We evaluated the effects of treatment for 12 weeks with 10 mg/kg/day of either losartan or doxazosin on vascular function in senescent spontaneously hypertensive rats (SHR). Both doxazosin and losartan reduced blood pressure, although the former was more effective. In contrast, both drugs reduced relative aortic weight and increased plasma nitrates to a similar extent. Losartan, but not doxazosin, increased the magnitude of the response to acetylcholine ($10^{-9}$ to $10^{-5}$ mol/L). Both treatments increased relaxations to sodium nitroprusside ($10^{-10}$ to $10^{-6}$ mol/L). These data show that losartan may possess advantages over doxazosin in improving vascular function in senescent SHR. This report emphasizes the importance of angiotensin II in vascular function alterations induced by aging in SHR. Am J Hypertens 1999;12:1105–1108 © 1999 American Journal of Hypertension, Ltd.

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consecutive weeks with 10 mg/kg per day of either losartan or doxazosin in drinking water. A group of untreated animals was run in parallel. The animals were maintained under controlled light and temperature conditions, and were fed a normal rat chow (A.04, Panlab, Barcelona, Spain). All experimental procedures were approved by the Institutional Animal Care and Use Committee, according to the guidelines for ethical care of experimental animals of the European Community.

**Blood Pressure Measurement Procedure** Systolic blood pressure (SBP) was estimated basally and at the end of the study by use of a tail-cuff plethysmograph (Narco Bio-Systems, Houston, TX) in unrestrained animals. Rats were trained daily before the beginning of measurements of blood pressure, as described elsewhere.3 The method was previously validated by comparing the values with direct measurements obtained in chronically catheterized animals.3

**Plasma Nitrites Concentration** Plasma samples were obtained in tubes containing citrate (3.8%) when the animals were killed. Plasma nitrite concentrations were measured using Griess reagent after the quantitative conversion of nitrites to nitrates by using dihydroxy-aminotanone adenine dinucleotide (NADH)-dependent nitrate reductase. Thus, the results are expressed in terms of plasma concentrations of nitrites plus nitrates ([NOx] in mmol per liter).

**Vascular Measurements** Concentration–response curves to Ach (10⁻⁹ to 10⁻⁵ mol/L) and SNP (10⁻¹⁰ to 10⁻⁶ mol/L) were studied in aortic rings contracted with a submaximal dose of PE and prepared as described elsewhere. The degree of preconstriction of rings was similar in all groups. As an index of aortic hypertrophy the weight per 10-mm length per 100 g body weight ratio was used.7

**Data Analysis** Single-variable comparisons were made using a one-way analysis of variance; all other data were analyzed by two-way analysis of variance for multiple comparisons, followed by a Newman-Keuls test if differences were noted. Values of \( P < .05 \) were considered statistically significant. Results are presented as mean ± SEM of 6 rats.

**RESULTS**

Chronic treatment with either losartan or doxazosin decreased SBP levels as compared with the untreated group (157.6 ± 6.9, 133.7 ± 9.6, 195.5 ± 7.7 mm Hg, respectively), although the effect of doxazosin tended to be more prominent than that observed with losartan (in the limit of significance). This hypotensive effect was associated with a similar reduction (\( P < .05 \)) in the relative weight of the aortic rings as compared with the control group (1.49 ± 0.08, 1.45 ± 0.06, 1.88 ± 0.08 mg/10 mm/100 g body weight, losartan, doxazosin, and control group, respectively). Likewise, both losartan and doxazosin treatment increased \( (P < .05) \) plasma nitrate levels to the same extent as compared with the untreated group (49.1 ± 8.3, 45.0 ± 10.3, 18.6 ± 4.9 mmol/L, respectively).

As shown in Figure 1 (right top), losartan administration increased the magnitude of the response to Ach, as suggested by the increase in the maximal response. Likewise, rings from losartan-treated animals were more sensitive to acetylcholine, as shown by a higher pD₂ value (7.8 ± 0.2 vs 6.9 ± 0.1; \( P < .05 \)). In contrast, doxazosin treatment enhanced the sensitivity to this agent only (7.6 ± 0.1 vs 6.9 ± 0.1; \( P < .05 \)). Both treatments increased the relaxation to SNP as shown by an increase in maximal response (Figure 1, bottom) and pD₂ value (7.9 ± 0.2, 7.8 ± 0.1, 7.3 ± 0.04, losartan, doxazosin, and control group, respectively).

**DISCUSSION**

The present study shows that losartan, the AT₁ receptor antagonist, was more effective than doxazosin in improving vascular function in senescent SHR. This suggests the importance of angiotensin II in the alterations of vascular function in senescent SHR. Moreover, these data confirm previous observations indicating that a reduction in blood pressure is not always associated with amelioration of endothelial dysfunction.8,9

Several mechanisms can be underlying the beneficial effects induced by doxazosin and losartan on the relaxation induced by Ach and SNP. The first could be attributable to a decrease in blood pressure, which implies a reduction in the physical stress targeting the vascular wall. This effect could also account for the reduction in the aortic hypertrophy induced by both drugs. Moreover, these changes in the vascular wall can also participate in the amelioration of vascular function by reducing the response to vasoconstrictor agents, which can antagonize the responses to vaso-dilatory factors. An enhancement in NO availability, as suggested by an increase in plasma nitrates, could be an additional mechanism involved in the amelioration of the endothelial function induced by both drugs. This increase could be the consequence of an elevation in the synthesis or a reduction in its degradation. In fact, it has been shown that doxazosin is not only able to increase nitric oxide synthase (NOS) activity,10 but also reduce NO degradation through its antioxidant ability.11 Likewise, losartan can prevent NO degradation by inhibiting the vascular production of superoxide via NADH/NADPH oxidase activation.12 Indeed, we have provided supporting evidence for the involvement of NO in the actions of losartan in SHR.13,14

The fact that losartan was more effective than dox-
azosin in improving relaxation to Ach could be explained by a major production or sensitivity to angiotensin II in senescent SHR, which, in turn, antagonizes the actions of NO. Indeed, we have previously reported a greater response to angiotensin II in senescent SHR as compared with that in adult animals in both conduit and resistance arteries.3,6 This response was reduced by losartan. Likewise, aging increases the activity of angiotensin converting enzyme in resistance arteries from SHR.15

In summary, these data show that in senescent SHR, blocking of AT₁ receptors with losartan may improve vascular function to a greater extent than by blocking α₁-adrenergic receptors with doxazosin, and emphasize the importance of angiotensin II in vascular function alterations observed in senescent SHR.

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