Effects of Angiotensin II on Isolated Rabbit Afferent Arterioles

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ABSTRACT—We examined the effects of angiotensin II (Ang II) on isolated rabbit afferent arterioles to assess the direct effect of Ang II at the resistance vessel level in the kidney. We microdissected the superficial afferent arteriole from the kidney of New Zealand White rabbits. The afferent arteriole was cannulated with a micropipette system, and the intraluminal pressure was set at 80 mmHg. Ang II did not change the lumen diameter of the afferent arterioles. After the afferent arterioles were pretreated with aspirin DL-lysine or indomethacin, Ang II (10⁻⁷ M) caused transient vasoconstriction in the afferent arterioles. Ang II (10⁻⁷ M) caused persistent constriction in the afferent arterioles pretreated with N⁶-nitro-L-arginine (10⁻⁴ M). Physiological doses of Ang II decreased the lumen diameter of the isolated afferent arterioles pretreated with N⁶-nitro-L-arginine and aspirin DL-lysine. Dup753 (10⁻⁶ M), an AT1-receptor antagonist, abolished the vasoconstrictor effects of Ang II. These findings suggest that the isolated rabbit afferent arteriole has AT1 receptors, and the vasoconstrictor response of Ang II is counteracted by vasodilatory prostaglandins and nitric oxide.

Keywords: Afferent arteriole (isolated), Angiotensin II, N⁶-Nitro-L-arginine, Aspirin DL-lysine

Angiotensin II (Ang II) is the most powerful biological active peptide of the renin-angiotensin system, and it plays an important role in regulating renal hemodynamics and urine formation. Exogenous infusion of Ang II has been shown to decrease renal blood flow (RBF) in both humans (1, 2) and experimental animals (3–5). Intrarenal infusion of Ang II to the dog kidney caused a marked decrease in RBF and a smaller decrease in glomerular filtration rate (GFR), with consequent increases in the filtration fraction (FF) (4). Based on in vivo experiments, the effect arterioles are thought to be more sensitive to Ang II than the afferent arterioles (AAs) (6). However, it is not clear whether or not Ang II has a direct vasoconstrictor effect on the AA.

Recent advances in methodology have enabled us to evaluate the direct actions of vasoactive substances on the resistance vessels of the renal circulation (7–18). In 1983, Edwards reported that Ang II did not change the lumen diameter of the isolated rabbit AAs (11). Since then, many subsequent studies have been performed. In rat experiments, Ang II was reported to cause a dose-dependent constriction of AA (14, 19). Ito et al. (13) reported that Ang II caused a transient vasoconstriction of microperfused rabbit AA with glomerulus. What accounts for this discrepancy?

One possible reason for the differing results may be due to the presence of several vasoactive substances that are produced within the kidney, because several types of cells other than arterioles in the kidney, for example, mesangium, renal tubule and interstitial cells, are known to produce vasoactive substances. Ang II caused a relaxation in the preconstricted dog renal artery, and the vasodilatory response to Ang II was postulated to derive from a release of vasodilatory prostaglandins (PGs) in the helical strip preparation of dog renal artery (20). Isolated AAs have the ability to produce PGE₂ and PGI₂ and Ang II stimulates the release of PGI₂ from isolated AAs (21). These findings suggest that vasodilatory PGs modulate the vasoconstrictor effect of Ang II in the renal resistance vessels. Moreover, we reported that nitric oxide (NO) is synthesized and/or released in the rabbit AA under basal conditions and that this basal release of NO plays an important role in the basal tone of the AA (12). This effect of NO may modulate the action of Ang II on the AA.

