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Antihypertensive activity of a nonpeptide angiotensin II receptor antagonist, YM358, in rats and dogs

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Abstract

The antihypertensive activity of YM358, 2,7-diethyl-5-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-5*H*-pyrazolo[1,5-*b*][1,2,4]triazole potassium salt monohydrate, a new nonpeptide angiotensin II receptor antagonist, was characterized in rats and dogs. In conscious rats, YM358 after a single oral administration (1–30 mg/kg) lowered blood pressure. The rank order of hypotensive potency of YM358 in conscious rats was 2-kidney, 1-clip renal hypertensive rats > spontaneously hypertensive rats > normotensive rats on the basis of maximum hypotension. YM358 also caused decreases in blood pressure in 2-kidney, 1-clip renal hypertensive dogs and furosemide-treated dogs. Repeated administration of YM358 to 2-kidney, 1-clip renal hypertensive rats for 28 days produced a stable and long-lasting antihypertensive effect without influencing circadian blood pressure and heart rate rhythms. No reflex tachycardia was observed in any animals of either species treated with YM358. Therefore, the pharmacological profile of this compound indicates that YM358 has potential as a useful antihypertensive agent. © 1997 Elsevier Science B.V.

Keywords: Angiotensin II receptor antagonist; Antihypertensive activity; YM358

1. Introduction

The therapeutic success of angiotensin I converting enzyme inhibitors has highlighted the importance of the renin–angiotensin system in a number of diseases including hypertension, congestive heart failure and chronic renal failure. However, angiotensin I converting enzyme inhibitors are associated with inherent side effects. These adverse effects, which include dry cough and angioedema are a result of the nonspecific effects of angiotensin I converting enzyme on substrates other than angiotensin I (Skidgel and Erdos, 1987; Williams, 1988). A logical approach to overcoming these effects is the specific blockade of angiotensin II receptors. Recent reports on the discovery of the nonpeptide angiotensin II receptor antagonists losartan and analogues have stimulated extensive research interest into the development of new therapeutic agents for the treatment of cardiovascular diseases (Duncia et al., 1990; Weinstock et al., 1991).

Our efforts into the development of a nonpeptide angiotensin II receptor antagonist led to the discovery of YM358, 2,7-diethyl-5-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-5*H*-pyrazolo[1,5-*b*][1,2,4]triazole potassium salt monohydrate, which was shown to possess potent angiotensin II antagonism in the rabbit aorta assay. We previously showed that YM358 is an orally active, selective and competitive angiotensin II receptor antagonist (Shibasaki et al., 1997). In the present study, to investigate further the therapeutic utility of YM358, we characterized the antihypertensive activity of this compound in both rats and dogs. In addition, we also compared the antihypertensive activity of YM358 with that of the well-characterized angiotensin II receptor antagonist losartan (Wong et al., 1990a,b, 1991).

2. Materials and methods

2.1. Acute hypotensive effect in rats

2.1.1. Hypotensive effect in normotensive rats

Male Wistar rats aged 16–21 weeks, were anesthetized with sodium pentobarbital (60 mg/kg i.p.), and the abdominal aorta was cannulated with a polyethylene tube

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(PE-50) via the left carotid artery. A catheter was passed subcutaneously, exteriorized via the neck, and filled with saline containing heparin. The animals were allowed to recover from surgery for at least 3–4 days before the experiment was begun. The arterial catheter was connected to a pressure transducer (TP-400T, Nihon Kohden, Japan), and mean blood pressure was recorded with a polygraph (RM-6000, Nihon Kohden, Japan). Heart rate was determined on-line using a cardiotachometer (AT-601G, Nihon Kohden, Japan) triggered by the pulse pressure wave. Mean blood pressure and heart rate were measured before and after oral administration of various doses of YM358 or losartan.

2.1.2. Antihypertensive action in renal hypertensive rats

Male Wistar rats aged 5 weeks were anesthetized with sodium pentobarbital (60 mg/kg i.p) and a dorsal incision was made, while the left renal artery was stenosed by application of a silver clip (internal diameter, 0.2 mm). The right kidney was left intact, producing 2-kidney, 1-clip renal hypertensive rats. Four weeks after the renal artery stenosis, blood pressure in the animals was measured directly as described above. Rats with mean blood pressure over 150 mmHg were used.

2.1.3. Antihypertensive effect in spontaneously hypertensive rats

Male spontaneously hypertensive rats aged 17–24 weeks with mean blood pressure of 133–178 mmHg were used. Mean blood pressure and heart rate were measured directly as described above.

2.2. Acute hypotensive effect in dogs

2.2.1. Hypotensive effect in sodium-depleted dogs

Beagle dogs of either sex weighing 8.0–13.5 kg were used. The animals were anesthetized with sodium thiopental (30 mg/kg i.v.). Anesthesia was maintained with 0.5–1% halothane in oxygen and room air during surgical operation. Under sterile surgical procedures, the right femoral artery was exposed. The abdominal aorta was cannulated with a polyvinyl tube (internal diameter 0.8 mm, Imamura, Japan) via the femoral artery. The catheter was passed subcutaneously, exteriorized via the neck, and filled with saline containing heparin. The skin incision was closed and the dog allowed to recover from surgery for at least 3–4 d. The dogs received an intramuscular dose and intravenous dose of furosemide (10 mg/kg) at 16 h and 2 h before the administration of test drugs, respectively. The animals were deprived of water from 18 h before to 8 h after dosing. The arterial catheter was connected to a pressure transducer (TP-400T, Nihon Kohden, Japan), and mean blood pressure was recorded with a polygraph (RM-6200, Nihon Kohden, Japan). Heart rate was determined on-line using a cardiotachometer (AT-601G, Nihon Kohden, Japan) triggered by the pulse pressure wave. Mean blood pressure and heart rate were measured before and after oral administration of various doses of YM358 or losartan.

