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Renal effect of YM435, a new dopamine D_1 receptor agonist, in anesthetized dogs

Takeyuki Yatsu [a,*], Yukinori Arai [a], Kenji Takizawa [b], Chieko Kasai-Nakagawa [a], Masahiro Takanashi [a], Wataru Uchida [a], Osamu Inagaki [a], Akihiro Tanaka [a], Masaharu Asano [b], Kazuo Honda [a], Toichi Takenaka [a]

[a] *Cardiovascular Diseases Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305, Japan*

[b] *Clinical Development Division, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki 305, Japan*

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Abstract

The renal effects of YM435 ((−)-(*S*)-4-(3,4-dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride hydrate), a dopamine D_1 receptor agonist, were investigated in anesthetized dogs. Intravenous infusion of YM435 (0.1–3 μg/kg per min) increased renal blood flow and decreased mean blood pressure in a dose-dependent manner with little effect on heart rate. Glomerular filtration rate, urine flow and urinary sodium excretion were concomitantly increased. The renal effect of YM435 by intravenous infusion at 0.3 μg/kg per min was completely blocked by treatment with the selective dopamine D_1 receptor antagonist SCH 23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine hydrochloride). Furthermore, intravenous infusion of YM435 (0.3 μg/kg per min) reversed the angiotensin II-induced decreases in renal blood flow, glomerular filtration rate, urine flow and urinary sodium excretion, and prevented the decrease in renal blood flow, glomerular filtration rate and urine flow induced by renal nerve stimulation and platelet-activating factor (PAF). These results suggest that intravenous administration of YM435 produces renal vasodilating and diuretic/natriuretic effects by stimulation of dopamine D_1 receptors, and demonstrate that YM435 can inhibit angiotensin II-, renal nerve stimulation- and PAF-induced renal dysfunction.

Keywords: YM435; Dopamine D_1 receptor agonist; Renal vasodilator; Angiotensin II; Renal nerve stimulation; PAF (platelet-activating factor)

1. Introduction

It is generally recognized that relatively low doses of dopamine increase glomerular filtration rate, renal blood flow and urinary sodium excretion (McDonald et al., 1964). As a consequence, dopamine is especially useful in the management of low cardiac output states with compromised renal function associated with decreased renal blood flow, such as cardiogenic or hypovolemic shock (Goldberg et al., 1977). At high doses, however, dopamine stimulates α-adrenoceptors and thereby constricts peripheral vascular beds including the renal vascular bed (Makabali et al., 1982). This breadth of receptor activity limits the clinical usefulness of dopamine (Goldberg et al., 1977; Makabali et al., 1982). To reduce the undesirable adrenoceptor and D_2 receptor agonist properties of the naturally occurring agonist dopamine, fenoldopam (Hahn et al., 1982), a dopamine D_1 receptor agonist from a series of benzazepines, has been developed. We have developed YM435 ((−)-(*S*)-4-(3,4-dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride hydrate), a selective and potent dopamine D_1 receptor agonist with a novel chemical structure (Yatsu et al., 1997a,b; Anan et al., 1991, 1996).

In the present study, the renal effect of YM435 was evaluated in anesthetized dogs. Our data demonstrate that YM435 increases renal blood flow, urine flow and urinary sodium excretion by stimulation of dopamine D_1 receptors.

When renal blood flow and/or blood pressure is decreased for any reason, a number of neurohormonal mechanisms, such as the renin-angiotensin system and the sympathetic nervous system and platelet-activating factor (PAF), are activated and the synthesis of angiotensin II and

* Corresponding author. Tel.: (81-298) 52-5111; Fax: (81-298) 52-2955; e-mail: yatsu@yamanouchi.co.jp

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the secretion of norepinephrine are increased (DiBona and Sawin, 1971; Truniger et al., 1971). These vasoactive substances potently constrict the renal vasculature, further worsening renal hemodynamics, and eventually causing renal dysfunction.

Therefore, we determined the effects of YM435 on the changes in renal hemodynamics and function induced by angiotensin II, renal nerve stimulation and PAF.

2. Materials and methods

2.1. General

Mongrel dogs of either sex weighing 8–18 kg were used. The animals were anesthetized by intravenous injection of pentobarbital sodium (30 mg/kg). A constant level of anesthesia was maintained by intravenous infusion of pentobarbital sodium at a rate of 3–5 mg/kg per h. After endotracheal intubation, artificial respiration was performed by means of a respiration pump (SN-480-4; Shinano Seisakusho, Tokyo, Japan) with room air at 18 strokes/min (20 ml/kg tidal volume). The right femoral artery was catheterized for measurement of systemic blood pressure with a pressure transducer (AP-200 T; Nihon Kohden, Tokyo, Japan) and heart rate with a tachometer (AP-600 G; Nihon Kohden) triggered by the arterial pulse wave. The left renal artery and left ureter were exposed by a flank incision using the retroperitoneal approach, and the renal artery was carefully dissected free from surrounding tissue. An electromagnetic blood flow probe (Nihon Kohden) was attached at the renal artery to measure renal blood flow with an electromagnetic flowmeter (MFV-3100; Nihon Kohden). Blood pressure, heart rate and renal blood flow were recorded on a polygraph (RM-6000; Nihon Kohden). A catheter was inserted into the right femoral vein for infusion of YM435 or vehicle (0.9% saline). A polyethylene catheter was inserted into the ureter for urine collection.

