the weight of upper aorta per mm length (A) and angiotensin-converting enzyme (ACE) activity in the aorta (B), and the influence thereon of enalapril and trandolapril treatments. [**]: 8 weeks after sham-operation (n=5 each). [***]: 8 weeks after aortic banding (n=6 each). Data are shown as the mean ± S.E.M. *P < 0.05, **P < 0.01 vs sham-operated group. †P < 0.05 and ‡P < 0.01 vs [banded + vehicle] group.
control ACE level in LV, whereas it was as high as 265% in the aorta. Although the regulatory mechanism of ACE gene expression is poorly understood, stretching is a suggested stimulus to induce ACE gene expression (15, 26). Thus, the observed difference between the heart and aorta may be ascribed to a presumable difference in stretch load between them. The pressure overload stretches the aortic wall continually both at systolic and diastolic phases, thereby substantially stimulating the ACE gene expression. Continuous stretching is suspected from the fact that intra-aortic DBP was increased as well as the SBP. LV systolic pressure also must have been elevated due to an increased afterload. However, LV end-diastolic pressure is unlikely, if any, to be elevated as long as the LV is in compensation. This is supported by the fact that no sign of LV failure was evident in the aorta-banded rats (Table 1 and ref 10). Moreover, even if LV end-diastolic pressure (normally approx. 5 mmHg) is doubled, it still is at an obviously lower level than end-diastolic aortic pressure because aortic valves separate these 2 compartments during diastole. Thus, the LV wall should have received less stretching than did the aorta during the diastolic phase, thereby less stimulus to ACE gene expression (15, 27, 28). Another line of evidence supporting our idea is that the cardiac ACE mRNA level was increased in cardiomyopathic hamsters only after congestive heart failure became evident (29). Much less induction of cardiac ACE than aortic ACE may indicate less importance of tissue ACE in development of cardiac hypertrophy unless complicated with heart failure.

Notwithstanding the above argument, another possibility that may not be excluded is that the observed difference between the heart and aorta can be ascribed to the difference in different cells (cardiomyocytes vs vascular smooth muscle cells) or merely to the difference in the quantitative levels of tissue ACE activity.

Failure of trandolapril to completely prevent the cardiac hypertrophy despite its complete inhibition of cardiac ACE activity can be ascribed to the fact that the drug could not totally suppress the pressure load onto the LV. Pressure stress may induce cardiotoxic factors other than ACE (21, 30, 31). In fact, ACE (and its catalytic product angiotensin II) is not the sole factor that is induced by pressure overload to promote cardiac hypertrophy (21, 32–34). Recent reports (34, 35) demonstrated that pressure load induced cardiac hypertrophy in the mice whose angiotensin AT1-receptor gene was knocked out, indicating that angiotensin II signaling is not essential for cardiac hypertrophy. It is lately suggested that the ACE-angiotensin II-AT1-receptor system may be just a co-stimulatory signal to the MAP kinase signaling cascade which is essentially responsible for pressure-overload cardiac hypertrophy (33, 34).

In contrast to the anti-cardiotoxic effect of trandolapril, the agent completely depressed the collagen accumulation and increase of hydroxyproline content in LV. Enalapril also suppressed hydroxyproline concentration in the hypertrophic LV partially yet significantly; this finding may appear inconsistent with the fact that enalapril did not inhibit the LV ACE activity. It should be noted, however, that the LV ACE activity was measured ex vivo as late as 24 hr after the final dosing, when the enalapril effect on cardiac ACE no longer persisted (22). It is reasonable to suppose that enalapril (20 mg/kg, present study) inhibited cardiac ACE activity at least in part for some while after oral administration, because enalapril (10 mg/kg) inhibited rat cardiac ACE activity at least up to 6 hr after an oral dose (22). Thus, it may be concluded that regulation of collagen synthesis depends on tissue ACE activity to a much higher extent than does myocardial hypertrophy. This notion is supported by many other investigations that indicate the profibrotic action of angiotensin II (19, 36) and the anti-fibrotic effect of ACE inhibitors (37–40). The molecular mechanism by which tissue ACE upregulates collagen synthesis remains an open question.

In the aortic hypertrophy, the role of upregulated ACE seems more important than in the cardiac hypertrophy. As already mentioned, the aorta responded to pressure load with a much larger increase in ACE activity than the heart. Enalapril and trandolapril were similarly effective in preventing almost completely the aortic hypertrophy, although trandolapril showed more marked ACE inhibition than enalapril. These results indicate that the pressure overload-induced increase in aortic ACE is primarily responsible for aortic hypertrophy. Our contention is strongly supported by the fact that the ACE inhibitor perindopril, but not the β-blocker atenolol, reduced the vascular hypertrophy in patients with essential hypertension even though atenolol was more hypotensive than perindopril (14). It should be noted that trandolapril did not affect the normal construction of the sham-operated aorta, although the agent suppressed the aortic ACE activity to a subnormal level. Thus, it is the excessive, upregulated ACE that may contribute to cardiovascular hypertrophy, but not the physiological ACE which is normally present in non-hypertrophic tissues.

In conclusion, pressure overload induced the cardiovascular hypertrophy in association with upregulation of tissue ACE. The upregulated ACE is an important yet not essential factor for cardiac hypertrophy, whereas it is the critical factor for LV collagen accumulation and aortic hypertrophy. To attain more benefit for the treatment of patients with hypertensive cardiovascular diseases, those ACE inhibitors which have high efficiency in tissue ACE inhibition would be indicated to be beneficial.
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