2.2.2. Antihypertensive effect in renal hypertensive dogs

Beagle dogs of either sex weighing 7.0–13.5 kg were used. The animals were anesthetized as described above. A dorsal incision was made, and the left renal artery was ligated with a silver ribbon such that renal blood flow as measured with an electromagnetic blood flowmeter (MFV-3100, Nihon Kohden, Japan) was reduced by 60–80%. The right kidney was left intact to produce 2-kidney, 1-clip renal hypertensive dogs. Four weeks after renal artery ligation, blood pressure in the animals was measured directly as described above. Dogs with systolic blood pressure over 160 mmHg were used.

2.3. Chronic antihypertensive effect in renal hypertensive rats

Male Wistar rats aged 5 weeks were anesthetized with sodium pentobarbital (60 mg/kg i.p). A dorsal incision was made, and the left renal artery was stenosed by applying a silver clip (internal diameter, 0.2 mm). The right kidney was left intact to produce 2-kidney, 1-clip renal hypertensive rats. Blood pressure and heart rate were measured by a telemetry system. The system consists of 4 parts: a battery-operated transmitter, a receiver, a pressure reference module and data acquisition software (Dataquest III; Data Science, St. Paul, MN) running on an IBM PC/AT compatible computer. The battery-operated transmitter was placed in the abdominal cavity in each rat 1 week after the renal artery stenosis under sodium pentobarbital (60 mg/kg i.p.) anesthesia. Blood pressure was measured via the cannula inserted into the descending aorta. The output from the transmitter was monitored with the receiver. The telemetered pressure data were collected with a computer (386AX model A, Kyocera, Japan), converted into millimeters of mercury units, and adjusted for atmospheric pressure.

Sampling time of the pressure signal was 5 s. Mean blood pressure and heart rate were measured on a beat-by-beat basis. The data were collected every 20 min to obtain mean values for the analysis of the diurnal variability. The 24 h mean values of mean blood pressure and heart rate were presented as the average of 72 points (3 points/h × 24 h) for the evaluation of chronic treatment with drugs. Each rat was placed in an activity cage inside a cabinet under of 13 h light cycle (5:30–18:30). Four weeks after renal stenosis, rats showing hypertension and circadian rhythm in blood pressure were selected for use. Drugs were orally administered once a day at 17:30 for 4 weeks.

2.4. Effect on the renin–angiotensin–aldosterone system in normal rats

Male Wistar rats aged 13–15 weeks were anesthetized with sodium pentobarbital (60 mg/kg i.p.), and the ab-

dominal aorta was cannulated with a polyethylene tube (PE-50) via the left carotid artery. The catheter was passed subcutaneously, exteriorized via the neck, and filled with saline containing heparin. The animals were allowed to recover from surgery for at least 3–4 days before beginning the experiment. A single sample of arterial blood was taken from each rat via the catheter at the indicated time after oral dosing of the drug.

Blood samples were transferred to a tube containing disodium EDTA as anticoagulant and centrifuged at 1000 $\times g$ for 10 min at 4°C. The plasma was separated and stored frozen (−20°C) until plasma renin activity and plasma aldosterone concentration were measured. The plasma renin activity and plasma aldosterone concentration were measured by radioimmunoassay using a renin activity assay Kit (Sorin Biomedica RIA Kit, Saluggia, Italy) and an aldosterone assay Kit (Aldosterone RiakitII, Dainabot, Japan).

All experiments were performed under the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical.

2.5. Drugs

YM358 and losartan were synthesized in Institute for Drug Discovery Research, Yamanouchi Pharmaceutical, Japan. The drug was suspended in a 0.5% methylcellulose solution and administered by oral gavage in a volume of 5 ml/kg for rats and 1 ml/kg for dogs.

2.6. Statistical analysis

The results are expressed as the mean ± S.E.M. Statistical analysis of the data was performed using one way analysis of variance. When overall statistical significance was achieved ($P < 0.05$), the Dunnett multiple range test was used to compare each of the doses to the vehicle control. Probability values less than 0.05 were considered to be significant.

Table 1
Pretreatment values of mean blood pressure and heart rate in normotensive rats, spontaneously hypertensive rats and 2-kidney, 1-clip renal hypertensive rats

Rat	*n*	Mean blood pressure (mmHg)	Heart rate (beats/min)
normotensive	20	107 ± 1	343 ± 4
spontaneously hypertensive	24	155 ± 3 [a]	342 ± 4
2-kidney, 1-clip renal hypertensive	40	169 ± 3 [a]	374 ± 6 [a]

[a] $P < 0.01$, significantly different from the normotensive rats.

3. Results

3.1. Acute hypotensive effect in rats

Baseline mean blood pressure and heart rate in rats are shown in Table 1. The mean blood pressures in 2-kidney, 1-clip renal hypertensive rats and spontaneously hypertensive rats were significantly higher than that in normotensive rats, but no significant difference in heart rate was observed in these animals.

