The Pharmacological Characterization of FK 739, a New Angiotensin II-Receptor Antagonist

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ABSTRACT—The pharmacological properties of FK 739, a new angiotensin II-receptor antagonist, were examined. FK 739 inhibited the specific binding of [125I]-angiotensin II to rat aortic smooth muscle cell membrane with an IC50 value of 8.6 nM, but did not displace the specific binding of [125I]-angiotensin II to bovine cerebellum membrane. In isolated helical strips of rabbit aorta, FK 739 shifted the concentration-response curve of angiotensin II-induced contraction in parallel to the right, and the values of the slope and pA2 were 1.06 and 8.45, respectively. In in vivo studies, oral administration of FK 739 at 10 mg/kg significantly inhibited the angiotensin I-induced pressor response in normotensive rats and dogs, and it caused a fall of mean blood pressure in renal hypertensive rats and dogs. In spontaneously hypertensive rats, FK 739 at 32 and 100 mg/kg significantly decreased the mean blood pressure in a dose-dependent manner. Additionally, we studied whether FK 739 would cause side effects such as dry cough, like other ACE inhibitors did. Oral administration of FK 739 (10 and 32 mg/kg) did not affect the capsaicin-induced bronchial edema. On the other hand, captopril (10 mg/kg) significantly enhanced capsaicin-induced bronchial edema. These results indicate that FK 739 is a potent and competitive antagonist for AT1-type receptors, and suggest that FK 739 might be a safe and useful agent for the treatment of hypertension in clinical trials.

Keywords: FK 739, Angiotensin II-receptor antagonist, Hypertension

The renin angiotensin system (RAS) plays an important role in the pathogenesis of hypertension. Angiotensin converting enzyme (ACE) inhibitors have been used for more than a decade in the clinical treatment of hypertension, and they have also been used with favorable effects on congestive heart failure (1, 2). However, ACE cleaves not only angiotensin I (Ang I), but also hydrolyzes bradykinin, substance P and enkephalins (3, 4), so the blockade of ACE may cause side effects such as dry cough (5). Accordingly, selectively preventing the binding of angiotensin II (Ang II) to the receptor would provide a safe and rational way to block the RAS.

Ang II elicits numerous physiological responses such as vasoconstriction, aldosterone release from the adrenal cortex, facilitation of adrenergic neurotransmission and stimulation of the growth of vascular smooth muscle cells (vSMCs) (6–8). Recently, Ang II receptors have been classified into at least two subtypes, AT1 and AT2, following the discovery of the nonpeptide Ang II-receptor antagonists DuP 753 and PD 123319 (9, 10). The AT1 receptors are located in the rat vSMCs and lung and are also expressed in bovine adrenal medulla, cortex and kidney (11–13). AT2 receptors, on the other hand, are detectable in human myometrium and bovine cerebellum (14, 15). At present, based on the distribution of AT2 receptors, it seems that AT2 receptors do not mainly contribute to the pathogenesis of cardiovascular disease, so a specific AT1-receptor antagonist might be preferable for the treatment of hypertension.

Fig. 1. Chemical structure of FK 739.
We used an alternative approach to design a new and potent specific AT₁-receptor antagonist and discovered a new nonpeptide Ang II-receptor antagonist, 2-butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-3H-imidazo[4,5-b]pyridine (FK 739) (Fig. 1). In this study, we describe the in vitro and in vivo pharmacological profile of the new Ang II-receptor antagonist FK 739.

MATERIALS AND METHODS

Preparation of rat vSMC membrane and bovine cerebellum membrane for Ang II receptor binding assay

Rat vSMCs were obtained from male Wistar rats (7-week-old) using the previously described procedure (16). Briefly, cells were cultured in Dulbecco's modified Eagle's medium (10% fetal calf serum, 1% penicillin G and 1% streptomycin) and used for the binding assay. For the preparation of the vSMC membrane, cells were homogenized in sucrose buffer (50 mM Tris/HCl, 1 mM EDTA and 250 mM sucrose, pH 7.4) of 5 volumes to the wet weight of cells and centrifuged at 1,000 x g for 10 min at 4°C. The supernatant was centrifuged at 100,000 x g for 60 min at 4°C. After centrifugation, the pellet was suspended in a small amount of 50 mM Tris/HCl-0.25% bovine serum albumin buffer (50 mM Tris/HCl and 5 mM MgCl₂, pH 7.4) and recentrifuged at 100,000 x g for 60 min at 4°C. The resulting pellet was resuspended in 50 mM Tris/HCl-0.25% bovine serum albumin buffer (pH 7.4) at a protein concentration of 5 mg/ml and stored at −80°C until used.

