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International Journal of Cardiology 81 (2001) 123–129

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Diverse effects of chronic treatment with losartan, fosinopril, and amlodipine on apoptosis, angiotensin II in the left ventricle of hypertensive rats☆

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Received 28 February 2001; received in revised form 15 May 2001; accepted 8 August 2001

Abstract

This study was designed to investigate diverse effects of angiotensin II (AngII) type I receptor antagonists, losartan, angiotensin converting enzyme (ACE) inhibitors, fosinopril, and calcium channel blockade, amlodipine on cardiomyocyte apoptosis and AngII in the left ventricle of spontaneously hypertensive rats (SHR). The SHRs were randomized to four groups: SHR-L (treated with losartan, 30 mg kg^{-1} d^{-1}), SHR-F (with fosinopril, 10 mg kg^{-1} d^{-1}), SHR-A (with amlodipine, 10 mg kg^{-1} d^{-1}) and SHR-C (with placebo). The cardiomyocyte apoptosis was examined by in situ TDT-mediated dUTP nick end labeling, AngII concentrations of plasma and myocardium were measured by radio immunoassay at 8 and 16 weeks of the study respectively. The results showed that: (1) compared with SHR-C at 8 and 16 weeks respectively; the systolic blood pressure was decreased similarly in the three treatment groups. Left ventricular weight and mass indexes were reduced in the three treatment groups. The latter parameter at 16 weeks was lower in SHR-F than that in the other two treatment groups. (2) Compared with SHR-C, the cardiomyocyte apoptotic index (APOI) was reduced significantly at 8 weeks only in SHR-F, and at 16 weeks in all three treatment groups. The APOI of SHR-F was lowest among the three treatment groups examined at latter endpoint. (3) Compared with SHR-C at both endpoints of this study, plasma and myocardium AngII levels were increased in SHR-L. However, plasma AngII concentrations were not altered in SHR-F and SHR-A, myocardium AngII concentrations were reduced significantly at 8 weeks only in SHR-F, and at 16 weeks in SHR-F and SHR-A. Meanwhile, myocardium AngII in SHR-F at 16 weeks was lower than that in SHR-A. The results of this study indicate that losartan, fosinopril, and amlodipine each effectively reverses heart hypertrophy and inhibits cardiomyocyte apoptosis, and fosinopril may be most effective in these cardioprotective effects. These findings suggest that the effects of the three blockers on myocardiocyte apoptosis and left ventricular hypertrophy were related to inhibition of the myocardium rennin–angiotensin–aldsterone system.

Keywords: Apoptosis; Cardiac hypertrophy; Angiotensin II; Drug therapy

Increased apoptotic myocytes have been observed in myocardium obtained from patients with end-stage heart failure [1] and myocardial infarction [2] and in myocardium from experimental models of myocardial hypertrophy and failure including the aortic-banded rat [3], the spontaneously hypertensive rat (SHR) [4], rats with myocardial infarction [5], and dogs with pacing-induced failure [6]. Apoptosis is now being considered as one of the determinants of the transition from compensated cardiac hypertrophy to the development of heart failure [4,7]. Inhibition on myocardiocyte apoptosis may prevent and restrain left ventricular hypertrophy and heart failure [7,8]. Several antihypertensive drugs such as ACE in-

☆PII of linked article: S0167-5273(01)00538-1

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0167-5273/01/$ – see front matter
PII: S0167-5273(01)00539-3

hibitors [9], AT_1 receptor antagonists [10,11] and calcium channel blockades [9,11] have beneficial effects on myocardiocyte apoptosis, but the diverse effects of the three blockers on the prevention of apoptosis in hypertensive rats has not been studied. The SHR is an inbred strain of genetically hypertensive rats that achieves plateau elevations in blood pressure at 16–20 weeks of age associated with compensatory cardiac hypertrophy [12]. In the present study, we sought to investigate the diverse effects of AT_1 receptor antagonist, losartan, ACE inhibitor, fosinopril, and calcium channel antagonist, amlodipine on apoptosis and AngII of the left ventricle during progression of cardiac hypertrophy in SHR.