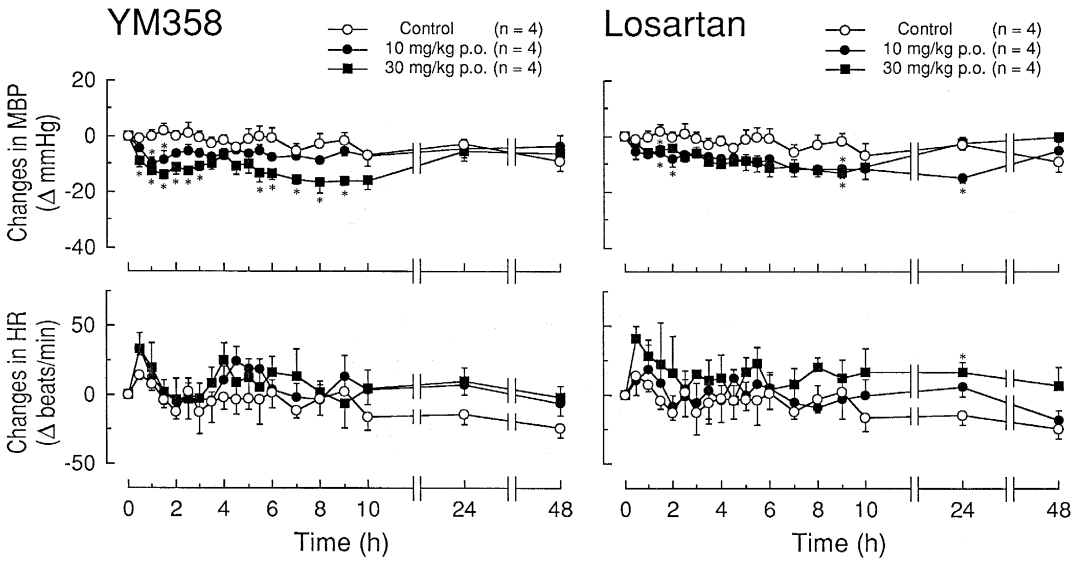

Fig. 1. Effect of YM358 and losartan on mean blood pressure and heart rate in conscious normotensive rats. * $P < 0.01$, significantly different from the control values.

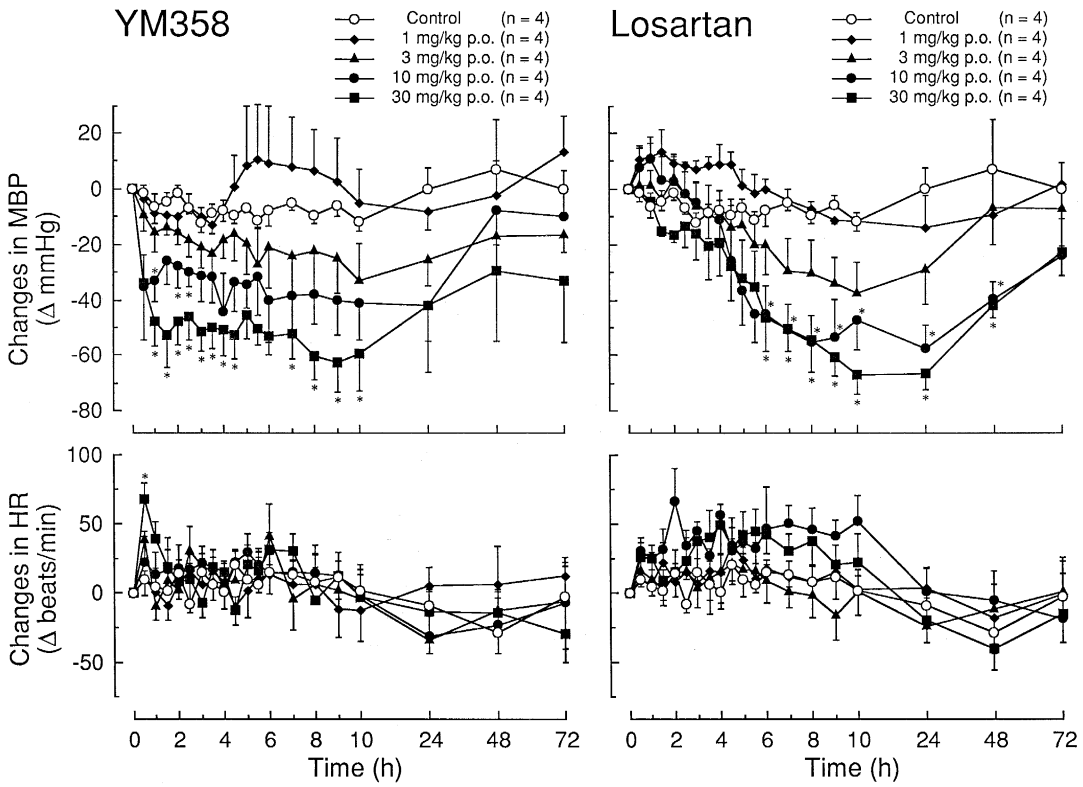

Fig. 2. Effect of YM358 and losartan on mean blood pressure and heart rate in conscious 2-kidney, 1-clip renal hypertensive rats. * $P < 0.01$, significantly different from the control values.

3.1.1. Hypotensive effect in normotensive rats

YM358 (10 and 30 mg/kg p.o.) slightly but significantly decreased mean blood pressure without affecting heart rate in conscious normotensive rats (Fig. 1). Losartan (10 and 30 mg/kg p.o.) also slightly decreased mean blood pressure without causing any change in heart rate.

