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Urotensin II is a nitric oxide-dependent vasodilator and natriuretic peptide in the rat kidney

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Zhang, Andrew Y., Ya-Fei Chen, David X. Zhang, Fu-Xian Yi, Jenson Qi, Patricia Andrade-Gordon, Lawrence de Garavilla, Pin-Lan Li, and Ai-Ping Zou. Urotensin II is a nitric oxide-dependent vasodilator and natriuretic peptide in the rat kidney. *Am J Physiol Renal Physiol* 285: F792–F798, 2003. First published June 3, 2003; 10.1152/ajprenal.00342.2002.—Recent studies have indicated that urotensin II (UII), a cyclic peptide, is vasoactive and may be involved in cardiovascular dysfunctions. It remains unknown, however, whether UII plays a role in the control of renal vascular tone and tubular function. In the present study, a continuous infusion of synthetic human UII (hUII) into the renal artery (RA) in anesthetized rats was found to increase renal blood flow (RBF) and urinary water and sodium excretion (UV and $U_{Na}V$) in a dose-dependent manner. At a dose of 20 $ng \cdot kg^{-1} \cdot min^{-1}$, it increased RBF by 20% and UV and $U_{Na}V$ by 94 and 109%, respectively. Nitric oxide (NO) synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) completely abolished hUII-induced increases in RBF and water/sodium excretion. In isolated, pressurized, and phenylephrine-precontracted small RA with internal diameter of ~200 μm, hUII produced a concentration-dependent vasodilation with a maximal response of 55% at 1.5 μM. L-NAME significantly blocked this hUII-induced vasodilation by 60%. In denuded RA, hUII had neither vasodilator nor vasoconstrictor effect. With the use of 4,5-diaminofluorescein diacetate-based fluorescence imaging analysis of NO levels, hUII (1 μM) was shown to double the NO levels within the endothelium of freshly dissected small RA, and L-NAME blocked this UII-induced production of endothelial NO. These results indicate that UII produces vasodilator and natriuretic effects in the kidney and that UII-induced vasodilation is associated with increased endothelial NO in the RA.

natriuretic factor; renal circulation; sodium reabsorption; renal tubule; renal hemodynamics

UROTENSIN II (UII) is a cyclic peptide with a COOH-terminal hexapeptide sequence, which is conserved across species, including fish, frog, mouse, rat, pig, and human (6, 7, 23). This cyclic peptide was originally isolated from fish spinal cord and had a structure similar to somatostatin (27). Recently, UII was identified as an endogenous ligand for G protein-coupled receptor (GPR14), which is one of these types of orphan receptors and was first cloned from rat cDNA library (18, 21, 23). A human receptor that has 75% homology with rat GPR14 was also characterized (2), and the mRNA for this receptor is widely expressed in human heart, brain, pancreas, skeletal muscle, vascular smooth muscle and endothelial cells, spinal cord, and endocrine tissues (2, 18, 20). This wide distribution of GPR14 suggested that UII may serve as a circulating hormone to participate in the regulation of many physiological processes.

Indeed, early studies reported that human UII (hUII) produced a marked vasoconstriction in many arteries from nonhuman primates, including large coronary, pulmonary, and carotid arteries (2, 8). It was found that hUII induced vasoconstriction in the isolated large arteries from both rat and human with a potency of 6- to 28-fold greater than endothelin-1 (2). In anesthetized nonhuman primates, this cyclic peptide was shown to markedly increase total peripheral resistance (2). These studies indicated that UII is one of the most potent vasoconstrictors in mammals, which may play an important role in the regulation of cardiovascular homeostasis and be importantly involved in circulatory dysfunction. However, recent studies demonstrated that hUII also causes vasodilation in rat small arteries and human pulmonary arteries (4, 30). It appears that the effects of UII depend on different vascular beds, vessel sizes, or species. Despite extensive studies on the effects of UII on different vascular beds, little is known regarding the action of UII on renal vascular tone. It remains unknown whether this cyclic peptide participates in the control of renal hemodynamics and urinary excretion of electrolytes.

