Angiotensin-(1–7) modulates vascular resistance and sympathetic neurotransmission in kidneys of spontaneously hypertensive rats

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Abstract

Objective: Angiotensin (Ang)-(1–7) generated from Ang I and II is reported to act as an endogenous angiotensin-converting enzyme (ACE) inhibitor and angiotensin type 1 (AT1)-receptor antagonist in vitro and in vivo. Ang-(1–7) has been suggested to play an important role in hypertension. Methods and results: Therefore, we tested whether Ang-(1–7) differentially modulates vascular resistance and neurotransmission in isolated kidneys of spontaneously hypertensive rats stroke prone (SHR-SP) and Wistar–Kyoto rats (WKY). Ang-(1–7) was administered in three concentrations (0.1, 1 and 10 μmol/l) to prevent Ang I- and Ang II-induced pressor responses and facilitation of noradrenaline release. There were indeed concentration-dependent strain differences. Ang-(1–7) prevented Ang I- and Ang II-mediated changes in vascular resistance more potently in SHR-SP than in WKY by inhibiting ACE and by blocking AT1-receptors. Ang-(1–7) by itself had no influence on renal vascular tone in both strains. Ang-(1–7) inhibited Ang I-mediated facilitation of noradrenaline release more potently than Ang II-mediated facilitation of noradrenaline release. Ang-(1–7) by itself enhanced noradrenaline release from SHR-SP, but not from WKY kidneys. Conclusion: Ang-(1–7) had a greater impact on Ang I and Ang II modulation of renal vascular resistance in SHR-SP than in normotensive rats. Furthermore, Ang-(1–7) by itself has facilitatory presynaptic effects on noradrenaline release but no postsynaptic effects on renal vascular resistance in SHR-SP. Since plasma levels of Ang-(1–7) accumulate during ACE-inhibitor or AT1-receptor antagonist therapy, Ang-(1–7) could contribute to antihypertensive effects of these agents.

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Keywords: Angiotensin-(1–7); Renin-angiotensin-system; Noradrenaline release; Vascular resistance; Experimental hypertension

1. Introduction

Angiotensin II (Ang II) is believed to be the major effector molecule of the renin–angiotensin system (RAS) [1,2]. Most of its known actions, i.e. regulation of vascular resistance, sympathetic neurotransmitter release, cell proliferation and differentiation, as well as osmo- and volume homeostasis, are mediated via AT1- and AT2-receptors [3–5]. However, Ang II is not the only active metabolite of the RAS. Other degradation products of Ang I and Ang II, such as the heptapeptide Ang-(1–7), have received more and more attention as active peptides of the RAS [6,7]. Ang-(1–7), which can be formed from either Ang I or Ang II by endopeptidases and carboxypeptidases, is further metabolized by angiotensin-converting enzyme (ACE). Recent studies suggest that Ang-(1–7) acts as an endogenous antagonist of Ang I and II and blocks Ang II-mediated vasoconstriction and cell proliferation [8–11]. In contrast, others have reported that Ang-(1–7) seemed to induce vasoconstriction in human forearm [12] and rat renal microvessels [13]. However, these effects are not easily attributable to a single mode of action. Thus, it was proposed that besides activation of a new Ang II (Ang-(1–7)-receptor), ACE-inhibition and AT1-receptor blockade could be responsible for the effects mediated by Ang-(1–7) [9,14–17]. Another important observation was that Ang-(1–7) plasma levels increase during antihypertensive therapy involving ACE-inhibitors alone or in combination with AT1-receptor antagonists [18–20]. Thus, two main areas of research interest have developed. First, a lack of the endog-
enous antagonist Ang-(1–7) may be one pathophysiological mechanism for the development and maintenance of hypertension. Accordingly, Benter et al. [21] and Kost et al. [22] reported that intravenous infusion of Ang-(1–7) decreases blood pressure in spontaneously hypertensive rats (SHR), but not in normotensive Wistar–Kyoto rats (WKY). The second area of interests concerns the possibility that Ang-(1–7) contributes to beneficial effects of antihypertensive treatment with inhibitors of the RAS. For instance, several studies have demonstrated that ACE inhibitor therapy does not totally prevent Ang II formation [23–25] and data supporting a primary role of bradykinin in mediating its antihypertensive and antihypertrophic effects remain controversial [7]. Thus, one could speculate that Ang-(1–7) is involved in preventing target organ failure in hypertension during chronic ACE inhibitor therapy. In chronic renal failure, hypertension is a result of both an activated RAS and activated sympathetic nervous system [26]. As many studies demonstrated that Ang II is more potent in kidneys of SHR, the primary aim of our study was to investigate whether Ang-(1–7) is capable to prevent Ang I- and Ang II-mediated renal vasoconstriction and enhancement of noradrenaline release in spontaneously hypertensive kidneys. Moreover, we explored the possibility that Ang-(1–7) by itself contributes to hypertension by facilitating renal sympathetic neurotransmission.