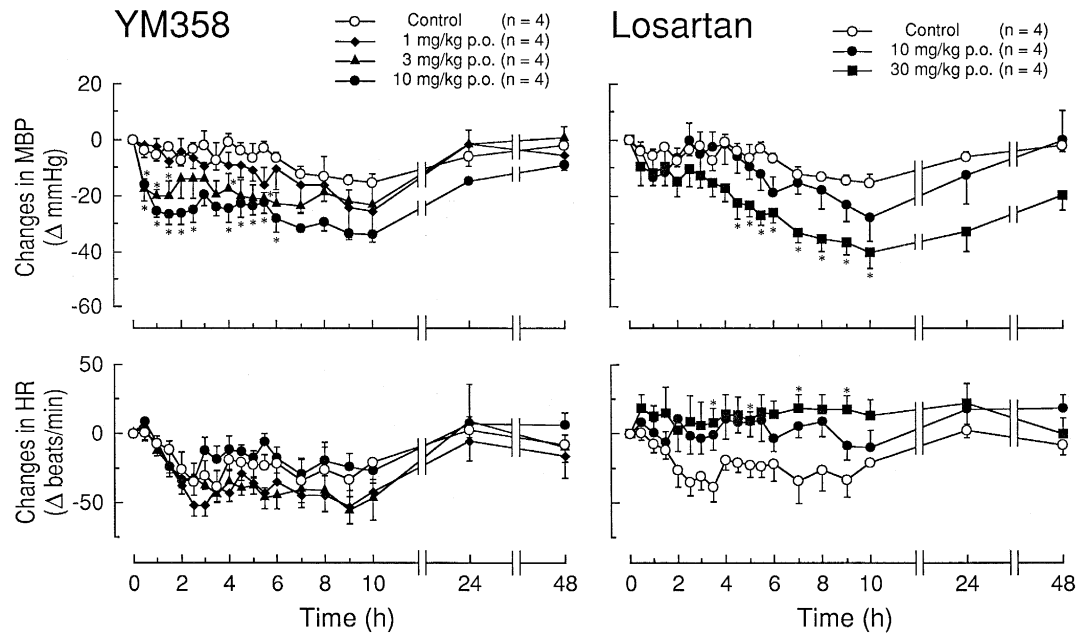

Fig. 3. Effect of YM358 and losartan on mean blood pressure and heart rate in conscious spontaneously hypertensive rats. * $P < 0.01$, significantly different from the control values.

3.1.2. Antihypertensive effect in 2-kidney, 1-clip renal hypertensive rats

Plasma renin activity in 2-kidney, 1-clip renal hypertensive rats ($n = 12$) at 4 weeks of renal artery stenosis was 28.6 ± 7.0 ng angiotensin I/ml per h, significantly higher than that in normotensive rats ($n = 8$, 7.0 ± 1.1 ng angiotensin I/ml per h). Oral administration of YM358 (1–30 mg/kg) produced a significant and dose-dependent decrease in mean blood pressure in conscious 2-kidney, 1-clip renal hypertensive rats but there was no change in heart rate (Fig. 2). Losartan (1–30 mg/kg p.o.) also lowered mean blood pressure in a significant and dose-dependent manner without affecting heart rate. YM358 first decreased mean blood pressure significantly after oral administration of 10 mg/kg and 30 mg/kg was at 1 h and 3 h, respectively. On the other hand losartan lowered mean blood pressure significantly from 6 h and 8 h after oral administration of 10 mg/kg and 30 mg/kg, respectively, indicating that the onset of hypotensive effect of oral YM358 was more rapid than that of losartan. The antihypertensive activity of YM358 at 30 mg/kg p.o. was maintained for over 24 h.

3.1.3. Antihypertensive effect in spontaneously hypertensive rats

In spontaneously hypertensive rats, YM358 (1–10 mg/kg p.o.) decreased mean blood pressure in a significant and dose-dependent manner without affecting heart rate (Fig. 3). Losartan (1–30 mg/kg p.o.) also produced a significant and dose-dependent decrease in mean blood pressure, but unlike YM358 with a slow onset of the effect. In contrast to YM358, heart rate in the losartan treated rats was increased significantly.

Table 2
Pretreatment values of mean blood pressure and heart rate in sodium-depleted dogs and 2-kidney, 1-clip renal hypertensive dogs

Dog	*n*	Mean blood pressure (mm Hg)	Heart rate (beats/min)
Sodium-depleted	21	107 ± 3	116 ± 5
2-kidney, 1-clip renal hypertensive	32	125 ± 2	126 ± 4

3.2. Acute hypotensive effect in dogs

Baseline mean blood pressure and heart rate in dogs are shown in Table 2.

3.2.1. Hypotensive effect in sodium-depleted dogs

Conscious sodium-depleted dogs showed a significant increase in plasma renin activity (from 1.1 ± 0.4 to 10.3 ± 0.8 ng angiotensin I/ml per h, $n = 11$) but no appreciable change in mean blood pressure. As shown in Fig. 4, YM358 (10 and 30 mg/kg p.o.) decreased mean blood pressure in a significant and dose-dependent fashion without any effect on heart rate. The hypotensive effect of YM358 at 30 mg/kg p.o. lasted significantly for more than 8 h. Losartan (10 and 30 mg/kg) also decreased