1. Material and methods

1.1. Animal and reagents

Forty SHRs of 16-week-old were provided by the animal laboratory center of Beijing Fuwai Cardiovascular Hospital (Beijing, China) and bred in our laboratory. All rats were housed in individual cages and were fed a standard rat chow and tap water ad libitum. They were maintained in a quiet room at constant temperature (20–22°C)and humidity (50–60%) with 12:12-h light–dark cycle. Losartan, fosinopril and amlodipine were given as presents by Sino-American Shanghai Suibb Pharmaceuticals, MSD and Pfizer Pharmaceuticals USA respectively. An in situ cell apoptosis detection kit was obtained from Sino-American Biotechnology, Beijing, China. AngII radio immunoassay kit was obtained from Northern Biotechnology, Beijing, China. All manipulations were carried out in accordance with institutional guidelines for ethical animal care and use of laboratory animals.

1.2. Experimental design

The rats were randomly divided into four groups: SHR-L (treated with losartan, 30 mg kg^{-1} d^{-1}), SHR-F (with fosinopril, 10 mg kg^{-1} d^{-1}), SHR-A (with amlodipine, 10 mg kg^{-1} d^{-1}) and SHR-C (with placebo, acted as a control group), each group consisted of 10 rats. All treatments were administered once daily by gastric gavage, and animals were weighed weekly to adjust dose accordingly. At 8 and 16 weeks of such a regime, 5 rats randomly obtained from each group were killed respectively under anesthesia with sodium pentobarbital (50 mg kg^{-1} i.p.) by removal of the heart.

1.3. Measurement of blood pressure (BP)

Systolic BP was measured in all animals by the standard tail-cuff method with HX-II sphygmomanometer (made in the cardiovascular physiological research center of Hunan Medical College, China) in conscious animals. Ambient temperature was maintained at 30°C. The animals were acclimated to the restraining cages and tail-cuff apparatus before BP was determined.

1.4. Fixation procedure

Under pentobarbital anesthesia the chest cavity was opened, and the heart was arrested in diastole by intraventricular injection of potassium chloride 1 mol L^{-1} and placed into ice-cold saline for removal of blood. The left ventricle (including interventricular septum) samples were weighed after the right and left atria, right ventricular free wall were dissected. The left ventricular mass index was calculated by dividing the left ventricular weight by the body weight in each animal.

For histopathological investigation, a transmural specimen of the left ventricular myocardium obtained from the free wall at the medium of the left ventricle was fixed in 10% buffered formalin and embedded in paraffin.

1.5. In situ detection of apoptosis

For each heart, 5-μm cross sections which included the endmyocardium, midmyocardium, and epimyocardium of left ventricle were cut by microtome and examined for apoptosis. Apoptosis was detected by an in situ terminal deoxynucleotidyl-transferase-mediated 2′-deoxyuridine 5′-triphosphate (dUTP) nick end labeling (TUNEL) technique. The procedure was performed according to the manufacturer's instructions. Briefly, slides were deparaffinized and rehydrated by serial changes of xylene and ethanol. The tissue was treated with 0.25% proteinase K (Sigma) in phosphate-buffered saline at room

temperature for 20 min. To block endogenous peroxidase, the slides were incubated with 3% hydrogen peroxide in methanol for 20 min and then incubated with 300 U/ml of terminal deoxynucleotidyl transferase (TdT) and 20 μM biotin-16-dUTP in TdT buffer (30 mM tris(hydroxymethylaminiomethane), pH 7.2, 140 mM sodium cacodylate, and 1 mM cobalt chloride). The incubation was carried out in a humidified chamber at 37°C for 60 min. On another slide, the TdT incubation was omitted to serve as a negative control. After end-labeling, the section was incubated with avidin–biotin complex containing horseradish peroxidase, stained with diaminobenzidine, and counterstained with benatoxylin. Apoptotic nuclei stained brown, and nonapoptotic nuclei blue.