Thus, the present study was designed to evaluate the direct effect of Ang II on the microdissected rabbit AA without glomerulus and renal tubule. We also examined the effects of PGs and NO on the action of Ang II on the isolated AA.
MATERIALS AND METHODS

Adult male New Zealand White rabbits (2.0–2.5 kg), maintained on standard rabbit chow, were anesthetized with intravenous sodium pentobarbital (25 mg/kg), followed by a maintenance dose when necessary. We used a method similar to that described previously to isolate and cannulate AA (12). Briefly, the kidney was exposed through a retroperitoneal flank incision, and the kidney was quickly removed and placed in iced modified Krebs-Ringer solution. The kidney was flushed with chilled modified Krebs-Ringer solution to remove the cell components from the blood. The kidney was then perfused with an isosmotic Krebs-Ringer solution containing human albumin (Green Cross, Osaka), dextran blue 2,000 (Pharman isosmotic Krebs-Ringer solution containing human albumin to remove the dye solution and blood components. The superficial AA was dissected free from the surrounding tissue under a stereoscopic microscope (SZH; Olympus, Tokyo) using thin steel needles and sharpened forceps (No. 5; Dumont, Basel, Switzerland) at 10°C. Using a micropipette, arteriole was transferred to a temperature-regulated chamber (ITM; San Antonio, TX, USA) mounted on the stage of an inverted microscope with Hoffman modulation (Diaphot; Nikon, Tokyo). Fresh bath medium was supplied to the bottom right side of the chamber at 0.5 ml/min, while the medium in the chamber was drained by gently sucking it out of the top of the left side of the chamber. The bath medium was a modified Krebs-Ringer solution (pH 7.4) consisting of 105 mM NaCl, 5 mM KCl, 25 mM NaHCO3, 2.3 mM Na2HPO4, 10 mM Na acetate, 1 mM MgSO4, 2 mM CaCl2, 8.3 mM glucose, 5 mM alanine, 0.01 mM EDTA and 10 mM HEPES. The superficial AA was dissected free from the top of the left side of the chamber. The bath medium was a modified Krebs-Ringer solution identical to the dissection solution, bubbled with 95% O2 and 5% CO2. During the experiment, water-saturated gas (90% O2 and 10% CO2) was gently blown over the surface of the bath to maintain the pH at 7.4.

One end of the AA was drawn into the holding pipette and the AA was sealed between the holding pipette and the perfusion pipette. The AA was perfused with the modified Krebs-Ringer containing 1% of bovine serum albumin to remove the dye solution and blood components. After perfusion of the AA was stopped, the other end of the AA was captured and sealed in another holding pipette that had a larger constriction. After completion of cannulation, the intraluminal pressure was controlled with a screw driven syringe and set at 80 mmHg. The intraluminal pressure was continuously monitored with a pressure transducer and monitor (Digic VPC; Valcom, Tokyo). If the intraluminal pressure could not be maintained at a constant level, the experiment was discarded. After the pressure was set, the pipettes were adjusted so that all bends in the vessel were removed. Microdissection and cannulation of the AA were completed within 90 min at 10°C. The temperature of the bath was gradually raised to 37°C and monitored during the experiment (E5CS; Omron, Kyoto). A 30-min equilibration period was allowed before each experiment. The image of the AA was recorded with a video system, consisting of a camera adaptor and CCD camera and control unit (CCD-10; Olympus, Tokyo), monitor (NV-0930Z; Mitsubishi, Tokyo) and video recorder (Timelapse BR-9000; JVC, Tokyo). The lumen diameter of the AA was measured directly on the video monitor screen. At the end of experiment, the viability of the vessel was assessed by the response to 10−6 M norepinephrine (NE).

Experimental protocols

Response of AA to Ang II: Following a 30-min equilibration, control measurements of the lumen diameter were made at 1-min intervals for 3 min. Repeat measurements were made at the same point. The control value is the third value of the three measurements. During the control measurements, we confirmed that the lumen diameter was stable. If the lumen diameter was not stable during the control observation, the experiment was discarded. To determine the dose-response curve of Ang II, Ang II was applied to the bath in increasing concentrations. After control measurements, continuous bath exchange was stopped, and the bath medium was rapidly changed to one containing the lowest concentration of Ang II (10−10 M). The bath exchange was restarted using medium containing the same concentration of Ang II, and the arteriole was observed for 3 min. Every 3 min, the concentration was increased by one order of magnitude up to 10−6 M. The lumen diameter was measured 1 min after the application.