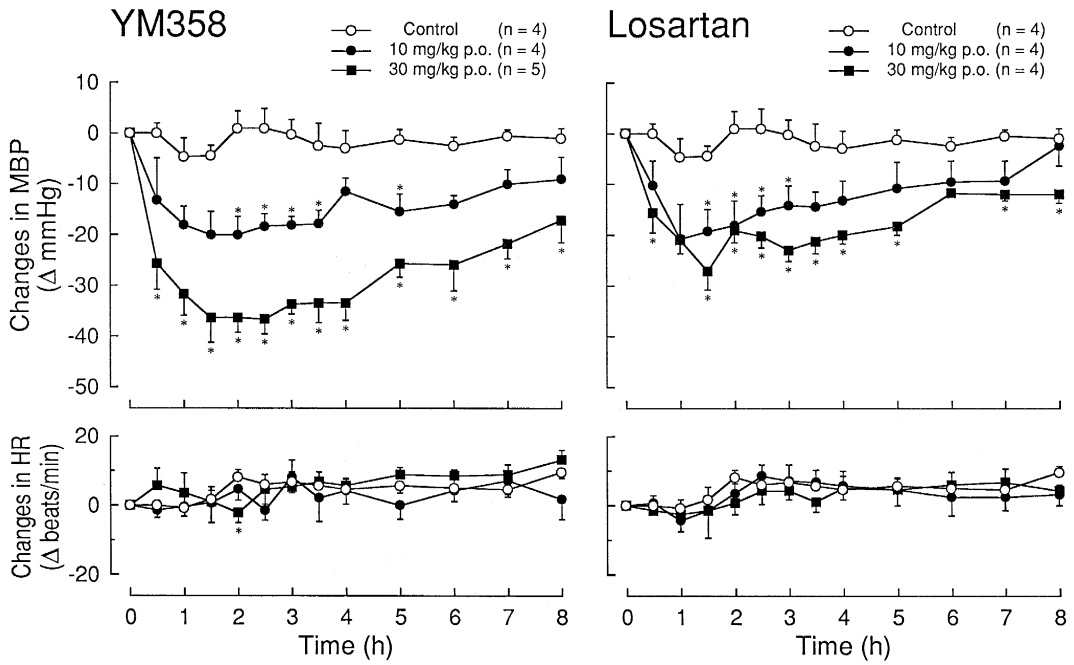

Fig. 4. Effect of YM358 and losartan on mean blood pressure and heart rate in conscious sodium-depleted dogs. * $P < 0.01$, significantly different from the control values.

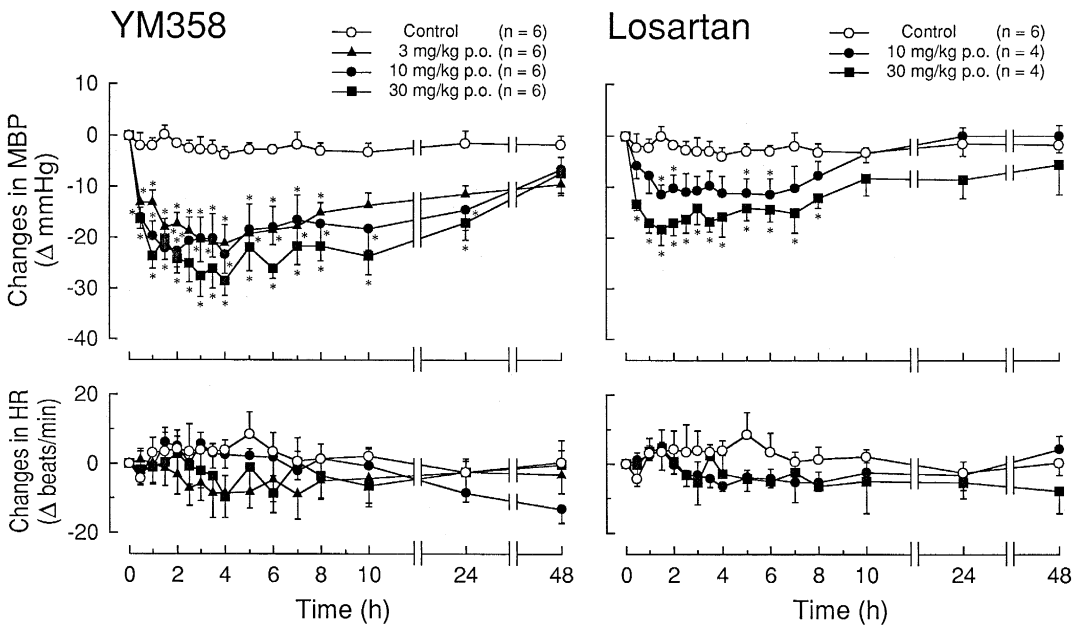

Fig. 5. Effect of YM358 and losartan on mean blood pressure and heart rate in conscious 2-kidney, 1-clip renal hypertensive dogs. * $P < 0.01$, significantly different from the control values.

mean blood pressure significantly without affecting heart rate. Compared to the effect of YM358, the maximum decrease in mean blood pressure was smaller and the duration of effect was shorter, but these differences were not statistically significant.

3.2.2. Antihypertensive effect in 2-kidney, 1-clip renal hypertensive dogs

Before renal artery stenosis, plasma renin activity in conscious 2-kidney, 1-clip renal hypertensive dogs was 2.5 ± 0.3 ng angiotensin I/ml per h ($n = 18$). Three days

