Effects of a New Dihydropyridine Derivative, CV-4093·2HCl, on Renal Hemodynamics in Spontaneously Hypertensive Rats

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Abstract—The effects of a new calcium antagonist, CV-4093·2HCl, on renal hemodynamics were examined in anesthetized and conscious spontaneously hypertensive rats (SHR). In the anesthetized rats, CV-4093·2HCl (5 and 10 μg/kg, i.v.) showed a long-lasting hypotensive action, dilated renal vasculature, and increased renal blood flow. These renal hemodynamic actions of CV-4093·2HCl were more prominent than those of nicardipine (5 and 10 μg/kg). Moreover, CV-4093·2HCl (10 μg/kg, i.v.) inhibited renal vascular contractions induced by intravenous norepinephrine and angiotensin II. The inhibitory effect of CV-4093·2HCl was much more marked than that of nicardipine, although the inhibitory effects of both calcium antagonists on systemic pressor responses induced by the vasoactive substances were almost the same. In addition, CV-4093·2HCl (1 and 3 mg/kg, p.o.) increased blood flow in the kidneys but not in the other organs except for the small intestine in conscious SHR. These results suggest that CV-4093·2HCl has a relatively higher affinity for the renal vascular bed (renal resistance vessels), and its effect on renal hemodynamics seems to be beneficial for treating hypertension.

Renal hemodynamic changes are greatly involved in chronic regulation of the levels of systemic blood pressure through factors such as electrolyte metabolism and the release of renin (1-4). In our previous studies, we demonstrated that the development and maintenance of hypertension in spontaneously hypertensive rats (SHR) are closely related to alterations in electrolyte metabolism and vascular reactivity to vasoactive substances in the kidneys (5, 6). Furthermore, the development of severe hypertension in stroke-prone SHR was also implicated in renal vascular change and its related hemodynamic and biochemical alterations (7-9). From these findings, we speculated that antihypertensive agents that acted to improve renal hemodynamic alterations are therapeutically beneficial in hypertensive patients.

The dihydropyridine derivative, CV-4093·2HCl, discovered on the basis of this speculation, is a new calcium antagonist with a long-lasting antihypertensive action (10, 11). The calcium antagonist shows little cardiodepressant action, but a highly selective vascular effect (12), and it also has long-lasting inhibitory actions on calcium inward currents in smooth muscle cells of the rabbit pulmonary artery (13). In the study reported here, we examined the effect of CV-4093·2HCl on renal hemodynamics and renal vascular contraction induced by vasoactive substances in rats with spontaneous hypertension.

Materials and Methods

Animals: Spontaneously hypertensive rats (SHR), a stroke-prone strain, 9-11-week-old males, were used in all experiments. The source of the animals has been reported elsewhere (14, 15).

Renal hemodynamics in anesthetized rats: The rats were anesthetized by an intraperitoneal injection of sodium pentobarbital (50 mg/kg body wt.), and a small dose of the barbiturate (6 mg/kg/hr) was added to the sustaining infusion of saline at 0.03 ml/min to maintain a stable renal perfusion pressure. A rectal temperature between 37 and 38°C...
was maintained with infrared lamps. The femoral artery was cannulated with polyethylene tubing (PE-50) to measure systemic arterial pressure. The left kidney was exposed by an abdominal incision. Blood flow in the left renal artery was measured by a small-diameter electromagnetic flow transducer (lumen size, 0.5 mm internal diameter) connected to an electromagnetic flowmeter and polygraph. In situ calibration of the flowmeter system has been reported elsewhere (7). In the present experiments, the measurement of renal blood flow was intermittently performed because of a technical limitation in the thermo-generation of the flow transducer. Heart rate was monitored with a pulse-triggered tachograph. Renal vascular resistance was calculated by dividing the mean blood pressure by renal blood flow. When the effect of vasoactive substances (norepinephrine and angiotensin II) on renal vascular resistance was examined, peak values of changes in the blood pressure and renal blood flow were used for calculation of renal vascular resistance.

In addition to observing the renal hemodynamic effect of calcium antagonists, their effects on renal vasoconstriction induced by exogenous norepinephrine (0.2–1.0 μg/kg) and angiotensin II (0.01–0.05 μg/kg) were examined in anesthetized SHR. In the latter experiment, the vasoactive agents were intravenously injected before and after the calcium antagonists were administered through a cannula inserted into the left femoral vein. The vasoconstrictor effect in the kidneys was evaluated by a decrease in blood flow and an increase in vascular resistance. Moreover, the effect of calcium antagonists on pressor response (increase in systemic blood pressure) induced by the vasoactive agents was also examined.