Tissue sections from each myocardial specimen were examined microscopically at ×40 magnification. Cardiomyocytes, which were well-shaped, elongated and strained cells, were easily distinguished morphologically, under a light microscope at high magnification, from other nonmyocytes. Apoptotic cells were quantified by counting the positive-staining nuclei in each whole section. The percentage of apoptotic cells was determined with apoptotic index (APOI), which was calculated by dividing the number of positive-staining cardiomyocyte nuclei by the total number of cardiomyocyte nuclei and multiplying that value by 100.

1.6. Determination of AngII in myocardium and plasma

After weighing and blotting, a transmural specimen of the left ventricle was homogenized with 0.9% NaCl (10 ml g^{-1}), adding enzyme inhibitors (contained 0.3 mmol L^{-1} Na_2-edetic acid, 0.3 mmol L^{-1} dimercarprol, and 0.3 mmol L^{-1} oxine sulphate), the homogenates were boiled, centrifuged, then the supernatant was shifted to prechilled polyethylene tubes and stored at −20°C or a colder temperature. Blood was collected from the right ventricle before the heart was arrested. Two ml of blood were placed into a chilled tube containing the enzyme inhibitors, then centrifuged within 1 h at 4°C, 2500 rpm for 10 min. The supernatant plasma was stored at −20°C or a colder temperature. AngII concentration was determined by radio immunoassay using Type SIV0682 (Shanghai, China) radio-γ-counter. The sensitivity was 10 pg ml^{-1} with a confidence of variation less than 5%. The rate of cross action with angiotensin I was less than 0.01%.

All samples were analyzed in a blinded manner without knowledge of the experimental group for all the rats examined.

1.7. Statistical analysis

Data were fed into a database (Foxpro 2.5) for further statistical analysis. All data were expressed as mean±S.D. Mean comparisons were performed by means of ANOVA. A P-value<0.05 was considered of statistical significance. All data were analyzed by use of the SPSS statistical package.

2. Results

2.1. Effects on systolic BP and left ventricular hypertrophy

There were no differences in the values of the body weights of the rats in four groups at both endpoints examined (Table 1). All rats showed similar high systolic BP before the beginning of treatment (Table 1). Compared with that of the control group, systolic BP were significantly reduced at 8 and 16 weeks of losartan, fonsinpril and amlodipine respectively (Table 1), and not different among three treatment groups over the course of the experiment (Table 1).

The effects of the three drugs on left ventricular hypertrophic parameters are summarized in Table 1. Compared with those of the control group, left ventricular weight and left ventricular mass indexes were significantly reduced at 8 and 16 weeks of losartan, fonsinpril, and amlodipine respectively, and the latter parameter at 16 weeks in rats with fonsinpril was lower than that in rats with either losartan or amlodipine.

2.2. Effects on apoptosis and AngII

Compared with the control group, apoptotic index at 8 weeks was significantly decreased only in the rats with fosinopril (Table 2). The parameters at 16 weeks were significantly reduced in all three treatment groups (Table 2). However, the parameter in

Table 1
Effects on systolic BP and left ventricular hypertrophy

	Number of rats	Body weight (g)	SBP (mmHg)	LVW (g)	LVMI (mg/g)
SHR with untreated					
Baseline	10	233.53±27.94	198.43±16.76		
At 8 weeks	5	256.75±30.19	205.25±14.50	1.00±0.12	3.69±0.35
At 16 weeks	5	270.50±35.12	217.33±36.88	1.13±0.11	4.18±0.35
SHR with Losartan					
Baseline	10	230.06±28.45	192.75±18.95		
At 8 weeks	5	254.25±29.68	165.53±8.63**	0.91±0.09*	3.44±0.37*
At 16 weeks	5	267.66±32.97	150.00±10.00**$^{\triangle}$	0.94±0.13*	3.38±0.42*
SHR with Fosinopril					
Baseline	10	234.53±29.55	193.84±19.64		
At 8 weeks	5	255.50±31.97	169.44±10.46**	0.90±0.11*	3.38±0.33*
At 16 weeks	5	269.16±34.55	153.33±11.69**$^{\triangle}$	0.90±0.13**	3.07±0.37*$^{\#\triangle}$
SHR with Amlodipine					
Baseline	10	228.23±28.84	199.73±16.69		
At 8 weeks	5	257.75±34.37	166.33±13.37**	0.94±0.12*	3.51±0.40*
At 16 weeks	5	263.63±33.24	154.11±9.60**$^{\triangle}$	0.97±0.11*	3.46±0.31*