2.2. Renal effects

The animal was infused intravenously with 0.9% saline (6 ml/kg per h) throughout the experiments. After an equilibration period, 10-min urine was collected. At the mid-point of each 10-min urine collection period, blood pressure, heart rate and renal blood flow were measured and a blood sample (3 ml) was obtained. After the 10-min baseline clearance period, YM435 (0.1, 0.3, 1 and 3 μg/kg per min) was administered by continuous intravenous infusion in stepwise increasing doses, for 20 min at each dose level, using an infusion pump (STC-521; Terumo, Tokyo, Japan). Urine collection was made over the latter 10 min of infusion at each dose level. Another group of animals received continuous intravenous infusion of 0.9% saline (0.05 ml/kg per min) in place of the YM435 over 80 min to serve as a vehicle control group. In a third group of dogs, intravenous infusion of YM435 (0.3 μg/kg per min for 20 min) was repeated sequentially after dopamine D_1 receptor blockade with SCH 23390 (10 μg/kg per min i.v. bolus + 0.5 μg/kg per min i.v.).

2.3. Effect against renal dysfunction

2.3.1. Effect against angiotensin II-induced renal dysfunction

A curved 25-gauge needle connected to a polyethylene tube was inserted into the renal artery proximal to the flow probe for infusion of angiotensin II. A priming administration of 0.9% saline (8 ml/kg) was given intravenously and immediately followed by a continuous infusion (18 ml/kg per h) throughout the experiments. After a baseline urine collection period, an intrarenal arterial infusion of angiotensin II (0.1 μg/min) was started for 30 min using an infusion pump. Ten minutes after the start of angiotensin II infusion into the renal artery, intravenous infusion of YM435 (0.3 μg/kg per min) or vehicle (0.9% saline, 0.05 ml/kg per min) was started for 20 min using an infusion pump. Ten-minute urine collections were obtained from each animal immediately before and after the start of angiotensin II infusion, and during the latter half of the YM435 (or 0.9% saline) infusion period. At the middle point of each 10-min urine collection period, blood pressure, heart rate and renal blood flow were measured and a blood sample (3 ml) was obtained.

2.3.2. Effect against renal nerve stimulation-induced renal dysfunction

Visible renal nerve bundle along the renal artery was carefully dissected and cut after ligation. For renal nerve stimulation, the distal cut portion was placed on bipolar platinum electrodes connected to an electric stimulator. A priming administration of 0.9% saline (8 ml/kg) was given intravenously and immediately followed by continuous infusion (18 ml/kg per h) throughout the experiments.

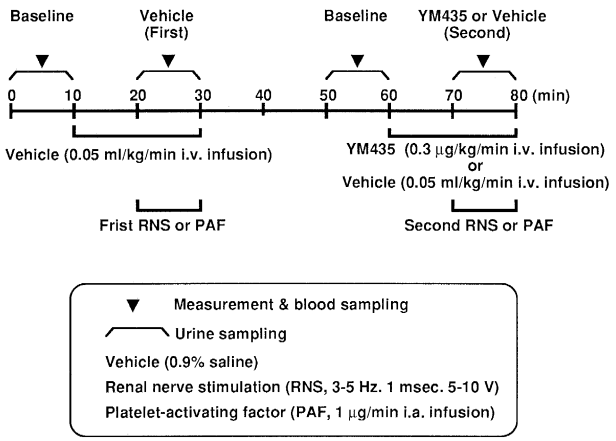

Fig. 1. Experimental protocol.

After a basal urine collection period, vehicle (0.9% saline) was infused intravenously at 0.05 ml/kg per min for 20 min with an infusion pump. At 10 min after the start of intravenous infusion of vehicle, electrical stimulation (5–10 V; duration, 1 ms) was made for 10 min at a frequency of 3–5 Hz. The renal nerve stimulation frequency was adjusted to produce an approximately 40% reduction of the renal blood flow from the baseline value. At 30 min after completion of the first renal nerve stimulation, YM435 (0.3 μg/kg per min) or vehicle (0.9% saline, 0.05 ml/kg per min) was infused intravenously for 20 min. At 10 min after the start of infusion of YM435 or vehicle, a second period of renal nerve stimulation was done for 10 min under identical conditions as the first renal nerve stimula-

