Angiotensin II receptor antagonists and sympathetic neurotransmission
Balt, J.C.

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CHAPTER 3

Inhibition of angiotensin II-induced facilitation of sympathetic neurotransmission in the pithed rat; A comparison between losartan, irbesartan, telmisartan and captopril

Introduction

The renin-angiotensin-system (RAS) plays an important role in the regulation of blood pressure and volume and of the electrolyte balance [1]. ACE-inhibitors and the recently developed AT₁-receptor antagonists are widely used in the treatment of hypertension and heart failure. Moreover, they are sophisticated tools in the analysis of the RAS and its various activities. Numerous studies have shown that angiotensin II (Ang II) enhances the influence of the sympathetic nervous system (SNS) at various levels. Ang II has been shown to enhance ganglionic transmission, to facilitate NA release from synaptic nerve terminals, block NA-uptake, enhance NA-synthesis, and enhance the post-synaptic effects of noradrenaline [2-5]. Angiotensin II, which is the endogenous stimulator of AT₁ receptors, is known to be a potent vasoconstrictor. It seems likely, however, that part of the vasoconstrictor effect of angiotensin II is brought about by the synergistic interaction between angiotensin II and various components of the SNS and its receptors. Conversely, it can be imagined that part of the vasodilator effects of the AT₁-blockers is caused by direct or indirect suppression of the sympathetic nervous system. This interaction may be clinically relevant taking into account the important role of SNS-activity in the genesis and maintenance of hypertension [6-8] and even more so of congestive heart failure [9-11].

The pithed rat is a model which is suitable to study interactions between angiotensin II and the peripheral nervous system. The vascular system in this model is extremely sensitive to all kinds of vasoconstrictor agents. Both plasma renin activity and plasma angiotensin II levels are elevated [12,13]. Endogenously generated angiotensin II facilitates neuronally mediated increments in vascular resistance [14]. Additionally, in this model, noradrenaline release was shown to be modulated by endogenously released angiotensin II [15]. In the propranolol-treated pithed rat, potential central effects [16] and indirect cardiac effects [17] of Ang II are known to be suppressed or even abolished. In this model, the increase in blood pressure caused by stimulation of the sympathetic nervous system can be attenuated in normotensive animals by both ACE-inhibition [14,18,19] and by AT₁-receptor blockade [20-22]. In pithed spontaneously hypertensive rats (SHR), similar results were observed with ACE-inhibition [23-24].

In the pithed rat model, effects of Ang II on blood pressure responses to exogenous noradrenaline are less clear. Responses can be attenuated by captopril treatment, saralasin and losartan [12,14,20]. However, Yokoyama et al. observed no effect of losartan on NA-induced pressor responses [22], whereas Antonaccio & Kerwin observed that chronic but not acute treatment with captopril attenuated NA-induced blood pressure increase [23]. These various
results indicate a facilitation of sympathetic neurotransmission in the pithed rat that may occur both at the pre- and postsynaptic levels.

Several new, non-peptidergic AT₁-selective receptor blockers are now available. Certain differences between the various AT₁-blockers with respect to the inhibition of direct actions of angiotensin II on smooth muscle have been reported. For instance, in rabbit aortic ring studies, the IC₅₀-value of losartan on Ang II-mediated contractions was reported to be 26.4 nM, whereas that of irbesartan amounted to 4.1 nM [25]. The Kᵦ value of telmisartan was reported to be 0.33 nM [26]. However, hardly any evidence is available concerning a comparison of the potency of these drugs with respect to the attenuation of the facilitation by Ang II of sympathetic neurotransmission. In SHR, angiotensin II was shown to increase sympathetic outflow as reflected by plasma noradrenaline concentrations. This effect could be inhibited by losartan and HR720 [27], where HR720 appeared to be more potent.

Ohlstein et al. reported that in the pithed rat model, eprosartan inhibited sympathetic outflow, whereas losartan, valsartan and irbesartan did not [28]. However, these authors used only one dose of each drug (0.3 mg/kg). In contrast, it was reported by Wong et al. and Christophe et al. that single doses of losartan 10 mg/kg and irbesartan 30 mg/kg, respectively, could indeed attenuate the sequelae of stimulated sympathetic activity in this model [20,21].

