Reduction of Vascular Noradrenaline Sensitivity by AT1 Antagonists Depends on Functional Sympathetic Innervation

Walter Raasch, Peter Dominiak, Andreas Ziegler, Andreas Dendorfer

Abstract—Blockade of angiotensin II type-1 (AT1) receptors has been shown to reduce the magnitude of the blood pressure response to noradrenaline in pithed rats via an unidentified mechanism. Dose-response curves were established for the noradrenaline-induced (10^-12 to 10^-7 mol/kg) increase of diastolic blood pressure in pithed rats treated with tubocurarine, propranolol, and atropine. Candesartan (1 mg/kg) increased the ED50 of the noradrenaline response (1.3±0.1 nmol/kg) up to 20-fold. Vasopressor responsiveness to noradrenaline was attenuated specifically, whereas the vasopressin-induced increase in diastolic blood pressure was maintained. Specific involvement of AT1 receptors was confirmed by equivalent actions of losartan. Blockade of norepinephrine transporter or α1-adrenoceptors using desipramine or rauwolscine reduced the losartan-induced shifts in the ED50 values of noradrenaline by 63% and 21%, respectively. Combined blockade of norepinephrine transporter and α1-adrenoceptors eliminated the influence of losartan on noradrenaline sensitivity (ED50 5.5±1.3 versus 5.6±1.2 nmol/kg), a result also observed after sympathetic denervation by reserpine (ED50 7.1±0.8 versus 7.8±0.8 nmol/kg). Our experiments show that the reduction of vascular noradrenaline sensitivity by AT1 blockade is dependent on the intact functioning of both neuronal noradrenaline uptake via norepinephrine transporter and presynaptic α1-mediated autoinhibition, exclusively provided by the sympathetic innervation. These newly identified mechanisms may contribute to the antihypertensive and protective actions of AT1 blockers. (Hypertension. 2004;44:346-351.)

Key Words: angiotensin antagonist receptors, angiotensin catecholamines vasopressins

Many clinical trials have evaluated the pronounced antihypertensive and cardioprotective effects of angiotensin-converting enzyme inhibitors and angiotensin II type-1 (AT1) receptor blockers. The significance of diminished plasma noradrenaline levels and of the antiadrenergic actions for therapeutic success with antihypertension and cardioprotection have been discussed.1 The mechanisms of the various interactions between the renin-angiotensin-aldosterone system and the sympathetic system have been established at different levels and have been shown to bear prominent pathophysiological implications. Angiotensin II (Ang II) stimulates the sympathetic system by activating central nervous tone and catecholamine release2 and by facilitating the release of catecholamines from peripheral sympathetic neurons via ganglionic3,4 and axonal presynaptic receptors.5,6 Ang II has been shown to increase vascular sensitivity to noradrenaline in rats and isolated vessels,7,8 so that Ang II and noradrenaline exert synergistic actions on vascular tone. As such, it could be proposed that blockade of endogenous Ang II by AT1 blockers might alter vascular reactivity to exogenous noradrenaline. Indeed AT1 blockers provoked a reduction in vascular sensitivity to noradrenaline in pithed rats,6 although discrepant findings were obtained even where similar experimental approaches were pursued.10 This controversy still requires clarification, particularly as regards the mechanisms by which AT1 blockers might reduce vascular catecholamine sensitivity.

In arterial smooth muscle, Ang II has been shown to potentiate noradrenaline sensitivity by activating protein kinase C and thereby increasing calcium sensitivity.6 Moreover, short-duration in vivo pretreatment with Ang II also primes the isolated rat portal vein for an enhanced adrenergic vasoconstriction.9 On the other hand, there is evidence that an increase in vascular noradrenaline sensitivity by Ang II may be attributed to a reduction of catecholamine clearance, because Ang II diminishes neuronal catecholamine uptake.11-13 We therefore hypothesized that blockade of AT1 receptors might enhance catecholamine uptake and consequently attenuate noradrenaline-induced vasoconstriction. To verify this hypothesis, we endeavored to confirm a reduction of noradrenaline reactivity during AT1 blockade and to determine the role of sympathetic innervation in this effect. Furthermore, the contributions of the 2 major regulators of noradrenaline availability and release, neuronal noradrenaline uptake and α1-autoinhibitory feedback, were differentiated.

