Antihypertensive Action of a Non-Sulfhydryl Angiotensin Converting Enzyme Inhibitor (CV-3317) in Various Hypertensive Models

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Abstract—The antihypertensive action of N-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-N-(indan-2-yl)glycine hydrochloride (CV-3317), a nonsulfhydryl compound characterized as an angiotensin converting enzyme inhibitor in our previous work, was examined in hypertensive animal models. In 2-kidney, 1 clip hypertensive rats and dogs, CV-3317 (3 and/or 10 mg/kg, p.o.) produced a sustained antihypertensive action of about 15 to 25 mmHg. Daily oral administrations of CV-3317 (1 to 10 mg/kg/day) to spontaneously hypertensive rats (SHR) for 5 weeks produced a sustained antihypertensive action of 20 to 40 mmHg. When CV-3317 (3 mg/kg) was combined with hydrochlorothiazide (10 mg/kg), its antihypertensive action was intensified in potency and duration. CV-3317 (30 mg/kg) induced a slight hypotension (5 to 10 mmHg) in normotensive rats, but had no effect on the blood pressure of 1-kidney, 1 clip hypertensive rats and on that of a low renin type of DOCA/salt hypertensive rat. The antihypertensive activity of CV-3317 was more potent than that of captopril. In pithed SHR, the pressor response induced by an electrical stimulation of the preganglionic sympathetic nerve, but not the pressor response to norepinephrine, was attenuated by both agents (0.3 mg/kg, i.v.). Both agents may exert their antihypertensive action not only primarily by inhibiting the renin-angiotensin system, but also by inhibiting norepinephrine release from the sympathetic nerve terminals indirectly by reducing the formation of vascular angiotensin II.

The renin angiotensin aldosterone system plays an important role in the pathogenesis of hypertension. Long term trials to control hypertensive diseases through regulation of this system have led to the discovery of orally active angiotensin converting enzyme inhibitors, exemplified by captopril. Recent clinical research indicates that this class of agent is extremely useful for treating hypertension (1, 2) and may be suitable for treating congestive heart failure (3). Captopril is effective in treating hypertension, but has some side effects, which have been attributed to the sulfhydryl moiety of the drug (4). N-

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Further, we discuss the possibility that CV-3317 may also exert a hypotensive action by inhibiting the release of norepinephrine from the sympathetic nerve terminals.

Materials and Methods

Hypotensive action in normotensive rats

Male Wistar rats (Jcl), 12 to 23 weeks old, were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the abdominal aorta was cannulated with a polyethylene tube (PE-10 fused to PE-50) via the femoral artery. A catheter was passed subcutaneously, exteriorized on the neck, and filled with saline containing heparin. The catheter was protected by a harness and spring and attached to water tight swivel (Instech 375/22, U.S.A.). The animals were allowed to recover for 1 to 2 days in single plastic cages. The catheter was connected to pressure transducer (Sanei, 45277, Japan) and blood pressure was recorded on a pen-writing oscillograph (Sanei 8662E, Japan) for 6 hr after the drugs were administered. The animals were allowed free access to a diet (CE-2, Japan Clea Laboratories) and tap water during the experiments. CV-3317 (30 mg/kg) and captopril (100 mg/kg) were orally administered in a volume of 2 ml/kg of water as a suspension with gum arabic. Control rats were given vehicle (2 ml/kg of water) alone.

Antihypertensive action in experimental hypertensive animals

Renal hypertensive rats and dogs: Male Wistar rats (Jcl), 5 weeks old, were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). A dorsal incision was made, and the left renal artery was stenosed by applying a silver clip (internal diameter, 0.22 to 0.27 mm). The right kidney was left intact for 2-kidney, 1 clip hypertensive rats (2K,1C-RHR) and removed for 1-kidney, 1 clip hypertensive rats (1K,1C-RHR). After surgery, the rats were maintained on the standard diet (CE-2), tap water, and 1% NaCl solution ad libitum for 3 to 7 weeks. Rats with systolic blood pressures of 160 to 240 mmHg (measured by the tail cuff method) were used.

