Original Article

Effects of Vasopeptidase Inhibition on Renal Function and Tubuloglomerular Feedback in Spontaneously Hypertensive Rats

Tao WANG and Toshikazu TAKABATAKE

Vasopeptidase inhibitors are a novel class of antihypertensive agents that concomitantly inhibit angiotensin converting enzyme and neutral endopeptidase. Our purpose was to investigate the effects of omapatrilat, a vasopeptidase inhibitor, on renal function and tubuloglomerular feedback (TGF) response in anesthetized 9–10-week-old spontaneously hypertensive rats (SHR). Intravenous injection of omapatrilat at 10 μmol/kg decreased systemic blood pressure and renal vascular resistance. Renal plasma flow was unchanged, whereas glomerular filtration rate (GFR) and filtration fraction (FF) were reduced. Increased urinary sodium excretion of tubular origin was observed. These parameters remained unaltered with vehicle treatment. Micropuncture study revealed that the maximal reduction of early proximal flow rate (EPFR) induced by orthograde perfusion of Henle's loop with artificial tubular fluid (ATF) was significantly reduced by omapatrilat treatment (28.5±3.1% *vs.* 72.0±2.8% of control) and was not significantly changed in the vehicle-treated group (vehicle 70.8±1.7% *vs.* control 71.0±2.1%). EPFR at zero perfusion was comparable between omapatrilat and vehicle treatment (29.7±2.2 *vs.* 31.3±2.1 nl/min, respectively). Luminal perfusion of 10^{-4} mol/l 7-nitroindazole in ATF abrogated the blunting of TGF response by omapatrilat but elicited no change in the vehicle-treated group. The suppression of the TGF mechanism and the reduction in FF suggest that omapatrilat respectively dilates the afferent and efferent arterioles. Under such conditions, reduction of GFR may indicate a fall in intraglomerular pressure. The restoration of nitric oxide signaling in the juxtaglomerular apparatus of SHR seems to participate in the inhibition of TGF by omapatrilat. These findings suggest that omapatrilat may provide a novel approach to the treatment of systemic and glomerular hypertension. (*Hypertens Res* 2005; 28: 611–618)

***Key Words*: vasopeptidase inhibitor, omapatrilat, tubuloglomerular feedback, macula densa, spontaneously hypertensive rat**

Introduction

Vasopeptidase inhibitors (VPI) are single molecules that simultaneously inhibit angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP). ACE, found in abundance in the lungs and kidneys, catalyzes the conversion of angiotensin I to angiotensin II and the inactivation of bradykinin. NEP, localized principally in the brush border membrane of renal tubule cells, catabolizes several vasodilator molecules, including the natriuretic peptides, bradykinin and adrenomedullin (*1*, *2*). Therefore, the application of VPI is associated with reduced production of vasoconstrictor angiotensin II and accumulation of the aforementioned vasodilators. In a rodent model of low-, normal-, and high-renin hypertension, VPI treatment lowered blood pressure regardless of renin levels or sodium balance (*3*, *4*), and a clinical study has shown that VPI reduces blood pressure in humans (*5*). Experimental

From the Fourth Department of Internal Medicine, Shimane University School of Medicine, Izumo, Japan.

Address for Reprints: Tao Wang, M.D., Ph.D., the Fourth Department of Internal Medicine, Shimane University School of Medicine, 89−1 Enya-cho, Izumo 693−8501, Japan. E-mail: wangtao@med.shimane-u.ac.jp

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Table 1. Effects of Intravenous Omapatrilat and Vehicle on Whole Kidney Function

