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European Journal of Pharmacology 437 (2002) 79–84

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DOI, a 5-HT_2 receptor agonist, induces renal vasodilation via nitric oxide in anesthetized dogs

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Received 16 July 2001; received in revised form 18 December 2001; accepted 21 December 2001

Abstract

We have previously reported that (±)-1-(2.5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-HT_2 receptor agonist, induced renal vasodilation in anesthetized dogs. The present study was designed to investigate whether DOI-induced renal vasodilation might be mediated by increased nitric oxide (NO) release/production in renal tissue. The experiments were performed in anesthetized dogs. A 23-gauge needle was inserted into the left renal artery for infusion of drug solutions. Renal blood flow was measured with an electromagnetic flowmeter. The microdialysis probes were implanted into the renal cortex to collect the dialysate for measurement of guanosine 3′,5′ -cyclic monophosphate (cGMP) and nitrite/nitrate (NO_2/NO_3) concentration. Intrarenal infusion of DOI at a rate of 5 μg/kg/min resulted in a significant increase, by 30 ± 4%, in renal blood flow, indicating renal vasodilation. The renal interstitial concentrations of NO_2/NO_3 and cGMP also increased by 70 ± 6% and 60 ± 6%, respectively. These changes induced by DOI were completely abolished by the intrarenal pretreatment with N^{ω}-nitro-L-arginine methyl ester (L-NAME, a NO synthase inhibitor, 100 μg/kg/min) or sarpogrelate (100 μg/kg/min, a highly selective 5-HT_2 receptor antagonist). DOI infusion increased urine volume and urinary excretion of Na^+, which were also blocked by L-NAME or sarpogrelate. These results suggest that DOI caused renal vasodilation due to increased NO release/production by stimulation of 5-HT_2 receptors in the kidney. The natriuretic effect of DOI might also be related to increased intrarenal NO production.

Keywords: DOI; 5-HT_2 receptor; Renal hemodynamics; Nitric oxide (NO); Sarpogrelate; Microdialysis

1. Introduction

Serotonin (5-hydroxytryptamine: 5-HT) has been well demonstrated to affect renal function (Sole et al., 1986; Shoji et al., 1989). However, reports concerning its renal vascular action vary widely as to both direction and magnitude. Pharmacological doses of 5-HT cause renal vasodilation in dogs and vasoconstriction in rats (Shoji et al., 1989; Cambridge et al., 1995; Verbeke et al., 1996; Moran et al., 1997). It appears that various renal responses to 5-HT may depend on species variation. We have reported that an intrarenal infusion of 5-HT in dogs resulted in a biphasic response of renal blood flow that decreased transiently then increased to above the control level during prolonged infusion. Since the increase of renal blood flow was abolished by infusion of ketanserin or methysergide, we concluded that 5-HT-induced renal vasorelaxation might be mediated via a 5-HT_2 receptor (Shoji et al., 1989). This was further confirmed by the fact that (±)-1-(2.5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a selective 5-HT_2 receptor agonist, produces renal vasodilation in anesthetized dogs (Shoji et al., 1990). However, the mechanisms underlying DOI-induced renal vasodilation remain unclear.

Nitric oxide (NO) is synthesized in the kidney and plays an important role in regulation of renal hemodynamics and function (Baylis and Qin, 1996; Tamaki and Abe, 1994). Inhibition of NO synthase causes a greater reduction in renal blood flow than in glomerular filtration rate with a greater rise in renal vascular resistance (Kiyomoto et al., 1992). In addition, NO modulates the effects of vasoconstrictors on renal hemodynamics (Deng et al., 1994). There have been some reports that 5-HT-induced vasodilation is mediated by increased NO release in endothelial cells of vascular vessels (Verbeuren et al., 1991a) and the release of NO by 5-HT has been considered to be mediated via 5-HT_1 receptors. On the

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0014-2999/02/$ - see front matter
PII: S0014-2999(01)01616-8