DOCA/salt hypertensive rats: Male Sprague-Dawley rats, 5 weeks old, were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Immediately after the left kidney was removed, a 25 mg pellet of desoxycorticosterone acetate (DOCA) was implanted into the dorsum of the rat. The rats were maintained on the standard diet (CE-2), tap water, and 1% NaCl solution ad libitum for 4 weeks. The rats were given the test compounds orally immediately after the surgery and then once a day for 4 weeks. Blood pressure was measured once weekly by the tail cuff method.

Antihypertensive action in spontaneously hypertensive rats (SHR)

Male SHR, 13 weeks old, with blood pressure of about 180 to 200 mmHg were used in groups of 6 to 7 animals each. The rats were given the test compounds orally once a day at about 9:00 a.m. for 5 weeks at doses of 1 to 10 mg/kg/5 ml of water as a suspension with a small amount of gum arabic. Blood pressure was measured by the tail cuff method (37°C, 6 to 9 min), and heart rate was measured with a pulse rate meter. The conscious rats were guillotined 5 hr after the final dose of a 5-week treatment regimen, and samples of blood and lung tissues were removed. The ACE activity of plasma and lung homogenates was measured by a radioenzymatic assay (7), as described in...
detail in the second paper (6). Plasma renin activity (PRA) and angiotensin I (A-I) concentration were measured by radioimmunoassay with a commercial assay kit (CEA-IRE-SORIN, France). When CV-3317 was used combined with a diuretic, CV-3317 (3 mg/kg, p.o.) and hydrochlorothiazide (10 mg/kg, p.o.), they were administered daily concurrently to 17 weeks old SHR for 15 days. On the 1st and 15th days, the first 5 hr urine after each dosing was collected, and the urinary sodium and potassium contents were determined with a flame photometer (Hitachi, 205DT, Japan).

Experiments in pithed rats
Male SHR, 20 to 23 weeks old, were used. Under pentobarbital anesthesia (50 mg/kg, i.p.), the left carotid artery and the right jugular vein were cannulated for blood pressure measurements and i.v. injection of drugs, respectively. After bilateral vagotomy was performed, rats were pithed by inserting a steel rod into the spinal column via the orbit and maintained by artificial respiration. Atropine sulfate (1 mg/kg) and d-tubocurarine chloride (1 mg/kg) were administered i.v. After the animals had been allowed to stabilize for about 1 hr, the entire sympathetic outflow was activated with 50V square wave pulses of 0.5 msec in duration and 2 and 20 Hz in frequency delivered with an electronic stimulator (Nihon Kohden, MSE-3R) for periods of 20 sec using the pithing rod and a hypodermic needle inserted under the skin of the back as the cathode. Norepinephrine (0.1 to 10 µg/kg) was injected i.v. The dose of CV-3317 and captopril used was 0.3 mg/kg, i.v.

Data analysis
All results in the text are expressed as the mean±S.E.M. The values among the different groups were analyzed using the one-way analysis of variance and Dunnett's test and Student's paired t-test. P values less than 0.05 were considered significant.

Drugs
The drugs used were (-)-norepinephrine bitartrate (Sigma), atropine sulfate (Wako), d-tubocurarine chloride (Sigma), hydrochlorothiazide (Esidrex powder, Ciba-Geigy), and desoxycorticosterone acetate (Tokyo-Kasei). CV-3317 and captopril were supplied from the Chemistry Laboratories of this Division.

Results
Hypotensive action in normotensive rats
CV-3317 (30 mg/kg) and captopril (100 mg/kg) slightly reduced blood pressure (<10 mmHg) for 4 hr in normotensive Wistar rats (Table 1).

Antihypertensive action in experimental hypertension
Renal hypertensive rats and dogs: In 2K,1C-RHR (Fig. 1), CV-3317 at a dose of 3 mg/kg caused significant antihypertensive action, which disappeared within 5 hr. Captopril (3 mg/kg) was not effective. CV-3317 at a dose of 10 mg/kg produced a marked and sustained hypotension of 15 to 25 mmHg over 8 hr; the effect was longer in duration than that of captopril (10 mg/kg). Neither drug had antihypertensive action in 1K,1C-RHR (Table 1). In the acute phase of 2K,1C-RHD (Fig. 2a), CV-3317 and captopril, at a dose of 3 mg/kg, both caused a significant fall of about 25 mmHg in both systolic and diastolic blood pressures. The hypotensive action was rapid in onset and lasted for at least 8 hr. Heart rate was not significantly altered by the agents. In the chronic phase of 2K,1C-RHD (Fig. 2b), CV-3317 (3 mg/kg) decreased blood pressure by a maximum of 20 to 25 mmHg. The duration of the hypotensive effect was shorter in this model than in the high renin model of hypertension (Fig. 2a). The blood pressure lowering effect of captopril was less potent.
Table 1. Effects of CV-3317 and captopril on blood pressure in normotensive rats and 1-kidney, 1 clip hypertensive rats (1K,1C-RHR)