	Vehicle			Omapatrilat		
	Control	E1	E2	Control	E1	E2
MBP (mmHg)	148±5	136±4	133±4	150±2	124±3*	114±3*
RVR (mmHg ml^{-1} min g KW)	15.4±0.7	14.4±1.0	13.8±0.8	16.0±1.0	11.8±1.1*	10.8±1.0*
RBF (ml min^{-1} g^{-1} KW)	9.80±0.44	9.77±0.84	9.76±0.73	9.58±0.86	10.78±1.09	10.65±0.96
RPF (ml min^{-1} g^{-1} KW)	4.30±0.21	4.29±0.21	4.31±0.19	4.17±0.24	4.68±0.20	4.68±0.20
GFR (ml min^{-1} g^{-1} KW)	0.90±0.03	0.92±0.01	0.92±0.02	0.93±0.03	0.92±0.02	0.87±0.02*
FF	0.21±0.01	0.22±0.01	0.22±0.01	0.23±0.01	0.20±0.02	0.19±0.01*
UV (μl min^{-1} g^{-1} KW)	3.3±0.1	3.6±0.3	3.4±0.2	3.5±0.1	3.5±0.1	3.0±0.2*
$U_{Na}V$ (nEq min^{-1} g^{-1} KW)	60±15	63±16	70±16	93±9	275±29*	204±38†
FE_{Na} (%)	0.054±0.011	0.057±0.012	0.061±0.011	0.063±0.006	0.206±0.021*	0.163±0.022*
Ht (%)	56±1	57±1	56±1	57±1	57±1	56±1
KW (g)			1.14±0.02			1.13±0.03

Data are means±SEM; $n=7$ for vehicle and $n=9$ for omapatrilat. Control, control period; E1 and E2, first and second 60-min clearance period, respectively; vehicle and omapatrilat, intraveneous injection of vehicle or omapatrilat (10 μmol/kg) after control period, respectively; MBP, mean blood pressure; RVR, renal vascular resistance; RBF, renal blood flow; RPF, renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction; UV, urine volume; $U_{Na}V$, urinary sodium excretion; FE_{Na}, fractional excretion of sodium; Ht, hematocrit; KW, kidney weight. *$p<0.05$ *vs.* the control value. $^{\dagger}0.05<p<0.10$ *vs.* the control value.

and clinical studies have also suggested that VPI have potential applications in the treatment of heart failure (*4*, *6*).

Glomerular hemodynamics are controlled by the tubuloglomerular feedback (TGF) mechanism, which alters the glomerular hydraulic pressure and the single nephron glomerular filtration rate (SNGFR) by changing afferent arteriole resistance in response to delivery and reabsorption of sodium chloride at the macula densa (MD) segment (*7*). The TGF mechanism is believed to play an important role in the regulation of water and electrolytes. In spontaneously hypertensive rats (SHR), TGF activity is enhanced compared with that in age-matched normotensive Wistar-Kyoto rats (*8*, *9*). The enhanced TGF activity results in a higher tonus of the afferent arterioles at any given level of salt and water delivery to the distal nephrons, which may underlie the increased preglomerular vascular resistance and reduced SNGFR observed in SHR. It has been suggested that the renin-angiotensin system is responsible for the enhanced TGF activity in young SHR (*10*).

Nitric oxide (NO) generated from a neuronal or type 1 constitutive nitric oxide synthase (nNOS) that is heavily expressed in MD cells is activated during MD solute reabsorption. It normally counteracts the TGF-mediated vasoconstriction (*11*). However, the blunting effect of MD-derived NO on TGF response is impaired in SHR (*12*). And the defect in NO generation in the juxtaglomerular apparatus (JGA) could contribute to the heightened TGF responses, enhanced renal vascular resistance, and hypertension (*13*).

Despite the extensive studies of VPI, the effects of simultaneous ACE and NEP inhibition on renal microcirculation and the TGF mechanism in hypertension have not hitherto been reported. And the impact of VPI on nNOS activity in JGA is also unclear due to the alteration of a diverse range of vasoactive agents that are regulated by VPI. Any change of NO synthesis in JGA may conceivably affect the TGF mechanism, since MD-derived NO is one of the major determinants of TGF response. The purpose of the present study was to investigate the acute effects of omapatrilat, the most clinically advanced VPI, on renal microcirculation and the TGF mechanism in anesthetized SHR. The role of NO in the context of TGF response under the influence of omapatrilat is also examined.