2. Materials and methods

Male Wistar–Kyoto rats (Charles River, Sulzfeld, Germany) and 16-week-old spontaneously hypertensive stroke prone rats (SHR-SP) (Max Delbrück Institut, Berlin) weighting between 220 and 310 g were used. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Rats were anesthetized with sodium pentobarbital (60 mg/kg, intraperitoneally) and then the kidneys were isolated and perfused with Krebs–Henseleit solution according to a method described previously [27]. Bipolar platinum electrodes were placed around the renal arteries to stimulate the renal sympathetic nerves. Perfusion pressure was monitored continuously with a Statham P23 Db pressure transducer (Gould, Oxnard, CA) coupled to a Watanabe pen recorder (Graphitec, Tokyo, Japan).

2.1. Experimental protocol (Part A): effects of Ang I, Ang II and Ang-(1–7) on renal vascular resistance

The kidneys were perfused with drug-free Krebs–Henseleit solution at 37 °C with a constant flow rate of 4.2 ml/min g kidney weight. Kidney wet weights were calculated according to data of previously published experiments [27], showing that they correspond to approximately 0.5% of whole body weight. The perfusion solution was continuously gassed with carbogen (5% CO2/95% O2) and passed through a 0.45-μm filter before it reached the kidneys. Immediately after preparation, a bolus injection of ANG II (3 nmol/l) was delivered to test the viability of the preparation followed by a stabilization period of 30 min. The agonists, Ang I, Ang II and Ang-(1–7) were added to the perfusion solution in a cumulative manner expressed in a dose response curve. The time interval between application of the different agonist concentrations was 2.5 min. The perfusion of drugs was stopped when the pressor responses had reached a maximum, or when no effects were observed respectively. When dose response curves for Ang I and Ang II were determined in the presence of Ang-(1–7) (acting as an antagonist), Ang-(1–7) was added to the perfusion solution 10 min before determination of the second dose response curve.

2.2. Calculations

The pressor responses of Ang I, Ang II and Ang-(1–7) were measured as the maximum increase of perfusion pressure above basal perfusion pressure (ΔPmax = Pmax – Pbasal). This increase was expressed as a percentage of ΔPmax (ΔPmax set as 100%). The increase in the perfusion pressure induced by either Ang I or Ang II in the presence of Ang-(1–7) was calculated as percentage to the control dose response curve (ΔPmax(antagonist)/ΔPmax(control) * 100).

Fig. 1. Enhancement of noradrenaline (NA) release after RNS (S1–5) induced by Ang-(1–7) in SHR (n = 4) isolated perfused kidneys, but not in WKY (n = 4). The RNS-induced noradrenaline release was calculated as a percentage of control stimulation S0 (S0 as % of S0) as described in Section 2. Ang-(1–7) was added to the perfusion solution in a cumulative manner 10 min before the next stimulation. In SHR, Ang-(1–7) induces a significant greater enhancement of noradrenaline release compared to WKY (two-factorial ANOVA for repeated measurements P < 0.05); mean ± S.E.M.
**pKᵦ-values for Ang I and Ang II against Ang-(1–7)** were determined according a method of Furchgott as described elsewhere [28].