Notes: LVW indicates left ventricular weight: LVMI, the ratio of left ventricular weight to body weight; compared with control group: *$P<0.05$, **$P<0.01$. Compared with 8 weeks in same group: $^{\triangle}P<0.05$, compared between treatment groups: $^{\#}P<0.05$.

the rats with fosinopril at the latter endpoint was less than that in the rats with either of losartan or amlodipine (Table 2).

The group with losartan showed higher levels of AngII in LV myocardium and plasma than the control and other two treatment groups at both endpoints (Table 2). Whereas, compared with control group, myocardium AngII at 8 weeks was decreased only in the rats with fosinopril (Table 2). Myocardium AngII at 16 weeks was significantly decreased in the rats with fosinopril or amlodipine, and the former rats exhibited a lower level than the latter (Table 2). However, neither fosinopril nor amlodipine affected the plasma AngII concentrations at both endpoints examined (Table 2).

3. Discussion

The present study has three major findings: (1) losartan, fosinopril and amlodipine each effectively lowered blood pressure, regress left ventricular hypertrophy and reduced myocardiocyte apoptosis in SHR. (2) The three blockers produced a similar

Table 2
Effects on apoptosis, bcl-2, c-fos proteins expression, and myocardium and Plasma AngII

	Number of rats	APOI (%)	PAngII (pg/ml)	M AngII (ng/g)
SHR with untreated				
At 8 weeks	5	3.49±0.85	432.29±74.45	8.29±1.48
At 16 weeks	5	4.63±1.03$^{\triangle}$	457.03±79.11	10.16±2.19
SHR with Losartan				
At 8 weeks	5	3.05±0.67	496.96±78.35*$^{\#}$	9.78±2.82*$^{\#}$
At 16 weeks	5	2.69±0.84*	547.40±81.09*$^{\#\#}$	13.64±3.91*$^{\triangle\#}$
SHR with Fosinopril				
At 8 weeks	5	2.42±0.58*	415.77±74.82	6.91±1.58*
At 16 weeks	5	1.81±0.48**$^{\triangle\#}$	397.11±91.44	4.12±1.32**$^{\triangle\star}$
SHR with Amlodipine				
At 8 weeks	5	3.41±0.79	432.90±67.26	7.75±1.82
At 16 weeks	5	2.73±0.67*	409.71±5.55	6.22±1.95*

Notes: APOI indicates myocardiocyte apoptotic index; PAngII, plasma ATII concentration; M AngII, Myocardium AngII concentration. Compared with control group: *$P<0.05$, **$P<0.01$, compared with 8 weeks in same group: $^{\triangle}P<0.05$, compared between treatment groups: $^{\#}P<0.05$, $^{\#\#}P<0.01$, compared with SHR with Amlodipine: $^{\star}P<0.05$.

decrease in systolic BP. However, fosinopril was much more effective in the regression of left ventricular hypertrophy and the reduction of myocardiocyte apoptosis than either of the other two drugs. (3) Losartan produced significant increases of AngII concentrations in the left ventricular myocardium and plasma, whereas, both fosinopril and amlodipine resulted in the reduction of AngII concentrations in LV myocardium associated with no significant changes of plasma AngII. These findings are in agreement with the results of the previous studies [4,10,11,13,14] and suggest that the effects of the three blockers on myocardiocyte apoptosis and left ventricular hypertrophy were related to suppressing rennin angiotensive system in myocardium.