Methods

Omapatrilat (BMS-186716) was provided by Bristol-Myers Squibb K.K., Tokyo, Japan.

Animal Preparations

This study was performed in accordance with our institutional guidelines for animal experimentation. Experiments were carried out on 9–10 week-old male SHR of Izumo origin (Japan SLC, Inc., Hamamatsu, Japan), which were fed a commercial chow diet (MF; Oriental Yeast, Chiba, Japan) and had free access to tap water. The rats were prepared as previously described (*9*). Anesthesia was induced with thiopental sodium (110 mg/kg body weight i.p.; Ravonal, Tanabe, Osaka, Japan) and supplemented *via* the rectum if needed. Anesthetization with thiopental is a well-established method for the study of renal function at both the whole-organ and the nephron levels (*14*). Rectal temperature was maintained at 37.5°C by a thermostatically controlled heated table. A tracheostomy tube was inserted and a PE-50 polyethylene catheter (Clay Adams, Parsippany, USA) was placed in the right external jugular vein for the infusion of 10% polyfructosan (Inutest, Frese-

Table 2. EPFR to Intravenous Application of Omapatrilat or Vehicle during Microperfusion of ATF or ATF Containing 7-Nitroindazole (7-NI) into the Loop of Henle

	Vehicle group			Omapatrilat group		
	Control	Vehicle i.v.	7-NI	Control	Omapatrilat i.v.	7-NI
$EPRR_0$ (nl/min)	31.5±2.2	31.3±2.1	29.7±2.1	32.5±2.0	29.7±2.2	28.6±2.0
$EPFR_{40}$ (nl/min)	9.1±0.8	9.2±0.8	7.3±0.4‡	9.1±1.1	21.0±1.5*,†	9.3±0.8
ΔEPFR (%)	71.0±2.1	70.8±1.7	74.7±1.9	72.0±2.8	28.5±3.1*,†	67.1±2.4§
$EPFR_0$ *vs.* $EPFR_{40}$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.05$	$p<0.001$
Nephrons	8	12	12	10	14	15

Data are means±SEM. $EPFR_0$, early proximal flow rate (EPFR) measured in the absence of loop flow; $EPFR_{40}$, EPFR measured during loop perfusion of 40 nl/min; ΔEPFR, percent reduction of $EPFR_0$ during loop perfusion; 7-NI, intraluminal perfusion of 10^{-4} mol/l 7-NI in ATF. ATF is the artificial tubular fluid perfused orthograde and through the loop of Henle. *$p<0.05$ compared with corresponding control value. †$p<0.05$ *vs.* data of 7-NI in the same group. ‡$p<0.05$ *vs.* respective $EPFR_{40}$ value of control and vehicle. §$p<0.05$ *vs.* data of 7-NI in the vehicle group.

nius, Linz, Austria) in 0.9% saline at a rate of 4.5 ml/kg body weight/h as well as for the administration of omapatrilat or vehicle. The right femoral artery was cannulated with a PE-50 catheter for monitoring arterial pressure and collecting blood samples. The left kidney was exposed through a flank incision, placed in a plastic cup, immobilized in agar and bathed in warmed (37.5°C) mineral oil. The pelvis was cannulated with a PE-10 (Clay Adams) catheter to collect urine samples. A 25-gauge needle connected to a PE-50 catheter was inserted into the left renal vein to obtain renal venous blood samples. Clearance and micropuncture studies were started 1 h after the completion of all surgical procedures.