**2.3. Experimental protocol (Part B): renal nerve stimulation (RNS) and sympathetic neurotransmission**

The kidneys were perfused as described in Section 2.2. Immediately after preparation, a priming stimulation of 5 Hz for 30 s (1 ms pulse width, 40 mA) was delivered to renal nerves to test the viability of the preparation. After a stabilization period of 30 min, cocaine (10 μmol/l) and corticosterone (20 μmol/l) were added to the perfusion solution in order to prevent neuronal and extraneuronal uptake of released noradrenaline, respectively. After another 20 min, 1-min fractions of the effluent were collected by a fraction collector (LKB, Bromma, Sweden) into vials con-

![Graph](https://example.com/graph1.png)

**Fig. 2.** Absolute noradrenaline (NA) release after RNS in the absence (control; Sₒ) of Ang-(1–7) and presence of Ang-(1–7) (10 μmol/l) (S₅) (WKY: control, n = 3; Ang-(1–7) (10 μmol/l), n = 4; SHR control, n = 4; Ang-(1–7) (10 μmol/l) n = 4). The absolute RNS-induced noradrenaline release was calculated as the total RNS-induced noradrenaline release per gram kidney. *Shows a significant greater RNS-induced noradrenaline release for the control as well as for Ang-(1–7)-induced noradrenaline release in SHR than in WKY. + Indicates a significant greater absolute increase of noradrenaline release induced by Ang-(1–7) compared to the control in SHR than in WKY kidneys (ANOVA, P < 0.05).

![Graph](https://example.com/graph2.png)

**Fig. 3. Influence of Ang-(1–7), tested in three different concentrations (0.1, 1 and 10 μmol/l) on Ang I (A)- and Ang II (B)-mediated renal vascular resistance (Ang I, n = 17; Ang I + Ang-(1–7) (0.1 μmol/l), n = 4; Ang I + Ang-(1–7) (1 μmol/l), n = 4; Ang I + Ang-(1–7) (10 μmol/l), n = 5; Ang II, n = 30; Ang II + Ang-(1–7) (0.1 μmol/l), n = 5; Ang II + Ang-(1–7) (1 μmol/l), n = 8; Ang II + Ang-(1–7) (10 μmol/l), n = 10) in WKY isolated perfused kidneys. Ang-(1–7) was added to the perfusion solution 10 min before measuring the second renal dose response curve. The increase in the renal resistance was calculated as a percentage of ΔPₘₐₓ (ΔPₘₐₓ set as 100%) as described in Section 2. Ang-(1–7) (1 and 10 μmol/l) shifted the dose response–curve of Ang I and Ang II significantly to the right (two-factorial ANOVA for repeated measurements, P < 0.05); mean ± S.E.M. The lowest concentration of Ang-(1–7) showed no inhibitory potency in WKY kidneys.
taining 167 µl of 1 M HCl, 13.3 µl of 0.067 M EDTA and 3.3 µl of 1 M Na₂SO₃. Six electrical RNS (S₀–S₅) each at 2 Hz for 30 s (1 ms pulse width, 40 mA) were applied 2, 16, 30, 44 and 58 min after the start of fraction collection. Cumulative concentrations response curves for Ang I, Ang II and Ang-(1–7) were determined. The substances were directly added to the perfusion solution in a cumulative manner starting 10 min before S₁, S₂, S₃, S₄ and S₅.

When Ang-(1–7) (used as an antagonist) was present throughout the experiment, it was added to the perfusion solution 8 min before the start of fraction collection.

2.4. Determination of endogenous noradrenaline

The noradrenaline in the isolated kidney samples was extracted (adsorption onto alumina, elution with HCLO₄). Noradrenaline content was determined by reversed-phase HPLC detection [29]. The amount of noradrenaline (pg/g kidney) present in each samples was corrected for recoveries (average percent recovery of noradrenaline–HCl was 0.562 ± 0.2; n = 33).