Methods

Pithed Rat Preparation

This study followed the National Institutes of Health guidelines for the care and use of laboratory animals. Male Wistar rats (250 to

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300 g. Charles River, Sulzfeld, Germany) were pithed as described. Briefly, the animals were anesthetized with ether and artificially respirated. The medulla and thoracolumbar portion of the spinal cord were destroyed using a steel pitting rod. Catheters were placed into a carotid artery and a femoral vein, and both vagal nerves were severed. Blood pressure was measured via the carotid catheter. Animals were pretreated with tubocurarine (3 mg/kg IV), propranolol (1 mg/kg IV), and atropine (2 mg/kg IP).

**Experimental Procedures**

**Protocol 1**
Acute increases in blood pressure were provoked by 30-s bolus injections of noradrenaline (1 pmol/kg to 100 nmol/kg IV) given sequentially at 10-minute intervals. One dose of candesartan (1 to 3000 μg/kg), losartan (30 mg/kg), or saline was administered 20 minutes before the first noradrenaline injection.

**Protocol 2**
Noradrenaline (1 mmol/kg) or vasopressin (130 ng/kg) was infused in repetitive applications to provoke acute increases (~50 mm Hg) in blood pressure. Candesartan (1 to 3000 μg/kg) was given in cumulatively increasing doses 3 minutes before each injection of noradrenaline or vasopressin.

**Protocol 3**
Noradrenaline dose-response curves were determined as in protocol 1 after application of saline or losartan (30 mg/kg). Twenty minutes before the first noradrenaline injection, rats received desipramine (0.5 mg/kg) and rauwolscine (3 mg/kg) either alone or in combination.

**Protocol 4**
Protocol 3 was repeated using losartan and desipramine, but rats were pretreated with reserpine (5 mg/kg IP) or vehicle 24 hours beforehand.

**Determination of Catecholamines**
To confirm the efficacy of reserpine treatment, tissue contents of noradrenaline and adrenaline were determined by high-pressure liquid chromatography/electrochemical detection after completion of the experiments in hearts and adrenal glands.

**Substances**
The AT1 antagonists candesartan and losartan were provided by AstraZeneca (Wedel, Germany) and MSD Sharp&Dohme (München, Germany), respectively. Stock concentrations of 10 mg/mL were prepared in 50 mmol/L Na2CO3 and were diluted with physiological saline to achieve infusion volumes of 1 mL/kg for each application. Reserpine (5 mg/kg) was dissolved in 20% saline to achieve infusion volumes of 1 mL/kg for each application. All chemicals were obtained at the highest quality from Sigma or Merck.

**Calculations and Statistics**
Diastolic blood pressure was chosen as the parameter of vascular response because it shows the highest degree of independence from heart rate and inotropy. Differences in diastolic blood pressure before and after each noradrenaline stimulation are generally depicted. Parameters of the dose-response relationships were calculated from nonlinear fits using Prism (GraphPad Software). Comparisons between treatment groups were performed by 2 sample t tests or ANOVA followed by Dunnett multiple comparison test. An error level of P<0.05 was considered significant. A nonparametric bootstrap procedure with 100 000 replicates was applied to investigate significant deviation of the ratio of ED50 values between losartan and control with samples drawn separately for the different treatment groups. Ninety-five percent confidence intervals (CI) were taken from the empirical bootstrap distribution of ED50 ratios. Two-sided P for treatment comparisons and group comparisons were determined from percentiles of the bootstrap distributions.

**Results**
Baseline Parameters
After surgical preparation, animals stabilized at an average mean arterial blood pressure of 65.5±1.2 mm Hg and a heart rate of 433.8±7.4 minutes⁻¹; no differences were found between the groups. Within the time course of the experiments (110±1.1 minutes), blood pressure dropped slightly (57.3±1.6 mm Hg, P>0.05), whereas heart rate (418.8±4.1 minute⁻¹) was stable.