Whole Kidney Clearance Studies

Two 30-min clearances were performed as a control with saline infused at a rate of 4.5 ml/kg body weight/h, and the data were later pooled together for analysis. Omapatrilat was then injected intravenously at 10 μmol/kg within 2 min ($n=9$ rats), followed by the infusion of saline. This dose of omapatrilat was previously found to markedly decrease mean blood pressure (MBP) 30 min after application without discernibly affecting heart rate (*15*). In addition, urinary excretion of atrial natriuretic peptide (ANP) was previously found to be increased followed by that of cyclic guanosine monophosphate, and both were sustained at 150 min (*16*). Accordingly, two 60-min clearances were started 30 min after omapatrilat administration. In another group of rats ($n=7$), the same procedure was repeated by replacing omapatrilat with vehicle. Repeated blood samples were taken from the femoral artery and renal vein at the midpoint of each clearance period for determination of the hematocrit and the plasma polyfructosan concentration, and timed urine collections into preweighed tubes were made at 60-min intervals. The glomerular filtration rate (GFR) was derived from polyfructosan clearance. Blood pressure (BP) was recorded on an electronic BP recorder (NEC San-ei, Tokyo, Japan) by connecting the femoral tube to a pressure transducer (Gould, Cleveland, USA). Renal plasma flow (RPF) was calculated as $RPF = GFR \times a/(a - v)$, where a and v are the systemic arterial and renal venous polyfructosan concentration. Renal blood flow (RBF) and renal vascular resistance (RVR) were calculated as RBF = RPF/(1 – hematocrit) and RVR = MBP/RBF. Urine volume was determined gravimetrically. Polyfructosan concentration was measured in the plasma and the urine by the anthrone methods. Sodium and potassium concentration in blood and urine were measured by a flame photometer (Model 775; Hitachi, Tokyo, Japan). Each measurement was made in duplicate.

Measurement of Early Proximal Flow Rate (EPFR) during Loop Perfusion

During the clearance study, TGF response was estimated by measuring the changes in EPFR, an index of SNGFR, while perfusing the loop of Henle with artificial tubular fluid (ATF) from the last accessible proximal segment at a rate of 40 nl/min as described elsewhere (*9*). The ATF was a modified Ringer's solution with the following composition (in mmol/l): 136 NaCl, 4 $NaHCO_3$, 4 KCl, 2 $CaCl_2$ and 7.5 urea with the addition of 0.1% FD & C Green (Keystone, Chicago, USA) to visualize the tubular flow. Successive, 3-min collections of tubular fluid were made from the early proximal segment during microperfusion at 0 or 40 nl/ml. Tubular fluid was collected spontaneously in 8 to 10-μl pipettes, proximal to a mobile, 4 to 5-tubular diameter block of Sudan Black-stained mineral oil. The volume of tubular fluid was determined in a constant-bore capillary tube (Microcaps 1.0 μl; Drummond, Broomall, USA). The feedback response was expressed as the change in EPFR when the loop perfusion rate was increased from 0 to 40 nl/min. Our preliminary study showed a fall of MBP of about 31–39 mmHg by the current dose of omapatrilat in the second 60-min clearance period. To obviate the confounding effects of a profound BP decrease on the TGF response, EPFR measurements were performed during the control and initial 60-min clearance period.