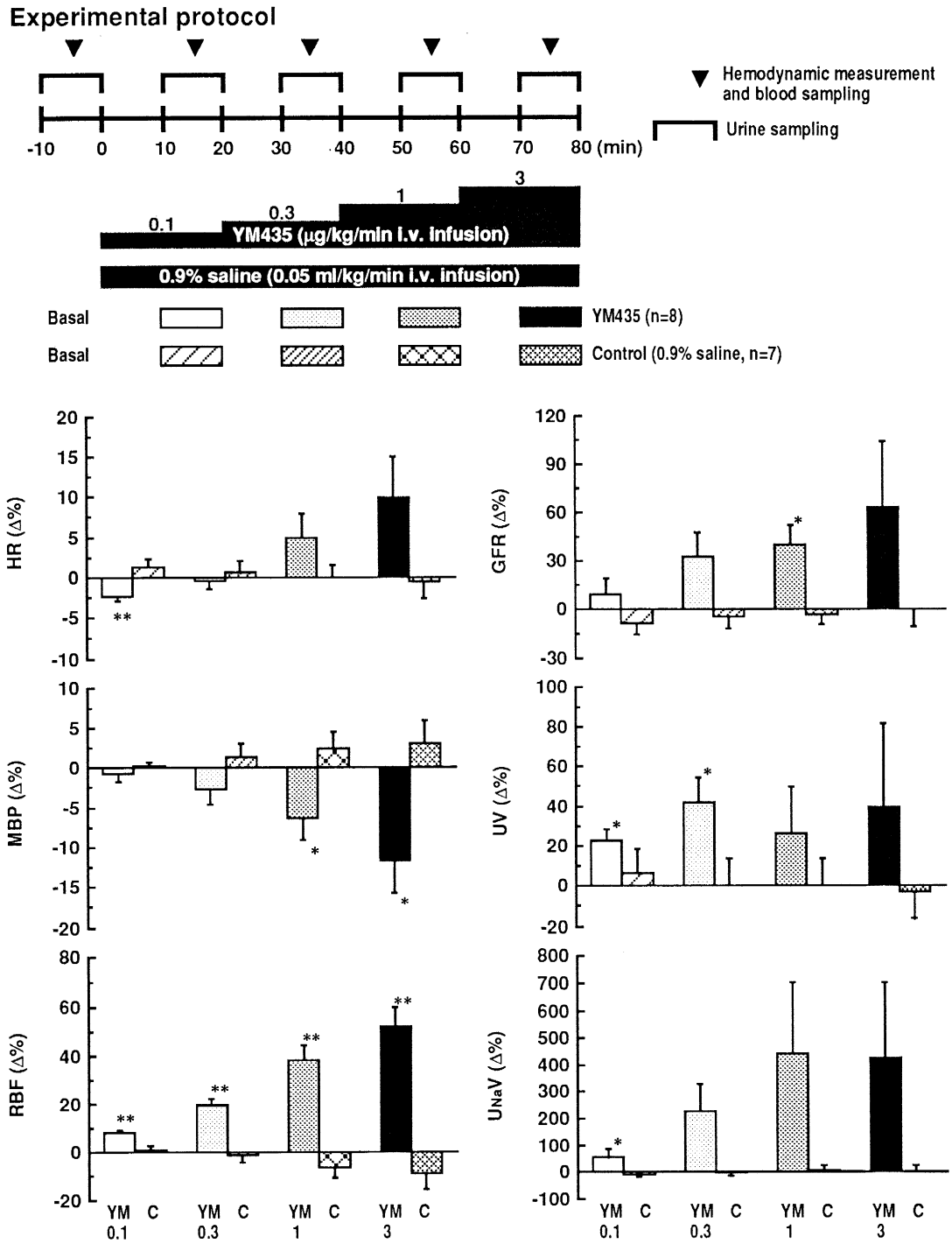

Fig. 2. Effects of YM435 (YM, $n = 8$) and vehicle control (C, $n = 7$) on heart rate (HR), mean blood pressure (MBP), renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) in anesthetized dogs. Columns represent the mean Δ% change ± S.E.M. from baseline values (see Table 1). * $P < 0.05$, ** $P < 0.01$, Student's unpaired *t*-test, YM435-treated groups vs. vehicle controls.

tion. As illustrated in the protocol (Fig. 1), 10-min urine collections were performed 4 times from each animal. Urine samples were collected for 10 min immediately before the start of infusion of vehicle, during the 10 min of the first renal nerve stimulation, for 10 min immediately before the start of infusion of YM435 or vehicle, and during the 10 min of the second renal nerve stimulation. At the middle point of each 10-min urine collection period, blood pressure, heart rate and renal blood flow were measured and a blood sample (3 ml) was obtained.

2.3.3. Effect against PAF-induced renal dysfunction

A curved 25-gauge needle connected to a polyethylene tube was inserted into the renal artery proximal to the flow probe for infusion of PAF. Effects of YM435 on the PAF-induced renal actions were examined in the same manner as for the study on renal nerve stimulation (Fig. 1). In these experiments, PAF (1 μg/min) was infused into the renal artery.