Organ blood flows in conscious rats: Blood flows in various organs of SHR were measured by the method reported by Tsuchiya et al. (16). The day before the measurements were made, cannulas were inserted under ether anesthesia into the right carotid artery and into the left ventricle (PE-10) to inject 141 Ce-labelled microspheres (15±3 μm in diameter, 10 mCi/g, New England Nuclear Co.) and into the abdominal aorta via the left femoral artery (PE-50) to measure mean arterial pressure and to sample blood. On the day of experiments, the rats were placed in a plastic chamber (22 cm in diameter, 35 cm high) and following an initial 30-min stabilization period for the rats to adapt to the chamber, systemic hemodynamics were measured under conscious conditions. Mean arterial pressure was recorded using a pressure transducer and a polygraph. The microspheres (45,000, 1 μCi), suspended in 50 μl of 10% dextran solution containing 0.01% Tween 80, were injected into the left ventricular cannula and flushed with 0.4 ml saline over a 30-sec period. The blood was sampled at a constant rate of 0.81 ml/min from 5 sec before the start of injection of the microspheres to 10 sec after the injection was finished. After the blood sampling was stopped, the rats were killed with ether and the organs (brain, heart, kidneys, small intestine, stomach, pancreas, liver, femoral skeletal muscle and abdominal skin) were removed. 141 Ce-radioactivity in the organs and the sampled blood was measured using a gamma-counter (Packard Co.). Organ blood flows and cardiac output were calculated according to the following formulae:

Organ blood flow (ml/min/g) = \[
\frac{141\text{Ce in the tissue (cpm)}}{\text{Wet wt. of the tissue (g)}} \times \frac{0.81\text{ (ml/min)}}{141\text{Ce in the blood (cpm)}}
\]

Cardiac output (ml/min/kg) = \[
\frac{141\text{Ce injected (cpm)}}{\text{Body wt. (kg)}} \times \frac{0.81\text{ (ml/min)}}{141\text{Ce in the blood (cpm)}}
\]

Total peripheral resistance was obtained by dividing the mean arterial pressure by cardiac output, and vascular resistance in each organ was calculated from the mean pressure and the organ blood flow.

Drugs: Methyl 2-(4-diphenylmethyl-1-piperazinyl) ethyl (-)-1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride (CV-4093·2HCl) (10) is 683.63 in molecular weight, a white to pale yellow crystal, and relatively stable to light. CV-4093·2HCl and nicardipine hydrochloride, synthesized in our
Chemistry Research Laboratories, were suspended in a 5% gum arabic solution for oral administration and were dissolved in 20% polyethyleneglycol-400 for intravenous injection (injection volume, 0.05 ml/100 g body wt.). The vehicle solution was administered to control rats. Norepinephrine bitartrate (NE, Wako) and angiotensin II (ang. II, Peptide Institute) were dissolved in saline and injected intravenously. In the present experiments, relatively small doses of CV-4093·2HCl and nicardipine were used, because the larger doses decreased blood pressure to a level below the lower limit of autoregulation of renal blood flow (7, 11). The doses of the calcium antagonists were 5–10 μg/kg by intravenous injection and 1–3 mg/kg by oral administration.

**Statistical analysis:** All values were expressed as the mean and standard error (S.E.). Statistical significance, evaluated by two way analysis of variance followed by Scheffe's test, was taken as P<0.05.

**Results**

1. Effects on blood pressure and renal hemodynamic in anesthetized SHR

Systemic blood pressure, heart rate, renal blood flow and renal vascular resistance before the drug administration showed no statistically significant differences among the control, CV-4093·2HCl-treated and nicardipine-treated groups of rats (legends of Figs. 1–3).

**Effects on systemic blood pressure:** Blood pressure changes at 1, 5, 20 and 40 min after intravenous administration of CV-4093·2HCl and nicardipine (5 and 10 μg/kg) are shown in Fig. 1. CV-4093·2HCl exerted a dose-dependent hypotensive action, which was slow in onset and long-lasting even when administered intravenously. The hypotensive action was more pronounced at 5 min than at 1 min after the administration, and it recovered gradually thereafter. Nicardipine showed very steep hypotensive actions; the pronounced effect was observed at 1 min after the administration, and the hypotensive effect of the lower dose of nicardipine had disappeared by 40 min. Hypotensive effects of CV-4093·2HCl and nicardipine at the higher dose lasted for over 40 min.