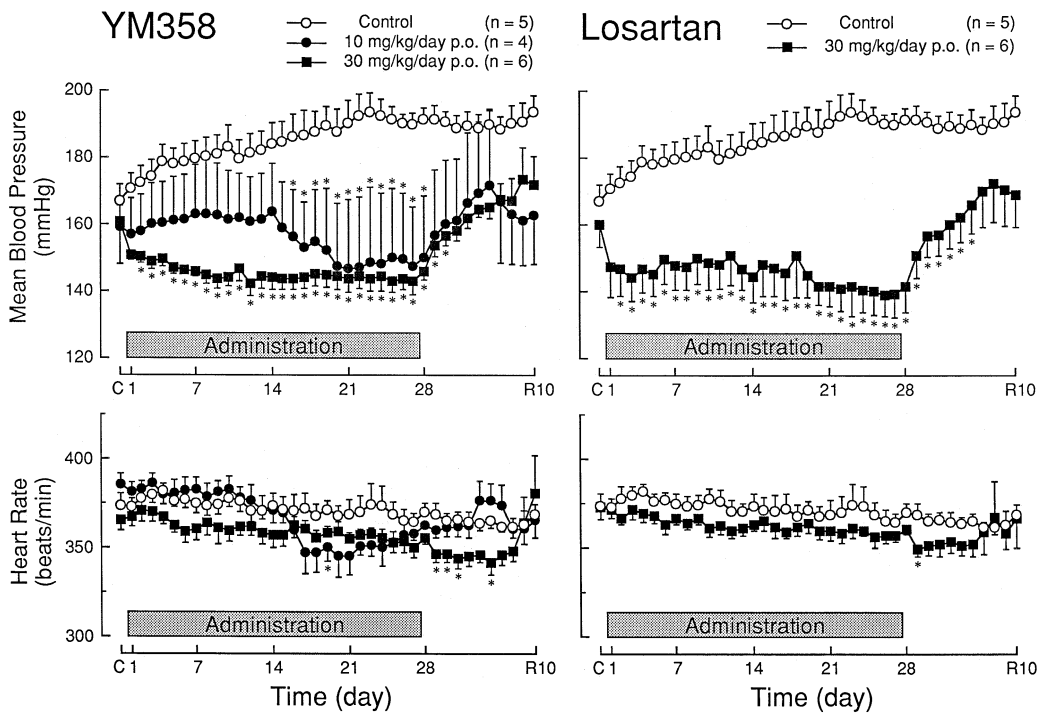

Fig. 6. Effect of repeated daily oral administration of YM358 or losartan on mean blood pressure and heart rate in conscious, unrestrained 2-kidney, 1-clip renal hypertensive rats. These parameters were measured with a telemetry system. Each point represents the 24 h mean value of mean blood pressure and heart rate. C1; the day before the start of administration. R10; 10 days after the cessation of administration. * $P < 0.01$, significantly different from the control values.

after stenosis, plasma renin activity was increased significantly to 5.3 ± 0.6 ng angiotensin I/ml per h, and after 4 weeks was slightly increased (2.9 ± 0.4 ng angiotensin I/ml per h), but not significantly. Baseline mean blood pressure in these animals was increased to 125 ± 2 mmHg (Table 2). YM358 (3–30 mg/kg p.o.) decreased mean blood pressure in a significant and dose-dependent manner without any effect on heart rate (Fig. 5). The antihypertensive effect persisted significantly for over 8 h even at a dose of 3 mg/kg p.o. Losartan (10 and 30 mg/kg p.o.) also produced a significant and dose-dependent decrease in mean blood pressure, and based on the hypotensive effect at 30 mg/kg p.o. the maximal effect (−18.3 ± 3.3 mmHg at 1.5 h after dosing) was significantly smaller than that of YM358 (−28.6 ± 2.8 mmHg at 4 h after dosing) and the duration of effect (significant until 8 h after dosing) was significantly shorter than that of YM358 (significant until 24 h after dosing).

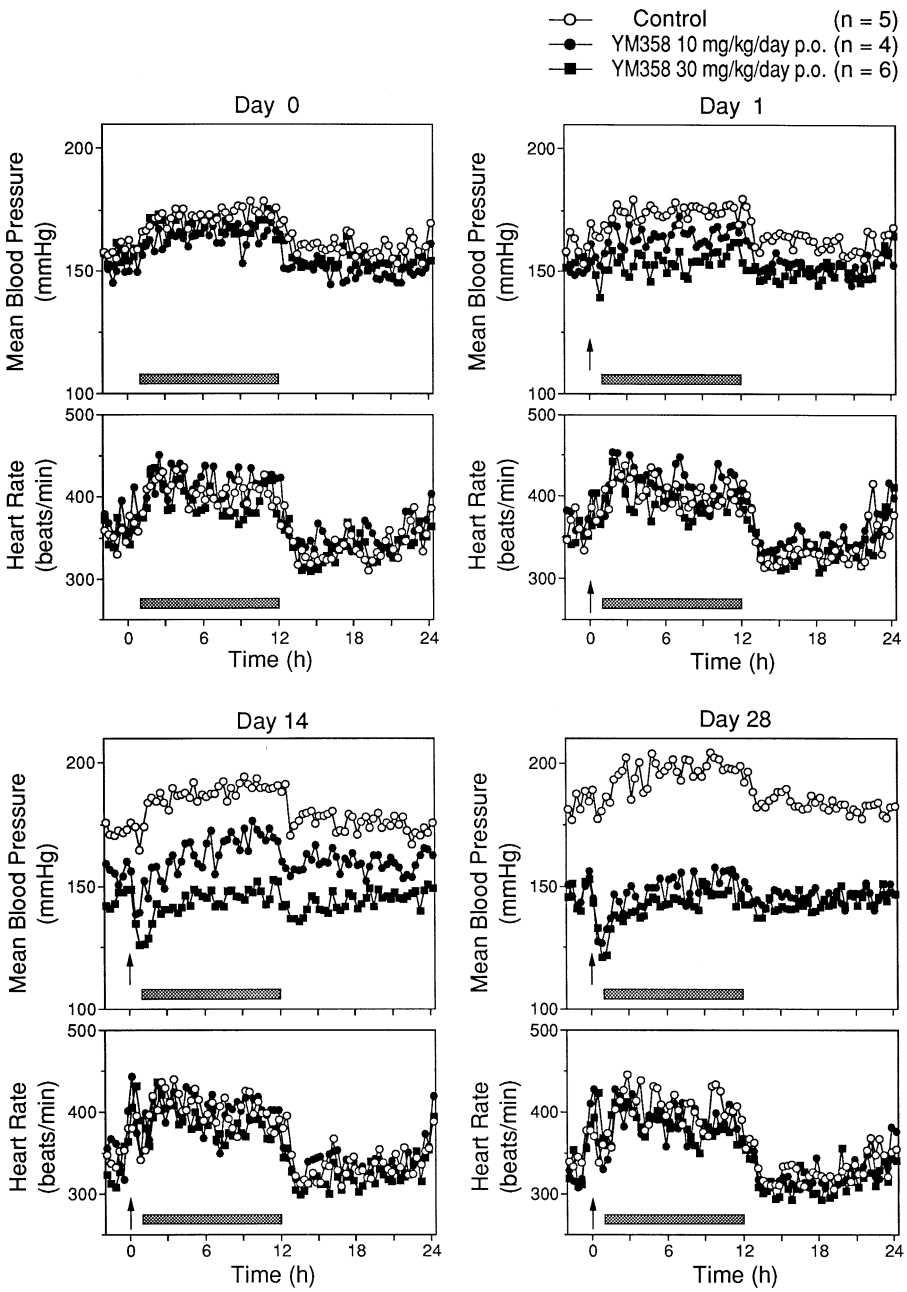

Fig. 7. Time sequence data of mean blood pressure and heart rate after single administration of YM358 in conscious and unrestrained 2-kidney, 1-clip renal hypertensive rats. These parameters were measured with a telemetry system. Each point represents the 20 min mean value of mean blood pressure and heart rate. Day 0; the day before the start of administration, Day 1, 14, 28; the 1st, 14th and 28th day after the start of administration. Shadow column: darkness (light off). Vertical arrow; the time of administration.