In the present study, the inhibitory effects of the AT₁-receptor blockers losartan, irbesartan and telmisartan on sympathetic neurotransmission were quantitatively compared in the pithed rat model. For this purpose, dose-response curves describing the effect of each compound on stimulation-induced DBP-increase were constructed.

In addition, the inhibitory effects of the ACE-inhibitor captopril were studied. Presynaptic as well as postsynaptic interactions were investigated, by using both electrical stimulation of the spinal cord and exogenous noradrenaline, respectively.
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Methods

Male, normotensive Wistar rats (255-320g) which were kept on a normal rat chow diet and had water ad libitum, were used throughout. Rats were anaesthetised with hexobarbital 150 mg/kg i.p. The cervical region was anaesthetised with lidocaine 2% and the trachea was cannulated. Subsequently the animals were pithed by introducing a steel rod through the right orbita and foramen magnum into the spinal canal. The pithing rod was insulated except for a 3.5 cm area, 2.5 cm from the tip in order to allow the selective stimulation of thoracolumbar sympathetic segments. The animals were ventilated with room air at a frequency of 40 cycles/min with a volume of 200 ml/min using a Braun Melsungen pump. Body temperature was kept at 37 °C by means of thermostat-equipped tables. The left carotid artery was cannulated, heparin 150 IU/kg was administered and blood pressure was monitored continuously using a Powerlab data acquisition system (Chart 3.4, ADI instruments). The heart rate was derived from this signal. The left internal jugular vein was cannulated for the administration of drugs. Bilateral vagotomy and bilateral adrenalectomy were performed. Rats were treated with propranolol 1 mg/kg i.v. to rule out β-adrenoceptor-mediated effects, tubocurarine 2.5 mg/kg i.v. to prevent muscle contraction during electrical stimulation and atropine 2 mg/kg i.p. to inhibit parasympathetic effects. Animals were left to recover for 15 minutes. Subsequently, either saline, one of the three AT1-blockers or the ACE-inhibitor captopril was administered i.v. in various concentrations. Groups consisted of 6-8 animals. Only one concentration of a drug was used in each animal. Fifteen minutes after drug administration, the sympathetic nervous system was stimulated at 0.25, 0.5, 1, 2, 4 and 8 Hz (15 seconds per frequency) at 50V with square wave pulses of 2 ms delivered by a HSE stimulator I at the level of the T5-L4 segments. After each period of stimulation at a given frequency, blood pressure was allowed to return to baseline. The following dose ranges were studied: losartan 1, 3, 10 and 30 mg/kg, irbesartan 3, 10, 30 and 60 mg/kg, telmisartan 0.3, 1, 3 and 10 mg/kg and captopril 1.5, 5, 15 and 45 mg/kg, respectively. All doses were administered in a volume of 1 ml/kg, except losartan 30 and irbesartan 60 mg/kg which were administered in 2 ml/kg volumes.

In order to investigate the effect of the various compounds on postjunctional vasopressor responses to α-adrenoceptor stimulation we applied noradrenaline intravenously in increasing dosages. Pithing and pretreatment with propranolol, tubocurarine and atropine were identical as in stimulation experiments. The pithed animals were allowed to recover for 15 minutes. Subsequently, either saline or losartan (3, 10 or 30 mg/kg), irbesartan (30 mg/kg), telmisartan (3
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mg/kg) or captopril (15 or 45 mg/kg) were administered, in a volume of 1 ml/kg. Another 15 minutes later, 0.5 ml/kg saline was injected i.v. in each animal as a volume challenge. Subsequently, intravenous administration of increasing doses of noradrenaline 0.03 nmol/kg – 0.3 µmol/kg was started, injected in volumes of 0.5 ml/kg. Between doses, blood pressure was allowed to return to baseline. Only the highest doses were injected in a cumulative manner. One complete dose-response curve was constructed in each animal.

Drugs

Losartan (MSD, USA) and captopril (Sigma, USA) were dissolved in saline. Irbesartan (Sanofi, France) and telmisartan (Boehringer Ingelheim, Germany) were dissolved in NaOH 1 M. Using HCl 0.01 M, the pH of the solution was lowered to 8 and saline was added. (±)-Propranolol HCl (RBI, USA), Atropine Sulfate (Sigma, USA) and d-Tubocurarine Chloride (Sigma, USA) were dissolved in saline. (-)-Noradrenaline bitartrate (Sigma, USA) was dissolved in saline containing L(+) ascorbic acid 100 µg/ml.