**Fig. 1.** Effects of CV-4093·2HCl (5, 10 μg/kg, i.v.) and nicardipine (5, 10 μg/kg, i.v.) on blood pressure in anesthetized spontaneously hypertensive rats. Values are percent changes of mean blood pressure. The average values of the blood pressure before drug administration are 132±4, 136±3, 134±8, 126±7 and 130±8 mmHg in the control (x, n=11), low-dose group of CV-4093·2HCl (○, n=5), high-dose group of CV-4093·2HCl (●, n=5), low-dose group of nicardipine (▲, n=5) and high-dose group of nicardipine (△, n=5), respectively. *P<0.05 vs. control. †P<0.05 vs. nicardipine. Mean±S.E.

**Fig. 2.** Effects of CV-4093·2HCl (5, 10 μg/kg, i.v.) and nicardipine (5, 10 μg/kg, i.v.) on renal blood flow in anesthetized spontaneously hypertensive rats. Values are percent changes of mean renal blood flow. The average values of the renal blood flow before drug administration are 6.77±0.50, 6.86±0.78, 7.27±1.02, 6.72±0.84 and 7.29±0.64 ml/min in the control (x, n=11), low-dose group of CV-4093·2HCl (○, n=5), high-dose group of CV-4093·2HCl (●, n=5), low-dose group of nicardipine (▲, n=5) and high-dose group of nicardipine (△, n=5), respectively. *P<0.05 vs. control. †P<0.05 vs. nicardipine. Mean±S.E.
Effects on renal blood flow: As illustrated in Fig. 2, CV-4093-2HCl increased renal blood flow in a sustained manner, and the increase of renal blood flow at the early but not late observation period was dose-dependent and statistically significant. Nicardipine, especially at the higher dose, decreased renal blood flow 1 min after its administration. Aside from the lower dose at 40 min, nicardipine did not increase renal blood flow significantly at 5 to 40 min after its administration.

Effects on renal vascular resistance: CV-4093-2HCl caused dose-dependent decrease in renal vascular resistance at all measuring points; the most pronounced effect was observed at 5 min after the administration. Nicardipine markedly decreased renal vascular resistance immediately after the injection. The duration of its action was shorter than of CV-4093-2HCl (Fig. 3).

Effects on heart rate: The lower dose of CV-4093-2HCl slightly but significantly increased heart rate at 5 to 40 min and the higher dose, at 1 to 40 min after the injection. The percent increase was 2% to 4% of the initial values (about 350 beats/min). Nicardipine also increased the heart rate at 1 and 5 min in the lower dose and at 1 to 20 min in the higher dose (1% to 4%). Thus, the effects of calcium antagonists on heart rate were very slight under conditions of anesthesia.

2. Effects on renal vascular constriction induced by vasoactive substances

Basal values of systemic blood pressure, renal blood flow and renal vascular resistance before the vasoactive substance were administered showed no statistically significant differences among the control and calcium antagonist-treated groups. The changes of these parameters after the treatment of calcium antagonists were similar to those described above (footnotes of Tables 1–4 and legends of Figs. 4 and 5).

Inhibitory actions against vasoconstriction induced by NE: The effects of CV-4093-2HCl and nicardipine on the elevation of systemic blood pressure (pressor response) and the decrease of renal blood flow by NE (0.2, 0.5 and 1.0 μg/kg, i.v.) were examined in anesthetized SHR at 10 and 30 min after the calcium antagonists were administered. As shown in Table 1, the pressor responses to NE before the calcium antagonists were administered were similar in the control group and the CV-4093-2HCl and nicardipine-treated groups of rats. CV-4093-2HCl significantly inhibited the pressor responses induced by the 3 doses of NE; the percent inhibitions were 33% to 37% at 10 min and 34% to 38% at 30 min after the treatment. Nicardipine also inhibited the pressor responses by 29% to 32% and 15% to 22% at 10 and 30 min, respectively.