The present study was designed to test whether UII alters renal hemodynamics and influences excretory function of the kidney, thereby participating in the regulation of renal function. To address these questions, we first examined the effects of hUII infusion into the renal artery on renal blood flow (RBF), glomerular filtration rate (GFR), and sodium and water ex-

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cretion (UV and $U_{Na}V$) in anesthetized Sprague-Dawley rats. With the use of isolated small renal arterial preparation, we then observed the direct vasodilator effects of hUII on small renal arteries. To explore the mechanism of hUII-induced renal vasodilation, a fluorescent video microscopy was performed to determine the effects of hUII on intracellular nitric oxide (NO) levels in the intact endothelium of these small renal arteries. These experiments provided direct evidence that hUII dilates renal arteries through a NO-dependent mechanism, which may participate in the regulation of renal functions in concert with its natriuretic effect.

MATERIALS AND METHODS

Determination of renal hemodynamics. Male Sprague-Dawley rats (purchased from Harlan Sprague Dawley, Madison, WI) weighing between 250 and 300 g were fasted overnight but allowed free access to water. They were anesthetized with ketamine (30 mg/kg body wt im) and Inactin (50 mg/kg body wt ip) and placed on a thermostatically controlled warming table to maintain body temperature at 37°C. After tracheotomy, cannulas were placed in the right femoral vein and artery for intravenous infusions and measurements of arterial pressure. An abdominal incision was made, the left kidney was placed in a stainless steel cup to stabilize the organ, and an electromagnetic flow probe (2 mm) was placed around the left renal artery to measure RBF as we described previously (5). The two ureters were isolated and catheterized for collection of urine during experiments. After surgery, the animals received an intravenous infusion of 2% bovine serum albumin in a 0.9% sodium chloride solution at a rate of 3 ml/h throughout the experiment to replace fluid losses and maintain a stable hematocrit of ~43 ± 3%.

Analysis of renal function. Sprague-Dawley rats were anesthetized, and the surgery for renal function study was performed as described above. After surgery and equilibration period, continuous measurements of mean arterial pressure (MAP) and RBF were obtained throughout the experiment. To measure GFR, a 0.5-ml bolus of FITC-inulin (8.0 mg/ml) was given, and then a steady intravenous infusion of FITC-inulin (4.0 mg/ml) at 3.0 ml/h continued throughout the experiment. After a 1.5-h equilibration period, two 20-min timed collections of urine were made. Blood samples (100 μl) were taken in heparinized hematocrit tubes after each urine collection period. Then, hUII (2.5, 5, 10, or 20 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused into the renal artery for 60 min, and late urine and blood collections were repeated. At the end of each experiment, the kidneys were removed and weighed, blood samples were centrifuged, and 20-μl plasma and 1:50 diluted urine samples were pipetted into a microtiter plate and mixed with 200 μl HEPES buffer (10 mM) for FITC-inulin measurement with excitation and emission wavelengths of 480 and 530, respectively, using an automatic microplate reader (KC4; Bio-Tek Instruments, Winooski, VT). The urine flow rate was determined gravimetrically, and sodium (Na^+) and potassium (K^+) concentrations of urine samples were measured using a flame photometer. GFR was calculated as the product of urine flow and the ratio of urine-to-plasma FITC-inulin concentrations. GFR, urine flow, and urinary Na^+ and K^+ excretion were factored per gram kidney weight. In an additional group of rats, nitric oxide synthase (NOS) inhibitor N^G-nitro-L-arginine methyl ester (L-NAME; 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused into the renal artery for 30 min, and then the effects of hUII (2.5, 5, 10, or 20 $ng \cdot kg^{-1} \cdot min^{-1}$) on renal hemodynamics and renal function were examined. The hUII (peptide sequence, ETPDCFWKYCV) used in this study was demonstrated to have an HPLC purity of 95.64%. The identity of this cyclic peptide was confirmed by electrospray ionization-mass spectrometry analysis with a molecular weight of 1387.7, which was consistent with the theoretical molecular weight of 1387.6 (data not shown).