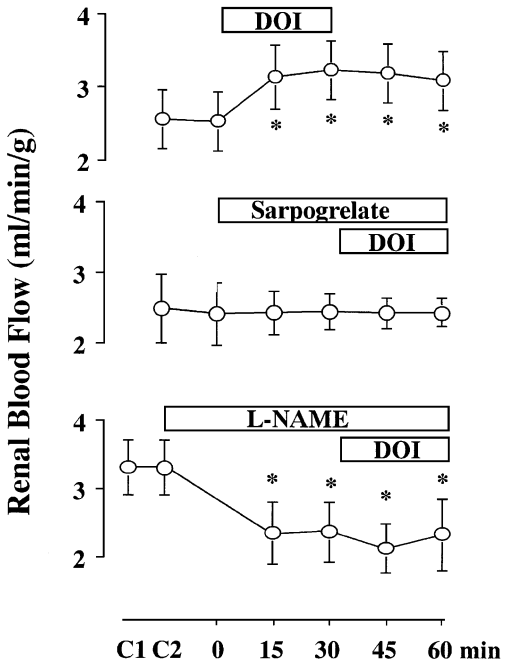

Fig. 1. Effects of DOI (5 μg/kg/min) on the renal blood flow. Upper: Renal blood flow responses to DOI. Middle: Renal blood flow responses to DOI after the pretreatment with sarpogrelate (100 μg/kg/min). Lower: Renal blood flow responses to DOI after the L-NAME pretreatment. C1 and C2 indicate control 1 and control 2, respectively; * indicates significant difference from control 2 ($P<0.05$).

other hand, a recent study by Ishida et al. (1998) has shown that the 5-HT_2 receptor agonist, DOI, stimulates NO release in endothelial cells and produces vasodilation in coronary arteries of rats. Thus, it is still unknown via which receptor subtypes of 5-HT receptor in the renal vasculature NO production is stimulated.

We now hypothesized that DOI-induced renal vasodilation might be mediated via NO release/production. To test this hypothesis, we used an in vivo microdialysis method (Nishiyama et al., 1999a), which allowed us to measure the dynamics of renal interstitial NO under various conditions (Siragy and Carey, 1997; Nishiyama et al., 1999b). Using this method, we investigated the effects of DOI on renal hemodynamics and on the renal interstitial concentrations of guanosine 3′ ,5′ -cyclic monophosphate (cGMP) and nitrite/nitrate (NO_2/NO_3).

2. Materials and methods

2.1. General procedures

All surgical and experimental procedures were performed under the guidelines for the care and use of animals as established by the Kagawa Medical University.

Experiments were carried out with adult mongrel dogs of both sexes weighting 9–13 kg. The animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and artificially ventilated. Catheters were inserted into the right brachial artery and vein for arterial blood sampling and infusion of isotonic saline or for the administration of agents. Isotonic saline was infused at a rate of 0.15 ml/kg/min throughout the experiment. A catheter was placed in the abdominal aorta at the level of the left renal artery bifurcation via the right femoral artery. The renal arterial pressure was considered equal to the aortic pressure and was continuously recorded with a polygraph (NEC-San-ei Model NO. 361, Japan). The left kidney was exposed through a retroperitoneal flank incision. The kidney was carefully denervated by dissecting all visible nerve fibers as well as the tissue connecting the renal hilum cephalic to the renal artery. An electromagnetic flowmeter (MFV-1200, Nihon Kohden, Japan) was positioned around the renal artery and renal blood flow was continuously monitored. A polyethylene catheter was inserted into the left ureter and urine samples were collected at 15-min intervals throughout the experiment. At the midpoint of each period, systemic arterial blood was collected from the right brachial artery. A 23-gauge needle was introduced into the left renal artery proximal to the flow probe for administration of saline or drug solution. A loading

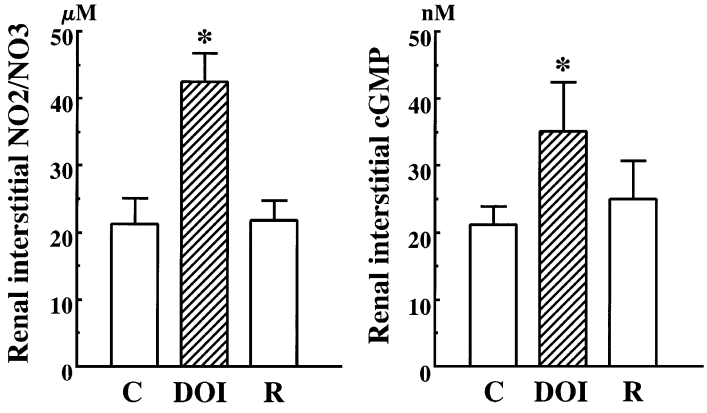

Fig. 2. Effects of DOI (5 μg/kg/min) on the renal interstitial concentrations of NO_2/NO_3 (left side panel) and cGMP (right side panel); * indicates significant difference from C ($P<0.05$). C: control, R: recovery.