The effect of the calcium antagonists on the decrease of renal blood flow induced by intravenous NE are summarized in Table 2. CV-4093-2HCl significantly inhibited the decrease in renal blood flow induced by the vasoactive substance. The percent inhibitions at 10 min after the administration were 62% and 63% for 0.2 and 0.5 μg/kg of NE, respectively, and 45% for 1.0 μg/kg of the vasoactive substance. The percent inhibitions of nicardipine were 33% and 26% for the small doses of NE and 9% for the highest dose of NE. Moreover, at 30 min after the administration, CV-4093-2HCl significantly inhibited the decrease in renal blood flow, but nicardipine
did not. These inhibitory effects of the calcium antagonist on renal vascular constriction were also observed when the changes in renal vascular resistance were taken as a measure of the NE-induced vasoconstriction in the kidney (Fig. 4). The inhibitory actions of CV-

Table 1. Inhibitory effects of intravenous treatments of CV-4093·2HCI and nicardipine on pressor response (mmHg) induced by norepinephrine (NE)

| Intravenous dose of NE (µg/kg) | 0.2 | 0.5 | 1.0 |
|-------------------------------|-----|-----|-----|
|                               |     |     |     |
| Before treatments             |     |     |     |
| Control                       | 17.5±0.7 | 27.5±0.7 | 33.7±0.9 |
| CV-4093·2HCI                  | 16.6±0.2 | 25.8±1.7 | 32.0±2.5 |
| Nicardipine                   | 17.6±0.9 | 27.8±1.4 | 32.8±2.0 |
| 10 min after treatments       |     |     |     |
| Control                       | 19.2±0.6 | 29.2±1.3 | 38.5±1.8 |
| CV-4093·2HCI                  | 12.8±1.0* | 19.0±1.0* | 24.4±0.8* |
| Nicardipine                   | 13.0±0.7* | 20.6±1.4* | 27.2±1.7* |
| 30 min after treatments       |     |     |     |
| Control                       | 20.5±1.1 | 29.0±1.1 | 40.2±0.8 |
| CV-4093·2HCI                  | 12.8±1.2* | 19.2±1.1* | 26.4±1.3* |
| Nicardipine                   | 16.0±1.2* | 24.6±2.2 | 31.4±2.3* |

Basal values of mean blood pressure in the control, CV-4093·2HCI and nicardipine treated groups were 140±3, 141±2 and 144±3 mmHg before treatments of calcium antagonists; 136±4, 111±6 and 123±1 mmHg at 10 min; and 119±4, 118±4 and 128±4 mmHg, respectively. Dose of CV-4093·2HCI or nicardipine: 10 µg/kg. N=5-6. *P<0.05 vs. control. Mean±S.E.

Table 2. Inhibitory effects of intravenous treatments of CV-4093·2HCI and nicardipine on decrease in renal blood flow (ml/min) induced by norepinephrine (NE)

| Intravenous dose of NE (µg/kg) | 0.2 | 0.5 | 1.0 |
|-------------------------------|-----|-----|-----|
|                               |     |     |     |
| Before treatments             |     |     |     |
| Control                       | -1.32±0.11 | -2.99±0.19 | -4.73±0.28 |
| CV-4093·2HCI                  | -1.17±0.12 | -2.61±0.30 | -4.04±0.39 |
| Nicardipine                   | -1.16±0.09 | -2.80±0.16 | -4.51±0.25 |
| 10 min after treatments       |     |     |     |
| Control                       | -1.41±0.10 | -3.30±0.23 | -4.70±0.42 |
| CV-4093·2HCI                  | -0.53±0.12* | -1.21±0.10* | -2.60±0.31* |
| Nicardipine                   | -0.95±0.04* | -2.45±0.20* | -4.28±0.20 |
| 30 min after treatments       |     |     |     |
| Control                       | -1.43±0.12 | -3.20±0.23 | -4.70±0.36 |
| CV-4093·2HCI                  | -0.94±0.11* | -2.14±0.24* | -3.49±0.32* |
| Nicardipine                   | -1.26±0.10 | -2.87±0.12 | -4.61±0.22 |

Basal values of renal blood flow in the control, CV-4093·2HCI and nicardipine treated groups were 6.97±0.59, 6.45±0.52 and 7.19±0.41 ml/min before treatment of calcium antagonists; 7.03±0.62, 7.20±0.46 and 7.54±0.25 ml/min at 10 min; and 7.07±0.61, 7.11±0.42 and 7.26±0.29 ml/min at 30 min, respectively. Dose of CV-4093·2HCI or nicardipine: 10 µg/kg. N=5-6. *P<0.05 vs. control, †P<0.05 vs. nicardipine. Mean±S.E.
4093-2HCl were more prominent than those of nicardipine.