Preparation of small renal arteries. Male Sprague-Dawley rats weighing between 250 and 300 g were anesthetized with pentobarbital sodium (80 mg/kg body wt ip), and the kidneys were rapidly removed and kept in ice-cold HEPES-buffered physiological saline solution (PSS) that consisted of the following composition (in mM): 140 NaCl, 4.7 KCl, 1.6 $CaCl_2$, 1.17 $MgSO_4$, 1.18 NaH_2PO_4, 5.5 glucose, 10 HEPES, pH 7.4. The small renal arteries (250- to 300-μm internal diameter) were carefully dissected on ice and transferred to a 35-mm Sylgard-coated dissecting dish containing ice-cold PSS. In an additional group of rats, the aorta below the left renal artery was isolated and cannulated. After the aorta at a site above the right renal artery was ligated, the kidneys were flushed with 10 ml of ice-cold PSS following 60 ml of air perfusion to remove the endothelium of the renal arteries. Then, the small renal arteries were dissected to measure agonist-induced NO production. These experiments were performed to confirm that NO was derived from the renal arterial endothelium. All these procedures were described in great detail in our previous studies (16).

Video microscopy of isolated and perfused renal arteries. Dissected segments of small renal arteries were mounted on glass pipettes in a water-jacketed perfusion chamber. The small arteries were perfused and bathed with PSS that was equilibrated with a 95% O_2-5% CO_2 mixture and maintained at 37°C. This arterial preparation has been shown to have an intact endothelium (12, 17, 37) in 95% of the arteries as determined by a vasodilator response to bradykinin (data not shown). After the artery was mounted, the outflow cannula was clamped, and the artery was pressurized to 80 mmHg and equilibrated for 1.5 h. Internal diameter of the artery was measured using a video system composed of a stereomicroscope (Leica MZ8, Leica), a CCD camera (KP-MI AU, Hitachi), a video monitor (VM-1221, Hitachi), a video measuring apparatus (VIA-170, Boeckeler Instrument, Tucson, AZ), and a video printer (UP890 MD, Sony). The arterial images were recorded continuously with a video cassette recorder (M-674, Toshiba). The effects of hUII on arterial diameters were studied by cumulative additions of hUII (0.25–1.5 μM) into the bath solution.

Measurement of NO levels within the endothelium of small renal arteries. A fluorescent NO indicator, 4,5-diaminofluorescein diacetate (DAF-2DA), which was recently developed by Kojima et al. (15), was used to measure NO levels within the endothelial cells of freshly isolated small renal arteries as we described previously (16). Small renal arteries were dissected as described above. The arterial segment was cut open along its longitudinal axis and pinned onto the dish with lumen side upward. Care was taken not to disrupt the endothelium. After a 1-h equilibrium period, the arterial segment was incubated with DAF-2DA (10 μM, Calbiochem) in 1 ml of PSS at room temperature for 30 min. The segment was then rinsed three times with PSS, and the dish was mounted on the stage of an epifluorescence microscope (Nicon E600) equipped with a ×20 objective and a 490-nm excitation and a 535-nm emission filter. Digital images were acquired and analyzed using a PC-controlled digital CCD camera (Roper Scientific RTE/CCD-1300-Y/HS) by MetaMorph imaging analysis software (Universal Imaging) as we described pre-

viously (35). NO fluorescence was measured every 5 min in the same area of endothelial layer.

Statistics. Data are presented as means ± SE. The significance of differences within and between groups in multiple groups of experiments was evaluated using an analysis of variance for repeated measures, followed by Duncan's multiple range tests (Sigmastat). $P < 0.05$ was considered statistically significant.

RESULTS

Effect of hUII on MAP, RBF, and GFR. The effects of hUII on renal hemodynamics in rats are presented in Fig. 1. A continuous infusion of hUII (2.5, 5, 10, or 20 $ng \cdot kg^{-1} \cdot min^{-1}$) into the renal artery in anesthetized rats had no significant effect on MAP regardless of the presence or absence of L-NAME ($n = 7$; Fig. 1*A*). However, this continuous infusion of hUII produced a concentration-dependent increase in RBF (Fig. 1*B*). It also increased GFR with a maximum increase of 23% at 2.5 $ng \cdot kg^{-1} \cdot min^{-1}$. At higher concentrations of hUII over 10 $ng \cdot kg^{-1} \cdot min^{-1}$, GRF returned to baseline (Fig. 1*C*). After treatment of the rats with L-NAME, hUII-induced alterations of RBF and GFR were completely blocked. Fractional filtration (FF) rate was calculated as a ratio of GFR and renal plasma flow, and no significant change was found on this ratio by hUII administration.