Statistical analysis

All data are shown as means ± SEM of the number of observations. Comparison of means was performed using Student's t-test. For comparison of the potency between drugs, linear regression was performed and analysis of covariance was used to determine differences between regression lines. A p value < 0.05 was considered to indicate statistical significance.
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Results

Baseline diastolic blood pressure (DBP) and heart rate (HR) (after pithing, treatment with propranolol, tubocurarine and atropine) amounted to 45.6 ± 1.8 mmHg and 308.5 ± 4.5 beats per minute (BPM), respectively. Administration of the AT₁-blocking drugs or captopril caused a significant, dose dependent reduction in blood pressure (see table 1). All compounds used caused very similar maximal hypotensive effects (p>0.05). Heart rate was unaffected by either AT₁-receptor blockade or ACE-inhibition (table 2).

Stimulation experiments

Stimulation of the thoraco-lumbar spinal cord (T5-L4) caused a frequency-dependent increase in diastolic blood pressure and heart rate. In the control group as well in the animals subjected to AT₁-receptor blockade or ACE-inhibition, the heart rate increased frequency-dependently, with a maximal increase of 23.7 ± 3.7 BPM in the control group observed at a stimulation frequency of 8 Hz. No significant difference was observed between groups (data not shown).

The increase in DBP could be dose-dependently and significantly attenuated by all three AT₁-receptor blockers, in the lower three concentrations used (fig. 1A-C). For instance, losartan 1 mg/kg showed no difference with control-values, but losartan 3 and 10 mg increasingly attenuated the stimulation-induced rise in DBP. This attenuation was more pronounced at the lower frequencies (0.25-2 Hz). Interestingly, the highest doses of all three AT₁-receptor antagonists did not further attenuate the rise in DBP. Conversely, the rise in DBP was stronger than observed after administration of the lower dose.

A comparable attenuation of DBP-rise was reached with the three AT₁-blockers, but with dosages which differed about threefold. For instance, telmisartan 1 mg/kg showed a degree of attenuation comparable to that of losartan 3 mg/kg and irbesartan 10 mg/kg, whereas telmisartan 3 mg/kg showed comparable attenuation to losartan 10 mg/kg and irbesartan 30 mg/kg.

The most pronounced effect of AT₁-receptor blockade was observed at a stimulation frequency of 2 Hz. In fig. 2A, the rise in DBP observed at 2 Hz is plotted against the various doses used of the three compounds studied. For comparison between AT₁-antagonists on a molar base, we expressed the doses in log mol/kg. When the lower three doses are considered, a linear correlation was observed between their doses and Δ DBP (fig. 2B). There was a significant difference between regression lines. (losartan vs. telmisartan p<0.01, losartan vs. irbesartan p<0.05, telmisartan vs. irbesartan p<0.01).
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Table 1. Baseline diastolic blood pressure (mmHg) in the pithed normotensive rat after administration of saline (control) or a single dose of either losartan, irbesartan, telmisartan or captopril, respectively.

<table>
<thead>
<tr>
<th>Dose AT₁-antagonist (mg/kg i.v.)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>45.6 ± 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>24.6 ± 1.3 *</td>
</tr>
<tr>
<td>1</td>
<td>22.6 ± 2.5 *</td>
</tr>
<tr>
<td>3</td>
<td>23.1 ± 2.0 *</td>
</tr>
<tr>
<td>10</td>
<td>24.2 ± 1.7 *</td>
</tr>
<tr>
<td>30</td>
<td>17.5 ± 1.4 *</td>
</tr>
<tr>
<td>60</td>
<td>19.9 ± 0.8 *</td>
</tr>
</tbody>
</table>

Pooled data from groups before spinal cord stimulation or noradrenaline administration. N = 6 - 12 animals per group. Values are expressed as mean ± SEM. * p<0.05 compared to control.

Table 2. Baseline heart rate (BPM) in the pithed normotensive rat after administration of saline (control) or a single dose of either losartan, irbesartan, telmisartan or captopril, respectively.