At the present time, the mechanisms responsible for increased apoptosis in hypertensive hearts are not well known. Previous studies [3,4] have documented that apoptosis can be induced in cardiac cells by pressure overload. The stretching of cardiac myocytes in vitro, which mimics an elevation of diastolic stress in vivo, induced apoptosis of these cells [15]. Teiger et al. [3] showed that apoptosis is induced selectively in cardiomyocytes after acute homodynamic stimulation secondary to aortic stenosis in the rat. Therefore, it is possible that the physical forces may induce apoptosis in conditions of experimentally induced pressure overload of the heart. However, others [10,16] have indicated that changes in blood pressure were unrelated to apoptosis in the left ventricle of SHRs. In the present study, our findings confirmed that the antihypertensive effects were not responsible for the different influences on apoptosis and left ventricular hypertrophy. Although the antihypertensive effects were not responsible for the differences, a role of long-term homodynamic decreases can not be excluded in the reduction of apoptosis and the regression of cardiac remodelling.

An alternative explanation may arise from several previous observations [17,18]. These findings showed that increased cardiomyocyte apoptosis is related to increased AngII concentration and exaggerated ACE activity in the left ventricle of rats with long-term pressure overload. AngII can trigger apoptosis in cultured cardiomyocytes by activating Ca^{2+}-dependent endogenous DNA endonuclease I [19]. AngII could also result in increased protein synthesis and cell volume of myocytes without cell proliferation, and markedly stimulate collagen synthesis and the proliferation of fibroblasts associated with the accumulation of fibrillar collagens in the extracellar matrix [20,21]. Cardiomyocyte hypertrophy, diffuse cardiac interstitial and perivascular fibrosis lead to hypoxia of the collagen-encircled cardiomyocytes. Hypoxia can specially induce cardiomyocyte apoptosis [22]. Thus, it can be considered that AngII may induce not only left ventricular growth and fibrosis but also apoptosis of the heart with hypertension. The results of the present study have further confirmed that the decreased AngII in myocardium or antagonizing AT1 receptors may be the main mechanism for the inhibition of cardiomyocyte apoptosis and cardiac hypertrophy.

The aim of this study was to observe the diverse effects of different antihypertensive drugs on cardiac hypertrophy and myocardiocyte apoptosis of rats with genetic hypertension. These results have shown that fosinopril was much more effective in these effects than either of the other two agents. Our data was similar to previous observations [11,23]. A recent report by Bastien [23], showed that the ACE inhibitor, quinapril, induced more reduction in cardiac hypertrophy than the AT1 receptor antagonist, losartan, in progressive heart failure models. Kim et al. [11] reported that the ACE inhibitor, perindopril, decreased left ventricular weight and AngII level to a greater extent than amlodipine alone.

The mechanisms underlying the different effects on apoptosis and cardiac hypertrophy between ACE inhibitors and AT1 receptor antagonists are not well known. It has been confirmed that the effect of ACE inhibitors is suppression of AngII formation by inhibition of ACE [24]. But clearly, ACE inhibitors will not prevent AngII being formed from other pathways such as chymase, cathepsin G and CAGE (chymostat in sensitive angiotensin II generating enzyme) [24]. The pharmacological profile of AT_1 receptor antagonists differs substantially from the ACE inhibitors. AT_1 receptor antagonists block directly the actions of AngII at the AT_1 receptor, irrespective of which enzyme produced the AngII [24]. Theoretically, AT_1 receptor antagonists are likely to be able to block the apoptosis and cardiac hypertrophy mediated by AngII more effectively than ACE inhibitors. However, ACE inhibitors not only suppress AngII formation but they also cause significant bradykinin accumulations which induce cardiac regression [25]. A recent report by Sugimoto [26] has