**Reduction of Vascular Noradrenaline Sensitivity by AT1 Blockers**
In rats treated with candesartan, dose-response curves of noradrenaline-induced increases in blood pressure were dose-dependently shifted to the right (Figure 1). ED50 values of noradrenaline (control 1.4±0.1 nmol/kg) were enhanced significantly by candesartan at doses >1 μg/kg (Table 1). Maximum noradrenaline-induced increases in blood pressure showed no significant differences between the groups (Table 1). Similarly, the increase in blood pressure induced by noradrenaline (1 nmol/kg) was dose-dependently diminished after candesartan treatment, resulting in an ID50 value of 3.0

| TABLE 1. Influence of Candesartan on Vascular Sensitivity |
|---------------------------------|----------------|----------------|
| Candesartan (mg/kg)             | ED50 Values for NA (nmol/kg) | Emax Values (mm Hg) |
| 0 (n=10)                        | 1.4±0.1         | 118.1±1.3      |
| 1 (n=6)                         | 3.8±2.3         | 119.8±4.4      |
| 10 (n=7)                        | 9.5±2.9*        | 125.4±4.2      |
| 100 (n=5)                       | 31.6±6.1*       | 127.6±3.0      |
| 1000 (n=7)                      | 29.0±5.6*       | 122.8±3.7      |
| 3000 (n=6)                      | 35.5±9.8*       | 126.5±4.7      |

Induced by increasing intravenous injections of noradrenaline after pretreatment with candesartan at doses of 0 to 3000 μg/kg, respectively. Mean±SEM. *P<0.05 vs controls, receiving no candesartan.
blood pressure response to vasopressin was not reduced by candesartan (Figure 2). As with the candesartan experiments, dose-response curves for noradrenaline during losartan treatment (30 mg/kg) were clearly displaced compared with controls (Figure 3A). Thus, the ratio of the ED\textsubscript{50} values of noradrenaline between control and losartan pretreated rats was 14.8 (95% CI, 10.0 to 21.2; Table 2).

Losartan-Induced Desensitization Depends on Norepinephrine Transporter and α\textsubscript{2}-Adrenoceptors

The significance of norepinephrine uptake in the desensitization of blood pressure responses by losartan was tested by blocking norepinephrine transporter (NET) with desipramine. In rats pretreated with desipramine, losartan still increased the ED\textsubscript{50} values of the vasopressor effect of noradrenaline (ratio losartan versus control 5.4; 95% CI, 3.5 to 8.6; Table 2) and did not affect \textit{E}\textsubscript{max} (Figure 3B). However, the losartan-induced shift in ED\textsubscript{50} values (ratio 5.4) was significantly reduced compared with saline-pretreated rats (ratio 14.8, P<0.05, Table 2). When α\textsubscript{2}-autoreceptors were blocked by rauwolscine, neither the ratio of noradrenaline ED\textsubscript{50} values between losartan-treated and control rats (11.7; 95% CI, 6.3 to 19.7; Table 2) nor \textit{E}\textsubscript{max} values were altered in comparison to rauwolscine-free animals (Figure 3C). Under combined blockade of uptake-1 and α\textsubscript{2}-autoreceptors, dose-response curves of noradrenaline in losartan and control groups were congruent, and the ED\textsubscript{50} and \textit{E}\textsubscript{max} values were identical (ratio 1.0; 95% CI, 0.5 to 1.7; P=0.88; Figure 3D, Table 2).

Effects of Losartan on Noradrenaline Sensitivity in Reserpine-Treated Rats

Pretreatment with reserpine had no effect on baseline mean arterial blood pressure compared with controls (69.9±1.7 mm Hg), whereas the response to vasopressin was not affected. Pithed rats were pretreated with tubocurarine (3 mg/kg), propranolol (1 mg/kg), and atropine (2 mg/kg). Values are expressed as mean±SEM (n=5). *P<0.05 vs candesartan 0 μg/kg of corresponding experiments using noradrenaline or vasopressin.