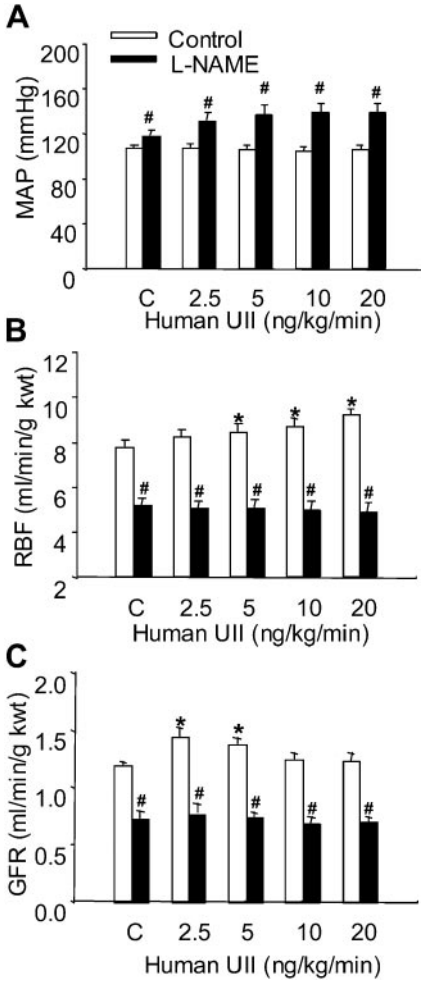

Fig. 1. Effects of intrarenal infusion of human urotensin II (hUII) on mean arterial pressure (MAP), renal blood flow (RBF), and glomerular filtration rate (GFR) in anesthetized rats. *A*-*C*: effects of hUII on MAP, RBF, and GFR under control conditions and after treatment of nitric oxide synthase (NOS) inhibitor N^G-nitro-L-arginine methyl ester (L-NAME), respectively. *$P < 0.05$ compared with the value obtained before infusion of UII (C); #$P < 0.05$ compared with the value obtained without L-NAME infusion (control; $n = 7$).

Effects of hUII on renal function. The results of these experiments are presented in Fig. 2. hUII markedly increased UV (Fig. 2*A*) and $U_{Na}V$ (Fig. 2*B*) in a dose-dependent manner, but it had no effect on potassium excretion (Fig. 2*C*). At the highest dose of hUII infusion, UV and $U_{Na}V$ were doubled. These hUII-induced increases in UV and $U_{Na}V$ were also completely blocked by L-NAME pretreatment. Consistently, the fractional excretion of sodium (FE_{Na}) was increased and doubled at the highest dose of hUII administration.

hUII-induced endothelium-dependent vasodilation in small renal arteries. hUII was found to induce an endothelium-dependent vasodilation in a dose-dependent manner. The isolated small renal arteries (with a basal internal diameter of 258 ± 15 μm) were precontracted with phenylephrine, then concentration-response curves of hUII were determined using these vessels. Figure 3*A* shows representative microscopic images showing the changes in the internal diameters of the small renal arteries treated with different compounds. Addition of hUII into the bath solution produced vasodilation in phenylnephrine-contracted arteries. In the presence of L-NAME, hUII-induced vasodilation was significantly blocked. Figure 3*B* summarizes the effects of hUII on vascular diameter of the small renal arteries with and without the intact endothelium. Addition of hUII into the bath solution produced a concentration-dependent vasodilation with maximal relaxation of 55%. Pretreatment with L-NAME (100 μM) for 30 min markedly inhibited the hUII-induced vasodilation in these phenylephrine-precontracted arteries with the maximal inhibition by 60%. To confirm that hUII-induced vasodilation is endothelium dependent, the denuded arteries were used to examine the effect of hUII. In these arteries, no significant vasorelaxation was observed.