dose of creatinine (100 mg/kg) was given intravenously, followed by a maintenance dose of 50 mg/kg/h. Glomerular filtration rate was measured based on creatinine clearance.

The microdialysis probes, which were made in our laboratory, were gently implanted into the renal cortex (Nishiyama et al., 2001). The probes were connected to a microinfusion pump (Carnergie Medicine, Stockholm, Sweden) and were perfused with isotonic saline solution with heparin (30 U/ml) at a rate of 5 μl/min. The dialysates were collected in chilled tubes for measurement of cGMP and NO_2/NO_3 concentration. Samples were stored at −70 °C until analysis. The dialysis membrane of the probe is made from cuprophan with a 5500-Da transmembrane cut-off. The recovery rates of cGMP and NO_2/NO_3 at a perfusion rate of 5 μl/min were 26.9 ± 1.9% and 29.7 ± 3.2%, respectively, as previously reported (Nishiyama et al., 1999b).

At the end of the experiment, the animals were killed with an excess dose of sodium pentobarbital. The kidney was excised to confirm the position of the dialysis membrane. If the membranes were positioned incorrectly in the cortex, we omitted the data from these dialysates.

2.2. Experimental protocols

The experiments were carried out according to the following protocols.

2.2.1. Effects of DOI on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

After two 15-min sampling periods, DOI was infused into the renal artery at a rate of 5 μg/kg/min for 30 min, then a recovery period was allowed for 30 min after cessation of the infusion ($N=8$). The dialysates were collected at 15-min intervals during DOI infusion and after cessation of the infusion.

2.2.2. Effects of DOI with sarpogrelate pretreatment on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

This protocol was designed to clarify whether DOI alters renal hemodynamics and NO release via 5-HT_2 receptor stimulation in seven dogs. After two 15-min control sampling periods, sarpogrelate, a highly selective 5-HT_2 receptor antagonist (Pertz and Elz, 1994), was infused into the renal artery at a rate of 100 μg/kg/min for 30 min, then DOI (5 μg/kg/min) was superimposed to sarpogrelate for an additional 30 min. The dialysates were collected at 15-min intervals during the infusion of sarpogrelate or of DOI plus sarpogrelate infusion.

2.2.3. Effects of DOI with N^w-nitro-L-arginine methyl ester (L-NAME) pretreatment on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

To determine the role of NO in DOI-induced renal vasodilation, we performed this protocol in seven animals. Following two 15-min sampling periods, L-NAME was infused into the renal artery at a rate of 100 μg/kg/min. The dialysates were collected at 30 and 60 min after the start of the L-NAME infusion. Then, DOI (5 μg/kg/min) was superimposed to L-NAME for an additional 30 min. Two dialysates were collected, again at a 15-min interval, after the start of the DOI infusion.

2.3. Analytical procedures

The cGMP in dialysate was measured with radioimmunoassay kits (Amersham, USA). NO_2/NO_3 was analyzed using an automated procedure based on the Griess reaction after reduction of nitrate to nitrite on a cadmium column (Kosaka et al., 1989). Na^+ concentrations in urine and plasma were measured with a flame photometer (Model 750, Hitachi, Japan). Creatinine in the plasma and urine was determined by the method of Bonsnes and Taussky (1945).