The prepared vSMC membrane (5 mg protein/ml, 50 µl) was incubated with 0.5 nM [125I]-Ang II (50 µl) and vehicle solution or test compounds (50 µl) for 60 min at 25°C in 0.1 ml of Tris/HCl-0.25% bovine serum albumin buffer. Nonspecific binding was defined as the binding in the presence of 1.0 µM saralasin. After incubation, the reaction was stopped with ice cold 50 mM Tris/HCl buffer. The membrane-bound [125I]-Ang II was separated from free ligand with a glass filter (GF/B, Whatman). Radioactivity was measured with a gamma counter. As assays were performed in duplicate. IC₅₀ values were determined by the data from three independent experiments.

Effect on Ang II-induced contractile response in isolated rabbit aorta

The descending thoracic aorta was removed from male Japanese white rabbits (2.0–2.5 kg) and cut into helical strips 4- to 5-mm-wide and 20- to 25-mm-long. Each helical strip was mounted in a 25-ml tissue bath containing Tyrode's solution (136.9 mM NaCl, 2.7 mM KCl, 1.8 mM CaCl₂, 1.0 mM MgCl₂, 11.9 mM NaHCO₃, 0.4 mM NaH₂PO₄ and 5.6 mM dextrose, pH 7.4). The Tyrode's solution was kept at 37°C and bubbled continuously with 5% CO₂ in oxygen. Initial resting tension was set at 1.0 g, and the aortic helical strip was allowed to equilibrate for 60 min. At 10 to 15 min intervals, the strip was stimulated by adding 50 mM KCl to the bath and then washed. At the end of the equilibration period, a control cumulative concentration-contractile response curve for Ang II (3.2 x 10⁻¹⁰ to 1.0 x 10⁻⁵ M) was obtained. After washing the tissue several times, FK 739 (1.0 x 10⁻⁸ to 1.0 x 10⁻⁷ M) was added, and the tissue was incubated with the drug for 15 min. The concentration-contractile response curve for Ang II (3.2 x 10⁻¹⁰ to 1.0 x 10⁻⁵ M) was then repeated in the presence of FK 739. The tension of the strips was measured isometrically with a force-displacement transducer connected to a polygraph (RPM-6008; Nihon Kohden, Tokyo). The response was expressed as a percentage of the maximal Ang II response. The pA₂ value of FK 739 was determined according to the method of Arunlakshana and Schild (17).

Effect on Ang I-induced pressor response in normotensive rats

Male Wistar rats (220–270 g) were used and fasted for 24 hr before this experiment. The animals were anesthetized with ether. A polyethylene catheter (PE 50) was placed into the right femoral artery for measurement of systemic blood pressure and into the right femoral vein for the dosing of Ang I. After a period of stabilization (about 2.5 hr), the experiment was started. Systemic blood pressure was measured via a pressure transducer (DX-312, Nihon Kohden) in the femoral artery. As the control response, Ang I (0.1 µg/kg) was intravenously injected at 30 min before oral administration of the test compounds. Then the same dose of Ang I was repeatedly injected at 15, 30, 60, 120, 240 and 360 min after administration of the test compounds. Effects of the test compounds were expressed as the percent change against the control pressor response.
Effect on Ang I-induced pressor response in normotensive dogs

This experiment in conscious normotensive male beagle dogs (8.0–12.0 kg) was carried out with a telemetry system (Multiplex; Primetech, Tokyo). A telemetric transmitter was implanted in the back of the dog, and its sensing catheter was inserted into the right femoral artery under anesthesia with sodium pentobarbital (35 mg/kg, i.v.). One week after surgery, the animals were fasted for 17 hr before administration of FK 739. Blood pressure and heart rate of the conscious animals were monitored with a receiver (RL2000, Primetech), and when blood pressure and heart rate were stable, Ang I (0.1 μg/kg/min) was infused for 1 hr to obtain the control response. The vehicle or FK 739 was given orally, and the same dose of Ang I was continuously infused for 6 hr. The data obtained was analyzed with DATEQUEST (Primetech). The effect of FK 739 was expressed as the percent change against the control pressor response.