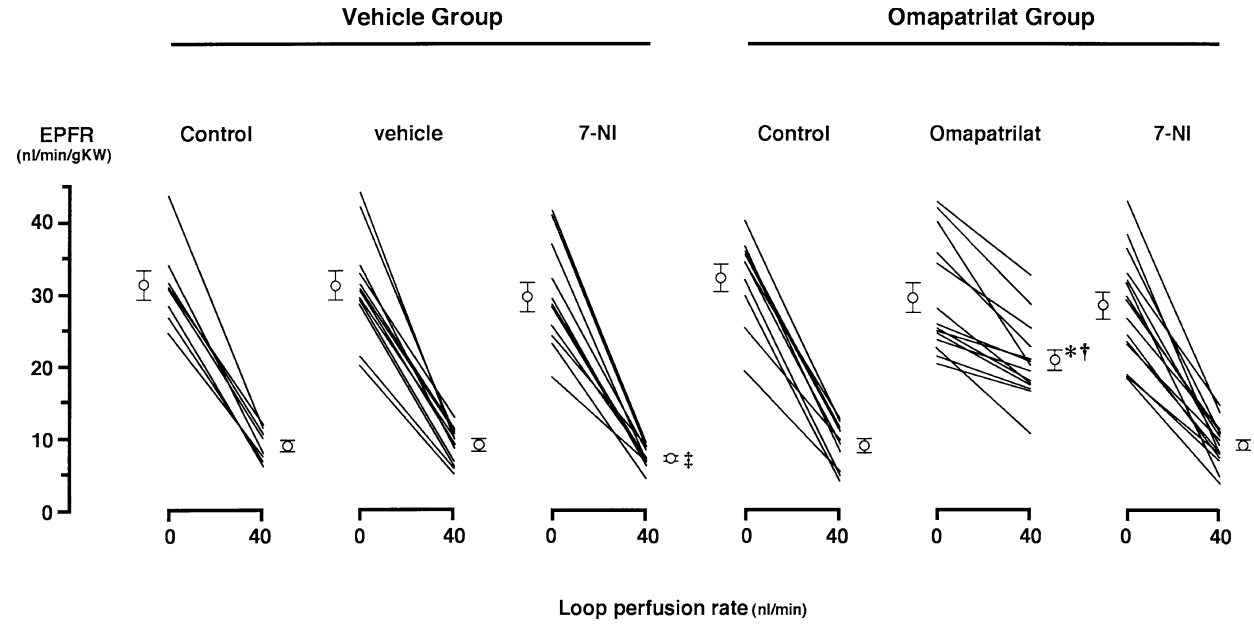

Fig. 1. *Response of EPFR to intravenous application of vehicle or omapatrilat during microperfusion of ATF or ATF containing 10^{-4} mol/l 7-NI into the loop of Henle. Lines connect individual EPFR values measured during loop perfusion at 0 ($EPFR_0$) and 40 nl/min ($EPFR_{40}$) in each nephron. Data are the mean±SEM.* *$p < 0.05$ vs. *$EPFR_{40}$ value of the corresponding control.* †$p < 0.05$ vs. *the corresponding $EPFR_{40}$ value during luminal perfusion of 7-NI.* ‡$p < 0.05$ vs. *the other two $EPFR_{40}$ values in the respective groups.*

Assessment of the Function of MD-Derived NO

The effects of MD-derived NO were deduced from the enhancement of TGF during luminal microperfusion of the relatively nNOS-selective inhibitor, 7-nitroindazole (7-NI, Sigma, St. Louis, USA) (*17*). 7-NI was perfused directly into a late proximal tubule of the nephron under investigation after administration of omapatrilat or vehicle. 7-NI (10^{-4} mol/l) in ATF was used since this dose of 7-NI was reported to be maximally effective and to reversibly entail a rapid increase in TGF responses (*18*).

Statistical Analysis

Results are expressed as the means±SEM. Student's paired *t*-tests were used for the comparison of paired variants. Analysis of variance (ANOVA) was performed to determine differences among groups. When ANOVA revealed a significant difference, Duncan's multiple-range comparison test was applied to the data to identify specific intergroup differences. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Whole Kidney Function

The results of the whole kidney clearance study are summarized in Table 1. Omapatrilat injection induced a significant reduction in MBP and RVR during both of the 60-min clearance periods (designated as E1 and E2). GFR was significantly decreased in E2 and RBF was unaltered; as a result, a diminished filtration fraction (FF) was observed. Urine volume was maintained in E1 but decreased in E2. Urinary excretion of sodium was increased in E1 and still tended to increase in E2 ($p = 0.06$). Fractional excretion of sodium (FE_{Na}) was increased in E1 and E2. Application of the vehicle affected neither renal hemodynamics nor urinary excretion, with the exception that MBP decreased by 15 mmHg in E2. The control values were similar between the omapatrilat and vehicle groups.