2.4. Statistical analysis

All data are expressed as means ± S.E.M. Statistical evaluations of the differences in responses were performed with one-way analysis of variance followed by a Fisher's

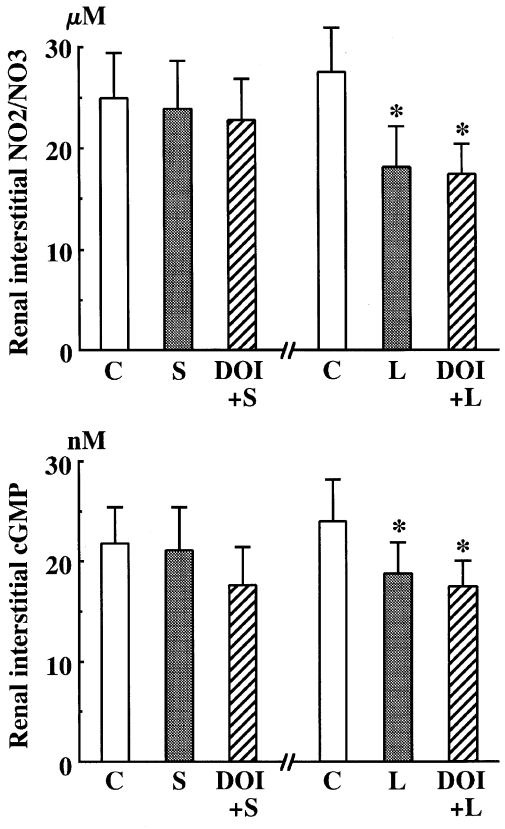

Fig. 3. Effects of DOI (5 μg/kg/min) on the renal interstitial concentrations of NO_2/NO_3 (upper panel) and cGMP (lower panel) after the pretreatment with sarpogrelate (100 μg/kg/min) or L-NAME (100 μg/kg/min); * indicates significant difference from each C ($P<0.05$). C: control, S: sarpogrelate, L: L-NAME.

Table 1
Effects of DOI on renal hemodynamics and urine formation

	MBP (mm Hg)	RBF (ml/g·min)	RVR (mm Hg·g·min/ml)	GFR (ml/g·min)	UF (μl/min)	$U_{Na}V$ (μEq/g·min)
Control	133 ± 5	2.86 ± 0.30	46.5 ± 4.7	0.89 ± 0.09	9.0 ± 1.8	1.07 ± 0.27
DOI	134 ± 6	3.51 ± 0.29[a]	38.1 ± 3.2[a]	0.90 ± 0.08	19.8 ± 4.1[a]	2.32 ± 0.41[a]
Recovery	135 ± 6	3.27 ± 0.28	41.3 ± 4.1	0.89 ± 0.01	11.7 ± 3.4	1.58 ± 0.46
Control	132 ± 5	2.78 ± 0.46	47.5 ± 3.8	0.79 ± 0.06	10.5 ± 3.0	1.55 ± 0.28
Sarpogrelate	132 ± 5	2.74 ± 0.31	48.2 ± 3.9	0.75 ± 0.05	9.8 ± 2.4	1.74 ± 0.39
DOI + Sarpogrelate	131 ± 4	2.72 ± 0.31	48.2 ± 4.2	0.73 ± 0.04	9.4 ± 2.1	1.20 ± 0.25
Control	133 ± 3	3.25 ± 0.42	40.9 ± 4.1	0.79 ± 0.01	9.0 ± 2.8	1.38 ± 0.31
L-NAME	147 ± 3[a]	2.35 ± 0.44[a]	62.7 ± 7.5[a]	0.71 ± 0.08	8.7 ± 3.7	1.17 ± 0.37
DOI + L-NAME	150 ± 4[a]	2.34 ± 0.47[a]	64.1 ± 7.0[a]	0.78 ± 0.08	9.8 ± 3.3	1.50 ± 0.34

All values are means ± S.E.M. MBP: mean blood pressure, RBF: renal blood flow, RVR: renal vascular resistance, GFR: glomerular filtration rate, UF: urine flow, $U_{Na}V$: urinary excretion rate of Na^+.
[a] $P < 0.05$ vs. control.

protected least significant difference test. A *P*-value below 0.05 was considered statistically significant.

3. Results

3.1. Effects of DOI on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

Intrarenal infusion of DOI at a rate of 5 μg/kg/min significantly increased renal blood flow immediately after the start of DOI infusion and maintained the high level of renal blood flow during the infusion (Fig. 1). Since renal arterial pressure did not change, the calculated renal vascular resistance was significantly decreased during DOI infusion. Urine flow was also increased without any change in glomerular filtration rate, indicating an inhibition of Na^+ reabsorption in the tubules (Table 1). DOI significantly increased the renal interstitial concentrations of cGMP and NO_2/NO_3. The concentrations of cGMP and NO_2/NO_3 increased by 70 ± 6 % and 60 ± 6% at 30 min after the start of the infusion, respectively (Fig. 2). After the cessation of DOI infusion, these parameters returned to their respective control level within 30 min.