In another experiment, we applied a single dose of Ang II (10−7 M) to the isolated AAs. After control measurements, continuous bath exchange was stopped, and the bath medium was rapidly changed to one containing Ang II (10−7 M). Then bath exchange was restarted using medium containing the same concentration of Ang II, and the arteriole was observed for 3 min. Every 3 min, the concentration was increased by one order of magnitude up to 10−6 M. The lumen diameter was measured every minute for 3 min.

Response of aspirin dl-lysine or indomethacin pretreated AA to Ang II: The rabbit received an intravenous injection of aspirin dl-lysine (50 mg/kg) or indomethacin (2 mg/kg) after anesthesia. Twenty minutes after cyclooxygenase inhibitor injection, a kidney was removed and an AA was dissected. Following cannulation of the AA, a bath medium containing cyclooxygenase inhibitor, either aspirin dl-lysine (10−4 M) or indomethacin (10−4 M), was...
continuously exchanged for 1 hr. Control measurements of the lumen diameter were made, and Ang II \((10^{-7} \text{ M})\) was added to the bath medium. The entire experiment was recorded with a video camera. After the application of Ang II, we measured the most constricted point of the lumen diameter every 30 sec for 3 min, because we found Ang II caused transient and segmental vasoconstriction using AA pretreated with cyclooxygenase inhibitors (Fig. 1). Repeat measurements were made at the same point of the lumen diameter.

Response of \(\text{N}^\text{G}\)-nitro-l-arginine (L-NNA) pretreated AA to Ang II: After control measurements, the infusion of bath medium containing L-NNA \((10^{-4} \text{ M})\) was initiated at 0.5 ml/min, and the arteriole was observed for 20 min. Second control measurements of lumen diameter were made, and Ang II \((10^{-7} \text{ M})\) was added to the bath medium. Then, the lumen diameter at the most constricted point was measured every minute for 5 min. After a 5 min application of Ang II \((10^{-7} \text{ M})\), the AA was rinsed well with plain bath medium for over 10 min, and the AA was perfused with perfusate containing DuP753 \((10^{-6} \text{ M})\), an AT1 antagonist. The bath medium was also changed to one containing L-NNA \((10^{-4} \text{ M})\) and DuP753 \((10^{-6} \text{ M})\). Following a 30-min equilibration, the measurement of lumen diameter was made, and then Ang II \((10^{-7} \text{ M})\) was added to the bath medium again. The lumen diameter at the most constricted point was again measured every minute for 5 min.

In another experiment, we examined the effect of Ang II on the lumen diameter of isolated AA pretreated with L-NNA \((10^{-4} \text{ M})\) and l-arginine \((10^{-2} \text{ M})\). After control measurements, the infusion of bath medium containing L-NNA \((10^{-4} \text{ M})\) and l-arginine \((10^{-2} \text{ M})\) was initiated at 0.5 ml/min, and the arteriole was observed for 20 min. A second control measurement of the lumen diameter was made, and then Ang II \((10^{-7} \text{ M})\) was added to the bath medium. The lumen diameter at the most constricted point was again measured every minute for 5 min.

In a separate set of experiments, we also examined the dose-response curve of Ang II on the lumen diameter of isolated AA. After pretreatment with L-NNA \((10^{-4} \text{ M})\) for 20 min, Ang II \((10^{-14} \text{ M})\) was added to the bath medium containing L-NNA \((10^{-4} \text{ M})\) for 3 min. The lumen diameter at the most constricted point was measured between 1 min and 2 min after Ang II application. Increasing doses of Ang II were added to the bath, and bath exchange of each dose of Ang II was continued at 3-min intervals. After the applications of Ang II, the AA was rinsed well with plain bath medium for over 10 min, and the AA was perfused with perfusate containing DuP753 \((10^{-6} \text{ M})\). The bath medium was also changed to one containing DuP753 \((10^{-6} \text{ M})\) and L-NNA \((10^{-4} \text{ M})\). Following a 30-min equilibration, we examined once again the dose-response curve of Ang II on the lumen diameter of AA.