EPFR during Loop Perfusion

The TGF parameters are presented in Table 2. The control values in the two groups were comparable. Figure 1 plots the changes of EPFR in the absence of distal flow ($EPFR_0$) and during perfusion of the loop of Henle at 40 nl/min ($EPFR_{40}$) with ATF. Loop perfusion significantly decreased EPFR in both the omapatrilat and vehicle groups. $EPFR_0$ did not differ among the control period, the period immediately after omapatrilat was given, and the period of luminal perfusion of 7-NI. The values of $EPFR_0$ in the vehicle group were also unchanged among these three periods. However, omapatrilat but not vehicle induced a significant increase in $EPFR_{40}$ during maximal loop perfusion. With luminal perfusion of 7-NI,

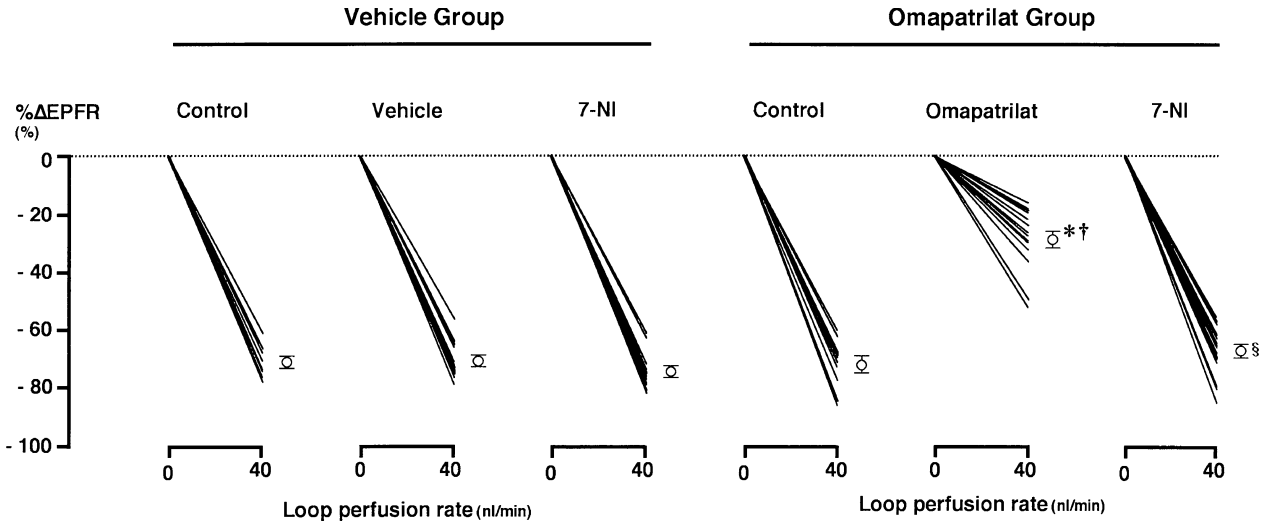

Fig. 2. *Percent reduction in EPFR in response to loop perfusion with ATF or ATF containing 10^{-4} mol/l 7-NI after intravenous injection of vehicle or omapatrilat. The line indicates a change of individual EPFR values. Data are the mean±SEM.* *$p < 0.05$ vs. *the control value in the same group.* †$p < 0.05$ vs. *the value obtained during luminal perfusion of 7-NI in the same group.* §$p < 0.05$ vs. *the value obtained during luminal perfusion of 7-NI in the vehicle group.*

the increased $EPFR_{40}$ in rats receiving omapatrilat returned to the control level, and the initially unaltered $EPFR_{40}$ in rats receiving vehicle showed a small but significant decrease. As depicted in Fig. 2, the 28.5±3.1% reduction in EPFR (*Δ*EPFR) by loop perfusion after omapatrilat application was significantly smaller than the 72.0±2.8% of the control value. Subsequent luminal perfusion of 7-NI significantly rendered *Δ*EPFR back to 67.1±2.4%, which was not significantly different from the control value. In the vehicle group, *Δ*EPFR was maintained to the same degree after vehicle was given. Ensuing luminal perfusion of 7-NI yielded a *Δ*EPFR of 74.7±1.9%, which was not significantly different from the other respective *Δ*EPFR values in the same group; however, it was significantly greater than the corresponding 7-NI induced *Δ*EPFR of 67.1±2.4% in the omapatrilat group.