3.3. Chronic antihypertensive effect in 2-kidney, 1-clip renal hypertensive rats

In 2-kidney, 1-clip renal hypertensive rats implanted with the telemetry transmitter, YM358 (10 and 30 mg/kg per day p.o.) decreased mean blood pressure significantly without affecting heart rate (Fig. 6). The antihypertensive effect of YM358 at 30 mg/kg per day gradually increased over the first 7 days of administration and thereafter remained rather constant until completion of the 28 day period, indicating no development of drug tolerance. In 10 mg/kg per day group, antihypertensive activity increased from day 14 of administration onwards and from day 21–28 it was similar to that of 30 mg/kg. Similarly, Losartan (30 mg/kg p.o) decreased mean blood pressure without any effect on heart rate. In the vehicle treated rats, mean blood pressure and heart rate were higher during darkness than during the light period, indicating the diurnal pattern of these parameters (Fig. 7). The antihypertensive effect of YM358 was sustained over 24 h daily from day 14 of administration onwards, and no effect on circadian variations of mean blood pressure and heart rate was observed during the experiment period.

3.4. Effect on the renin–angiotensin–aldosterone system in normal rats

In normal rats, YM358 (0.3–30 mg/kg p.o.) produced a significant and dose-dependent increase in plasma renin activity, but no effect on plasma aldosterone concentration was observed (Fig. 8). The increase in plasma renin activity was maximal at 1 h after dosing and disappeared by 24 h after dosing. Plasma renin activity was similarly increased in a dose-dependent manner with losartan, with this effect being marked at 1 h and 5 h after dosing.

4. Discussion

The present study describes the antihypertensive properties of the non-peptide angiotensin II receptor antagonist, YM358. In acute experiments in rats, the rank order of maximum hypotensive potency of YM358 was 2-kidney, 1-clip renal hypertensive rats > spontaneously hypertensive rats > normotensive rats. In particular, its antihypertensive effect in 2-kidney, 1-clip renal hypertensive rats was marked and sustained, indicating this to be a model of renin-dependent hypertension as indicated by the elevation of plasma renin activity. YM358 also induced a dose-dependent decrease in blood pressure in spontaneously hypertensive rats, even though this rat is normoreninemic. This antihypertensive effect in spontaneously hypertensive rats may be due to the effective blockade of angiotensin II produced by the tissue renin angiotensin system, as described previously (Dzau, 1986). Moreover, YM358 slightly but significantly decreased blood pressure in normotensive rats, suggesting that the renin angiotensin sys-

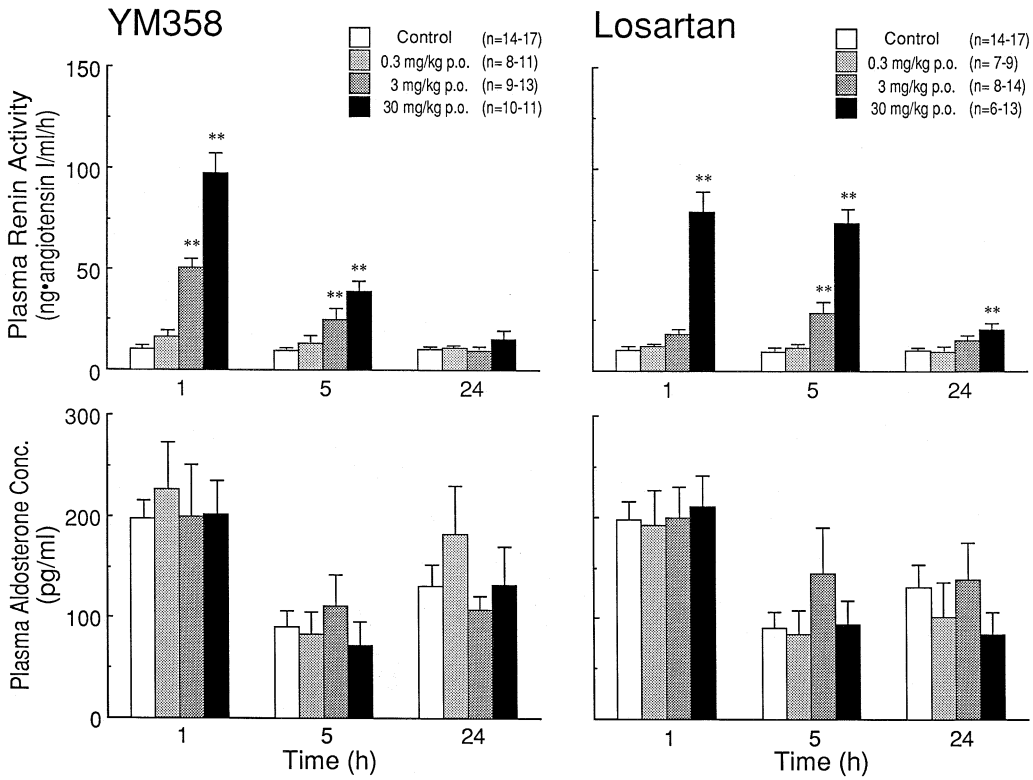

Fig. 8. Effects of YM358 and losartan on plasma renin activity and plasma aldosterone concentration in conscious normotensive rats. ** $P < 0.01$, significantly different from the control values.

tem, in particular the tissue renin angiotensin system, plays a role in the maintenance of blood pressure at normotensive levels. The antihypertensive activity of YM358 in rats was characterized by the normalization of blood pressure with a rapid onset and a long duration of effect. In contrast, the onset of antihypertensive response was slower with losartan, presumably due to the delay incurred in the metabolism of losartan to its active component, EXP3174 (Wong et al., 1990c).