2.4. Analytical measurements

Urinary sodium concentration was determined using a flame photometer (Model 710; Hitachi, Tokyo, Japan), and plasma and urinary creatinine concentration using an auto-analyzer (Model 736; Hitachi). The clearance of endogenous creatinine was calculated by using standard formulas and glomerular filtration rate was estimated from the clearance of endogenous creatinine.

2.5. Drugs and data analysis

YM435 was synthesized at Yamanouchi Pharmaceutical, SCH 23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine hydrochloride) and PAF were purchased from Funakoshi (Tokyo, Japan). Angiotensin II was purchased from Protein Institute (Osaka, Japan). All other chemicals were the best grade commercially available. All data are expressed as the mean ± S.E.M. Between-group differences were analyzed statistically using the Student's unpaired *t*-test. Within-group changes were analyzed statistically using the Student's paired *t*-test. Differences were considered significant at $P < 0.05$.

Table 1
Baseline values of parameters before intravenous infusion of YM435 or vehicle control (0.9% saline)

Parameter	YM435 ($n = 8$)	Control ($n = 7$)
Heart rate (beats/min)	157 ± 9	155 ± 8
Mean blood pressure (mmHg)	138 ± 4	128 ± 8
Renal blood flow (ml/min)	127 ± 14	113 ± 11
Glomerular filtration rate (ml/min)	16.1 ± 1.7	17.9 ± 1.6
Urine flow (ml/min)	0.20 ± 0.08	0.14 ± 0.04
Urinary sodium excretion (μEq/min)	28.6 ± 10.9	29.5 ± 9.3

Values are mean ± S.E.M.

Table 2
Baseline values of parameters before and after treatment with SCH 23390 ($n = 5$)

Parameter	Before treatment with SCH 23390	After treatment with SCH 23390
Heart rate (beats/min)	136 ± 9	130 ± 8
Mean blood pressure (mmHg)	131 ± 6	131 ± 6
Renal blood flow (ml/min)	113 ± 21	125 ± 24
Glomerular filtration rate (ml/min)	17.7 ± 3.1	19.9 ± 3.8
Urine flow (ml/min)	0.40 ± 0.31	0.46 ± 0.33
Urinary sodium excretion (μEq/min)	37.3 ± 17.4	52.1 ± 22.2

Values are mean ± S.E.M.

3. Results

3.1. Renal effect

Baseline values of the parameters before intravenous infusion of YM435 or vehicle control (0.9% saline) are shown in Table 1, with data expressed as percent changes from the baseline value. Fig. 2 illustrates renal and cardio-

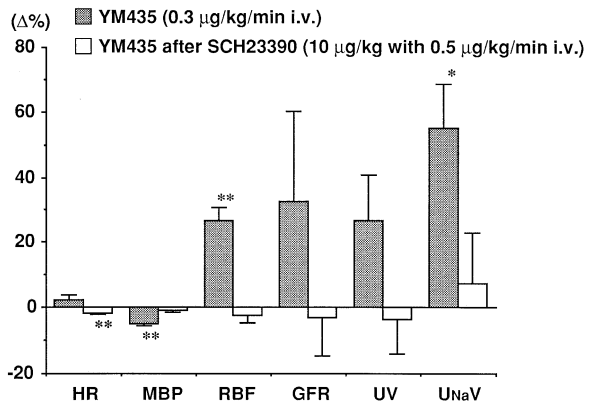

Fig. 3. Effect of YM435 on heart rate (HR), mean blood pressure (MBP), renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) in the absence and presence of the selective dopamine D_1 receptor antagonist SCH 23390 in anesthetized dogs ($n = 5$). Columns represent the mean Δ% change ± S.E.M. from baseline values (see Table 2). * $P < 0.05$, ** $P < 0.01$, Student's paired *t*-test, compared with the values observed before YM435 administration.

Table 3
Baseline values of parameters before infusion of angiotensin II in the YM435 and vehicle groups ($n = 6$)

Parameter	YM435	Vehicle
Heart rate (beats/min)	137 ± 8	121 ± 14
Mean blood pressure (mmHg)	130 ± 5	126 ± 8
Renal blood flow (ml/min)	146 ± 26	176 ± 42
Glomerular filtration rate (ml/min)	20.5 ± 2.3	23.5 ± 4.1
Urine flow (ml/min)	1.04 ± 0.27	0.89 ± 0.18
Urinary sodium excretion (μEq/min)	134.2 ± 42.4	110.6 ± 17.6

Values are mean ± S.E.M.

vascular changes resulting from YM435 (0.1–3 μg/kg per min i.v.) and 0.9% saline (0.05 ml/kg per min i.v.). Intravenous infusion of YM435 at 0.1–3 μg/kg per min increased renal blood flow and decreased mean blood pressure in a dose-dependent manner, with little effect on heart rate. Glomerular filtration rate, urine flow and urinary sodium excretion were concomitantly increased. In the vehicle control (0.9% saline) group, all renal and cardiovascular parameters were mostly stable over the 80-min period of experiments.