Effect on blood pressure in renal hypertensive rats (RHRs, 2kidney-1clip)

Male Wistar rats were anesthetized with sodium pentobarbital (30 mg/kg, i.p.). The left renal artery was constricted with a silver clip (internal diameter, 0.22 mm), and the right kidney was left intact. Six weeks after surgery, the rats were fasted for 24 hr before the experiments. Under anesthesia with ether, a polyethylene cannula (PE 50) was inserted into the femoral artery for measurement of blood pressure and plasma renin activity. For measuring the plasma renin activity (PRA), a blood sample (1 ml per time point) was collected into a plastic tube containing 50 μl of 50 mM EDTA and was centrifugated at 3,000 × g at 4°C for 20 min to separate the plasma. PRA was estimated enzymatically by measurement of the produced Ang I, which was quantified by a commercially available radioimmunoassay kit (RENNIN. RIABEAD; Dainabot, Tokyo). To evaluate the hypotensive activity of the test compounds, experiments were conducted in RHRs with a mean blood pressure of 160–240 mmHg. The vehicle or test compound was given orally. Blood pressure was measured for 6 hr after dosing. Effects of the test compounds on blood pressure were expressed as the percent change against the mean blood pressure under stable condition before administration of the test compounds.

Effect on blood pressure and heart rate in spontaneously hypertensive rats (SHRs)

Male SHRs (15- to 18-week-old, 180–250 g) with a mean blood pressure of 150–194 mmHg were used after deprivation of food for 24 hr before the experiments. The animals were anesthetized with ether, and a polyethylene cannula (PE 50) was inserted into the femoral artery for measurement of blood pressure. Heart rate was measured with a tachometer (AT-601G, Nihon Kohden) triggered by a pulse wave detector. After a period of stabilization (about 2.5 hr), the vehicle solution or FK 739 was given orally. Effects of FK 739 on blood pressure and heart rate were expressed as the percent change against the mean blood pressure under stable condition before administration of the test compounds.

Effect on blood pressure in renal hypertensive dogs (RHDs, 2kidney-1clip)

Male beagle dogs (8.5–12.5 kg) were used. Under sodium pentobarbital (35 mg/kg, i.v.) anesthesia, left renal blood flow was measured with an electromagnetic flow meter probe (MFV-3200, Nihon Kohden) and reduced to approximately 30% with a silver clip. A polyethylene tube filled with 3000 U/ml of heparin was inserted into the left femoral artery, and the tip of the tube was left exposed in preparation for measuring blood pressure and heart rate. PRA was determined as described above. Five days later, the cannula tube was connected to a pressure-transducer to measure the blood pressure of the conscious animals. Heart rate was measured with a tachometer (AT-601G, Nihon Kohden) triggered by a pulse wave detector. The experiments were conducted in RHDs with a steady diastolic pressure of 100 mmHg or more. Vehicle solution or FK 739 was given orally when the blood pressure and heart rate were stable. Effects of the test compounds on blood pressure were expressed as the percent change against mean blood pressure under stable condition before administration of the test compounds.

Effect on the capsaicin-induced bronchial edema

Male Hartley guinea pigs (300–350 g) were used. The vehicle solution or test compounds were given orally after depriving the animals of food for 24 hr. One hour later, the animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), and a polyethylene cannula (PE 50) was inserted into the right carotid vein. Evans blue dye (20 mg/kg, dissolved in saline) was given intravenously via the cannula tube, and then capsaicin (0.1 mg/kg) was given intravenously. Five minutes later, the bronchii and lungs were excised and perfused with saline. The isolated bronchii was incubated with formamide (4 ml) at 50°C for 24 hr to extract the Evans blue dye. The amount of Evans blue dye was determined by measuring the optical density at 640 nm with a spectrophotometer (U-3200; Hitachi, Tokyo).

Drugs

[125I]-Angiotensin II (specific activity 2200 Ci/mmol) was purchased from DuPont-NEN (Boston, MA, USA).
Angiotensin I, angiotensin II, saralasin and capsaicin were obtained from Sigma Chemical Company (St. Louis, MO, USA) and dissolved in deionized water or saline before use. FK 739, DuP 753 and captopril were synthesized at Fujisawa Pharmaceutical Company (Osaka) and dissolved in deionized water before use. Evans blue dye was purchased from Wako Pure Chemical Industries (Osaka).