Inhibitory actions against vasoconstriction induced by ang. II: CV-4093-2HCl and nicardipine slightly but not significantly inhibited pressor responses induced by ang. II. A difference in potency between the two calcium antagonists was not observed (Table 3); percent inhibitions at 10 min after the administration were 11% to 21% for CV-4093-2HCl and 15% to 16% for nicardipine. However, CV-4093-2HCl significantly inhibited the decrease in renal blood flow induced by the vasoactive substance, although nicardipine also slightly but not significantly inhibited the decrease in renal blood flow (Table 4). The percent inhibitions at 10 min after the administration were 32% to 40% for CV-4093-2HCl and 10% to 24% for nicardipine. Both calcium antagonists depressed the increase in renal vascular resistance caused by ang. II; the potency of CV-4093-2HCl tended to be greater than that of nicardipine (Fig. 5).

3. Effects on organ blood flows in conscious SHR

The organ blood flows were measured one hour after CV-4093-2HCl (1 and 3 mg/kg) or nicardipine (3 mg/kg) was orally administered. Mean blood pressure was decreased by
Table 3. Inhibitory effects of intravenous treatments of CV-4093-2HCl and nicardipine on pressor response (mmHg) induced by angiotensin II

| Intravenous dose of angiotensin II (μg/kg) | 0.01 | 0.02 | 0.05 |
|-------------------------------------------|------|------|------|
| (μg/kg)                                   |      |      |      |
| Control                                   | 12.5±0.8 | 19.5±1.4 | 29.3±2.8 |
| CV-4093-2HCl                              | 13.8±0.9 | 19.3±1.0 | 27.8±1.1 |
| Nicardipine                               | 13.8±1.0 | 21.0±0.5 | 29.0±1.2 |
| **Before treatments**                      |      |      |      |
| Control                                   | 13.5±1.0 | 19.8±0.7 | 29.7±0.9 |
| CV-4093-2HCl                              | 10.7±0.9 | 16.2±1.4 | 26.3±2.2 |
| Nicardipine                               | 11.4±1.1 | 16.6±1.1 | 25.2±1.6 |
| **10 min after treatments**                |      |      |      |
| Control                                   | 14.7±0.3 | 19.0±0.4 | 28.7±0.8 |
| CV-4093-2HCl                              | 12.3±0.7 | 18.7±1.4 | 26.8±2.0 |
| Nicardipine                               | 14.2±1.0 | 18.4±1.3 | 26.6±1.7 |
| **30 min after treatments**                |      |      |      |

Basal values of mean blood pressure in the control, CV-4093-2HCl and nicardipine treated groups were 138±5, 137±3 and 140±4 mmHg before treatments of calcium antagonists; 139±6, 114±1 and 120±2 mmHg at 10 min; and 125±4, 107±2 and 117±2 mmHg at 30 min, respectively. Dose of CV-4093-2HCl or nicardipine: 10 μg/kg. N=5–6. Mean±S.E.

Table 4. Inhibitory effects of intravenous treatments of CV-4093-2HCl and nicardipine on decrease in renal blood flow (ml/min) induced by angiotensin II

| Intravenous dose of angiotensin II (μg/kg) | 0.01 | 0.02 | 0.05 |
|-------------------------------------------|------|------|------|
| (μg/kg)                                   |      |      |      |
| Control                                   | -1.51±0.17 | -2.70±0.23 | -4.94±0.35 |
| CV-4093-2HCl                              | -2.14±0.22 | -3.49±0.27 | -5.65±0.37 |
| Nicardipine                               | -1.89±0.15 | -3.13±0.22 | -5.53±0.28 |
| **Before treatments**                      |      |      |      |
| Control                                   | -1.72±0.19 | -2.99±0.31 | -5.33±0.41 |
| CV-4093-2HCl                              | -1.17±0.08* | -1.78±0.14* | -3.65±0.19* |
| Nicardipine                               | -1.31±0.09 | -2.26±0.18 | -4.79±0.29 |
| **10 min after treatments**                |      |      |      |
| Control                                   | -1.66±0.17 | -3.00±0.31 | -5.18±0.41 |
| CV-4093-2HCl                              | -1.39±0.11 | -2.14±0.12* | -4.69±0.24 |
| Nicardipine                               | -1.41±0.13 | -2.86±0.18 | -5.26±0.30 |
| **30 min after treatments**                |      |      |      |