<table>
<thead>
<tr>
<th>Dose AT₁-antagonist (mg/kg i.v.)</th>
<th>Heart Rate (BPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>308.5 ± 4.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>302.2 ± 5.5</td>
</tr>
<tr>
<td>1</td>
<td>307.5 ± 6.45</td>
</tr>
<tr>
<td>3</td>
<td>306.7 ± 10.1</td>
</tr>
<tr>
<td>10</td>
<td>304.3 ± 7.3</td>
</tr>
<tr>
<td>30</td>
<td>295.8 ± 11.1</td>
</tr>
<tr>
<td>60</td>
<td>300.1 ± 8.6</td>
</tr>
</tbody>
</table>

Pooled data from groups before spinal cord stimulation or noradrenaline administration. N = 6 - 12 animals per group. Values are expressed as mean ± SEM.
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Fig. 1. Effect of either AT₁-receptor blockade or ACE-inhibition on the frequency-response curve induced by electrical stimulation of the spinal cord (T5-L4) in the pithed normotensive rat. The stimulation frequency (in Hz) is shown on the abcissa. The increase in diastolic blood pressure (expressed as mmHg) is shown on the ordinate.  
A: losartan (1, 3, 10 and 30 mg/kg). B: irbesartan (3, 10, 30 and 60 mg/kg).  
C: telmisartan (0.3, 1, 3 and 10 mg/kg). D: captopril (1.5, 5, 15 and 45 mg/kg).  
Values are expressed as mean ± SEM. * p<0.05 compared to control. N = 6-8 in each group.
Captopril (1.5 – 45 mg/kg) could also dose-dependently inhibit stimulation-induced increases of DBP (fig. 1D). The maximal attenuation was somewhat less than achieved by the AT₁-antagonists. However, this difference only reached statistical significance when compared with irbesartan (ΔDBP at 2 Hz: 60.2 ± 5.9 mmHg with captopril and 45.2 ± 4.7 mmHg with irbesartan; p<0.05).

Fig. 2. A: Effects of losartan, irbesartan, telmisartan and captopril on the diastolic blood pressure increase observed at a stimulation frequency of 2 Hz. Doses of each compound are shown on the abscissa and expressed as log mol/kg. The increase in diastolic blood pressure (expressed as mmHg) is shown on the ordinate. Note the reduction of the inhibitory effects by the highest doses of the AT₁-receptor blockers. B: The three lower doses of each compound and linear regression lines are shown. * p<0.05 between regression lines.

Exogenous noradrenaline
In these experiments, exogenous NA caused a dose-dependent increase in DBP (EC₅₀ 8.52 ± 0.09 –log mol/kg, Eₘₐₓ 120.2 ± 4.7 mmHg) (fig. 3). Losartan 3, 10 and 30 mg/kg did not alter the BP-response to administration of exogenous noradrenaline. Irbesartan 30 mg/kg, telmisartan 10 mg/kg and captopril 15 and 45 mg/kg (the doses that caused maximal suppression of stimulation curves) showed similar results.
Fig. 3. Effects of either losartan, irbesartan, telmisartan or captopril on the dose-response curve induced by intravenously administered noradrenaline in the pithed normotensive rat. The noradrenaline doses (expressed as log mol/kg) are shown on the abcissa. The increase in diastolic blood pressure (expressed as mmHg) is shown on the ordinate.

A: losartan (3, 10 and 30 mg/kg). B: irbesartan (30 mg/kg) C: telmisartan (3 mg/kg)
D: captopril (15 and 45 mg/kg). Values are expressed as mean ± SEM. N = 6 in each group.
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Discussion

In the present study, three selective AT₁ blockers (losartan, irbesartan and telmisartan) and the ACE-inhibitor captopril were compared quantitatively with respect to their inhibitory effects on the sequelae of sympathetic nervous system activation. In the pithed rat model, neuronally mediated increments in vascular resistance are known to be facilitated by endogenously formed Ang II [14]. So far, very little is known about differences in sympatho-inhibitory potency between the various AT₁-receptor blockers. Ohlstein et al. found eprosartan, but not losartan, valsartan and irbesartan to be effective [28]. However, in their experiments only one dose of each compound was used (0.3 mg/kg). Both losartan and irbesartan had previously been shown to attenuate sympathetic neurotransmission at higher doses of 10 mg/kg and 30 mg/kg, respectively [20,21]. In the present study, multiple doses of each compound were used, enabling us to quantitatively compare their potencies on the basis of dose-response relationships.

