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Different Contributions of the Endothelin ET_A Receptor to Hypertension Induced by Acute or Chronic Inhibition of Nitric Oxide Synthesis

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Abstract

The effects of FR139317((*R*)2-[(*R*)-2-[(S)-2-[[1-(hexahydro-1*H*-azepinyl)]carbonyl] amino-4-methyl-pentanoyl] amino-3-[3-(1-methyl-1*H*-indoyl)]propionyl]-amino-3-(2-pyridyl)propionic acid), an endothelin ET_A receptor antagonist, on systemic and renal haemodynamic responses and excretory responses to chronic or acute nitric oxide (NO) synthase inhibition with N^G-nitro-L-arginine (NOARG) have been examined.

An intravenous bolus injection of FR139317 ($10\,mg\,kg^{-1}$) to chronic NO-deficient hypertensive rats (2·74 mM NOARG in drinking water for 4 weeks) elicited only a slight decrease in mean arterial pressure (MAP), to the same extent as seen in normotensive control rats. Injection of this drug induced no alteration of the renal haemodynamics of this chronic hypertensive model. Urine formation in control rats was significantly reduced by administration of FR139317. No significant decrease in urine formation was observed in the chronic NO-deficient rats. Acute intravenous injection of NOARG ($5\,mg\,kg^{-1}$) induced a gradual and significant increase in MAP, with a significant decrease in renal blood flow. A slight but insignificant diuretic effect was observed. In animals pretreated with FR139317 ($10\,mg\,kg^{-1}$ i.v.) NOARG induced a significantly less potent increase in MAP, whereas similar renal haemodynamic responses to NOARG were observed. In contrast to the FR139317-untreated group, urine formation tended to decrease after administration of NOARG. These results suggest that endothelin, via the ET_A receptor, contributes to the systemic pressor response to acute NO synthase inhibition, although renal vasoconstriction and functional changes induced by acute NO synthase inhibition are independent of ET_A receptor-related effects.

These results imply that action of endothelin via the ET_A receptor is not involved in the maintenance of sustained hypertension induced by chronic NO synthase inhibition.

In the vascular endothelium nitric oxide (NO) is synthesized from the amino acid L-arginine by the enzyme NO synthase (Moncada et al 1991). This NO is responsible for the biological effects of endothelium-derived relaxing factor (EDRF) and acts via stimulation of soluble guanylate cyclase in vascular smooth muscle cells (Ignarro 1990; Moncada et al 1991). Inhibition of NO synthesis by N^G-nitro-L-arginine (NOARG) and other arginine analogues induces a hypertensive response and reduces local blood flow in laboratory animals (Gardiner et al 1990; Lahera et al 1991). These observations indicate that the synthesis and release of NO at the basal level contribute tonically to the regulation of vascular tone in the cardiovascular system. In the kidney intrarenal arterial infusion of NO synthase inhibitors induces potent renal vasoconstriction and antidiuresis (Baylis et al 1990; Egi et al 1994). The NO synthase inhibitor NOARG has been reported to impair pressure-induced natriuresis and renal autoregulation in anaesthetized dogs (Salom et al 1992; Majid et al 1993), implying that endogenous NO plays an important role in the regulation of renal vascular tone and renal tubular re-absorption of sodium or water, or both. Most of the evidence of the functional role of NO in the kidney has been obtained from experiments using NO synthase inhibitors.

There is accumulating evidence of functional interaction between NO and endothelin 1 in some pathophysiological conditions. NO not only opposes

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the actions of endothelin by independently inducing vasodilation (Moncada et al 1991), but directly modulates the production of endothelin 1 in endothelial cells. This view is based on findings in in-vitro studies which indicate that NO reduces the formation of endothelin 1 via a cyclic GMP-dependent mechanism (Boulanger & Lüscher 1990; Yokokawa et al 1993). In addition, endothelin promotes NO synthesis via activation of the ET_B receptor in an autocrine fashion (Hirata et al 1993). Recent studies have demonstrated that the hypertensive effect of acute blockade of NO synthesis with NO synthase inhibitors is efficiently suppressed by a non-selective ET_A/ET_B receptor antagonist or a selective ET_A receptor antagonist (Richard et al 1995; Thompson et al 1995; Banting et al 1996; Filep 1997), suggesting that endogenously enhanced production of endothelin contributes to the above hypertensive effect, mainly via the ET_A receptor.