Baseline values of the renal and cardiovascular parameters before and after treatment with SCH 23390 are shown in Table 2. As shown in Fig. 3, the renal and cardiovascular effects of YM435 by intravenous infusion at 0.3 μg/kg per min were almost completely inhibited by pretreatment with the selective dopamine D_1 receptor antagonist SCH 23390 (10 μg/kg i.v. bolus + 0.5 μg/kg per min i.v.).

3.2. Effect against renal dysfunction

3.2.1. Effect against angiotensin II-induced renal dysfunction

Baseline values of the parameters prior to the start of angiotensin II infusion in the YM435 group and vehicle group are shown in Table 3, with data expressed as percent change from baseline values. Intrarenal arterial infusion of

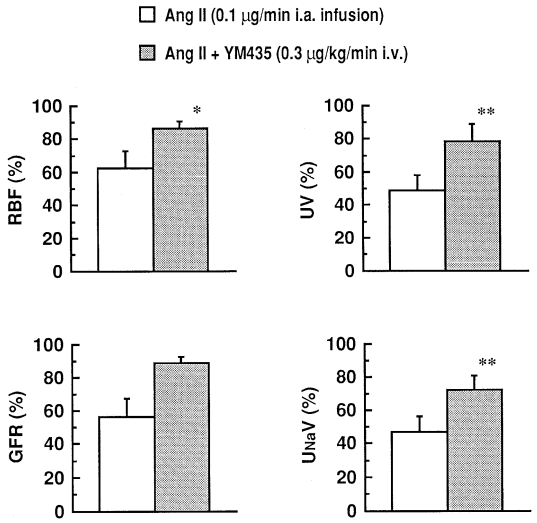

Fig. 4. Effect of YM435 on angiotensin II (Ang II)-induced decreases in renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) in anesthetized dogs ($n = 6$). Columns represent the mean % change ± S.E.M. from baseline values (see Table 3). * $P < 0.05$, ** $P < 0.01$, Student's paired t-test, compared with the values observed before YM435 administration.

angiotensin II (0.1 μg/min) rapidly reduced renal blood flow and also decreased glomerular filtration rate, urine flow and urinary sodium excretion. Intravenous infusion of YM435 (0.3 μg/kg per min) significantly reversed the angiotensin II-induced decreases in renal blood flow, urine flow and urinary sodium excretion (Fig. 4). The decreased glomerular filtration rate by angiotensin II also tended to be reversed but without significance. In the vehicle group, no significant change in the angiotensin II-induced decreases in renal blood flow, glomerular filtration rate, urine flow and urinary sodium excretion was observed following vehicle infusion; the effects by angiotensin II continued throughout the course of experiments (Table 6). Heart rate and mean blood pressure remained relatively stable during the experiment in both YM435 and vehicle groups (data not shown).

3.2.2. Effect against renal nerve stimulation-induced renal dysfunction

Table 4 shows the baseline values of parameters before the first and second renal nerve stimulation in the YM435

Table 4
Baseline values of parameters before the first and second renal nerve stimulation in the YM435 and vehicle groups

Parameter	YM435 ($n = 6$)		Vehicle ($n = 5$)	
	First RNS	Second RNS	First RNS	Second RNS
Heart rate (beats/min)	135 ± 8	126 ± 11	144 ± 18	150 ± 19
Mean blood pressure (mmHg)	135 ± 8	138 ± 10	136 ± 7	140 ± 9
Renal blood flow (ml/min)	115 ± 14	96 ± 7	152 ± 31	147 ± 29
Glomerular filtration rate (ml/min)	17.1 ± 1.3	16.9 ± 1.7	20.6 ± 2.8	20.9 ± 2.4
Urine volume (ml/min)	0.68 ± 0.18	0.45 ± 0.14	0.79 ± 0.23	0.99 ± 0.33
Urinary sodium excretion (μEq/min)	75.6 ± 28.6	49.6 ± 17.7	112.8 ± 25.4	111.4 ± 24.6

Values are mean ± S.E.M. RNS: renal nerve stimulation.

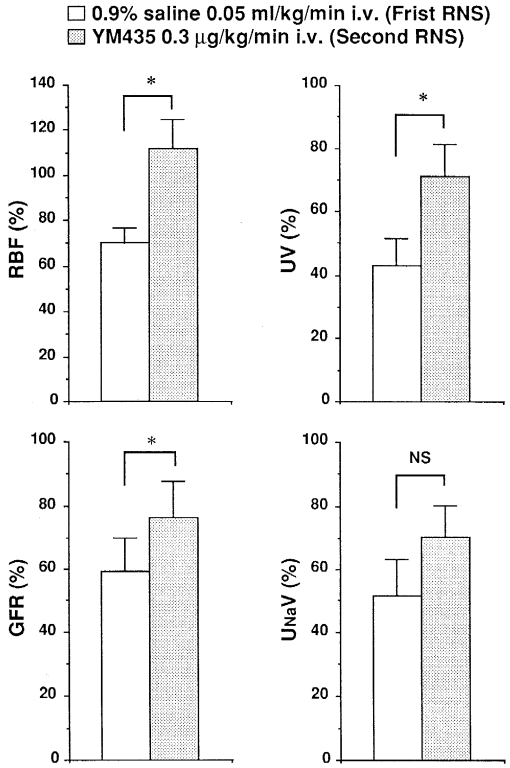

Fig. 5. Effects of YM435 on the decrease in renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) induced by renal nerve stimulation (RNS) in anesthetized dogs ($n = 6$). Columns represent the mean % change ± S.E.M. from baseline values (see Table 4). * $P < 0.05$, Student's paired *t*-test. NS: not significant.