As shown in table 1, the three selective AT₁-receptor antagonists as well as captopril significantly lowered baseline blood pressure. However, heart rate was unaffected (table 2). Apparently, in this model HR is not modulated by Ang II. Indeed, effects of Ang II on HR were shown to be mediated by β-adrenoceptors in this model [17], which in the present study was prevented by propranolol.

The decrease in blood pressure was comparable to that described in other studies in which either AT₁-blockers or ACE-inhibitors were used. There was no difference in maximal BP-lowering effect between the compounds.

In our investigation, as in other studies, electrical stimulation of the thoracolumbar spinal cord caused stimulation-frequency dependent increases in diastolic blood pressure and heart rate. In the present study, the increase in HR was very small compared to other studies [14,20] which can be explained by the pretreatment with propranolol in the present study. We found no significant differences in ΔHR between the control group and in the animals subjected to AT₁-receptor blockade or ACE-inhibition. These findings are in accordance with Kaufman & Vollmer and Wong et al., who also concluded that the stimulation-induced increase in HR was unaffected by blockade of the RAS [14,20].

The increase in DBP could be dose-dependently attenuated by both AT₁-blockade and ACE-inhibition (fig 1). At the lower frequencies (0.25-2 Hz), the attenuation was more pronounced, indicating a more important facilitating role of Ang II in the lower frequency range. In other studies in which the pithed rat model was also used, frequencies of 1-5 Hz have been shown to
be most sensitive to facilitation [14,15,20,18]. At the higher frequencies, NA release seems to be maximal and less sensitive to facilitation by Ang II. However, both losartan 10 mg/kg and irbesartan 30 mg/kg could decrease DBP-rise at 8 Hz.

In order to compare the potency of the compounds used, effects observed at 2 Hz were plotted separately (fig. 2). The degree of attenuation was similar for all three AT$_1$-blockers used in this study. Maximum inhibition achieved by captopril was somewhat less than with AT$_1$-blockade, although the difference only reached statistical significance compared to maximum inhibition achieved by irbesartan (ΔDBP at 2 Hz: 60.2 ± 5.9 mmHg with captopril and 45.2 ± 4.7 mmHg with irbesartan; p<0.05). Hence, the efficacy of sympato-inhibition does not differ between the AT$_1$-blockers, but appears to be higher for irbesartan than for captopril. A linear correlation was observed between the doses administered and ΔDBP, for all compounds used. Regression lines between the AT$_1$ blockers differed significantly (fig. 2B). Compared to losartan, telmisartan exerts similar effects in a lower dose range (p<0.01), whereas for irbesartan higher doses are needed (p<0.05 compared to losartan, p<0.01 compared to telmisartan). Captopril exerts its effects in a similar dose range as irbesartan (0.01-0.1 μmol/kg), and therefore seems equipotent. However, the regression lines differ significantly, largely due to significantly different slopes (p<0.01). It is unclear what the significance of this finding might be.

Accordingly, on a molar basis, the order of potency of the selective AT$_1$-blockers regarding inhibition of sympathetic neurotransmission is telmisartan>losartan>irbesartan. However, the order of potency, concerning the inhibition of angiotensin II-induced contraction of vascular smooth muscle, was reported to be telmisartan>irbesartan>losartan [25-26]. Consequently, for losartan and irbesartan, the order of potency regarding direct action on smooth muscle and sympato-inhibition appears to be reversed. This difference in order of potency might be explained by the conversion of losartan into its more potent metabolite EXP 3174 in the in vivo model used in the present study. Telmisartan is more potent than the other two compounds in inhibiting both direct action of Ang II on vascular smooth muscle and inhibition of Ang II-mediated facilitation of sympathetic neurotransmission.

A rather surprising finding was obtained for the highest doses of the various AT$_1$-receptor blockers used in the present study. These doses caused less than maximal suppression (fig. 2A), and no plateau was reached. Conversely, with captopril, the highest doses caused a very similar reduction of DBP-rise, indicating that a maximum inhibition has indeed been achieved.
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The fact that the highest dosages of the AT₁-receptor antagonists still caused a significant fall in baseline blood pressure implies that AT₁-blockade was indeed achieved. The consistency of this observation for all three AT₁-blockers suggests that it is a class effect.