UII-induced NO production in the intact endothelium of renal arteries. As shown in Fig. 4*A*, a 30-min infusion of hUII (1 μM) with the renal arteries (internal diameter = 340 ± 35 μm) produced a marked increase in green NO fluorescence in the endothelium. In the presence of L-NAME, hUII-induced increase in NO green fluorescence was significantly attenuated, suggesting that L-NAME is capable of blocking the hUII-induced increase in NO within the intact endothelium of these freshly isolated renal arteries. Figure 4*B* summarizes hUII-induced alterations of NO levels measured by DAF-2T fluorescence intensity in the absence or presence of L-NAME ($n = 7$). hUII time dependently produced a significant increase in NO levels within the endothelium of the renal arteries. In the denuded renal arteries, there was no detectable hUII-induced increase in DAF-2T fluorescence.

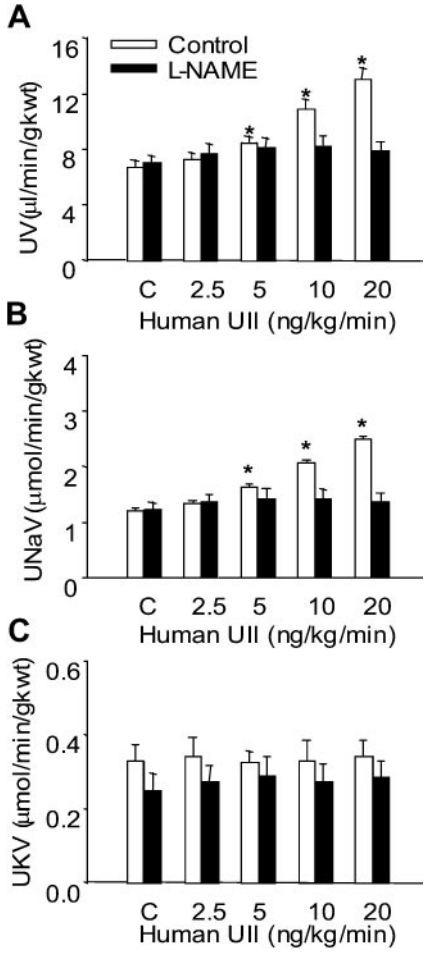

Fig. 2. Effects of intrarenal infusion of hUII on urine flow rate (UV) and urinary sodium excretion ($U_{Na}V$). *A-C*: effects of hUII on UV, $U_{Na}V$, and potassium excretion (U_KV) under control conditions and after treatment of NOS inhibitor L-NAME, respectively. *$P < 0.05$ compared with the value obtained before infusion of UII (C; $n = 6$). gkwt, Grams kidney weight.

DISCUSSION

In contrast to the vasoconstrictor effect in large vessels from different species, the present study demonstrated that hUII produced a marked NO-dependent vasodilator response in isolated small renal arteries of rats. We also found that hUII induced a strong natriuretic response when directly administrated into the renal artery. These results indicate that hUII is a NO-dependent vasodilator and natriuretic peptide in the rat kidney.

In anesthetized rats, we first examined the effects of infusion of hUII into the renal arteries on renal hemodynamics and renal functions. It was demonstrated that hUII markedly increased RBF in a dose-dependent manner, indicating that hUII may produce renal vasodilation. After pretreatment of the rat kidney with NOS inhibitor L-NAME, hUII-induced actions on renal hemodynamics were substantially blocked. It appears that the effect of hUII in this preparation is associated with NO-dependent mechanism. This is consistent with previous observations in cerebral and other vascular beds, showing that the vascular effects of hUII could be blocked by L-NAME (4). It is well known that NO plays a critical role in the regulation of renal vascular tone and RBF (36). Renal vascular resistance is increased following inhibition of NOS, whereas stimulation of endogenous NO leads to a decrease in renal vascular resistance and increase in RBF. Many stimuli or agonists such as bradykinin, acetylcholine, ANG II, norepinephrine, endothelin, or shear stress have been reported to activate NOS and produce NO in the kidney (26, 33). The results from the present in vivo animal experiments suggest that hUII may be another possible agonist to stimulate NO production in renal vascular bed.