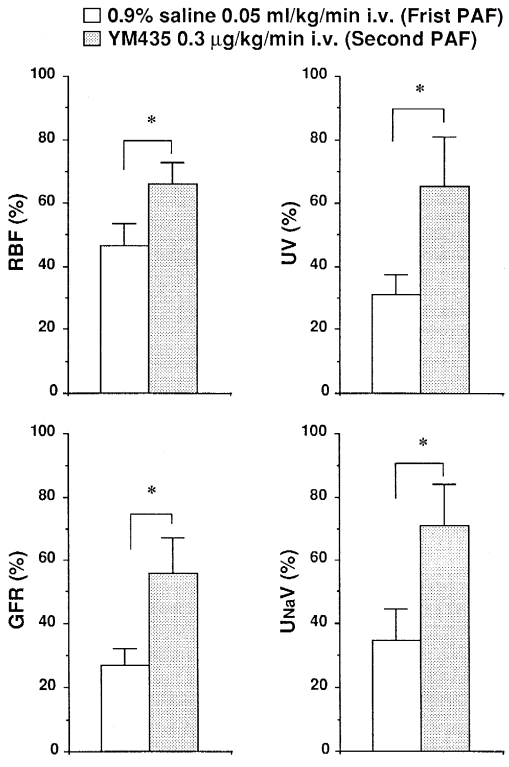

Fig. 6. Effects of YM435 on the decrease in renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) induced by platelet-activating factor (PAF) in anesthetized dogs ($n = 6$). Columns represent the mean % change ± S.E.M. from baseline values (see Table 5). * $P < 0.05$, Student's paired *t*-test.

and vehicle groups. Data are expressed as percent change from baseline values before the first and second renal nerve stimulations. The first renal nerve stimulation for 10 min (3–5 Hz; 5–10 V; duration, 1 ms) produced a decrease in renal blood flow, glomerular filtration rate, urine flow and urinary sodium excretion (Fig. 5). Intravenous infusion of YM435 (0.3 μg/kg per min) significantly prevented this decrease in renal blood flow, glomerular filtration rate and urine flow induced by the second renal nerve stimulation. The decrease in urinary sodium excretion by renal nerve stimulation also tended to be prevented but without significance. In the vehicle group, no significant differences were observed in renal hemodynamic disturbance and renal dysfunction induced by the first and second renal nerve stimulations (Table 6). Therefore, the renal response to renal nerve stimulation was reproducible. Heart rate and mean blood pressure remained relatively stable during the experiments in both the YM435 and vehicle groups (data not shown).

3.2.3. Effect against PAF-induced renal dysfunction

Table 5 shows the baseline values of parameters before the first and second PAF infusions into the renal artery in the YM435 and vehicle groups. Data are expressed as percent change from baseline values before the first and

Table 5
Baseline values of parameters before the first and second PAF infusions in the YM435 and vehicle groups ($n = 6$)

Parameter	YM435		Vehicle	
	First PAF	Second PAF	First PAF	Second PAF
Heart rate (beats/min)	133 ± 8	137 ± 6	126 ± 10	131 ± 6
Mean blood pressure (mmHg)	135 ± 8	139 ± 8	124 ± 7	117 ± 4
Renal blood flow (ml/min)	111 ± 12	90 ± 6	92 ± 9	88 ± 8
Glomerular filtration rate (ml/min)	17.5 ± 1.4	17.1 ± 1.8	12.4 ± 0.6	13.0 ± 0.6
Urine volume (ml/min)	0.62 ± 0.23	0.52 ± 0.21	0.73 ± 0.20	0.48 ± 0.09
Urinary sodium excretion (μEq/min)	57.3 ± 17.9	40.2 ± 10.9	70.7 ± 18.8	55.9 ± 13.4

Values are mean ± S.E.M. PAF: platelet-activating factor.