3.2. Effects of DOI with sarpogrelate pretreatment on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

Intrarenal infusion of sarpogrelate alone did not affect renal arterial pressure, renal blood flow, urine flow or renal interstitial concentrations of cGMP and NO_2/NO_3. During sarpogrelate infusion, DOI did not affect any of the above parameters (Figs. 1 and 3, and Table 1).

3.3. Effects of DOI with L-NAME pretreatment on renal hemodynamics and the renal interstitial concentrations of cGMP and NO_2/NO_3

L-NAME infusion significantly increased renal arterial pressure and decreased renal blood flow (Fig. 1 and Table 1). As a result, renal vascular resistance was increased significantly at 60 min after the start of the infusion. The renal interstitial concentrations of cGMP and NO_2/NO_3 decreased significantly as expected. Superimposition of DOI on L-NAME failed to increase renal blood flow or renal interstitial concentrations of cGMP and NO_2/NO_3 (Fig. 3). The increases in urine flow and urinary excretion of Na^+ induced by DOI were abolished after the L-NAME treatment (Table 1).

4. Discussion

The present study demonstrated that an intrarenal infusion of DOI induced renal vasodilation which was completely abolished by the selective 5-HT_2 receptor antagonist, sarpogrelate, suggesting the involvement of 5-HT_2 receptors in renal vasorelaxation. DOI significantly increased the renal interstitial concentrations of cGMP and NO_2/NO_3, which were diminished by L-NAME. In addition, DOI did not increase renal blood flow after the L-NAME treatment, suggesting that DOI-induced renal vasorelaxation was achieved by the increased NO release/production via 5-HT_2 receptors.

Although the renal vascular response to various 5-HT receptor agonists is controversial (Blackshear et al., 1991; Cambridge et al., 1995), our results demonstrated clearly that stimulation of 5-HT_2 receptors significantly increased renal blood flow, and the increase could not be explained by alterations in systemic hemodynamics, because systemic blood pressure was not changed after DOI infusion and the renal nerves were dissected. Furthermore, the effect was blocked by a selective 5-HT_2 receptor antagonist, indicating involvement of 5-HT_2 receptor in renal vasorelaxation of the dog. These results are consistent with our previous reports (Shoji et al., 1989).

Some studies have shown that the L-arginine-NO pathway in endothelial cells mediates vascular responses to 5-HT (Verbeuren et al., 1991b; Ishida et al., 1998). Our results show that DOI induced renal vasodilation along with the increases of renal interstitial cGMP and NO_2/NO_3 concen-

tration, suggesting that DOI plays a role in the renal vasorelaxation associated with increased NO production. There are three possible explanations for the DOI-induced renal vasodilation. First, DOI might induce renal vasodilation by stimulating other 5-HT receptors except for 5-HT_2, because it has been reported that DOI at a large dose can activate the 5-HT_{1B} receptor (Ishida et al., 1998). This is unlikely, because a highly selective 5-HT_2 receptor antagonist, sarpogrelate, not only blocked the renal hemodynamic effects of DOI but also inhibited the increases in renal interstitial concentrations of cGMP and NO_2/NO_3. Second, DOI might induce renal vasorelaxation via direct stimulation of 5-HT_2 receptors in vascular smooth muscle cells independent of the NO effect. Some studies have shown that stimulation of 5-HT_2 receptors in vascular smooth muscle cells causes a vasoconstrictor response but not vasorelaxation (Verbeuren et al., 1991b). Our results demonstrated that DOI-induced renal vasorelaxation was diminished after L-NAME treatment, suggesting that the effect of DOI was induced via NO. Therefore, it is also unlikely that DOI acts directly on vascular smooth muscle to cause vasorelaxation. Third, DOI might induce vasorelaxation due to the increased NO release/production via stimulation of 5-HT_2 receptors in endothelial cells. This idea is supported by the present results which show that the pretreatment with sarpogrelate or L-NAME abolished DOI-induced renal vasodilation and increases in renal interstitial concentrations of cGMP and NO_2/NO_3. NO is a very powerful renal vasodilator and its progressive vasodilator responses are accompanied by an augmentation of cGMP release (Moncada et al., 1991; Heuze-Joubert et al., 1992). This phenomenon was also observed during DOI infusion in the present study. As now seen in the renal vascular bed, Bruning et al. (1994) and Stroes et al. (1995) demonstrated that 5-HT induces nitric oxide-dependent vasodilation in the human forearm. In addition, Bruning et al. (1994) reported that 5-HT_{1A} receptors are not functionally involved in 5-HT-induced vasodilation.