Consistent with the increase in RBF, hUII also produced a significant increase in GFR, especially at a low dose. By calculating FF rate, we found that hUII only increased FF at low-dose range, indicating that low concentrations of hUII may produce greater vasodilation in preglomerular vessels compared with postglomerular vessels. When the dose of intrarenally infused hUII was increased, however, GFR and FF increase did

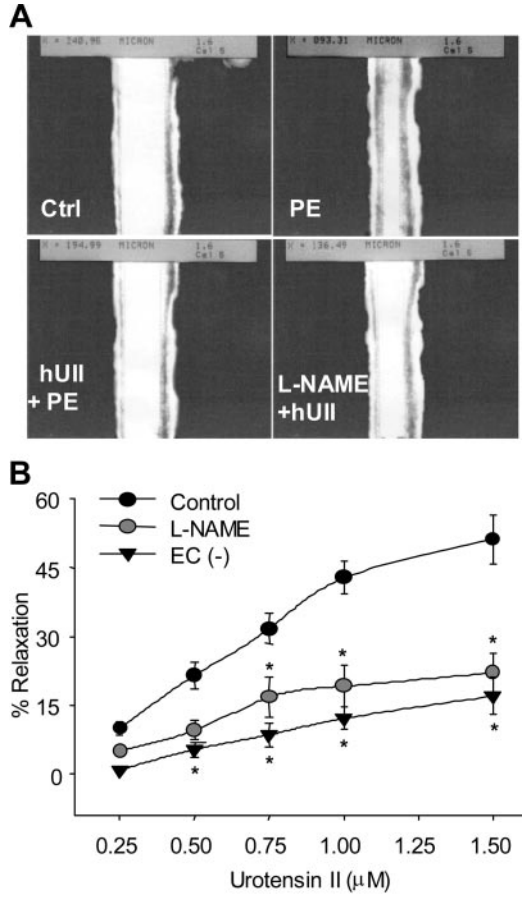

Fig. 3. hUII-induced vasodilation in isolated small renal arteries. *A*: representative photo prints showing the changes in internal diameters of small renal arteries treated with hUII or L-NAME + hUII. *B*: summarized data showing the effects of hUII on control (Ctrl), L-NAME-treated, or endothelium-denuded arteries. *$P < 0.05$ vs. control ($n = 5$). PE, precontraction with phenylephrine; EC, endothelial cells.