demonstrated that ACE inhibitor combination with bradykinin receptor antagonist, Icatibant, leads to the loss of the effects of ACE inhibitor on cardiac hypertrophy and fibrosis in SHRs, which suggested that the cardioprotective effects of ACE inhibitor, perhaps including inhibition of apoptosis, may be ascribed, at least mainly, to ACE inhibitor-induced bradykinin potentiation. However, AT_1 receptor antagonists induce a marked increase in AngII levels of left ventricular myocardium, which might theoretically lead to an excessive stimulation of the AngII type 2 (AT_2) receptor [24]. Until recently the role of the AT_2 receptor has remained unclear. There is evidence that the AT_2 receptor may be involved in antihypertrophic and pro-apoptotic effects on myocardium [27]. But a recent report [28] demonstrated that the AT_2 receptor did not alter apoptosis in normal and postinfarcted hypertrophied myocytes. Moreover, Ford et al. [29] reported that AT_2 receptor antagonist, PD123, 319, exerted cardioprotective effects after ischemia-reperfusion.

The mechanisms underlying the anti-apoptotic effect of calcium channel blockades remains undefined. Calcium channel blockades may produce cardioprotective effects by preventing the AngII-mediated increase in cytosolic calcium, attenuating activity of Ca^{2+}-dependent DNA endonuclease I and suppressing tissue RAS activity [30,31]. The explanations responsible for the different effects on apoptosis and cardiac hypertrophy between ACE inhibitors and calcium channel blockades remains undefined. Our data provides evidence that less suppression of the local rennin–angiotensin–aldsterone system in the rats with amlodipine than with fosinopril may be responsible for the difference.

In the present study, our data showed that losartan caused a significant increase of plasma and myocardium AngII levels. Whereas, fosinopril and amlodipine resulted in a reduction of myocardium AngII levels and no changes of plasma AngII concentrations. These findings were in agreement with the previous studies [32,33]. AT_1 receptor antagonists cause a significant increase of plasma and myocardium AngII levels through increasing renin activity led by AngII blockade at the receptor. ACE inhibitors act within the renin–angiotensin system to prevent the conversion of AngI to AngII. However, the AngII level in the circulation is mainly determined by an elevated level of AngI and any remaining ACE activity. The chronic administration of ACE inhibitor leads to a temporal reduction plasma level of aldosterone, which stimulates an increase in renin activity and AngI in plasma, and plasma AngII levels even return to baseline less than 24 h after drug administration [34]. Recent clinical and experimental studies found that chronic ACE inhibition with captopril, quinapril and lisinopril specifically affects angiotensinogen mRNA levels in cardiovascular tissues, and has marked effects on cardiac AngII level [35]. The probable mechanism responsible for decreasing myocardium AngII in the hypertensive rats by amlodipine is unclear. This result was related to the reduction of left ventricular load and the improvement of coronary circulation, which may lead to suppression of the local rennin–angiotensin–aldsterone system [36].

4. Conclusion

The results of this study indicate that long-term monotherapy with losartan, fosinopril, amlodipine effectively reverses heart hypertrophy and inhibits cardiomyocyte apoptosis, independently of blood pressure reduction. Our data suggest that the three antihypertensive drugs are not equally effective in terms of their effects on cardiac hypertrophy and apoptosis in SHRs, and fosinopril may be more effective in these cardioprotective effects. These findings also suggest that the effects of the three blockers on myocardiocyte apoptosis and left ventricular hypertrophy were related to inhibition of the myocardium rennin–angiotensin–aldsterone system.

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International Journal of Cardiology 81 (2001) 129–130

Editorial comment

Angiotensin II and cardiomyocyte apoptosis in the SHR☆

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Received 5 July 2001; accepted 8 August 2001

There is increasing evidence that cardiomyocyte (CM) apoptosis plays a significant role in cardiovascular pathophysiology and left ventricular (LV)

☆PII of linked article: S0167-5273(01)00539-3
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0167-5273/01/$ – see front matter
PII: S0167-5273(01)00538-1