The L-arginine-NO pathway is an important negative feedback mediator in response to various vasoconstrictors among humoral factors and neural transmitters (Nishida et al., 1998), which participate in the control of local vascular tone. L-NAME decreased renal blood flow as well as renal interstitial concentrations of cGMP and NO_2/NO_3, suggesting that basal NO release/production plays an important role in maintenance of renal blood flow. It has been reported that 5-HT_{1A} receptor in the canine renal artery, or 5-HT_{1B} receptor in the human coronary artery, regulates NO release/production in endothelial cells, which can regulate vascular responses to 5-HT (Verbeuren et al., 1991a; Ishida et al., 1998). To our knowledge, there have been no reports that 5-HT_2 receptors occur in endothelial cells of renal arteries. Our results suggested that DOI induced renal vasorelaxation via activation of 5-HT_2 receptors in endothelial cells. Ullmer et al. (1996) have reported that the 5-HT_{2B} receptor occurs in human pulmonary artery endothelial cells. Therefore, it is likely that 5-HT_2 receptors occur in endothelial cells of the renal artery in dogs, which may participate in pathophysiological regulation of renal hemodynamics. However, sarpogrelate has been demonstrated to show high affinity for the 5-HT_{2A} subtype among 5-HT_2 receptor subtypes (Nishio et al., 1996). Together, these findings allow the assumption that the 5-HT_{2A} receptor as well as the 5-HT_{2B} receptor may occur in enthothelial cells, and that a non-selective 5-HT_2 receptor agonist, DOI, dilates the renal artery, with nitric oxide production, via the 5-HT_{2A} receptor. Further research is necessary to prove the existence of the 5-HT_2 receptor in endothelial cells of renal artery.

The present study showed that an intrarenal infusion of DOI significantly increased urine flow and urinary excretion of Na^+, which were also blocked by L-NAME. One possibility is that the effects of DOI on urine formation were due to increased renal blood flow without any change in glomerular filtration rate. Another possibility is that DOI might stimulate NO production in the renal tubules, which contributes to the increases of urine flow and urinary excretion of Na^+. Many studies have reported that NO plays an important role in the regulation of water and Na^+ excretion in the kidney (Mattson et al., 1994; Manning and Hu, 1994; Hu and Manning, 1995). It has been reported that NO can decrease Na^+ reabsorption by inhibiting Na^+–H^+ exchange and Na^+/K^+-ATPase activity along the nephron (Stoos and Garvin, 1997). Our results showed that DOI significantly increased renal interstitial concentrations of cGMP and NO_2/NO_3. The increased NO might have originated not only from endothelial cells in the renal artery, but also from other sites in nephrons, which contributed to DOI-induced natriuresis.

In conclusion, DOI infusion significantly increased renal blood flow as well as renal interstitial concentrations of cGMP and NO_2/NO_3 in anesthetized dogs, which may have resulted from increased NO production by stimulation of 5-HT_2 receptors in endothelial cells of the renal artery. DOI also increased urinary sodium and water excretion, which may also have been related to increased intrarenal NO production.

Acknowledgements

We are grateful to H. Sakurai and M. Kyo (Toyobo K.K., Japan) for supplying the dialysis membrane and steel needles, and also to Tokyo-Mitsubusi Pharmaceutical for supplying Sarpogrelate. We thank Ms. Y. Ihara and Y. Moriyasu for secretarial service. Ms. J.A. Giffin reviewed this manuscript. This work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Science and Culture of Japan.

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