52.5±12.8 μg/kg candesartan. In contrast, blood pressure response to vasopressin was not reduced by candesartan (Figure 2). As with the candesartan experiments, dose-response curves for noradrenaline during losartan treatment (30 mg/kg) were clearly displaced compared with controls (Figure 3A). Thus, the ratio of the ED\textsubscript{50} values of noradrenaline between control and losartan pretreated rats was 14.8 (95% CI, 10.0 to 21.2; Table 2).

### Table 2. Influence of Losartan (30 mg/kg) on \textit{E}\textsubscript{50} Values of the Noradrenaline-Induced Increase in Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Pretreatment (mg/kg)</th>
<th>Control</th>
<th>Losartan</th>
<th>Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>3.4±0.8</td>
<td>50.6±9.1</td>
<td>14.8 (10.0–21.2)</td>
</tr>
<tr>
<td>Rauwolscine (3)</td>
<td>2.5±0.4</td>
<td>29.4±8.4</td>
<td>11.7 (6.3–19.7)</td>
</tr>
<tr>
<td>Desipramine (0.5)</td>
<td>1.4±0.5</td>
<td>7.6±1.4</td>
<td>5.4 (3.5–8.8)</td>
</tr>
<tr>
<td>Desipramine/rauwolscine (0.5/3)</td>
<td>5.5±1.3</td>
<td>5.6±1.2</td>
<td>1.0 (0.5–1.7)</td>
</tr>
</tbody>
</table>

The action of losartan was tested under conditions of uptake-1 blockade by desipramine, α\textsubscript{2}-adrenoceptor blockade by rauwolscine, or both (mean±SEM, n=5–11).

*CI indicates 95% confidence interval from 100,000 bootstrap samples in parenthesis.

**P<0.05 vs corresponding pretreatment not receiving losartan.

†P<0.05 vs \textit{E}\textsubscript{50} ratio of the saline-treated group.

Figure 3. Influence of losartan (●) and saline (○) on the noradrenaline (NA)-induced increase in diastolic blood pressure (ΔDBP) without pretreatment (A) and after blockade of uptake-1 with desipramine (0.5 mg/kg; B), after blocking α\textsubscript{2}-adrenoceptors using rauwolscine (3 mg/kg; C), and after combined blockade of uptake-1 and α\textsubscript{2}-adrenoceptors (D). Values are expressed as mean±SEM (n=5 to 8).

Figure 2. Influence of candesartan on vascular sensitivity to noradrenaline (○) or vasopressin (□). Increases in diastolic blood pressure (DBP) were induced by sequential intravenous injections of noradrenaline (1 nmol/kg) or vasopressin (17 ng/kg). Cumulatively increasing doses of candesartan greatly reduced the noradrenaline effect (ID\textsubscript{50}: 52.5±12.8 μg/kg), whereas the response to vasopressin was not affected. Pithed rats were pretreated with tubocurarine (3 mg/kg), propranolol (1 mg/kg), and atropine (2 mg/kg). Values are expressed as mean±SEM (n=5). *P<0.05 vs candesartan 0 μg/kg of corresponding experiments using noradrenaline or vasopressin.
TABLE 3. Influence of Reserpine (5 mg/kg) on the Dose-Response Curve for Noradrenaline-Induced Blood Pressure Increase in Pithed Rats Pretreated With Losartan (30 mg/kg), Desipramine (0.5 mg/kg), or a Combination

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>$ED_{50}$ (mmol/kg)</th>
<th>$E_{	ext{max}}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n=5)</td>
<td>10.6±1.1</td>
<td>115.8±5.1</td>
</tr>
<tr>
<td>Reserpine (n=5)</td>
<td>7.1±0.8*</td>
<td>118.0±0.9</td>
</tr>
<tr>
<td>Reserpine/losartan (n=5)</td>
<td>7.8±0.8*</td>
<td>119.7±3.4</td>
</tr>
<tr>
<td>Reserpine/desipramine (n=5)</td>
<td>5.2±0.4*</td>
<td>118.5±3.0</td>
</tr>
<tr>
<td>Reserpine/desipramine/losartan (n=7)</td>
<td>5.7±0.9*</td>
<td>120.6±2.2</td>
</tr>
</tbody>
</table>

*P<0.05 vs saline.