Basal values of renal blood flow in the control, CV-4093-2HCl and nicardipine treated groups were 7.03±0.32, 7.61±0.27 and 7.21±0.19 ml/min before treatment of calcium antagonists; 7.02±0.29, 8.35±0.23 and 7.53±0.23 ml/min at 10 min; and 7.19±0.33, 7.99±0.30 and 7.58±0.26 ml/min at 30 min, respectively. Dose of CV-4093-2HCl or nicardipine: 10 μg/kg. N=5–6. *P<0.05 vs. control. Mean±S.E.

11%, 18% and 12% of the initial values in the groups treated with lower and higher doses of CV-4093-2HCl and nicardipine, respectively (Table 5). Cardiac output in the rats treated with the higher dose of CV-4093-2HCl was slightly higher than that in the controls (Table
Table 5. Effects of CV-4093-2HCl and nicardipine on mean blood pressure (MBP) and cardiac output (CO) in conscious spontaneously hypertensive rats

|                | Control       | CV-4093-2HCl | Nicardipine |
|----------------|---------------|--------------|-------------|
|                | n=8           | n=5          | n=6         | n=6         |
| Body weight (g)| 221±6         | 233±4        | 229±5       | 220±7       |
| MBP (mmHg)     |               |              |             |             |
| 0 hr           | 147±2         | 142±4        | 146±2       | 148±3       |
| 1 hr           | 147±3         | 131±3*       | 120±3*      | 129±7*      |
| CO (ml/min/kg) | 275±14        | 253±14       | 323±29      | 268±25      |

MBP: mean blood pressure. CO: cardiac output. CO was measured 1 hr after oral administration of drugs. *P<0.05 vs. control. Mean±S.E.

Fig. 6. Effects of CV-4093-2HCl (1 and 3 mg/kg, p.o.) and nicardipine (3 mg/kg, p.o.) on blood flow in the cerebral cortex, heart, kidney and small intestine of conscious spontaneously hypertensive rats. The organ blood flow was measured 1 hr after oral administration of the calcium antagonists. ■: control (n=8). ■■■: CV-4093-2HCl (1 mg/kg, n=5). ■■■■: CV-4093-2HCl (3 mg/kg, n=6). □: nicardipine (3 mg/kg, n=6). *P<0.05 vs. control. Mean±S.E.

5). Total peripheral resistance in the higher dose group of CV-4093-2HCl (0.389±0.040 mmHg/ml/min/kg) was significantly lower than that in the control group (0.541±0.026 mmHg/ml/min/kg). However, the decrease in total peripheral resistance in the other two treated groups was not significant compared with the control.

The effects of CV-4093 2HCl and nicardipine on blood flow in the cerebral cortex, heart, kidney and intestine of conscious SHR are illustrated in Fig. 6. CV-4093-2HCl at 1 mg/kg increased blood flow in the small intestine (37% of the control, P<0.05), but not in the other organs and brain stem. The compound at 3 mg/kg increased blood flow in the kidney and intestine (18% and 47%, P<0.01). In addition, vascular resistance was significantly decreased in the intestine (36%, P<0.01) of rats treated with 1 mg/kg of CV-4093-2HCl and in the intestine and kidneys (44% and 30%, P<0.01) of rats treated with 3 mg/kg of the compound. However, CV-4093-2HCl (3 mg/kg) did not show any significant effect on blood flow in the brain stem, stomach, pancreas, liver, skeletal muscle and skin. Nicardipine did not affect blood flows and vascular resistance in the organs tested.

Discussion

The alteration of renal hemodynamics and function is one of the most important factors involved in the mechanism for developing and maintaining hypertension. A lowered ability to excrete sodium ions results in their accumulation in the body, increase in circulatory fluid volume, and enhancement of
vascular reactivity to vasoactive substances (3, 4, 17, 18). Moreover, an increase in the release of renin induced by the decreases in renal blood flow and/or renal perfusion pressure accelerates biosynthesis of angiotensins. Also, in SHR, altered electrolyte metabolism has been demonstrated in the developmental and early phases of hypertension (5, 7, 19). Renal vascular reactivity to vasoactive substances is enhanced in the SHR (6). An abnormal release of renin and damages such as proliferative narrowing in the afferent arterioles of the kidneys were observed in the malignant phase of hypertension in the rats (8, 9). These findings prompted us to develop antihypertensive drugs with the ability to improve alteration of renal circulation. CV-4093-2HCl was discovered in the process of evaluating drug effects on renal blood flow in SHR.