We have previously reported that intravenous injection of an ET_A receptor antagonist FR139317 ((*R*)2-[(*R*)-2-[(S)-2-[[1-(hexahydro-1*H*-azepinyl)]-carbonyl]amino-4-methyl-pentanoyl] amino-3-[3-(1-methyl-1*H*-indoyl)]propionyl]-amino-3-(2-pyridyl)propionic acid) to long-term NO synthase-blocked hypertensive rats elicited only a moderate hypotensive effect—similar to that seen in normotensive rats (Fujita et al 1995b). There have been reports that chronic treatment with a non-selective or a selective ET_A receptor antagonist did not induce a significant reduction of blood pressure in chronic NO-deficient rats (Moreau et al 1997; Sventek et al 1997), thus there seems to be a discrepancy between the roles of endothelin
under conditions of acute and chronic inhibition of NO synthase. In recent studies using
other hypertensive models such as deoxycorticosterone acetate (DOCA)-salt hypertensive rats we and others have demonstrated that ET_A receptor antagonists effectively suppress the development and maintenance of this hypertension (Fujita et al 1995a, 1996b; Schiffrin et al 1997). We also noted that effects of endothelin via the ET_A receptor play an important role in water and sodium retention, and in renal vasoconstriction in DOCA-salt-induced hypertension (Matsumura et al 1997).

In this study we have evaluated the involvement of endothelin via the ET_A receptor in systemic and renal haemodynamic responses and excretory responses to acute or chronic blockade of NO synthesis, using FR139317, a selective ET_A receptor antagonist.

Materials and Methods

Drugs and solutions

FR139317, a kind gift from Fujisawa Pharmaceutical, Osaka, Japan, was dissolved in NaOH (1 M) and diluted (1 : 10) with saline. Other chemicals were purchased from Nacalai Tesque (Kyoto, Japan).

Long-term NOARG treatment

Experiments were performed on male Sprague-Dawley rats, 160–180 g. For experiments on NO synthase inhibition these rats were given drinking water containing NOARG (2·74 mM; Dananberg et al 1993; Fujita et al 1995b). Control animals received plain tap water throughout the study. Systolic blood pressure was monitored by use of a tail cuff and a pneumatic pulse transducer. After 4 weeks treatment rats with systolic blood pressure > 180 mmHg were used for clearance studies.

Surgical procedure for renal clearance study

The rats were anaesthetized with sodium thiobutabarbital (Inactin, 100 mg kg^{-1}; i.p.) and placed on a surgical tray that maintained rectal temperature between 37 and 38°C. After tracheotomy the right femoral vein was cannulated for infusion of 0·9% NaCl (saline) containing 0·5% inulin (6 mL h^{-1}). The right and left femoral arteries were also cannulated for measurement of mean arterial pressure (MAP) and for blood sampling, respectively. After abdominal midline incision the left kidney was exposed and the renal artery was carefully stripped of connective tissue, followed by the application of 5% phenol in 70% ethanol to exclude the influence of renal sympathetic nerves. An electromagnetic flow probe (1·0 mm diam.; Nihon Kohden, Tokyo, Japan) connected to a square-wave flowmeter (MFV-2100; Nihon Kohden) was positioned on the renal artery to measure renal blood flow. A polyethylene cannula was inserted into the ureter for urine collection. The urinary bladder was cannulated to ensure free drainage of urine from the right kidney. MAP and renal blood flow were continuously recorded on a polygraph (RM 6000; Nihon Kohden) throughout the experiment. A period of approximately 60–90 min was allowed for stabilization of MAP, renal blood flow and urine flow.

Experimental protocol

In the first group of experiments we examined the effects of bolus injection of FR139317 on systemic and renal haemodynamics and urine formation in long-term NO-deficient hypertensive rats and in normotensive control rats. After an equilibration period urine samples were collected during two 15-min control clearance periods. Results for the second control period served as the basal values. After the control periods, FR139317 (10 mg kg^{-1}) was administered intravenously by slow bolus

injection. The dose of FR139317 used in this study has been reported to abolish the pressor response to exogenous endothelin 1 (Sogabe et al 1993). During the first 5 min after drug injection urine was not collected to take into account the dead space of the urine collection system. After this urine samples were collected during four consecutive 15-min periods (E1–E4). Blood samples (0·2 mL) were obtained 15 min before drug injection and 20 and 50 min thereafter. The blood loss was replaced by injecting an equal volume of blood from donor rats. Plasma was immediately separated by centrifugation. In the time-control study, the vehicle was administered to rats for which haemodynamic and excretory parameters were constant throughout the study (data not shown).