Response of L-NNA and aspirin \(\text{DL}\)-lysine pretreated AA to Ang II: The rabbit received an intravenous injection of aspirin \(\text{DL}\)-lysine \((50 \text{ mg/kg})\) after anesthesia. Twenty minutes after cyclooxygenase inhibitor injection, a kidney was removed and an AA was dissected. Following cannulation of the AA, a bath medium containing aspirin \(\text{DL}\)-lysine \((10^{-4} \text{ M})\) and L-NNA \((10^{-4} \text{ M})\) was con-

Fig. 1. Example of angiotensin II-induced changes in the lumen diameter of an afferent arteriole pretreated with aspirin \(\text{DL}\)-lysine \((10^{-4} \text{ M})\). The top panel shows the control condition of the cannulated afferent arteriole. The middle panel shows angiotensin II caused segmental vasoconstriction on the isolated afferent arteriole 30 sec after angiotensin II application. Angiotensin II-induced vasoconstriction is transient. The bottom panel shows the afferent arteriole 1 min after angiotensin II application. The lumen diameter of the afferent arteriole proceeded to increase to the diameter of the control condition, despite the continuous presence of angiotensin II in the bath.
Continuously exchanged for 1 hr. Control measurements of lumen diameter were made, and Ang II (10^{-7} M) was added to the bath medium. Then, the lumen diameter at the most constricted point was measured every minute for 5 min.

In another experiment, we examined the dose-response curve of Ang II on the lumen diameter of isolated AA pretreated with aspirin dl-lysine (10^{-4} M) and L-NNA (10^{-4} M). The rabbit received an intravenous injection of aspirin dl-lysine (50 mg/kg) after anesthesia. After pretreatment with aspirin dl-lysine and L-NNA for 1 hr, Ang II (10^{-15} M) was added to the bath medium for 3 min. Every 3 min the concentration was increased by one order of magnitude up to 10^{-8} M. The lumen diameter at the most constricted point was measured between 1 min and 2 min after Ang II application.

Chemicals
Aspirin dl-lysine was a gift from Green Cross (Osaka), and DuP753 was a gift from Dupont Merck Pharmaceuticals Co. (Wilmington, DE, USA). Indomethacin was purchased from Sigma Chemical Co. (St. Louis, MO, USA). N^G-nitro-l-arginine and l-arginine were purchased from the Peptide Institute (Osaka). Bovine albumin fraction V was purchased from Seikagaku Kogyo Co., Ltd. (Tokyo).

Statistics
Values are expressed as means ± S.E.M. The data were analyzed by one-way analysis of variance followed by a least significant difference test.

RESULTS

Response of AA to Ang II
The lumen diameter of the AAs under the control condition was 22.7 ± 1.1 μm (n = 6). After Ang II application, the wall of the AA started to move slightly, but we did not observe significant changes in the lumen diameter (10^{-10} M: 23.4 ± 1.2 μm, 10^{-9} M: 23.0 ± 1.2 μm, 10^{-8} M: 22.7 ± 1.1 μm, 10^{-7} M: 22.7 ± 1.2 μm, 10^{-6} M: 22.5 ± 1.1 μm, n = 6).

We also did not observe significant changes in the lumen diameter of AAs after the single dose of Ang II (10^{-7} M) (Fig. 2).

Response of aspirin dl-lysine or indomethacin pretreated- AA to Ang II
Ang II (10^{-7} M) caused strong and transient vasoconstriction in the AA pretreated with aspirin dl-lysine (Figs. 1 and 2). We did not observe any effect of Ang II on the lumen diameter of AA even when a higher concentration of Ang II was applied soon after the transient vasoconstriction. In preliminary experiments, we observed that application of aspirin dl-lysine (10^{-4} M) for 1 hr did not change the lumen diameter of the afferent arterioles (before: 20.6 ± 1.5 μm, after: 20.6 ± 1.2 μm, n = 5). Ang II (10^{-7} M) also caused almost the same transient vasoconstriction in the AA pretreated with indomethacin (n = 3, data not shown).