2.5. Calculation of data

The RNS-induced outflow of noradrenaline was determined in four 1-min samples collected immediately after the onset of stimulation. S₀ served as a control/reference stimulation for the following stimulations. The RNS-induced noradrenaline outflow during S₁, S₂, S₃, S₄ and S₅ was expressed as a percentage of that during S₀ (Sₙ as % of S₀). For further evaluations, the effects of Ang I, Ang II and Ang-(1–7) in the absence or presence of Ang-(1–7), the Sₙ/ S₀ ratios were calculated as a percentage of values, which were determined in the corresponding control experiments (Sₙ/ S₀ as % of control).

2.6. Statistical analysis

All data were expressed as mean ± S.E.M. Differences between dose response curves were analyzed by two-facto-
rial ANOVA for repeated measurements followed by unpaired Student's t-test. Probability levels of P<0.05 were consisted statistically significant. The number of experiments indicates the number of individual kidneys.

2.7. Drugs and vehicles

The Krebs–Henseleit solution had the following composition (mM): NaCl 118, KCl 4.7, CaCl₂ 2.5, MgSO₄ 0.45, NAHCO₃ 25, KH₂PO₄ 1.03, d-(+)-glucose 11.1, Na₂EDTA 0.067 and ascorbic acid 0.07. The following drugs were employed: (+)-noradrenaline HCl, corticosterone, Ang I (Sigma, Deisenhofen, Germany); cocaine HCl (Merk, Darmstadt, Germany); EXP 3174 (DU PONT, Wilmington, DE); Ang II (Angiotensinamid, Ciba-Geigy, Wehr, Germany); Ang-(1–7) (Bachem, Heidelberg, Germany). Drugs

Fig. 4. Influence of Ang-(1–7), tested in three different concentrations (0.1, 1 and 10 µmol/l) on Ang I (A)- and Ang II (B)-mediated renal vascular resistance (Ang I, n = 11; Ang I + Ang-(1–7) (0.1 µmol/l), n = 5; Ang I + Ang-(1–7) (1 µmol/l), n = 5; Ang I + Ang-(1–7) (10 µmol/l), n = 5; Ang II, n = 14; Ang II + Ang-(1–7) (0.1 µmol/l), n = 5; Ang II + Ang-(1–7) (1 µmol/l), n = 5; Ang II + Ang-(1–7) (10 µmol/l), n = 6) in SHR isolated perfused kidneys. Ang-(1–7) was added to the perfusion solution 10 min before measuring the second renal dose response curve. The increase in the renal resistance was calculated as a percentage of ΔPₚₘₓ (ΔPₚₘₓ set as 100%) as described in Section 2. All tested concentrations of Ang-(1–7) (0.1, 1 and 10 µmol/l) shifted the dose response–curve of Ang I and Ang II significantly to the right (two-factorial ANOVA for repeated measurements, P<0.05); mean ± S.E.M.
were dissolved in distilled water before being diluted with Krebs–Henseleit solution, except of corticosterone that was dissolved in absolute ethanol.

3. Results

SHR-SP and WKY rat kidneys were isolated and perfused with Krebs–Henseleit solution. The effects of Ang-(1–7) alone and against Ang I, Ang II on renal vascular resistance and RNS-induced noradrenaline release were analyzed.

3.1. Effects of Ang-(1–7) on pressor responses and RNS-induced noradrenaline release

Ang-(1–7) failed to induce vasodilation or vasoconstriction by itself as well as in noradrenaline preconstricted kidneys of WKY and SHR-SP (data not shown). In contrast, Ang-(1–7) significantly enhanced noradrenaline release in SHR-SP and not in WKY kidneys (Fig 1). The maximal absolute RNS-induced noradrenaline release (pg/g kidney weight) in the absence of Ang-(1–7) was greater in SHR-SP than in WKY (Fig. 2). Moreover, the absolute increase of noradrenaline release induced by Ang-(1–7) was also significantly greater in SHR-SP than in WKY kidneys (Fig 2) (control: WKY: 1837 ± 129, SHR: 2308 ± 192; Ang-(1–7): WKY 1597 ± 61, SHR 3292 ± 311 pg/g kidney).