Discussion

Acute administration of omapatrilat induced marked hypotension in SHR. In spite of the reduction in renal perfusion pressure, RBF remained constant, indicating vasodilation of the preglomerular vessels. GFR was also decreased, and as a result, a reduction in FF from 0.23 to 0.19 was observed in E2. In our previous studies (*19*, *20*), ANP was found to significantly increase both GFR and RBF, rendering FF unchanged. Therefore, the present findings of decreased FF may indicate vasodilation of the postglomerular efferent arterioles by omapatrilat, as reported by other laboratories (*21*, *22*). The effect of omapatrilat on the efferent arterioles seems to be due to ACE inhibition, because pure NEP inhibition has otherwise converse influences on the glomerular vasculatures (*23*). In rats subjected to 5/6 nephrectomy, omapatrilat was found to be more effective in lowering intraglomerular pressure than enalapril, though the precise mechanism of its effect remains to be determined (*21*). Consistently, combined blockade of ACE and NEP by VPI afforded greater renoprotection than the sole inhibition of ACE in the same model (*24*, *25*).

Omapatrilat treatment also produced a robust natriuretic response while GFR was maintained in E1 and decreased in E2. This response was associated with a significant increase in FE_{Na}, thus indicating direct tubular effects. The natriuretic effect of omapatrilat may be mediated by local enhancement of ANP within the kidney (*26*, *27*), since ANP has been shown to be the primary determinant of sodium excretion stimulated by combinations of NEP and ACE inhibition (*28*). This notion is supported by the finding of an increased urinary excretion of ANP and cyclic guanosine monophosphate in monkeys given the same dose of omapatrilat intravenously as in our study (*16*). Nevertheless, we cannot completely exclude the possibility that the tubular function was influenced by peptides rather than ANP, since it has been shown that NEP inhibition can also delay the degradation of endothelin and other peptides (*2*); this possibility may warrant future examination. The NEP inhibition protects ANP, either filtered by the glomerulus or locally synthesized, from degradation in the brush border and facilitates the peptide's tubular action of inhibiting sodium reabsorption at the inner medullary collecting duct (*26*). Alternatively, locally high ANP levels may antagonize the tubular effect of the remaining angiotensin II and the effects of aldosterone at the collecting ducts (*29*). However, the enhanced natriuretic response waned with time in our study. This was probably due to the prolonged decrease in systemic BP producing a decrease in renal perfusion pressure and blunting the natriuretic

responses to NEP inhibition. Indeed, the sensitivity of the natriuretic effects of ANP to changes in BP is well known (*30*). It is noteworthy that, in our study, the natriuresis was not completely abolished by the fall in BP.

Our study revealed that the natriuretic response was dissociated from the diuretic response. Similar findings have been reported previously in rats (*31*) and humans (*32*). The disparity between the two responses was likely due to the fact that the natriuresis is separate from the diuretic response, since the primary control of water reabsorption in the collecting ducts occurs *via* an antidiuretic hormone, *i.e.*, arginine vasopressin (AVP), and not the ANP-sensitive sodium channel (*33*). Since an acute decrease in arterial pressure stimulates AVP secretion in rats (*34*), our experiment might have induced an elevation in AVP, which would have acted to conserve urinary water. Thus, once the inhibition of collecting duct sodium transport by ANP proceeds independently of the tubular action of AVP, sodium excretion would remain increased without a concurrent rise in urine volume.