Response of L-NNA pretreated- AA to Ang II
Pretreatment with L-NNA (10^{-4} M) for 20 min decreased the lumen diameter of AA by 9% from the control condition. Ang II (10^{-7} M) caused a strong and continuous vasoconstriction on the AA pretreated with L-NNA (Figs. 3 and 4). DuP753 (10^{-6} M) inhibited this vasoconstriction (control: 17.3 ± 1.3 μm; 1 min after Ang II application: 15.3 ± 1.7 μm, 3 min: 17.0 ± 1.5 μm, 5 min: 16.3 ± 1.7 μm, n = 5).

Ang II decreased the lumen diameter of AAs pretreated with L-NNA in a dose-dependent manner, and DuP753 (10^{-6} M) completely abolished this vasoconstriction (Fig. 5).

Pretreatment with l-arginine (10^{-2} M) and L-NNA (10^{-4} M) did not alter the degree of Ang II-induced vasoconstriction. However, unlike the L-NNA alone pretreated- AA which had continuous vasoconstriction, Ang II-induced vasoconstriction on AA pretreated with L-arginine (10^{-2} M) and L-NNA (10^{-4} M) started to wane 2 min after Ang II application (Fig. 4).

Response of L-NNA and aspirin dl-lysine pretreated- AA to Ang II
Ang II (10^{-7} M) caused a strong and continuous vasoconstriction on the AA pretreated with L-NNA and
aspirin DL-lysine (Fig. 4). While the vasoconstriction of L-NNA pretreated-AA had begun to wane 4 min after Ang II application, the lumen of AA pretreated with L-NNA and aspirin DL-lysine was still closed after 5 min in 4 of 5 AAs.

After a 1-hr incubation with L-NNA (10^{-4} M) and aspirin DL-lysine (10^{-4} M), a low concentration of Ang II (10^{-13} M) significantly decreased the lumen diameter of AA pretreated with L-NNA (10^{-4} M) and aspirin DL-lysine (10^{-4} M) (Fig. 5). Ang II constricted AA pretreated with L-NNA (10^{-4} M) and aspirin DL-lysine (10^{-4} M) dose-dependently. The dose-response curve of Ang II-induced vasoconstriction in the experiment using AA pretreated with L-NNA alone (Fig. 5).
DISCUSSION

The participation of Ang II in the physiological control of renal hemodynamics has been discussed and the discussion is still ongoing (6, 23-25). Hall (6) concluded that Ang II did not directly constrict the AAs even when the renin-angiotensin system was activated physiologically in vivo experiments. However, the kidney has the ability to produce several vasoactive compounds that act as autacoids and modulate the effects of other vasoactive compounds. Moreover, in the kidney, there are intrinsic mechanisms, for example, autoregulation of RBF and tubuloglomerular feedback, to regulate renal circulation. According to these intrinsic mechanisms, changes in arterial blood pressure or in macula densa electrolyte concentration cause resistance changes of the AA. Thus, it is difficult to evaluate the direct effect of a vasoactive substance on AA using in vivo experiments. Several methodologies were developed to directly observe the changes of resistance vessels (16-18); and by these methodologies, the effect of Ang II on the AA has been evaluated. Edwards (11) reported that Ang II did not change the lumen diameter of the isolated rabbit AA even in pharmacological doses of Ang II. In the present experiment, we confirmed Edwards’ results. However, interestingly, Toda et al. (20, 26) reported that Ang II caused relaxation in the helically cut strip of dog renal artery, and this relaxation was mediated by vasodilatory PGs. In fact, isolated AA has the ability to produce vasodilatory PGs (21) and NO (12). Then, we hypothesized that vasodilatory PGs and NO counteract the vasoconstrictor effect of Ang II on the isolated AA. The present results clearly showed that a pharmacological dose of Ang II (10^-7 M) did not change the lumen diameter of isolated rabbit AA, but it did cause vasoconstriction when AA was pretreated with cyclooxygenase inhibitors and/or NO synthase inhibitor. Moreover, when AA was pretreated with a NO synthase inhibitor, Ang II caused a dose-dependent vasoconstriction. The dose-response curve of Ang II-induced vasoconstriction shifted to left when AA was pretreated with a cyclooxygenase inhibitor and a NO synthase inhibitor. Ang II-induced vasoconstriction was observed even at lower doses (maybe physiological doses) in L-NNA and aspirin DL-lysine pretreated AAs. Dup753, an AT1-receptor antagonist, inhibited the vasoconstrictor effect of Ang II. These results suggest that isolated rabbit AA has AT1 receptors, and vasodilatory PGs and NO counteract the vasoconstrictor action of Ang II in the isolated rabbit AA.