| Animals         | Drug    | Dose mg/kg. p.o. | 0 mmHg | 1      | 2      | 3      | 4      | 5      | 6      |
|-----------------|---------|------------------|--------|--------|--------|--------|--------|--------|--------|
| Control         | —       | 102±2            | 1.2±1.2| 1.0±1.9| 0.8±2.1| 1.2±2.0| -0.6±2.2| -2.4±2.4|
| Normotensive rats| CV-3317 | 30               | 105±2  | -3.6±2.5| -5.8±1.6| -4.2±2.1| -6.4±1.8| -3.4±2.9| -5.8±2.6|
|                 | Captopril| 100              | 113±3  | -8.2±1.9| -5.8±1.9| -6.8±2.0| -9.2±0.8| -7.2±2.9| -9.6±4.5|
| Control         | —       | 189±7            | 1.6±1.5| -3.0±2.3| -0.4±0.4| -4.0±1.9| 0.2±2.2| 1.3±3.5|
| 1K,1C-RHR       | CV-3317 | 30               | 188±10 | -1.0±2.3| -2.2±4.4| 0.5±6.1| 7.3±6.0| 5.2±3.3| 2.6±4.3|
|                 | Captopril| 100              | 189±5  | -3.2±3.2| -6.0±1.6| -2.0±3.7| -3.0±3.4| 1.8±3.8| 2.8±2.5|

The data show the means±S.E.M. (n=5). Dunnett's test: vs. control. *P<0.05, **P<0.01.
Fig. 2. Antihypertensive action of CV-3317 and captopril in 2-kidney, 1 clip hypertensive dogs (2K, 1C-RHD). (a) Acute phase: n=4, PRA (6.32±2.1 ng A-1/ml/hr. (b) Chronic phase: n=3, PRA (1.07 ±0.30 ng A-1/ml/hr. •, CV-3317; ■, captopril; ○, vehicle. Student’s paired t-test: vs. respective 0 time, *P<0.05, **P<0.01.

Table 2. Effects of CV-3317 and captopril on the development of hypertension in DOCA/salt hypertensive rats

| Dose        | Drug/kg/day, p.o. | Drug administration (weeks) (mmHg) |
|-------------|-------------------|-----------------------------------|
|             | 0                 | 1       | 2                      | 3       | 4                      |
| Control     | —                 | 115±3   | 137±2                 | 160±4   | 178±2                 | 190±4     |
| CV-3317     | 30                | 116±2   | 131±4                 | 157±7   | 187±8                 | 203±12    |
| Captopril   | 100               | 116±3   | 134±3                 | 175±10  | 198±10                | 220±11    |

The data show the means±S.E.M. (n=7). Blood pressure was measured 5 hr after each administration.

than that of CV-3317. Neither agent affected the heart rate.

DOCA/salt hypertensive rats: The consecutive administrations of CV-3317 and captopril had no effect on the development of DOCA/salt hypertension (Table 2).

Antihypertensive action in SHR

When CV-3317, at doses of 1 to 10 mg/kg/day, was administered once a day to SHR for 35 days, it produced a more pronounced antihypertensive action of 20 to 40 mmHg as the number of doses increased. The effect at 1 mg/kg/day lasted for more than 8 hr, and the effect at 10 mg/kg/day lasted for 24 hr. Captopril at a dose of 10 mg/kg/day produced a much reduced antihypertensive action (Fig. 3). As shown in Table 3, CV-3317 (3 and 10 mg/kg/day) markedly inhibited both plasma and lung ACEs after 5 weeks of treatment, whereas captopril activated plasma ACE and slightly inhibited lung ACE. CV-3317 markedly elevated and captopril slightly elevated plasma renin and A-I concentrations. When CV-3317 (3 mg/kg) was given daily for 2 weeks combined with hydrochlorothiazide (10 mg/kg), which by itself reduced blood pressure slightly, the antihypertensive effect of CV-3317 was intensified in potency and duration; the effect lasted for more than 24 hr (Fig. 4). As shown in Table 4, CV-3317 alone had no effect on the urinary excretion of water and electrolytes, and the diuretic action of hydrochlorothiazide was not altered by being combined with CV-3317.