The second group of experiments examined the effects of FR139317 on systemic and renal haemodynamic responses and excretory responses to intravenous injection of NOARG. FR139317 ($10\,mg\,kg^{-1}$) or vehicle (0·1 M NaOH) was injected intravenously ($1\,mL\,kg^{-1}$) and urine samples were collected during two 15-min periods (P1, P2). NOARG ($5\,mg\,kg^{-1}$) was then injected intravenously and three 15-min clearance periods (P3–P5) were monitored. The dose of NOARG was determined by examining the inhibitory effect on acetylcholine-induced vasodilation. Blood samples were obtained 20 and 55 min after injection of FR139317 or vehicle. During the first 5 min after injection of each drug urine was not collected to take into account the dead space of the urine collection system.

Analytical procedure

Urine and plasma inulin levels were measured by spectrofluorimetry (Hitachi 650-50; Tokyo, Japan) as described elsewhere (Matsumura et al 1997). Glomerular filtration rate (GFR) was calculated from the inulin clearance. Urine and plasma sodium concentrations were determined by flame photometry (Hitachi 205D).

Statistical analysis

All values are expressed as means ± s.e.m. For statistical analysis we used the unpaired Student's *t*-test for two-group comparison. Effects of drugs on each rat were analysed by repeated measures using one-way analysis of variance combined with Dunnett's multiple range test. Differences were considered significant when $P < 0.05$.

Results

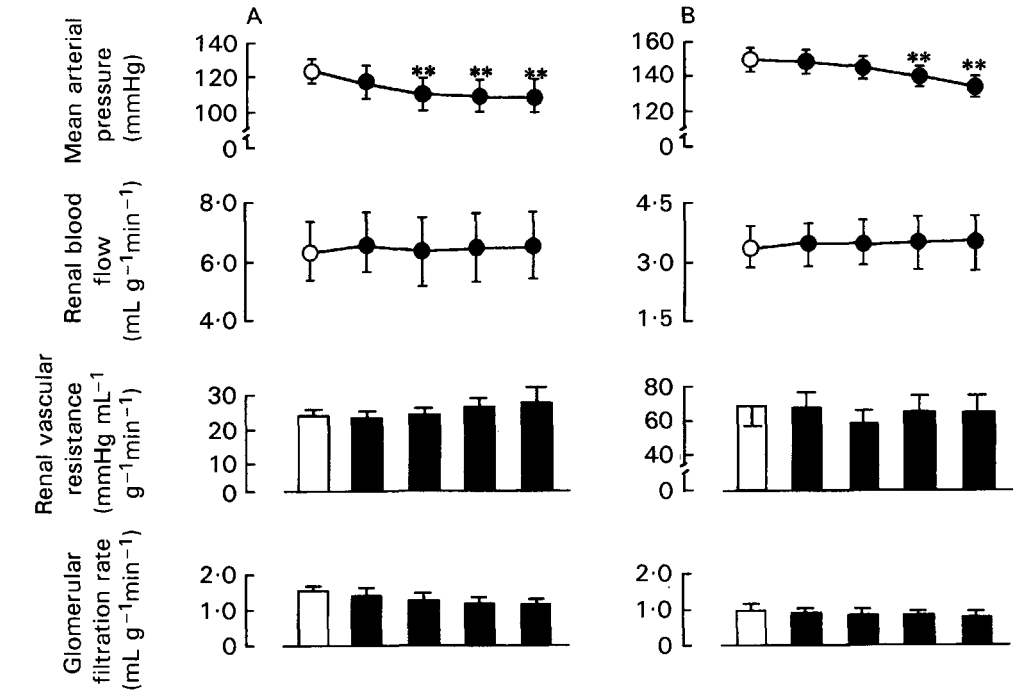
Effects of FR139317 on long-term NO-deficient hypertensive rats

