The effects of angiotensin converting enzyme inhibitor spirapril on vascular distensibility in normotensive and spontaneously hypertensive rats

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Introduction

It is now generally known that angiotensin converting enzyme inhibitors (ACEI) possess not only hypotensive and antihypertensive effects [4], but may furthermore reduce myocardial and vascular remodelling associated with arterial hypertension (AH) [3]. However, the mechanisms underlying beneficial effects of ACEI on arterial vessel wall remodelling are poorly understood. An excessive cyclic distension of vascular smooth myocytes leading to increased accumulation of collagens and glycosaminoglicans in the vascular wall has been recognized as one of most important factors promoting vascular remodelling in AH [5]. On the other hand, the major determinant of the ability of vascular wall to withstand increased pulses of blood pressure is vascular distensibility (VD), or compliance [3].

It follows, therefore, that the effects of ACEI on VD are of special interest. The extent of VD at every certain time point is now considered as a result of interaction of myogenic and endothelium-derived factors within the vascular wall. There is no doubt that among the endothelium-dependent mechanisms of vascular tone regulation the key role belongs to nitric oxide (NO), which is continuously produced by endothelial NO-synthase owing to shear stress [7]. ACEIs have been shown to stimulate endothelial NO synthesis via the bradykinin-independent mechanism [6].

It has been demonstrated that sulfhydryl-containing ACEIs possess the antioxidant properties and limit formation of the reactive oxygen species (ROS) during myocardial reperfusion [1].
Editor's Column

It is almost time for the big event of the year for neuroscientists: the Neuroscience Meetings. We at David Kopf Instruments hope to see you in Washington this year. Please stop by the Kopf booth to say hi to all of us and to look at the many new products that are to be shown. As usual, the booth will be inside the front entrance to the exhibit hall, #2802. We especially invite you to attend the special lecture on Neuroethics to be given from 10 to 11 am Monday, November 4 by Thomas H. Murray, Ph.D., titled “Thinking Better? The Ethics of Cognitive Enhancement”. David Kopf Instruments is pleased to sponsor this very important lecture in memory of David Kopf, company founder. 

The sun is finally shining in sunny south Florida. It has been quite a time here this hurricane season, although we did miss the real action of Katrina and Rita. As you may recall, we had two fairly major hurricanes last year that did a lot of damage just north of us here in Ft. Lauderdale, and two others that came across the state from the other side. This year, Katrina made landfall just about 10 miles south of Ft. Lauderdale as a category 1 storm, which meant that we had the highest winds here because we were on the north side of the eye. However, the winds were only about 90 miles per hour, not enough to do real damage. We go a long day of winds and rain, with some trees and limbs down, but no structural damage and only a few scattered electrical outages. However, of course, then Katrina went out into the Gulf and became one of the biggest storms in history and eventually destroyed much of the Gulf coast, including New Orleans.

How do we get ready for such a storm? Last year, after living here for 4 years, I thought that putting in some food, water and other supplies was enough. After going through 2 storms and watching the winds come across our lake and thinking about a piece of debris coming through a window, I decided to have hurricane shutters put on the house. Our house was built in 1995 and is supposed to withstand winds of up to 150 miles per hour. That supposes, however, that the windows are intact so wind does not get in to blow the roof off. This year, I felt much better with shutters closed when Katrina came by. Since we are 14 miles from the ocean, we now know that even in the worst storm, it would be better to shut up the house and stay put rather than try to evacuate. Those along the coast have to evacuate due to storm surges (that did so much damage along the Gulf Coast), but staying in a well-built house a few miles from the coast is the best policy. Hopefully, we will not have another storm this year and I will not have to test the theory. And I did purchase an electrical generator in case the electricity went out for an extended time.

This edition of the Carrier is from our Russian colleagues, Sonin, Syrenskii, Alexandrov and Galagudza in St. Petersburg. Their studies on the effects of angiotensis converting enzyme inhibitor are very interesting and provocative. I know you will enjoy reading the article.

I look forward to seeing you at the Neuroscience meeting. Please stop by to say hello.

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It is also known that along with other factors ROS are responsible for endothelial dysfunction, which is associated with reduced endothelial NO release. Therefore, one might assume that the net beneficial effect of sulfhydryl-containing ACEIs on endothelial function is actually a mixture of bradykinin-induced NO release and attenuation of ROS-mediated endothelial injury. Hence, the experimental utilization of non-sulfhydryl-containing ACEIs which lack antioxidant capacity provides an opportunity of more targeted investigation of the mechanisms of their vascular effects. The aim of this study was to examine the effects of non-sulfhydryl-containing ACEI spirapril on vascular distensibility in normotensive and spontaneously hypertensive rats.

**Materials and methods**

The experiments were performed on normotensive male Wistar rats, Wistar-Kyoto (WKY) rats, and spontaneously hypertensive rats (SHR) weighting 250-300 g under chloralose anaesthesia, mechanical ventilation and myorelaxation. Abdominal aorta below the renal arteries was dissected and cannulated. A hindquarter was perfused with blood taken from proximal part of aorta through distal aortic cannula using a peristaltic roller pump [2]. Mean arterial pressure (MAP) was registered through the catheter inserted into the left carotid artery, and perfusion pressure (PP) was measured in distal aortic cannula. Heart rate (HR) was derived from MAP recordings. Femoral vein was cannulated for drug administration. Before surgery, animals received intravenous injection of heparin (1500 IU/kg).