Experiments with pithed SHR

Stimulation of the preganglionic sympa-
thetic nerves (1 to 50 Hz, 0.5 msec, 50 V, 20 sec) produced frequency-related increases in blood pressure. Stimulation with 2 and 20 Hz increased blood pressure by about 30 and 80 mmHg, respectively; the latter was the maximum response. As shown in Fig. 5, the pressor responses to stimulation at the low (2 Hz) and maximum (20 Hz) frequency were reduced by i.v. pretreatment with 0.3 mg/kg of CV-3317 or captopril; the action of CV-3317 was most remarkable. In contrast, the pressor response to norepinephrine (0.1 to 3 \( \mu g/kg \), i.v.) in pithed SHR was slightly, but not significantly, reduced by CV-3317 (1 mg/kg, i.v.) (data not shown).

**Discussion**

We have already reported that CV-3317 is a potent orally effective angiotensin converting enzyme inhibitor and that the potency of this agent on the inhibitory effect of conversion from A-I to A-II is considered to be more potent and longer lasting than that of captopril (6). In the present study, the antihypertensive activity of CV-3317 was examined in normotensive rats and various hypertensive animal models.

CV-3317, as well as captopril, slightly but significantly lowered blood pressure in normotensive rats, indicating that this class of ACE inhibitors has a common hypotensive action (8). Both ACE inhibitors exerted marked, sustained antihypertensive action in renin-angiotensin dependent models of hypertension such as 2-kidney, 1 clip hyper-

![Fig. 3. Antihypertensive action of CV-3317 and captopril in spontaneously hypertensive rats (SHR). Each group consists of 6–7 rats. •, CV-3317; □, captopril; ○, vehicle. Dunnett’s test: vs. vehicle, *P<0.05, **P<0.01.

![Fig. 4. Potentiation of antihypertensive action of CV-3317 combined with hydrochlorothiazide. Each group consists of 10 rats. •, CV-3317 (3 mg/kg/day, p.o.); ■, HC (10 mg/kg/day, p.o.); ▲, CV-3317 plus HC; ○, vehicle. Dunnett’s test: vs. vehicle, *P<0.05, **P<0.01; vs. HC alone, +P<0.05; vs. CV-3317 alone, +P<0.05.

### Table 3. Plasma and lung angiotensin converting enzyme (ACE) activity and plasma renin and angiotensin I (A-I) concentrations following the 5-week-treatment with CV-3317 and captopril

| Drug     | Dose mg/kg/day, p.o. | Plasma ACE (HA nmol/ml/min) | Lung ACE (HA nmol/mg/mg protein/min) | Plasma renin concentration (A-I ng/ml/hr) | Plasma A-I concentration (ng/ml) |
|----------|----------------------|-------------------------------|--------------------------------------|------------------------------------------|---------------------------------|
| Control  | —                    | 49.8±2.3                      | 9.3±0.5                              | 23±5                                     | 0.48±0.23                      |
| CV-3317  | 3                    | 9.4±0.5**                     | 2.7±0.3**                            | 60±12                                    | 1.79±0.47                      |
|          | 10                   | 8.2±0.2**                     | 2.1±0.4**                            | 100±20                                   | 1.86±0.34                      |
| Captopril| 10                   | 66.9±1.8**                    | 7.5±0.5**                            | 37±9                                     | 0.71±0.26                      |