In acute studies in dogs, we examined the ability of YM358 to decrease blood pressure in two models, the renal artery-ligated dog and the furosemide-treated dog. Furosemide treatment induced an increase in plasma renin activity and, presumably an increase in plasma angiotensin II to maintain blood pressure at normotensive levels. In both models, YM358 produced a dose-dependent decrease in blood pressure in the same dose range. Whereas the antihypertensive activity of YM358 was similar in dogs to that in rats, that of losartan in dogs was extremely modest compared to that in rats. This species difference in the hypotension of losartan may involve its active metabolite, EXP3174: while EXP3174 may be responsible for much of its antihypertensive activity, it may not be produced in the dog. A species difference in the metabolism of losartan has also been suggested by Wong et al. (1991).

It is well known that normotensive subjects show a circadian rhythm in blood pressure (Millar et al., 1978). However, this pattern tends to disappear in hypertensive patients, and high blood pressure tends to be maintained during sleep at night (Messerli et al., 1982). The telemetry system used in the present study allows continuous recording of blood pressure and heart rate under near-normal or physiological states for long periods and is therefore considered useful for evaluating the influence of medication on circadian rhythm. As the rat is nocturnal, blood pressure and heart rate show higher diurnal values during darkness than during light. In the present study, in contrast to human subjects, 2-kidney, 1-clip renal hypertensive rats revealed diurnal patterns in the same way as spontaneously hypertensive rats and normotensive rats do (Henry et al., 1990; Kato et al., 1994). The present results showed that circadian rhythms in blood pressure and heart rate in 2-kidney, 1-clip renal hypertensive rats are dependent on the dark/light cycle. YM358 gradually decreased mean blood pressure without influencing the circadian rhythms of mean blood pressure and heart rate, indicating that the renin angiotensin system does not contribute to circadian blood pressure regulation in this model. The antihypertensive effect of YM358 gradually increased on repeated administration from days 1 to 7, showing saturation. In the acute study, in contrast, YM358 caused the same hypotensive effect after single oral administration. The cause for this difference in the time acquired to achieve maximal hypotension may be due to the method of blood pressure measurement: the use of restraint devices and a implanted catheter in the acute study may produce a stress-related increase in blood pressure. The reason for this discrepancy remains to be clarified.

YM358 showed a comparable antihypertensive effect to losartan in rats, but the duration of action of YM358 was a little shorter than that of losartan, which received a contribution from its active metabolite, EXP3174. In the binding and function studies, YM358 showed a competitive AT1 receptor antagonism, while EXP3174 is a non-competitive AT1 antagonist (Shibasaki et al., 1997). The relative efficacy of the competitive and non-competitive angiotensin AT1 receptor antagonists is currently under discussion, and no conclusion has been reached. A compensatory elevation of renin was observed with YM358 and losartan in the present study, and similar observations have been previously reported in animals and man (Wong et al., 1990b; Christein et al., 1991). With regard to the antihypertensive effect, therefore, due to the increase in angiotensin II levels in the case of compensation, attenuation of the effect of the competitive angiotensin AT1 receptor antagonists may occur during treatment, and a rebound increase in blood pressure may occur after discontinuation of treatment. In other words, it is possible that the increase in angiotensin II levels in the case of compensation may overcome the competitive antagonism but not non-competitive antagonism. However, in the present chronic experiments, YM358 showed a comparable effect to losartan in antihypertension without an attenuation of antihypertensive effect, and no rebound increase in blood pressure was observed during the recovery period, consistent with the result in stroke–prone spontaneously hypertensive rats (Yamaguchi et al., 1997). Thus, there appears to be no difference in antihypertensive efficacy between competitive and non-competitive angiotensin AT1 receptor antagonisms.

Both YM358 and losartan increased plasma renin activity in conscious normotensive rats. A large part of this response is thought to result from blockade of the inhibitory effect of angiotensin II on renin release, a calcium-mediated process at the renal juxtaglomerular cell (Churchill, 1985). However, plasma aldosterone concentration was unchanged by either drug in the present study, even though the production of aldosterone is known to be regulated mainly by angiotensin II, adrenocorticotropic hormone and potassium ions in the adrenocortical glomerular cells (Quinn and Williams, 1988). One explanation for this may be the existence of negative feedback factors, for example, fluid volume, Na ions, blood pressure and other hormonal and neuronal factors.

Despite large decreases in arterial blood pressure in both the acute and chronic study, YM358 caused no increase in heart rate in rats and dogs as compared to vehicle treatment. The occurrence of tachycardia induced by drugs affecting the renin angiotensin system is a complex matter. For example, some studies with losartan report no change in heart rate (Wong et al., 1990a,b) whereas others report an increase (Tomlinson et al., 1990). While

the present study cannot provide an explanation for the absence of reflex increases in heart rate accompanying the antihypertensive effect of YM358, the absence of a tachycardiac effect may be advantageous over vasodilator antihypertensive drugs, since the latter agents have limited therapeutic utility due to augmentation of reflex tachycardia, particularly in patients with insufficient coronary circulation (Gilmore et al., 1970).

In summary, we have demonstrated that the novel angiotensin II receptor antagonist YM358 has potent antihypertensive activity, in rats and dogs. The pharmacological profile of this compound indicates that it is a good candidate for development as a antihypertensive agent.

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