Analysis of data
The results were expressed as the mean±S.E.M. Statistical analysis was performed by Student's t-test for unpaired comparison. A value of P <0.05 was considered to be statistically significant. The IC50 value was the drug concentration required to produce 50% inhibition of the total specific binding of [125I]-Ang II.

RESULTS

[125I]-Ang II binding in rat vSMC membrane and bovine cerebellum membrane

In the rat aortic smooth muscle cell membrane, the binding of [125I]-Ang II was inhibited by saralasin (IC50, 9.1 × 10^-9 M) as well as by FK 739 and DuP 753 in a concentration dependent manner. IC50 values of FK 739 and DuP 753 were 8.6 nM and 11 nM, respectively (Fig. 2A).

In the bovine cerebellum membrane, saralasin at doses of 0.1 nM or more inhibited the specific binding of [125I]Ang II in a concentration-dependent manner with an IC50 value of 1.4 nM, but FK 739 (1.0 × 10^-6 M) and DuP 753 (1.0 × 10^-5 M) had no effects (Fig. 2B).

Inhibition of Ang II-induced the contractile response in rabbit aorta

In rabbit thoracic aorta (Fig. 3A), Ang II (3.2 × 10^-10 to 1.0 × 10^-7 M) caused concentration dependent contraction, while FK 739 caused a rightward parallel shift of the concentration response curve of Ang II. Schild analysis of these data indicated a mean pA2 value of 8.45 and a slope of 1.06 (Fig. 3B). High concentration of FK 739 (1.0 × 10^-6 M) did not change the contractile response curve of norepinephrine (3.2 × 10^-5 to 10^-3 M) or KCl (10 to 50 mM) (data are not shown).

Inhibition of Ang I-induced pressor response in normotensive rats and dogs

In conscious normotensive rats, the pressor response (25–37 mmHg) was induced by intravenous injection of Ang I (0.1 μg/kg). Oral administration of FK 739 (10 mg/kg) completely inhibited the Ang I-induced pressor response at 30 min after dosing (from 27±1.0 to 0±0 mmHg, n = 3), and this effect lasted at least 6 hr (Fig. 4A). Oral administration of DuP 753 also inhibited the pressor response of Ang I (from 25±5.0 to 2.0±1.0 mmHg, with the maximal effect at 10 mg/kg, n = 3), and this effect lasted 6 hr (Fig. 4B). Similarly, captopril inhibited the pressor response of Ang I (from 37±1.0 to 0±0 mmHg, n = 3) (Fig. 4C).

In conscious normotensive dogs, intravenous infusion of Ang I (0.1 μg/kg/min) caused a stable pressor response (approximately 40 to 50 mmHg). Oral administration of FK 739 (10 mg/kg) completely inhibited the Ang I-induced pressor response at 60 min after dosing.
Antihypertensive effect in RHRs, SHRs and RHDs

RHRs: Six weeks after renal artery clipping, PRA was elevated in RHRs (6.4 ± 0.4 ng Ang I/ml/hr in sham operated group (n = 3), 38.8 ± 15.2 ng Ang I/ml/hr in renal artery clipping group (n = 11)). Under this experimental condition, oral administration of FK 739 (10 or 32 mg/kg) significantly decreased the mean blood pressure in a dose-dependent manner (from 218 ± 12 to 202 ± 13 mmHg at 10 mg/kg and from 221 ± 7 to 159 ± 11 mmHg at 32 mg/kg, n = 3-4), with the latter effect lasting longer than 6 hr (Fig. 6A). Oral administration of DuP 753 (10 mg/kg) also decreased the mean blood pressure (from 197 ± 15 to 167 ± 6 mmHg, n = 3); and at a dose of 32 mg/kg, it significantly decreased the mean blood pressure for 6 hr after dosing (from 221 ± 13 to 158 ± 24 mmHg, n = 4) (Fig. 6B). Captopril (10 or 32 mg/kg) also elicited a significant antihypertensive effect (from 205 ± 7 to 169 ± 9 mmHg, n = 4), although it was short lived when compared with that of the same doses of FK 739 or DuP 753 (Fig. 6C).