TGF has been established as a mechanism that exerts prompt and efficient control over the afferent arteriolar tone and thereby over the glomerular plasma flow and filtration rate. Our micropuncture experiments demonstrated that EPFR decreases in response to an increase in distal tubular flow, both in the vehicle- and omapatrilat-treated SHR, supporting the existence of feedback regulation of glomerular hemodynamics (*7*). Our findings also showed that intravenous administration of omapatrilat decreases the maximal reduction in EPFR induced by loop perfusion, indicating attenuation of the TGF response. The blunted response of TGF may indicate dilation of the afferent arterioles by omapatrilat, since the TGF response involves the vasomotor response of this arteriolar segment (*7*). The enhanced TGF activity and reduced GFR in SHR may lead to resetting of the pressure-natriuresis relation and salt retention, which are thought to play an important role in the development and maintenance of hypertension (*8*, *35*). In the present study, a single intravenous bolus of omapatrilat further attenuated TGF responses to a level less than that recorded in normotensive Wistar-Kyoto rats (*9*, *36*). The blunted TGF response under the influence of omapatrilat in SHR permits a larger tubular load to pass the MD region with less activation of TGF and thus a lesser degree of afferent arteriolar constriction.

MD-derived NO established the set point for TGF during the long-term adaptation to the changes in the proximal reabsorption (*37*). Prolonged inhibition of nNOS with oral 7-NI in normal rats first enhanced TGF and later induced hypertension (*38*). These studies confirm that MD nNOS plays an important long-term role in modulating the TGF mechanism. The buffering of TGF by NO derived from nNOS is impaired in the JGA of the SHR (*12*, *18*). Our findings are in general agreement with these observations in that there was no significant change of TGF response to blockade of nNOS by luminal 7-NI in the vehicle-treated SHR. Nevertheless, 7-NI abolished the attenuation of TGF by omapatrilat, but it failed to increase the level of TGF to that seen in the vehicle-treated rats. We interpret this finding as meaning that the restoration of the NO signaling in the JGA by omapatrilat contributes, but not exclusively, to the suppression of TGF. That is, there was possible involvement of other vasoactive factor(s), such as direct effects of the elevated ANP level on the afferent arterioles (*29*). Using the pharmacokinetic parameters provided by the manufacturer, the plasma concentration of omapatrilat in our study was estimated to be 13 ng/ml at the midpoint of the first 60-min clearance period during which the micropuncture study was performed. This is roughly consistent with the plasma concentration in human subjects taking a single oral dose of 7.5–25 mg (*39*). Our findings could thus be of clinical importance in helping to establish a therapeutic regimen for this drug.

Reduction of arterial pressure has been shown to attenuate TGF response (*40*), and under such a condition, EPFR varies directly with BP when the loop flow is zero (*41*). In our study, however, omapatrilat did not decrease EPFR at zero perfusion in the face of decreased perfusion pressure, suggesting that omapatrilat maintains EPFR at zero perfusion by vasodilating the afferent arterioles and possibly more proximal arteriolar segments. ANP is known to elevate glomerular hydraulic pressure due to its divergent effects on the afferent and efferent arterioles (*29*) and to increase EPFR in the absence of loop perfusion (*19*, *20*). Our current finding that EPFR was unchanged at zero perfusion may further support the notion that the efferent arterioles participate in renal vasodilation, as did the finding that omapatrilat decreased FF in the clearance study.

In conclusion, the results of the present study demonstrate that the acute vasopeptidase inhibition induced by omapatrilat in SHR has hypotensive, vasodilatory and natriuretic effects. Omapatrilat attenuates the TGF response by dilating the afferent arterioles, contributing to the maintenance of RBF despite the reduction in renal perfusion pressure. The restoration of nitric oxide signaling in the JGA of the SHR seems to participate in the inhibition of TGF by omapatrilat. In addition, omapatrilat exhibits favorable renal hemodynamic and tubular effects, as it may reduce the intraglomerular pressure and promote sodium excretion. Thus vasopeptidase inhibition has potential as an effective therapeutic modality for the treatment of both systemic and glomerular hypertension.

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