3.2. Effects of Ang-(1–7) on pressor responses to Ang I and Ang II

Ang-(1–7) inhibited pressor responses to Ang I and Ang II in WKY and SHR-SP kidneys in a competitive manner (Figs. 3 and 4). However, there were different inhibitory potencies of Ang-(1–7) in WKY and SHR-SP kidneys. Furthermore, concentration-dependent differences in the effects of Ang-(1–7) against Ang I and Ang II were observed. Thus, the lowest concentration of Ang-(1–7) (0.1 μmol/l) shifted the dose response curves of Ang I and Ang II significantly to the right in SHR-SP but not in WKY (Figs. 3 and 4). Higher concentrations of Ang-(1–7) (1 and 10 μmol/l) shifted the dose response curves of Ang I and Ang II in both strains. Calculated pK_B-values (Table 1A and B) for Ang-(1–7) (1 μmol/l) against Ang I and Ang II suggest a similar inhibitory potency in WKY. In contrast, in SHR-SP Ang-(1–7) (1 μmol/l) appears to be more potent against Ang I than against Ang II (Table 1A and B). The highest concentration of Ang-(1–7) (10 μmol/l) shifted the dose response curves of Ang I more effectively to the right than the dose response curve of Ang II for both WKY (Fig. 3A and B) and SHR-SP (Fig. 4A and B). The corresponding pK_B-values for Ang-(1–7) were similar (Table 1A and B).

Table 1

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(A) and (B) shows pK_B-values of Ang 1–7 in two different concentrations (1 and 10 μmol/l) against Ang I and Ang II in WKY and SHR kidneys. In WKY, Ang 1–7 (1 μmol/l) was equipotent against Ang I and II. In all other groups, Ang-(1–7) was more potent against Ang I than against Ang II. pK_B values (−log K_B) were obtained according to the following equation: K_B = |A|/(concentration ratio − 1) where [A] is the concentration of the antagonist and concentration ratio is the EC50 in the presence of the antagonist divided by the EC50 in the absence of antagonist.

Fig. 5. Influence of Ang-(1–7) (10 μmol/l) on the Ang I-mediated induced noradrenaline (NA) release after RNS (WKY: Ang I, n = 3; Ang I + Ang-(1–7), n = 4; SHR: Ang I, n = 4; Ang 1 + Ang-(1–7), n = 5) in isolated perfused kidneys of WKY and SHR. Ang-(1–7) was added to the perfusion solution 10 min before the first RNS. The RNS-induced noradrenaline release was calculated as a percentage of control stimulation S_0 (Sn as % of S_0) as described in Section 2. Ang-(1–7) shifted the dose response– curve of Ang I in both strains significantly to the right (two-factorial ANOVA for repeated measurements, P<0.05); mean ± S.E.M. *Indicates in the presence of Ang-(1–7) (10 μmol/l) a significant smaller maximal Ang I-induced enhancement of noradrenaline release in SHR than in WKY.
release was calculated as a percentage of control stimulation $S_0$ (SN as % of solution 10 min before the first RNS. The RNS-induced noradrenaline perfused kidneys of WKY and SHR. Ang-(1–7) was added to the perfusion $S_0$) as described in Section 2. Ang-(1–7) shifted the dose response curve of Ang II in both strains significantly to the right (two-factorial ANOVA for repeated measurements, $P<0.05$); mean ± S.E.M. No difference in both strains was seen.

3.3. Effects of Ang-(1–7) on Ang I- and Ang II-mediated modulation of RNS-induced noradrenaline release

Ang-(1–7) (10 μmol/l) shifted the dose response curves of Ang I- and Ang II-induced noradrenaline release to the right in a significant manner in SHR-SP and WKY kidneys (Figs. 5 and 6). Ang-(1–7) (10 μmol/l) induced a greater shift of the dose response curve to Ang I than to Ang II in both strains (Figs. 5 and 6). Ang-(1–7) (10 μmol/l) seemed to be equally effective in WKY and SHR-SP kidneys with one exception, in the presence of Ang-(1–7) (10 μmol/l) the maximal Ang I-induced enhancement of noradrenaline release was significantly smaller in SHR-SP than in WKY (Fig. 6).