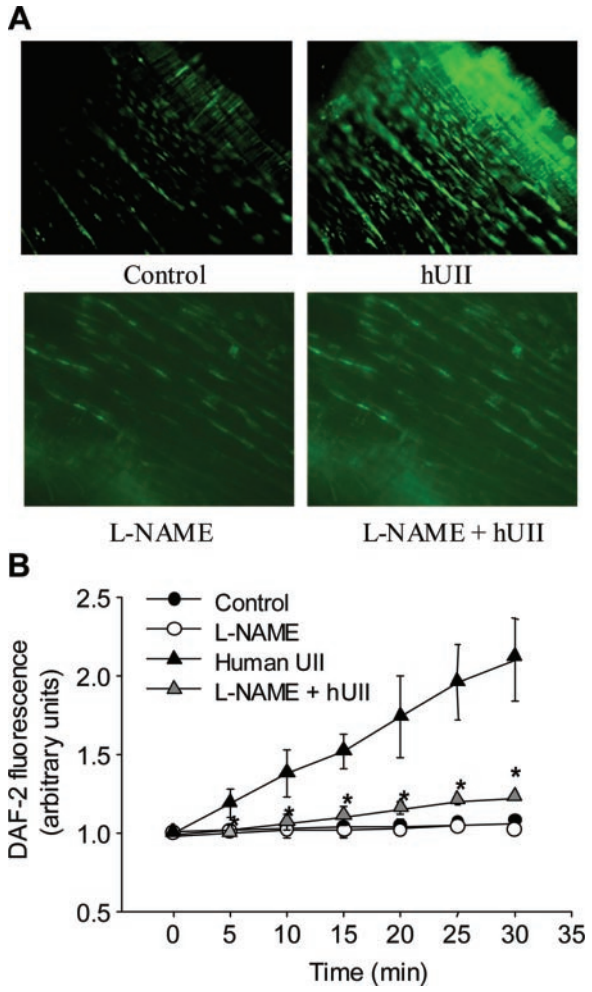

Fig. 4. hUII-induced NO increase in the endothelium of small renal arteries. *A*: typical fluorescent microscopic images showing NO-induced 4,5-diaminofluorescein diacetate (DAF-2) green fluorescence within endothelial cells. *B*: time course for hUII-induced change in NO levels in the renal arterial endothelium with different treatments. *$P < 0.05$ vs. control ($n = 7$).

not occur. This suggests that high concentrations of hUII may dilate both pre- and postglomerular vessels. The present study also demonstrated that hUII increased urinary water and sodium excretion, which was blockable by L-NAME. This hUII-induced increase in urinary sodium excretion may not simply be attributed to the increase in RBF or GFR; it may be associated with the direct inhibition of tubular ion transport activity. Indeed, FE_{Na} was found increased by administration of hUII. Given that hUII increased FE_{Na} but had no effect on potassium excretion, it is possible that the natriuretic action of this peptide is attributed to inhibition of the ion transport activity in the collecting duct. When the rat kidney was pretreated with L-NAME, the effect of hUII on sodium excretion was completely blocked. Therefore, NO may be involved in UII-induced changes in urinary sodium excretion. Numerous studies have demonstrated that NO can directly act on renal tubules to inhibit tubular ion transport activity. It has been indicated that the effects of NO on sodium reabsorption are associated with its direct inhibitory action on the Na^+/H^+ exchange, Na^+-K^+-ATPase, and amiloride-sensitive Na^+ channels in different tubules (36). It seems that hUII stimulates NO production in the kidney and thereby inhibits tubular sodium reabsorption, resulting in diuretic and natriuretic response in concert with its hemodynamic effects.

Despite intensive studies on the vasomotor response of hUII in other vascular beds, there is no direct evidence showing the effect of hUII on renal vascular tone or renal endothelial function. To provide direct evidence that hUII produced renal vasodilation and to explore the mechanism responsible for hUII-induced vasodilator response, we used isolated, perfused, and pressurized renal artery preparation to examine the effects of hUII on the diameter of these small arteries using video microscopy. It was found that addition of hUII into the lumen of the perfused arteries produced a concentration-dependent vasodilation in endothelium-intact renal arteries. When these arteries were denuded, hUII-induced vasodilation was completely blocked. Similarly, when these arteries were pretreated with L-NAME, hUII-induced vasodilation was substantially attenuated. These results indicate that hUII stimulates NO and produces endothelium-dependent vasodilation in the renal arteries, which is consistent with the results obtained from our in vivo animal experiments. Therefore, we conclude that hUII is a potent NO-dependent vasodilator in renal circulation.

In previous studies, however, hUII has been shown to be a potent vasoconstrictor in various arteries, including large coronary, pulmonary, and carotid arteries isolated from different species, such as rats, dogs, pigs, and monkeys (2, 9, 10, 19). In some studies, in contrast, this cyclic peptide was not found to have any vasomotor action in human arteries and veins of different sizes (13). This led to an assumption that a vasoconstrictor action of hUII may be masked by its potent vasodilator effects in these human vessels. Indeed, hUII has been reported to cause vasodilation in isolated human pulmonary and abdominal resistant arteries (30). Recent studies have demonstrated that hUII also dilates the small arteries from different vascular beds in rats (4, 11, 14, 30). The results from the present study support the view that hUII is a potent vasodilator in small resistance arteries. Taken together, hUII seems to cause vasoconstriction primarily in large conduit vessels but vasodilation predominantly in small resistance arteries.