After stabilization, perfusion volume (PV) was increased stepwise to achieve values of PP lying within a range between 30 and 250 mm Hg. Thereafter, PV was plotted against PP, and the resultant plots were mathematically analyzed. When baseline plots were obtained, spirapril was administered intravenously at a dose 1 mg/kg, and the test was repeated after 20-25 min. Before and after injection of spirapril PV was changed to identical level in each experiment. The following parameters were mathematically derived from volume-pressure relationships and calculated before and after drug administration: vascular distensibility (VD), hydraulic vascular resistance (HVR), and the index of intravascular pressure stability (IIPS) [8]. The IIPS is inversely related to the difference between maximal and minimal PP. VD reflects the degree to which the properties of the vessels correspond to the properties of linear hydraulic conductor. Biophysical properties of the vessels fully correspond to the properties of linear hydraulic conductor when VD is zero. Increase in the VD values quantitatively demonstrates that the HVR levels were decreased in response to PV increase, and occurrence of negative VD values demonstrates a situation when arterial vessels have a vasoconstriction response to PV increase.

Statistical evaluation of quantitative data was performed with Student and Wilcoxon-Mann-Whitney tests by software package “Microsoft Excel™”.

**Results**

Before injection of spirapril, MAP was 101+-8 mm Hg and HR was 421+-15 beats/min in normotensive rats. The MAP was 166+-10 mm Hg (64% greater than in normotensive animals) and HR was 384+-18 beats/min in SHR at baseline. After 20-25 min of intravenous bolus of the drug, the MAP was reduced to 18.6% (p<0.01), and the HR remained unchanged significantly (Table 1).

At the baseline, the increase in PV from 2.4+-0.5 to 15.0+-0.8 ml/min caused PP increase up to
221+/-23 mm Hg in normotensive rats. The same values of PP (217.5+/-20.9 mm Hg) could be achieved in SHRs with smaller PV (8.9+/-1.0 ml/min). Thereby we chose the similar ranges of PV changes (from 2.2+/-0.6 to 8.4+/-0.9 ml/min) in both groups to ensure proper comparisons.

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<tr>
<th>Table 1. Influence of spirapril on haemodynamic parameters</th>
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<td>Winter and WKY</td>
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<td>MAP, mm Hg</td>
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<td>Baseline</td>
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<td>After administration of spirapril (1 mg/kg)</td>
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Note: **p<0.01.

In normotensive rats the minimal PV corresponded to PP of 44+/-9 mm Hg (Figure 1), and the maximal PV corresponded to PP of 125+/-11 mm Hg. In this range of the PV changes, initial VD and IIPS were 0.36+/-0.04 and 12.3+/-0.9 mm Hg-1x1000, respectively. After 20-25 min of intravenous injection of spirapril (1.0 mg/kg), PP was not changed significantly at minimal PV (42+/-11 mm Hg), but it was significantly decreased at maximal PV (101+/-12 mm Hg, p<0.01). This was accompanied by significant increase of VD and IIPS up to 0.77+/-0.09 and 16.9+/-1.3 mm Hg-1x1000, respectively (Table 2).

In SHR group, the PP values of 66+/-6 and 229+/-9 mm Hg corresponded to minimal and maximal PV, respectively. The initial VD and IIPS within the chosen range of PV changes have appeared much less than in normotensive rats and were 0.08+/-0.01 and 6.6+/-1.0 mm Hg-1x1000, respectively (Figure 2). After spirapril administration, the PP in SHRs was slightly decreased (to 62+/-5 mm Hg) at minimal PV, but this reduction was significant (up to 192+/-15 mm Hg) at maximal PV. The IIPS and the VD increased up to 8.8+/-1.2 mm Hg-1x1000 and 0.31+/-0.6, respectively.

Discussion

The results obtained demonstrate that at baseline the arterial vessels of normotensive rats have greater distensibility in response to similar changes in perfusion volume than of SHRs. Thereby, the intravascular pressure stability was initially higher in normotensives.
It seems to be likely that the reduced vascular distensibility is a major cause of an excessive cyclic stretch of the vascular smooth myocytes that promotes vascular remodelling. It has been shown previously that endothelium-derived NO plays a primary role in the maintenance of vascular distensibility in normotensive animals [9]. Therefore, reduced vascular distensibility in hypertensive animals at baseline may evidence for diminished endothelial NO production in response to enhanced shear stress caused by PV increase. Based on this evidence one should expect to find significant differences in vascular effects of spirapril in normo- and hypertensive rats. However, our results have shown approximately similar degree of the hypotensive effect of spirapril in normotensive and hypertensive animals. Furthermore, the effect of the drug on dynamic characteristics of vascular tone in both groups of animals was similar. In both groups, the increase of intravascular pressure stability in response to injection of spirapril was similar, and the increase of vascular distensibility in hypertensive animals was more significant than in normotensives. In addition, in both groups, the hydraulic resistance of vascular region decreased only at the large perfusion volume rates after spirapril administration, and remained not different at the small volumes of perfusion. These data point to another important effect of spirapril, namely, the increase in flow-dependent vasodilatation. However, the exact mechanism whereby spirapril increases the distensibility of arterial vessels requires further studies.

In conclusion, our experiments show that non-sulfhydryl-containing ACEI spirapril has beneficial effects on static and dynamic parameters of vascular tone in normo- and hypertensive rats. The fact that spirapril causes greater increase in vascular distensibility in hypertensive animals provides an experimental basis for the use of this drug for prevention of functional and structural vascular remodelling in hypertension.

Summary

The experiments were performed on the anesthetized male Wistar, Wistar-Kyoto (WKY), and spontaneously hypertensive rats (SHR) under conditions of the hindlimb vascular bed perfusion. Intravenous injection of ACE inhibitor spirapril (1.0 mg/kg) caused the increase in vasodilatation stimulated by the elevation of perfusion flow rate in both normo- and hypertensive rats. The increased vasodilatation was associated with increased intravascular pressure stability. The results obtained show that spirapril may prevent excessive cyclic distension of the vascular smooth myocytes and decrease dynamic pressure overload of vascular myocytes.
References