We observed that pretreatment with a cyclooxygenase inhibitor altered the response of Ang II on the AA without glomerulus. However, Ito et al. (13), using microperfused rabbit AA with glomerulus, reported that a pharmacological dose of Ang II (10^-7 M) caused a transient constriction and pretreatment with indomethacin did not alter the vasoconstrictor action of 10^-7 M Ang II. The reason for this discrepancy is not clear. Because there are some anatomical differences between the proximal part and distal part of AA, differences in the preparations of AA may explain this discrepancy. Ito et al. (13) reported that Ang II caused segmental constrictions and the strongest was observed in the segment close to the glomerulus using microperfused AA. While Ito et al. isolated the AA with glomerulus, we isolated only the AA in our preparation (12), and both ends of the AA were cannulated with a pipette system (Figs. 1 and 3). So, we could not observe the distal segment of AA close to the glomerulus. Moreover, mesangial cells are known to produce a variety of vasoactive substances, for example, NO, PGs, endothelin and growth factors, so these substances may be responsible for the difference between our results and Ito’s results. Weihprecht et al. (27) reported that Ang II decreased the lumen diameter of rabbit AA with glomerulus, but the vasoconstrictor effect of Ang II was markedly attenuated in the AA without glomerulus. Concerning the interaction of Ang II and PGs, Ito’s group reported pretreatment with indomethacin did not alter vasoconstrictor action of 10^-7 M Ang II at first. However, they recently reported that indomethacin augmented the vasoconstrictor action of Ang II (10^-11 M to 10^-9 M) in microperfused rabbit AA (28). Although there are some discrepancies among reports, it is clear that there are angiotensin II receptors in the rabbit AA.

Many researchers suggest that NO and the renin-angiotensin system interact to influence renal hemodynamics. However, interaction between Ang II and NO in regulating renal hemodynamics is still unclear. In rat experiments, Sigmon et al. (29, 30) suggested that the renal response to a NO synthase inhibitor was predominantly mediated by Ang II, but Baylis et al. (31) reported that renal effects of a NO synthase inhibitor is independent of endogenous Ang II. In anesthetized rabbits, L-NNA partially blocked the renal vasodilatory effects of DuP753 (32). DuP753 did not alter the renal response of L-NNA in anesthetized dogs (33). An interaction between Ang II and NO in the AA has also been reported already, but the results are controversial. Ito et al. (13) reported that L-NNA augmented the vasoconstrictor action of Ang II in the isolated microperfused rabbit AA. However, Ohishi et al. (34) reported that the presence of L-NNA did not influence the vasoconstrictor response to Ang II in the rat AA. Our results concerning the interaction of Ang II and NO in the AA are consistent with the data reported by Ito et al. (13). However, L-arginine did not completely restore the effect of L-NNA in our experiment. This finding suggests that there is another mechanism(s), in addition...
to inhibiting NO synthase, involved in modulating the vasoconstrictor effect of Ang II on AA by L-NNA. However, the exact mechanism remains unclear.

In summary, Ang II did not constrict the rabbit isolated AA without glomerulus. However, Ang II caused vasoconstriction when AA was pretreated with cyclooxygenase inhibitors and/or a NO synthase inhibitor. DuP753, an AT1-receptor antagonist, abolished the vasoconstrictor action of Ang II. Physiological doses of Ang II decreased the lumen diameter of the isolated AAs pretreated with L-NNA and aspirin DL-lysine. These findings suggest that the isolated rabbit AA has AT1 receptors and vasoconstrictor response of Ang II is counteracted by vasodilatory prostaglandins and nitric oxide.

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