The basal MAP of anaesthetized long-term NOARG-treated hypertensive rats was significantly higher than that of normotensive control rats (153 ± 5 compared with 123 ± 5 mmHg; n = 7; $P < 0.01$). In these chronic NOARG-treated rats, there were marked reductions in basal renal blood flow (3·74 ± 0·84 compared with 6·16 ± 0·79 $mL\,g^{-1}\,min^{-1}$; $P < 0.05$) and GFR (1·00 ± 0·10 compared with 1·45 ± 0·15 $mL\,g^{-1}\,min^{-1}$; $P < 0.05$), whereas renal vascular resistance (RVR) was increased by long-term treatment with NOARG (63·2 ± 19·1 compared with 21·6 ± 2·5 $mmHg\,mL^{-1}\,g^{-1}\,min^{-1}$; $P < 0.05$). Basal levels of urine flow, urinary excretion of sodium ($U_{Na}V$) and fractional excretion of sodium (FE_{Na}) were not significantly different for NOARG-treated and control rats (Figure 1).

In normotensive control rats (Figure 1A), FR139317 induced slow-onset and slight decreases in MAP. Significant decreases in MAP were observed for periods E2–E4 (from a control value of 123 ± 5 mmHg to 109 ± 7 mmHg for period E4, $P < 0.01$). There were no significant changes in renal haemodynamic parameters. After injection of FR139317 urine flow decreased gradually over the experimental period, being about half the control value in period E4. $U_{Na}V$ and FE_{Na} fell gradually over the experimental period, but the changes were not statistically significant. In hypertensive rats treated long-term with NOARG (Figure 1B), a bolus injection of FR139317 induced a slight but significant decrease in MAP (periods E3 and E4), to the same extent as in normotensive rats. Urine flow and FE_{Na} decreased slightly after injection of FR139317 but the changes were not statistically significant. There were no alterations in renal blood flow, RVR, GFR and $U_{Na}V$ after treatment with FR139317.

Effect of FR139317 on hypertensive rats induced by acute inhibition of NO synthase

As shown in Figure 2A, intravenous injection of NOARG induced marked increases in MAP (from 108 ± 3 mmHg in P2 to 143 ± 3 mmHg in P5; $P < 0.01$) and RVR (from 25·3 ± 4·0 $mmHg\,mL^{-1}\,g^{-1}\,min^{-1}$ in P2 to 57·3 ± 13·2 $mmHg\,mL^{-1}\,g^{-1}\,min^{-1}$ in P5; $P < 0.01$), with a significant decrease in renal blood flow (from 5·06 ± 1·07 $mL\,g^{-1}\,min^{-1}$ in P2 to 3·59 ± 1·03 $mL\,g^{-1}\,min^{-1}$ in P5; $P < 0.01$). The GFR tended to decrease, but the changes were not statistically significant. After pretreatment with FR139317 the increase in MAP was considerably attenuated (from 111 ± 5 mmHg



	Control	E1	E2	E3	E4
Urine flow (μL g^{-1}min^{-1})	12·00 ±3.45	11·43 ±2.98	8·33 ±2.35	7·17* ±1.72	6·59* ±1.31
	11·75 ±1.91	10·77 ±1.23	9·81 ±1.24	9·14 ±1.01	8·85 ±0.95
Urinary excretion of sodium (μEq g^{-1}min^{-1})	1·52 ±0.53	1·70 ±0.70	1·33 ±0.35	1·01 ±0.35	1·05 ±0.36
	1·23 ±0.44	1·31 ±0.36	1·34 ±0.37	1·25 ±0.33	1·18 ±0.32
Fractional excretion of sodium %	0·71 ±0.27	0·76 ±0.30	0·55 ±0.24	0·45 ±0.15	0·48 ±0.16
	0·82 ±0.15	0·80 ±0.15	0·75 ±0.18	0·71 ±0.14	0·67 ±0.14

Figure 1. Systemic and renal haemodynamic responses and excretory responses to intravenous injection of FR139317 (10 mg kg^{-1}) in seven normotensive control (A) and in eight long-term NO-deficient hypertensive rats (B). Values are means ± s.e.m. *$P < 0.05$, **$P < 0.01$, significantly different from result for control period.

in P2 to 128 ± 7 mmHg in P5; $P < 0.01$). The observed change in P5 was 15·3 ± 3·8%, which was significantly smaller than that in vehicle-treated rats (37·1 ± 4·2%) (Figure 2B). Renal haemodynamic responses to NOARG were similar to those in vehicle-treated rats.