Table 6
Changes in renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV) and urinary sodium excretion ($U_{Na}V$) induced by angiotensin II, renal nerve stimulation and PAF in vehicle (0.9% saline)-treated groups

Parameter	Angiotensin II ($n = 6$)		RNS ($n = 5$)		PAF ($n = 6$)	
	Alone	+ 0.9% saline	First	Second	First	Second
RBF	78.0 ± 3.0	79.0 ± 3.6	54.4 ± 5.6	58.4 ± 6.7	70.4 ± 6.7	66.1 ± 7.9
GFR	74.2 ± 4.5	85.3 ± 3.6	23.2 ± 7.3	30.2 ± 9.8	44.0 ± 5.9	48.5 ± 5.2
UV	59.0 ± 1.9	58.5 ± 5.8	20.4 ± 8.1	17.6 ± 4.2	40.3 ± 3.7	49.9 ± 4.7
$U_{Na}V$	67.9 ± 1.9	70.7 ± 6.6	18.8 ± 6.4	18.7 ± 3.0	44.0 ± 5.7	50.4 ± 3.8

Values are mean % change ± S.E.M. from basal values (see Table 3Table 4Table 5). RNS: renal nerve stimulation; PAF: platelet-activating factor.

second infusions. The first intrarenal arterial infusion of PAF (1 μg/min) for 10 min produced a decrease in renal blood flow, glomerular filtration rate, urine flow and urinary sodium excretion (Fig. 6). Intravenous infusion of YM435 (0.3 μg/kg per min) significantly prevented the decrease in renal blood flow, glomerular filtration rate, urine flow, and urinary sodium excretion induced by the second PAF infusion. In the vehicle group, no significant differences were observed in renal hemodynamic disturbance and renal dysfunction induced by the first and second PAF infusions (Table 6). Therefore, the renal response to PAF was reproducible. Heart rate and mean blood pressure remained relatively stable during the experiments in both the YM435 and vehicle groups (data not shown).

4. Discussion

There is now good evidence that endogenous renal dopamine plays a physiological role in the handling of sodium by the kidney (Lokhandwala and Hegde, 1990; Lokhandwala et al., 1990). In the present study, YM435 produced natriuresis and diuresis with increased renal blood flow in anesthetized dogs. The renal effect of YM435 was almost completely blocked by treatment with the selective dopamine D_1 receptor antagonist SCH 23390. These results are consistent with previous studies which showed that intrarenal arterial infusion of SCH 23390 reduced sodium excretion and urine flow in conscious dogs (Siragy et al., 1988) and that intrarenal arterial infusion of dopamine caused an increase in renal blood flow and sodium excretion by stimulation of dopamine D_1 receptors in anesthetized dogs (Frederickson et al., 1985). In the kidney, dopamine D_1 receptors have been identified not only in the renal vasculature but also in the proximal renal tubules (Felder and Jose, 1988; Zdilar and Lackovic, 1989). Furthermore, evidence indicates that dopamine and the dopamine D_1 receptor agonist fenoldopam inhibit sodium reabsorption in proximal tubules through inhibition of Na^+/K^+-ATPase and/or the Na^+/H^+ antiporter, suggesting that the effects on sodium transport in proximal tubules are mediated by a dopamine D_1 receptor mechanism (Aperia et al., 1987; Felder et al., 1990; Gesek and Schoolwerth, 1990). YM435 has also been shown to inhibit sodium transport through dopamine D_1 receptors in the rat proximal tubule (Giammattei et al., 1991). The natriuretic and diuretic effects of YM435 may therefore involve dopamine D_1 receptor-mediated changes in renal hemodynamics and proximal tubular sodium reabsorption. Our data suggest that intravenous administration of YM435 produces renal vasodilating and diuretic/natriuretic effects by stimulation of dopamine D_1 receptors.

It is known that renal vasoconstriction caused for any reason induces impairment of renal hemodynamics and function in the kidney. In the present study, we therefore determined the effects of YM435 on the changes in renal hemodynamics and function induced by the vasoconstrictor stimuli such as angiotensin II, renal nerve stimulation and PAF.

Intrarenal arterial infusion of angiotensin II reduced renal blood flow and caused decreases in glomerular filtration rate, urine flow and urinary sodium excretion without affecting the heart rate or mean blood pressure. These results are consistent with a previous study showing that intrarenal arterial infusion of angiotensin II caused dose-related renal vasoconstriction, and decreases in urine flow, urinary sodium excretion, fractional excretion of sodium and glomerular filtration rate in anesthetized dogs (Clark et al., 1993). These findings suggest that angiotensin II-induced renal vasoconstriction causes a decrease in glomerular filtration rate, and that angiotensin II-induced reduction in urine/sodium excretion is probably a consequence of both changes in renal hemodynamics and direct enhancement of renal tubular sodium reabsorption, which together precipitate depression of kidney function. The dopamine D_1 receptor agonist YM435 significantly improved angiotensin II-induced renal dysfunction. Angiotensin II acts in the kidney to cause renal arteriolar constriction and increase proximal tubular sodium reabsorption (Navar et al., 1991; Harris, 1992). The effects of YM435 in the kidney, on the other hand, are renal vasodilation and inhibition of proximal tubular sodium reabsorption (Yatsu et al., 1997a,b; Giammattei et al., 1991; Takenaka et al., 1993). The beneficial effects of YM435 on angiotensin II-induced renal dysfunction are therefore presumably due to functional antagonism by YM435 of the action of angiotensin II on the renal vasculature and renal tubule.