Antihypertensive effect in RHRs, SHRs and RHDs

SHRs: Six weeks after renal artery clipping, PRA was elevated in SHRs (53 ± 5 to 0 ± 3 mmHg, n = 3) (Fig. 5).
Fig. 5. Effect of FK 739 on angiotensin I-induced pressor response in conscious normotensive dogs. Ordinate: percent change of angiotensin I-induced response before oral administration of deionized water (○) or FK 739 at 10 mg/kg (△). Abscissa: time after administration of FK 739. Each value represents the mean ± S.E.M. of 3 experiments. Significant differences from the group treated with deionized water are indicated: **P < 0.01.

Fig. 6. Effects of FK 739 (A), DuP 753 (B) and captopril (C) on mean arterial pressure in conscious renal hypertensive rats. The ordinate expresses the percent change after administration of vehicle or test compounds, and the abscissa expresses the time after dosing. Each value represents the mean ± S.E.M. of 3 to 4 experiments. Significant differences from the group treated with deionized water are indicated: *P < 0.05 and **P < 0.01. Vehicle (○), FK 739 (■, 32 mg/kg; ▲, 100 mg/kg).

Fig. 7. Effect of FK 739 on mean arterial pressure (A) and heart rate (B) in spontaneously hypertensive rats. Each value represents the mean ± S.E.M. of 5 to 6 experiments. Significant differences from the group treated with deionized water are indicated: *P < 0.05 and **P < 0.01. Vehicle (○), FK 739 (■, 32 mg/kg; ▲, 100 mg/kg).

SHRs: Oral administration of FK 739 decreased the mean blood pressure in a dose-dependent manner for 6 hr after dosing (from 166 ± 2 to 143 ± 7 mmHg at 32 mg/kg and from 176 ± 5 to 144 ± 6 mmHg at 100 mg/kg, n = 6), but did not significantly change the heart rate (from 390 ± 28 to 434 ± 20 beats/min in maximal change, n = 5–6) (Fig. 7, A and B).

RHDs: PRA and mean blood pressure rose rapidly at 3 days after renal artery clipping and were sustained for 7 days (PRA: 1.9 ± 0.6 ng Ang I/ml/hr at day 0, 12.4 ± 4.4 ng Ang I/ml/hr at day 3 and 7.3 ± 3.5 ng Ang I/ml/hr at day 7; mean blood pressure: 87 ± 2 mmHg at day 0, 135 ± 9 mmHg at day 3 and 125 ± 9 mmHg at day 7, respectively).
(n = 5). To reduce the influence of surgical stress on this experiment, for all animals, we evaluated the antihypertensive effect of FK 739 at 5 days after surgery. Oral administration of FK 739 (3.2 mg/kg) significantly decreased the mean blood pressure, and there was a rapid onset of the hypertensive effect of FK 739 after dosing (from 121 ± 1 to 113 ± 4 mmHg at 1.0 mg/kg, from 129 ± 9 to 100 ± 10 mmHg at 3.2 mg/kg, n = 3–4) (Fig. 8).

Effect on capsaicin-induced bronchial edema

As shown in Fig. 9, the amount of the Evans blue dye was 1.21 ± 0.23 µg/g tissue in the bronchia of guinea pigs in the vehicle treatment group (n = 8), and that in the FK 739 oral administration groups (10 mg/kg, n = 9 or 32 mg/kg, n = 3) was almost the same (1.08 ± 0.24 µg/g tissue at 10 mg/kg and 1.04 ± 0.20 µg/g tissue at 32 mg/kg). On the other hand, captopril (10 mg/kg) significantly increased the extravasation of Evans blue dye in the bronchia at 2.53 ± 0.24 ng/g tissue (n = 7).