The data show the means±S.E.M. (n=7). HA: hippuric acid. Dunnett’s test: vs. control, **P<0.01.
Table 4. Effects of CV-3317, hydrochlorothiazide (HC) and their combination on urinary excretion of water and electrolytes in spontaneously hypertensive rats (SHR)

| Days after Drug Dose V U\textsubscript{Na} V U\textsubscript{K} | Drug | mg/kg/day, p.o. | ml/5 hr/100 g | \(\mu\text{eq}/5 \text{ hr/100 g} \) |
|---|---|---|---|---|
| Control | --- | --- | 0.70±0.19 | 67±18 | 46±11 |
| CV-3317 | 3 | 0.71±0.21 | 66±19 | 39±8 |
| HC | 10 | 2.40±0.18** | 360±19** | 152±13** |
| CV-3317 plus HC | 3/10 | 2.66±0.27*** | 477±44*** | 173±17*** |
| Control | --- | --- | 1.15±0.11 | 83±6 | 78±8 |
| CV-3317 | 3 | 0.95±0.20 | 76±15 | 67±17 |
| HC | 10 | 2.62±0.07*** | 318±11*** | 149±5** |
| CV-3317 plus HC | 3/10 | 2.56±0.20*** | 387±29*** | 175±17*** |

The data show the means±S.E.M. (n=5). HC: hydrochlorothiazide. Dunnett's test: vs. control, **P<0.01; CV-3317 vs. CV-3317 plus HC, #P<0.01.

Fig. 5. Inhibitory action of CV-3317 and captopril on pressor action induced by an electrical stimulation of preganglionic sympathetic nerves in pithed spontaneously hypertensive rats (SHR). Each group consists of 5 rats. ●, CV-3317 (0.3 mg/kg, i.v.); ■, captopril (0.3 mg/kg, i.v.); ○, vehicle. Dunnett’s test: vs. vehicle, *P<0.05, **P<0.01.

Angiotensin II facilitates the transmission at sympathetic neuro-effector sites (16). The inhibition of A-II formation, i.e., by blockade of ACE, has been reported to suppress the response to sympathetic activation in animals (17, 18). CV-3317 caused significant reductions in the pressor effects in renin-angiotensin dependent models. CV-3317 and captopril did not reduce the blood pressure in renin-angiotensin independent models of hypertension such as 1-kidney, 1 clip hypertensive rats (9, 10) and DOCA/salt hypertensive rats. In particular, it has been reported that in DOCA/salt hypertensive rats, the renin-angiotensin system is suppressed (11).

In SHR, both ACE inhibitors induced marked, sustained blood pressure reduction in spite of normoreninemia (12). The antihypertensive effect of CV-3317 became more marked in potency and duration with repeated dosings. It has been reported that the vascular renin-angiotensin system is potentiated in SHR (13). The antihypertensive effect and its potentiation may be due to the more effective inhibition of tissue ACEs, especially of vascular ACE, as described in the previous paper (6). The antihypertensive effects of CV-3317 was intensified in potency and duration when the drug was combined with a diuretic. The antihypertensive responses to captopril were similar to those reported previously (14, 15).

Contrary to these marked antihypertensive effects in renin-angiotensin dependent models, CV-3317 and captopril did not reduce the blood pressure in renin-angiotensin independent models of hypertension such as 1-kidney, 1 clip hypertensive rats (9, 10) and DOCA/salt hypertensive rats. In particular, it has been reported that in DOCA/salt hypertensive rats, the renin-angiotensin system is suppressed (11).

In SHR, both ACE inhibitors induced marked, sustained blood pressure reduction in spite of normoreninemia (12). The antihypertensive effect of CV-3317 became more marked in potency and duration with repeated dosings. It has been reported that the vascular renin-angiotensin system is potentiated in SHR (13). The antihypertensive effect and its potentiation may be due to the more effective inhibition of tissue ACEs, especially of vascular ACE, as described in the previous paper (6). The antihypertensive effects of CV-3317 was intensified in potency and duration when the drug was combined with a diuretic. The antihypertensive responses to captopril were similar to those reported previously (14, 15).
response to sympathetic stimulation in pithed SHR. Since the postjunctional vascular responses to A-Il (6) and norepinephrine were unaffected by CV-3317, the inhibition of responses to sympathetic stimulation could not be the results of alpha-adrenergic receptor, ganglionic or adrenergic neuron blockade. Therefore, CV-3317 appears to cause a prejunctional inhibition of nor-epinephrine release by inhibiting the formation of vascular A-II in SHR. This would also explain why the consecutive administration of CV-3317 as well as captopril had no effect on heart rate despite of the reduction of blood pressure in SHR.

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