versus 65.7±3.0 mm Hg; P>0.05). Concentrations of noradrenaline in hearts and adrenals of controls were 50.7±5.6 ng/mg protein and 3.1±0.2 μg/mg protein, respectively, and that of adrenaline 753±69 pg/mg protein and 12.2±0.4 μg/mg protein, respectively. Effectiveness of reserpine injections was confirmed, because noradrenaline and adrenaline content were both extensively reduced in left ventricles (noradrenaline 0.7±0.2 ng/mg protein, adrenaline 64±11 pg/mg protein) and by more than two thirds in the adrenals (noradrenaline 1.2±0.1 μg/mg protein, adrenaline 3.8±0.6 μg/mg protein). Dose-response curves for the noradrenaline-induced blood pressure increase were slightly displaced leftwards in reserpine-pretreated rats when compared with reserpine-free animals. No displacement of dose-response curves could be observed in reserpine-pretreated animals under losartan, desipramine, or the combination of both compared with corresponding reserpine-pretreated controls (Table 3). The maximal blood pressure increase provoked by noradrenaline ($E_{\text{max}}$) was identical in all experimental regimes (Table 3).

Discussion

This study demonstrates that a noradrenaline-induced increase in blood pressure is reduced by AT$_1$ blockade. This is an important confirmation of our previous findings, which disagreed with similar experiments of Balt et al. In the present study, we avoided technical differences to those studies with regard to rat strains and experimental protocols but still observed prominent effects of losartan and candesartan. Furthermore, this activity of AT$_1$ antagonists has been confirmed by the identification of possible pathways whose significance for the vascular desensitization to noradrenaline must be differentially discussed.

First, the consequence of AT$_1$ blockade may be suspected to reflect a desensitization of $\alpha_1$-mediated contraction of vascular smooth muscle, rather than an alteration of sympathetic innervation. Concern has been expressed that a consequent vasoconstrictor membrane may attenuate the response to catecholamines. However, a general reduction of vascular tone does not seem to represent a limitation of the present study because an influence of AT$_1$ receptor blockade on total peripheral resistance had been excluded in the pithed rat model. In addition, the blood pressure-increasing potency of noradrenaline is maintained at basal diastolic blood pressure values considerably lower (ie, 20 mm Hg) than the minimum values reached in the present study (range 35 to 52 mm Hg). Furthermore, the reduction of noradrenaline sensitivity arises as an AT$_1$ specific effect, because it is produced by both candesartan and losartan at low doses. As a further support of specificity, AT$_1$ blockade did not affect the vasopressin-induced blood pressure increase, indicating a specific interaction between the sympathetic nervous system and the renin-angiotensin-aldosterone system rather than a general suppression of vasoconstrictor function by AT$_1$ blockers.

Second, the reduction of vascular noradrenaline sensitivity during AT$_1$ blockade clearly depends on an intact sympathetic innervation. Pretreatment of rats with reserpine depleted noradrenaline storage and impaired NET (as shown in this study and by other authors). The increase in noradrenaline sensitivity after reserpine-treatment (Table 3) is consistent with earlier findings and has been attributed to an enhancement of vasoconstriction due to upregulated vascular $\alpha_2$-adrenoceptors. In this condition, losartan had no further influence on vascular noradrenaline sensitivity (Table 3). This exclusive role of sympathetic innervation in determining the vascular response to exogenous noradrenaline provides an explanation why a similar influence of AT$_1$ receptors has not been observed in most isolated vascular preparations.