Table 1 summarizes the effects of intravenous injection of NOARG, with or without pretreatment with FR139317, on urine output. In the absence of FR139317 no significant alterations in urine flow, $U_{Na}V$ or FE_{Na} were observed after the injection of NOARG, although the level of urinary parameters tended to increase in period P5. After pretreatment with FR139317, the level of urine flow, $U_{Na}V$ and FE_{Na} gradually decreased after administration of NOARG, but these changes were not statistically significant except for $U_{Na}V$ in period P5.

Discussion

Our results showed that intravenous injection of FR139317 induced only a slight decrease in MAP in long-term NO-deficient rats, and that the decrease was similar to that seen in normotensive control rats. In contrast, the pressor response to acute inhibition of NO synthase was markedly attenuated by pretreatment with FR139317. It seems likely that endothelin actions via the ET_A receptor do not contribute to the maintenance of sustained hypertension induced by chronic NO synthase blockade, but are closely involved in the hypertensive effect induced by the acute blockade of NO synthase. This view is compatible with evidence from previous studies (Richard et al 1995; Thompson et al 1995; Banting et al 1996; Fujita et al 1996b; Filep 1997; Moreau et al 1997; Sventek et al 1997).

The mechanism underlying the elevation of vascular tone induced by acute blockade of NO synthase has not been fully elucidated. Because NO is synthesized continuously by endothelial cells and acts locally to modulate vascular smooth-muscle tone, a reduction in its supply seems to result in a