To further test the hypothesis that hUII stimulates NO production in renal arterial endothelium, we directly examined the intracellular NO response to hUII. In these experiments, DAF-2DA, a novel cell-permeable fluorescent indicator of NO, was loaded into endothelial cells, and then NO responses in these cells were monitored. We found that hUII (1 μM) stimulated the production of a strong green fluorescence in the endothelial layer of the renal arteries, which represented the increases in NO levels within renal arterial endothelial cells. The NOS inhibitor L-NAME or the re-

moval of the endothelium completely blocked the hUII-induced increase in NO levels in this preparation, suggesting that detected NO increases in response to hUII are derived from the endothelium of these arteries. To our knowledge, these results provide the first direct evidence that hUII increases NO levels in the renal arterial endothelium. It should be noted that the arteries used in this protocol were relatively large renal arteries. Therefore, the results may not necessarily suggest that this NO production in these large renal arteries contributes to UII-induced reduction of renal vascular resistance or increase in RBF, because these large vessels are not renal resistance arteries.

The mechanism by which hUII stimulates NO production remains unknown. Previous studies showed that hUII is an endogenous ligand for the orphan receptor GPR14 (18). This cyclic peptide caused concentration-dependent increases in intracellular $[Ca^{2+}]$ in HEK-293 cells expressing human GPR14 (2). In vascular smooth muscle cells, the action of hUII is mediated by an increase in $[Ca^{2+}]_i$ through the IP_3 signaling pathway (25). Therefore, it is possible that hUII activates its receptors on vascular endothelial cells and subsequently causes intracellular Ca^{2+} mobilization, resulting in the stimulation of endothelial NOS activity through a calmodulin-dependent mechanism. This Ca^{2+}-depenent activation of NOS in endothelial cells has been well documented (28). In a recent study, we provided direct evidence that NOS activation in the intact arterial endothelium is dependent on cytosolic $[Ca^{2+}]$ (34).

Although the present study did not determine the role of endogenous UII in the regulation of renal hemodynamics and renal excretory function due to lack of specific potent antagonists of UII, the finding that this peptide increases RBF and sodium and water excretion at least indicates that increases in plasma concentration of UII change renal vascular and tubular activities, which may represent the effects of activation of UII system on renal function. However, it remains unknown whether these actions of UII are physiological or pathological, because the plasma concentrations in human or different animals measured in many laboratories have shown the diversity even under physiological conditions, ranging from 1.9 pM to 2.5 nM depending on the methods used for its measurements. The disparity of the assay results may be related to the assay formats, reagents, and/or extraction (8). In the present study, the calculated concentrations of hUII in renal blood were ~75–600 pM, which seem to be at physiological range of UII plasma levels. However, we performed preliminary experiments to quantify rat plasma UII concentration using RIA and found that plasma concentrations of UII were 4.78 ± 1.2 pM in anesthetized rats (n = 6), which was much lower than calculated renal plasma concentrations. If the assay results are true, the high concentrations of UII during intrarenal infusion may represent a pathological condition related to activation of UII activation as seen in patients with chronic heart failure or chronic renal failure (8, 29, 31). As discussed above, nevertheless, the diversity of the assay results plagues an appropriate evaluation of physiological range of UII plasma levels. Interestingly, previous studies showed that prepro-urotensin II and GPR14 mRNAs and UII proteins exhibited a high abundance in human kidney (22, 24). Recent studies also found that hUII mRNAs were abundantly expressed in renal carcinoma cells and that plasma hUII concentrations were higher in patients with chronic renal failure compared with normal people (29, 31). By immunohistochemical examinations, hUII was found high in endothelial cell and in the distal convoluted tubules (29). All these results and our findings suggest that UII may be an important target molecule in studying renal physiology and pathophysiology.

In summary, the present study demonstrated that *1*) acute elevations of hUII in the kidney produced an increase in RBF, GFR, and urinary water/sodium excretion, which was blocked by L-NAME; *2*) hUII stimulated endothelium-dependent vasodilator responses in the small renal arteries when added into isolated, perfused, and pressurized renal arterial preparation; and *3*) hUII increased NO levels in the intact endothelium of the renal arteries. These results suggest that UII is a NO-dependent vasodilator and natriuretic peptide in the kidney, which may participate in the control of renal function.

DISCLOSURES

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