4. Discussion

In the present study, the effect of Ang-(1–7) on renal sympathetic neurotransmitter release and renal vascular resistance was investigated in SHR-SP and WKY isolated kidneys.

Previous studies showed that Ang-(1–7) blocks AT1-receptors and inhibits ACE [10,15,16,30,31]. Such an inhibitory effect of Ang-(1–7) on pressor responses to Ang I and II has been previously demonstrated in kidneys of normotensive rats. An involvement of specific Ang-(1–7)-receptors was excluded [17]. In the present study, several concentrations of Ang-(1–7) (0.1, 1 and 10 μmol/l) were tested to detect possible differences in the inhibitory potency of Ang-(1–7) on Ang I- and II-mediated pressor responses elicited in WKY versus SHR-SP. Ang-(1–7) in the lowest concentration (0.1 μmol/l) failed to shift the Ang I- and Ang II-mediated dose response curve significantly to the right in WKY kidneys, whereas the intermediate and highest concentrations of Ang-(1–7) caused a significant shift to the right. The intermediate concentration was equipotent against Ang I and II, however, the highest concentration of Ang-(1–7) revealed a more potent inhibitory effect against Ang I than against Ang II. The greater shift of the Ang I as compared to the Ang II dose response curve by Ang-(1–7) is most likely due to simultaneous AT1-receptor blockade and ACE inhibition [17]. The identical potency of the intermediate concentration (1 μmol/l) of Ang-(1–7) against Ang I and Ang II gives indirect evidence that in this concentration Ang-(1–7) blocks AT1-receptors only. The situation in SHR-SP was different. In the hypertensive strain the lowest concentration of Ang-(1–7) shifted the dose response of Ang-(1–7) revealed a more potent inhibitory effect against Ang I than against Ang II. The greater shift of the Ang I as compared to the Ang II dose response curve by Ang-(1–7) is most likely due to simultaneous AT1-receptor blockade and ACE inhibition [17]. The identical potency of the intermediate concentration (1 μmol/l) of Ang-(1–7) against Ang I and Ang II gives indirect evidence that in this concentration Ang-(1–7) blocks AT1-receptors only. The situation in SHR-SP was different. In the hypertensive strain the lowest concentration of Ang-(1–7) shifted the dose response curve of Ang I- and Ang II-mediated pressor responses to Ang I and II significantly to the right. The more potent effect of Ang-(1–7) in SHR-SP is consistent with results of Kost et al. [22], Benter et al. [21], Fernandes et al. [32] and Iyer et al. [14,19]. They suggested that the more potent effect of Ang-(1–7) in SHR was due to the release of prostanoids, kinines and/or nitric oxide by activation of putative Ang-(1–7)-receptors [6]. However, this is not a likely explanation for our findings in SHR-SP isolated kidneys, since Ang-(1–7) had no vasodilatory effect in noradrenaline preconstricted kidneys even in subnanomolar concentrations considered to be selective for Ang-(1–7)-receptors [9,32]. There seem to be also species differences, since Ang-(1–7) has been shown to dilate rabbit renal arteries in vitro [9]. In contrast to the almost identical inhibitory potency of an intermediate concentration of Ang-(1–7) (1 μmol/l) against Ang I and II in WKY, in SHR-SP Ang-(1–7) (1 μmol/l) was more potent against Ang I than against Ang II. This may suggest a higher affinity of Ang-(1–7) for ACE in SHR-SP than in WKY kidneys. The inhibitory effect of Ang-(1–7) in the highest concentration (10 μmol/l) showed no differences between both strains with respect to Ang I- and Ang II-induced pressor responses.