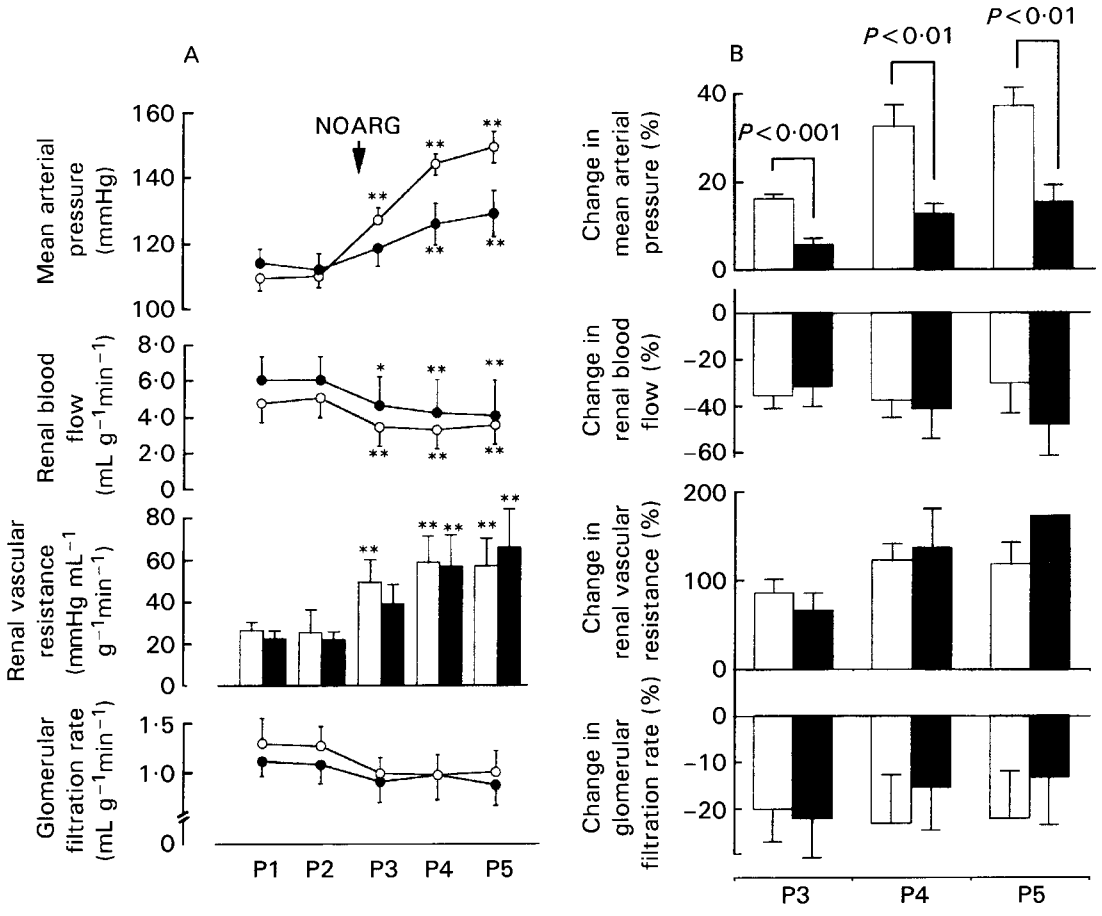


Figure 2. Systemic and renal haemodynamic responses of anaesthetized rats to intravenous injection of NOARG (5 mg kg^{-1}) after pretreatment with FR139317 (10 mg kg^{-1}; ●, ■) or with vehicle (○, □). Values are means ± s.e.m. of absolute changes (A) and percentage changes from the values in period P2 (B). *$P < 0.05$, **$P < 0.01$, significantly different from result for period P2.

higher setting of smooth muscle tone (Vane et al 1990). Alternatively, a decrease in NO supply might enhance the production or action, or both, of other vasoactive substances such as endothelin 1 to elevate vascular smooth-muscle tone. Several studies have indicated that inhibition of NO synthase increases release of endothelin 1 from cultured endothelial cells, thereby suggesting a role of endogenous NO as an inhibitory modulator on endothelin 1 production (Boulanger & Lüscher 1990; Yokokawa et al 1993). We have recently obtained evidence that an NO synthase inhibitor increases endothelial endothelin 1 mRNA expression by suppression of the endogenous NO/guanyl cyclase/cyclic GMP system (unpublished data). In addition, we noted that a spontaneous NO-donor can

Table 1. Effect on urine formation of intravenous injection of NOARG in the presence or absence of FR139317.

Time (min)	Urine flow (μL g^{-1} min^{-1})	Urinary excretion of sodium (μEq g^{-1} min^{-1})	Fractional excretion of sodium (%)	Urine flow (μL g^{-1} min^{-1})	Urinary excretion of sodium (μEq g^{-1} min^{-1})	Fractional excretion of sodium (%)
	Intravenous injection of vehicle			Intravenous injection of FR139317 (10 mg kg^{-1})		
5–20 (P1)	11·89 ± 1·94	1·86 ± 0·55	1·02 ± 0·24	10·81 ± 1·63	1·38 ± 0·29	0·79 ± 0·10
20–35 (P2)	13·63 ± 1·85	1·68 ± 0·33	0·93 ± 0·13	10·15 ± 1·57	1·37 ± 0·36	1·02 ± 0·26
	Intravenous injection of N^G-nitro-L-arginine (5 mg kg^{-1})					
40–55 (P3)	10·38 ± 1·85	1·41 ± 0·25	1·05 ± 0·21	6·73 ± 0·86	0·99 ± 0·15	0·84 ± 0·14
55–70 (P4)	14·59 ± 3·62	1·13 ± 0·17	0·85 ± 0·11	5·58 ± 0·83	0·95 ± 0·13	0·79 ± 0·24
70–85 (P5)	20·56 ± 5·40	1·77 ± 0·54	1·22 ± 0·20	6·66 ± 1·87	0·76 ± 0·15*	0·61 ± 0·17

Values are means ± s.e.m. of results from six rats. *$P < 0.05$, significantly different from result for period P2.

suppress production of endothelin 1 in endothelial cells (Takada et al 1996). Gratton et al (1997) found that in anaesthetized rabbits a single bolus injection of NO synthase inhibitor at a pressor dose caused an elevation of plasma big endothelin 1 level, probably via stimulation of its synthesis in endothelial cells. Taken together, it seems likely that enhanced production of endothelin 1 in endothelial cells is at least in part involved in the vasopressor responses to an acute blockade of NO synthase, although the mechanism underlying the elevation of vascular tone induced by long-term inhibition of NO synthesis seems not to involve the up-regulation of endothelin 1 activity.