DISCUSSION

Our study clearly showed that FK 739 is a potent, selective and competitive antagonist for the AT₁ receptor. To evaluate the selectivity of FK 739 for the subtypes of Ang II receptors, we used rat aortic smooth muscle cell membrane as the source of AT₁-type receptor and bovine cerebellum membrane as the source of AT₂-type receptor. In rat aortic smooth muscle cell membrane, FK 739 displaced the specific binding of [125I]-Ang II binding with an IC₅₀ value of 8.6 nM. Under the same conditions, DuP 753 and saralasin also inhibited [125I]-Ang II binding with IC₅₀ values of 11 and 9.1 nM, respectively. On the other hand, in bovine cerebellum membrane, FK 739 and DuP 753 did not inhibit the specific binding of [125I]-Ang II, but saralasin displaced the binding of [125I]-Ang II. These results indicate that FK 739 possesses a high selective affinity for DuP 753-sensitive Ang II receptor, namely the AT₁-type receptor. In isolated rabbit aorta, FK 739 caused a rightward parallel shift of the concentration-response curve of Ang II with a pA₂ value of 8.5 and the slope of the Schild plot was 1.06. This result indicates that FK 739 is a competitive antagonist for Ang II receptor. Furthermore, FK 739 itself did not show any contractile response in the isolated rabbit aorta at the highest concentration of 100 nM and also did not induce the pressor response in conscious normotensive rats, indicating a lack of agonistic activity for the Ang II receptor.

To evaluate the antihypertensive activity of FK 739, we used RHRs and SHRs. In RHRs, oral administration of FK 739 decreased the blood pressure in a dose-dependent manner for at least 6 hr, and the antihypertensive activity of FK 739 was almost the same as that of DuP 753, which had a more profound antihypertensive effect than captopril. Several studies have also demonstrated the important role of RAS in maintaining vascular tone (18–20). Mizuno et al. reported that captopril could not completely inhibit the formation of immunoreactive Ang II (21). This might explain the difference between the antihypertensive effects of FK 739 and DuP 753 in comparison with that of captopril in RHRs. In SHRs, moreover, oral administration of FK 739 decreased blood pressure in a dose-dependent manner without changing the heart rate, which indicates that this Ang II-receptor antagonist is useful for treating hypertensive patients with normal renin
activity as well as ACE inhibitors, although the qualitative
differences between the antihypertensive effects of
Ang II antagonist and ACE inhibitors have not been fully
ecluated.

To ascertain the Ang II-receptor antagonism of FK 739
in different species, we used Ang I-infused hypertensive
dogs and RHDs. Intravenous infusion of Ang I produced a
stable pressor response in conscious normotensive dogs.
Oral administration of FK 739 completely inhibited the
Ang I-induced pressor response for 1 hr after dosing.
Moreover, in RHDs, oral administration of FK 739 also
decreased the mean arterial pressure in a dose-dependent
manner. These results show that there is no species differ-
ence in the pharmacological characteristics of FK 739. In
normotensive dogs, FK 739 was almost completely ab-
sorbed after oral administration, and we could not detect
any active metabolites of FK 739 in either rats or dogs (data not shown). On the other hand, DuP 753 is metabo-
lized to the noncompetitive Ang II-receptor antagonist
EXP 3174 which contributes to the long lasting antihy-
tensive effect of this compound in RHRs (22). This meta-
abolic change may work against its clinical usefulness in
patients with impaired renal or hepatic function.

In the clinical application of ACE inhibitors, one well-
known side effect is persistent dry cough (23). The mecha-
nisms of dry cough after treatment with these inhibitors is
associated with the increase of bradykinin, substance P
and other bronchoconstrictor substances, and it has been
reported that captopril potentiates the bronchoconstric-
tion induced by exogenous bradykinin and substance P in
guinea pigs (5). In this study, the effect of FK 739 on cap-
saicin-induced bronchial edema in guinea pigs was eval-
uated and compared with that of captopril. We chose this
animal model based on the fact that capsaicin mainly
releases bronchoconstrictors such as substance P and
bradykinin (24); and furthermore, both enalapril and
remipril increase the cough reflex response to inhaled cap-
saicin in hypertensive patients (25). Oral administration of
captopril significantly enhanced capsaicin-induced bronchial edema. On the contrary, oral administration of FK 739 did not show any effect on the capsaicin induced bronchial edema. These results suggest that this new Ang II-receptor antagonist would not increase the sensitivity of the cough reflex and not cause symptoms such as those observed in patients treated with ACE inhibitor.

In conclusion, the present study showed that FK 739 is
a potent and selective AT1-receptor antagonist. FK 739
showed sufficient and long lasting antihypertensive activ-
ity without tachycardia in various hypertensive animal
models and species. FK 739 should prove to be a safe and
useful agent for the treatment of hypertension in clinical
trials.

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