In the present study, Ang-(1–7) neither induced vasodilation nor vasoconstriction. Thus, our results do not provide evidence for a vasoactive potency of Ang-(1–7) by itself in the renal vasculature of normotensive and hypertensive rats. These results are in contrast to findings...
of Ueda et al. [12], Abbas et al. [33] and van Rodijnen et al. [13] who showed a weak but significant AT1-receptor-mediated vasoconstriction of high Ang-(1–7) doses in the human forearm, anesthetized rats and rat renal microvessels. On the other hand recent studies showed that Ang-(1–7) induces AT1-/AT2-receptor independent relaxation in different tissues and species, including coronary arteries of canines and pigs [34,35] and isolated heart and aorta of rats [36,37]. Osei et al. [38] found apparently opposing vascular responses to Ang-(1–7) in mesenteric and hindlimb vascular beds, suggesting tissue selectivity.

4.2. Effects of Ang-(1–7) as a modulator of renal sympathetic neurotransmission

Ang-(1–7) (10 µmol/l) inhibited Ang I- and Ang II-mediated enhancement of RNS-induced noradrenaline release in both strains. There was a greater rightward shift of the dose response curve for Ang I than for Ang II by about one log unit in both strains. This greater shift of the Ang I dose response curve may be attributed to a simultaneous AT1-receptor blockade and ACE inhibition by the high concentration of Ang-(1–7) [17]. The inhibitory potency of Ang-(1–7) (10 µmol/l) against Ang I and Ang II was not different between SHR-SP and WKY. Thus, obvious differences of Ang-(1–7) as an antagonist of Ang I- and II-mediated modulation of renal sympathetic neurotransmitter release appear not to play a role for hypertension in the SHR-SP. Ang-(1–7) reduced the maximal Ang I- but not the maximal Ang II-mediated enhancement RNS-induced noradrenaline release in SHR-SP. This may suggest that Ang-(1–7) acts as a non competitive inhibitor in SHR-SH kidneys as previously described for Ang II-induced pressor effects in rabbit aortic rings by Mahon et al. [10].

It is noteworthy that Ang-(1–7) by itself enhanced RNS-induced noradrenaline release in SHR-SP but not in WKY kidneys. One explanation could be that Ang-(1–7) especially in high concentrations has an intrinsic activity at AT1- or AT2-receptors as suggested for rat atria and hypothalamic tissues [39–41]. However, this explanation seems not likely for several reasons. Even the highest concentration of Ang-(1–7) (10 µmol/l) did not have any facilitatory effects on RNS-induced noradrenaline in WKY kidneys. Furthermore, as outlined above, Ang-(1–7) had a similar inhibitory effect against AT1-receptor-mediated enhancement of noradrenaline release in WKY and SHR. Thus, there has to be an alternative explanation. One could speculate that there are presynaptic high affinity binding sites for Ang-(1–7) in SHR-SP, which might be responsible for these observed differences. Thus, the facilitatory effect of Ang-(1–7) in SHR-SP may play a pathophysiological role in this model of hypertension. In conclusion, Ang-(1–7) acts as an endogenous antagonist of ACE and AT1-receptors in WKY and SHR-SP kidneys and has a greater impact on Ang I- and Ang II-mediated modulation of renal vascular resistance in SHR-SP than in WKY. Furthermore, Ang-(1–7) by itself shows differential pre-and postsynaptic effects in SHR-SP, e.g. it facilitates noradrenaline release presynaptically but has no direct vasoactive effects. Since plasma levels of Ang-(1–7) accumulate during therapy with ACE-inhibitors and/or AT1-receptor antagonists [18–20,30,42], Ang-(1–7) could contribute to beneficial effects of this antihypertensive therapy. This view is supported by our findings that Ang-(1–7) inhibits Ang I- and II-mediated pressor responses more potently in a genetic model of hypertension. Admittedly, plasma levels of Ang-(1–7) reported even under therapy with ACE-inhibitors and/or AT1-receptor antagonists are lower than concentrations used in this study. Nevertheless, it may be that Ang-(1–7) tissue levels exceed Ang-(1–7) plasma levels in analogy to the situation with Ang II itself.

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References