It has been reported that long-term NO synthase-inhibited hypertension in rats was prevented by treatment with an angiotensin II receptor antagonist (Jover et al 1993) or with an angiotensin-converting enzyme inhibitor (Sventek et al 1997) and Beierwaltes & Carretero (1992) noted the increasing effect of inhibition of NO synthase on release of renin from rat renal cortical slices. It thus seems likely that the renin-angiotensin system partly contributes to the elevation of vascular tone in the chronic NO-deficient hypertensive model.

The increase in RVR and a decrease in renal blood flow induced by intravenous injection of NOARG were not affected by pretreatment with FR139317. Thompson et al (1995) also reported that a decrease in renal blood flow as a result of acute inhibition of NO synthase was not affected by subsequent injection of an ET_A receptor antagonist. In addition, FR139317 elicited no alteration of the renal haemodynamics of long-term NOARG-treated rats. These results suggest that action of endothelin via the ET_A receptor does not contribute to the renal vasoconstriction induced by NO synthase inhibition. Several researchers noted that a renal vasoconstrictive response to exogenous endothelin 1 in rats was attenuated by a non-selective endothelin receptor antagonist, but not by an ET_A receptor antagonist (Pollock & Opgenorth 1993; Wellings et al 1994), which suggests that endothelin 1-induced renal vasoconstriction is mediated by ET_B receptor subtypes. Gellai et al (1997) recently reported that an ET_A/ET_B non-selective receptor antagonist, but not a selective ET_A receptor antagonist, suppressed NO synthase inhibitor-induced renal vasoconstriction in rats. Taken together, this evidence implies that an ET_B, rather than ET_A, receptor subtype might be responsible for the renal vasoconstriction induced by blockade of NO synthase.

Intravenous injection of FR139317 induced decreases in urine flow and $U_{Na}V$ in normotensive control rats, as reported elsewhere (Fujita et al 1996a). These antidiuretic and antinatriuretic effects are a result of the agent-induced hypotension, because the same dose of FR139317 does not alter urine production when the renal perfusion pressure is constant (Matsumura et al 1997). FR139317 also tended to reduce urine flow in chronic NO-deficient hypertensive rats, but this effect was smaller than that seen in normotensive rats. It has been reported that chronic NO synthase inhibition leads to attenuation of water and sodium excretory responses to changes in blood pressure (García-Estañ et al 1996). This might account for our observation that the antidiuretic and antinatriuretic responses to FR139317-induced hypotension were attenuated in chronic NOARG-treated rats. This evidence implies that endothelin-mediated actions via the ET_A receptor are not directly responsible for renal tubular function in normotensive and chronic NO-deficient hypertensive rats. We have previously noted that the same dose of FR139317 elicited no alteration of urine formation in DOCA-salt hypertensive rats, despite marked agent-induced hypotension (Fujita et al 1996a). Rather, diuretic and natriuretic responses were observed after administration of FR139317 in this hypertensive model, in which renal perfusion pressure was protected from the agent-induced hypotension by means of an aortic clamp (Matsumura et al 1997), thereby implying that endogenous endothelin contributes to water and sodium retention in DOCA-salt hypertensive rats.

Our results showed that acute NO blockade with NOARG tended to increase urine flow. However, the direct action of NO would be diuretic and natriuretic, because renal arterial administration of an NO synthase inhibitor, at a dose which was without effect on blood pressure, elicited marked reductions in urine flow and $U_{Na}V$ (Baylis et al 1990; Egi et al 1994). NO has been reported to inhibit sodium re-absorption in renal tubules (Stoos et al 1992) and it is likely that the diuretic action of NOARG is a result of the agent-induced marked increase in blood pressure. FR139317 seems to blunt the diuretic response to acute administration of NOARG, possibly via attenuation of pressor response to NOARG.

In conclusion, our results suggest that the action of endothelin via the ET_A receptor contributes to the systemic pressor response to acute NO synthesis inhibition with NOARG, but not to the maintenance of hypertension induced by chronic NO synthase inhibition. Renal functional changes induced by acute or long-term blockade of NO synthase are independent of ET_A receptor-related effects, in contrast with those in other types of hypertensive model, for example DOCA-salt hypertension.

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