Third, Ang II is known to facilitate the release of endogenous noradrenaline by activation of presynaptic AT$_1$ receptors. Because the total postsynaptic availability of noradrenaline results from both, endogenous release and exogenous application, it is feasible that suppression of facilitation by AT$_1$ blockade increases the dose requirement of infused noradrenaline to maintain equivalent vascular responses. This mechanism would result in a vascular desensitization to exogenous noradrenaline, on the condition that a functionally relevant amount of endogenous noradrenaline is continuously released. In the pithed rat model, this basal release of noradrenaline is very low and results in hardly detectable plasma concentrations. To evaluate the significance of facilitated noradrenaline release, its dependency on presynaptic autoinhibition was used. Blockade of the neuronal feedback mechanism of noradrenaline release by $\alpha_2$-antagonists is known to abolish the facilitating activity of Ang II, suggesting that Ang II acts via an attenuation of autoinhibition. Pharmacological suppression of autoinhibition by the $\alpha_2$-antagonist rauwolscine in the present study did not reduce the desensitizing influence of losartan on vascular noradrenaline sensitivity (Table 3), indicating a minor contribution of endogenous noradrenaline release under basal conditions (Figure 4). In contrast, rauwolscine abolished the antiadrenergic action of losartan after blockade of NET by desipramine (Table 2), signifying that $\alpha_2$-mediated feedback and consequently AT$_1$ mediated facilitation became unmasked when the availability of endogenous noradrenaline was enhanced.

Fourth, the desensitizing influence of AT$_1$ blockade under basal conditions essentially involves the activity of NET, as demonstrated in despramine-pretreated rats (Table 2). This result implies that NET determines the availability of exogenous noradrenaline in the vascular wall. In support of this, an enhancement of noradrenaline responses after inhibition of NET has been reported earlier and is also reflected by a reduction of the $ED_{50}$ value of noradrenaline after pretreat-
ment with desipramine (Table 2). However, this influence of desipramine has not been statistically evaluated in the present study because it mainly focused on the influence of losartan on the potency of noradrenaline and consequently used parallel experiments in the absence and presence of losartan. Thus, we abstained from comparing the absolute ED_{50} values of noradrenaline between the different pretreatment regimes (saline, desipramine, rauwolscine, desipramine + rauwolscine) and restricted this analysis to the relative changes of noradrenaline ED_{50} values induced by losartan (ratio values in Table 2). Consequently, AT_{1} antagonists appear to attenuate vascular noradrenaline sensitivity by enhancing the efficacy of noradrenaline uptake, as schematically depicted (Figure 4). The prerequisite for this interpretation, a direct reduction of noradrenaline uptake by Ang II, had been demonstrated in isolated rabbit hearts.\(^{31}\) Reversely, an observed enhancement of NET during experimental or therapeutic AT_{1} blockade or angiotensin-converting enzyme inhibition strengthens our hypothesis of a presynaptic interaction between AT_{1} receptors and NET.\(^{12,13,32,33}\) However, noradrenaline uptake alone is not sufficient to explain all of the vascular desensitization by losartan. As discussed, \(\alpha_{2}\)-adrenoceptors may contribute by modulating the endogenous release of noradrenaline during NET blockade. The complete suppression of the antiadrenergic activity of losartan by a combination of desipramine and rauwolscine indicates that the essential role of sympathetic innervation (also reflected in reserpine-pretreated rats) is exclusively related on a modulation of NET activity and noradrenaline release. These interrelated neuronal mechanisms, which are known to modulate the secretory activity of the sympathetic nerve system, were also identified as important regulators of vascular noradrenaline sensitivity.

**Perspectives**

Angiotensin-converting enzyme inhibitors and AT_{1} blockers are established in the therapy of hypertension and heart failure because of their potential to diminish direct and indirect effects of Ang II. In this regard, both drug classes were shown to effectively reduce plasma noradrenaline levels in parallel to cardiovascular mortality. Our study indicates that this decrease in plasma noradrenaline may not only be attributed to an attenuation of noradrenaline sensitivity, but also involves an enhancement of neuronal noradrenaline clearance. Further consideration must be given to the fact that both mechanisms will not only modulate the availability of locally secreted but also that of circulating noradrenaline. In consequence, the influence of AT_{1} antagonists on a specific vascular property (the sensitivity to noradrenaline) reflects their interactions with the sympathetic system. An evaluation of different AT_{1} antagonists has revealed that they attenuate vascular noradrenaline sensitivity at slightly higher doses, as compared with their potencies to antagonize Ang II–provoked vasoconstriction.\(^{6}\) As such, it may be presumed that this newly recognized antiadrenergic mechanism of AT_{1} antagonists will contribute to their protective and antihypertensive properties, but the efficacy and dose dependency of these drugs in long-term therapy remain to be investigated.

**References**


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