To our knowledge, this is the first time that such a finding has been reported in vivo. However, a similar finding was reported for in vitro conditions by Cox et al., who demonstrated that, in the isolated perfused caudal artery of the rat, losartan (10 nM) increased the Ang II-induced stimulation-induced NA-efflux as well as nerve stimulated vasoconstriction [29,30]. This finding might be explained by an unmasking of a latent population of AT-receptors that further mediates Ang II-induced facilitation of sympathetic neurotransmission. The synergistic actions of losartan and Ang II could be abolished by adding PD123319, indicating a role for the AT₂ receptor. In the present study, less than maximal inhibition observed with the highest doses of selective AT₁-blockade might also be caused by a mechanism as proposed by Cox et al. Indeed, the phenomenon was not observed after ACE-inhibition.

To elucidate whether the attenuation of sympathetic neurotransmission by AT₁-blockade or ACE-inhibition was due to postsynaptic effects, experiments using exogenous noradrenaline were performed (fig. 3A-D). The three doses of losartan which caused a significant reduction of DBP-rise in the stimulation experiments were used. For irbesartan, telmisartan and captopril, the doses that caused maximal suppression in stimulation experiments were used. As to be expected, exogenous NA caused dose dependent increases in DBP. AT₁-blockade by losartan (3, 10 and 30 mg/kg), irbesartan (30 mg/kg), telmisartan (3 mg/kg) and captopril (15 and 45 mg/kg) did not affect DBP-responses to exogenous NA. After AT-blockade, E_max values were slightly, although not significantly increased in all groups. This probably reflects the differences in baseline blood pressure between control-experiments and those after AT₁-blockade or ACE-inhibition. Because the DBP after the highest doses of NA are very similar in each group, including the control group, (around 150 mmHg), the ADBP tend to be slightly higher after AT₁-blockade and captopril treatment.

Since no difference was observed in the responses to exogenous noradrenaline between control experiments and those after AT₁-blockade, the sensitivity of the postsynaptic α-receptors is not affected by angiotensin II in our experimental model. These findings are in accordance with the observations of Yokoyama et al., who did not establish any effect of losartan (1 mg/kg) on the pressor responses of NA [22]. Their figures show a slight, not significant increase in E_max. Others [14,20] reported that both losartan and captopril reduced BP-responses to NA, but they used very low doses of NA (1-3 µg/kg) and did not achieve maximal effects. Similarly as in our present
study, Antonaccio & Kerwin observed no effect of an acute captopril infusion on the response to the pressor effects to noradrenaline [23].

Some authors have suggested that the low initial BP after ACE-inhibition or AT₁-receptor blockade might be responsible for the attenuation of ΔDBP [12,13,18,31]. They suggested that the effect of the inhibitors was at least in part a consequence of the diminished arteriolar tone. However, in the present study, low doses of the AT₁-receptor antagonists caused a significant decrease of baseline BP, but the pressor response to spinal cord stimulation was the same as in control experiments. Accordingly, we found no inhibitory effect of the lowered baseline blood pressure on ΔDBP. In addition, both Wong et al. and Kaufman & Vollmer reported that in the pithed rat model, total peripheral resistance— and therefore arteriolar tone— was not affected by AT-receptor blockade. In our experiments with NA, we observed that the increase in DBP was not blunted after AT₁-blockade nor ACE-inhibition, despite a significant decrease in initial DBP. This finding indicates that DBP increase is not negatively affected by a low initial DBP.

In conclusion, in the pithed rat model, Ang II facilitates sympathetic neurotransmission. The observations in this study mainly reflect interactions between RAS and SNS at the peripheral level. The facilitation occurs via pre-synaptic AT₁-receptors, since the responses to exogenous NA could not be reduced by AT₁-blockade. The order of potency of the sympatho-inhibitory effect in this model proved to be telmisartan > losartan > irbesartan. The efficacy of the three AT₁-antagonists is very similar.

The fact that all three AT₁ blockers cause less than maximal inhibition in their highest doses, as opposed to captopril, suggest that this is a class effect of AT₁-antagonists.

The sympatho-inhibitory properties of both the AT₁-receptor antagonists losartan, irbesartan and telmisartan, as well as the ACE-inhibitor captopril, might contribute to the therapeutic effects of these drugs. This presumption appears to be relevant in particular if one considers the role of the sympathetic nervous system in the genesis and maintenance of hypertension [6-8] and even more so in congestive heart failure [9-11], two conditions in which AT₁-antagonists and ACE-inhibitors are known to be beneficial therapeutics.
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