In the present experiments, the effects of CV-4093-2HCl and nicardipine on renal circulation were investigated in the SHR. The effects in normal rats were not examined, since the mean blood pressure in normal rats is 95–105 mmHg under the anesthetized conditions, which is close to the lower limit of the autoregulation of renal blood flow (7). CV-4093-2HCl (5 and 10 μg/kg, i.v.) decreased blood pressure dose-dependently; its action was slow in onset and long-lasting, as observed in the previous experiments in which the drug was orally administered to unanesthetized SHR (11). Moreover, CV-4093-2HCl constantly increased renal blood flow even when the hypotensive effect of the drug was clearly observed in the SHR. Nicardipine especially at the higher dose (10 μg/kg) decreased renal blood flow immediately after it was administered. The effect seems to depend on the steep fall of blood pressure induced by nicardipine but not on renal vascular contraction. This view is supported by the fact that renal vascular resistance was clearly decreased by nicardipine. The drug did not apparently increase renal blood flow at the time when the degree of the hypotensive effect was similar to that in the rats treated with CV-4093-2HCl (see the results at 5 and 20 min in Figs. 1 and 2). These data suggest that CV-4093-2HCl increases renal blood flow in the SHR more effectively than does nicardipine, when compared at the same doses (5 and 10 μg/kg, i.v.).

These findings suggest that CV-4093-2HCl may have high affinity for the renal vascular bed. To elucidate this point, we examined the effects of CV-4093-2HCl on renal and systemic vascular contractions induced by vasoactive substances, NE and ang. II. CV-4093-2HCl and nicardipine inhibited the pressor response (elevation of systemic blood pressure) induced by NE by 33–37% and by 29–32% at 10 min after the administration, respectively. In contrast to this small difference, CV-4093-2HCl inhibited the decrease in renal blood flow induced by NE much more than did nicardipine: the percent inhibition was 45–63% for CV-4093-2HCl and 9–33% for nicardipine. In the case of ang. II, the percent inhibition of both calcium antagonists were much smaller than that observed in the case of NE, suggesting that involvement of extracellular calcium ions is less in the vasoconstriction induced by ang. II. The calcium antagonists slightly but not significantly inhibited pressor responses induced by ang. II to the same extent (11–22% and 15–16%). However, the percent inhibition for the renal vascular contraction was greater for CV-4093-2HCl (32–40%) than for nicardipine (10–24%). The differences of the inhibitory effects of the calcium antagonists became larger at 30 min after the administration. This difference is likely to depend on both the duration and potency of the inhibitory action of the two compounds. These results further suggest that CV-4093-2HCl has a relatively higher affinity for the renal vascular bed in SHR.

This speculation has been strongly supported by the present results indicating that in the conscious SHR rats, CV-4093-2HCl specifically increased renal and intestinal blood flows. Moreover, it has been reported that, as compared with nicardipine, the antagonizing effect of CV-4093-2HCl on potassium-induced vasocontraction was more marked in the isolated kidneys including the arterioles but less in the isolated large renal artery (20). Furthermore, the antagonizing effects of CV-4093-2HCl on potassium-induced vasocontraction were less prominent than those of other calcium antagonists in the aorta and coronary artery of dogs and rabbits.
These findings suggest that CV-4093-2HCl has a higher affinity for the resistant vessels (arterioles and small arteries) in the kidneys.

CV-4093-2HCl and nicardipine did not increase blood flows in the brain and heart in conscious SHR, at least at the doses used in the present study. However, the calcium antagonists, especially CV-4093-2HCl, markedly inhibited the onset of cerebrovascular lesions in stroke-prone SHR (21). These results suggest that CV-4093-2HCl may be able to prevent the development of hypertensive complications through inhibiting abnormal vasoconstriction in the brain and/or improving renal hemodynamic alteration.

In conclusion, CV-4093-2HCl, with long-lasting antihypertensive action, increases renal blood flow and inhibits renal vasoconstriction induced by vasoactive substances. These hemodynamic effects seem to be beneficial for treating patients with hypertension.

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