That is, the observed responses were consequent to improvement of renal blood flow and glomerular filtration rate and modification of altered renal hemodynamics via the renal vasodilation by YM435, and also to inhibition of proximal tubular sodium reabsorption by YM435. It has been demonstrated that YM435 dose-dependently reverses angiotensin II-induced afferent and efferent arteriole constriction in the isolated perfused hydronephrotic rat kidney (Takenaka et al., 1993). It therefore follows that the reversal by YM435 of the angiotensin II-induced reduction in renal blood flow observed in this study is attributable to the direct functional antagonism of the compound in renal arterioles.

Electrical stimulation of renal sympathetic nerves reduced renal blood flow and induced decreases in glomerular filtration rate, urine flow and urinary sodium excretion without any effect on heart rate or mean blood pressure. These results are consistent with previous findings that direct renal nerve stimulation at a low frequency (0.5–2.0 Hz) produces renal tubular sodium and water reabsorption with no alteration in renal hemodynamics, while renal nerve stimulation at a higher frequency (> 2.0 Hz) elicits more potent antinatriuresis and antidiuresis, and produces a decrease in renal blood flow and glomerular filtration rate as a result of renal vasoconstriction (DiBona, 1982; Osborn et al., 1983). YM435 significantly prevented the renal hemodynamic disturbance and renal dysfunction induced by renal nerve stimulation. It is therefore considered that the beneficial effects of YM435 on renal nerve stimulation-induced renal dysfunction are presumably due to functional antagonism by YM435 of the renal response to renal nerve stimulation in the renal vasculature and renal tubule. Moreover, we have confirmed that YM435 dose-dependently reversed the increase in renal vascular resistance by exogenous norepinephrine in anesthetized dogs (Yatsu et al., 1997b). Our findings strongly support the hypothesis that the improvement of the renal nerve stimulation-induced decrease in renal blood flow by YM435 may be due to direct functional antagonism of the renal vasoconstriction mediated by norepinephrine released in response to renal nerve stimulation. Intrarenal arterial infusion of norepinephrine-induced acute renal failure in dogs is characterized by low glomerular filtration rate, a secondary effect of renal vasoconstriction with reduced glomerular capillary pressure, and by tubular obstruction (Bruke et al., 1980). Based on this view and our finding that YM435 inhibited the renal response to renal nerve stimulation, it is strongly anticipated that YM435 will be effective against acute renal failure. However, further study is needed to examine the effect of YM435 on acute renal failure.

It is known that PAF is synthesized and released in the kidney (Prewitt et al., 1979; Lopez-Farre et al., 1988). Furthermore, it is reported that intrarenal arterial infusion of PAF reduces renal blood flow without a reduction in blood pressure (Baer and Cagen, 1987). Accordingly, it is considered that PAF acts as a potent vasoconstrictor in the renal vasculature, and that renal vasoconstriction due to PAF may impair renal hemodynamics and deteriorate renal function. Therefore, it is reasonable to consider PAF as a potential mediator of renal injury in pathophysiological states. In the present study, intrarenal arterial infusion of PAF reduced renal blood flow and induced decreases in glomerular filtration rate, urine flow and urinary sodium excretion without any effect on heart rate or mean blood pressure. These results are in agreement with a previous finding that PAF is a potent vasoconstrictor of the canine renal vasculature, and that the infusion of PAF into the renal artery causes dose-dependent reductions in renal blood flow, glomerular filtration rate, urine flow and urinary sodium excretion with no significant alterations in heart rate or mean blood pressure (Sherf et al., 1987). YM435 significantly prevented the renal hemodynamic disturbance and renal dysfunction induced by PAF. It is suggested that PAF may influence the net tubular transport of sodium through mechanisms independent of its actions on renal hemodynamics (Plante et al., 1986). Furthermore, it is also indicated that PAF receptors are expressed in the renal tubule (Jamil et al., 1992). Take together, it is conceivable that PAF-induced renal vasoconstriction causes a decrease in glomerular filtration rate, and that PAF-induced reduction in urine/sodium excretion is probably a consequence of both changes in renal hemodynamics and direct action on renal tubular sodium reabsorption. Therefore, it is considered that the beneficial effects of YM435 on PAF-induced renal dysfunction are presumably due to functional antagonism by YM435 of the action of PAF on the renal vasculature and renal tubule. PAF antagonists are effective in various models of acute renal failure, suggesting that PAF may be involved in the genesis of acute renal failure (Plante et al., 1988; Wang and Dunn, 1987; Lopez-Farre et al., 1990). Based on this view and our finding that YM435 inhibited the renal response to PAF, it is strongly anticipated that YM435 will be effective against acute renal failure. However, further study is required to elucidate the effect of YM435 on acute renal failure.

In conclusion, the results of the present study suggest that intravenous administration of YM435 produces renal vasodilating and diuretic/natriuretic effects by stimulation of dopamine D_1 receptors, and demonstrate that YM435 can inhibit angiotensin II-, renal nerve stimulation- and PAF-induced renal dysfunction.

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