Hemodynamic Changes Following Long-Term Administration of CS-905, a Novel Dihydropyridine Calcium Blocker, in Conscious SHR

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Abstract—To investigate the central and regional hemodynamics after long-term administration of CS-905, a novel calcium blocker, we administered the agent (1 and 3 mg/kg/day) for 15 weeks in spontaneously hypertensive rats. At the end of the dosing period, hemodynamic changes were examined using the radioactive microsphere technique. CS-905 produced a sustained dose-dependent antihypertensive effect without inducing tolerance during the 15-week dosing period and prevented cardiac hypertrophy. The agent increased cardiac output, decreased blood pressure and thus decreased total peripheral resistance in a dose-related manner. Regional blood flows measured by the microsphere technique were increased in the kidney and brain despite the lowered blood pressure. There was no organ where regional blood flow was decreased. These changes after chronic treatment with CS-905 would be beneficial in the long-term therapy of hypertension.

Dihydropyridine calcium blockers are widely used for the treatment of hypertensive diseases. Although the agents are administered for a long period of time in hypertensive patients, no data are available regarding regional hemodynamic changes after chronic therapy in both clinical and experimental hypertension. Central and regional hemodynamic changes induced by long-term therapy are an important aspect of an antihypertensive agent, particularly in view of the quality of life.

CS 905 ((±) 3-(1-diphenylmethylazetidin-3-yl)5-isopropyl-2-amino-1,4-dihydro-6-methyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate) is a novel dihydropyridine calcium blocker that has long-lasting antihypertensive action with little tachycardia in various hypertensive models and renal hypertensive dogs (1, 2). In the present study, we administered CS-905 for 15 weeks in spontaneously hypertensive rats (SHR) and observed the chronic effects of CS-905 on blood pressure and investigated central and peripheral hemodynamics using the radioactive microsphere technique in the conscious state.

Materials and Methods

Male 23 week-old SHR obtained from Hoshino Laboratory Animals (Japan) were used. Systolic blood pressure (SBP) was measured by the tail cuff method (Narco, PE-300). The rats were divided into 3 groups so that SBP were evenly distributed, and they were administered CS-905 (1 or 3 mg/kg/day, p.o., suspended in 0.3% carboxymethylcellulose (CMC)) or 0.3% CMC. SBP was measured at 2 days before and at 1, 3, 5, 9, 12 and 15 weeks after initiation of the dosing. The measurement of SBP was performed 24 hr after the previous administration of the agents.

Measurement of cardiac output and regional blood flows: At the end of the dosing period, the animals were anesthetized with sodium pentobarbital, 30 mg/kg, i.p. A polyethylene cannula (PE 10) was placed in
the left femoral artery to measure arterial pressure and to withdraw reference blood samples. Another polyethylene cannula (PE 50) was placed in the left ventricle via the right carotid artery for the injection of microspheres. The other ends of both cannulae were led under the skin and exteriorized at the back of the neck.

On the next day, about 24 hr after the final administration of the drug or vehicle and the operation, the arterial cannula was connected to a pressure transducer (MPU-0.5, Nihon Kohden, Tokyo, Japan). Mean blood pressure and heart rate were recorded on a rectocorder (Recti-Horiz-8K, NEC Sanei, Tokyo, Japan) in the conscious state. After blood pressure and heart rate were stabilized, approximately 100,000 to 200,000 microspheres labeled with $^{141}$Ce, having a diameter of $15\pm 1$ μm (New England Nuclear, 10 mCi/g), were injected with 0.7 ml of saline into the left ventricle within 30 sec. We measured regional blood flows and cardiac output according to the reference sample technique (3, 4). A reference arterial blood sample was withdrawn from the femoral artery at a rate of 0.67 ml/min for a period of 60 sec starting 5 sec before initiation of microsphere injection. With 15 min, the animal was killed and its organs excised. The excised organs were weighted, and the radioactivity due to $^{141}$Ce in the tissues and reference blood samples were measured in a multichannel auto-gamma scintillation counter (Gamma 8000, Beckman, California, U.S.A.).

Cardiac output, fractional distribution of cardiac output and regional blood flows were calculated according to the following equations:

Cardiac output (ml/min/kg) = reference flow rate x total radioactivity injected/radioactivity in reference blood sample/animal's body weight

Fractional distribution of cardiac output (%) = radioactivity in the tissue x 100/total radioactivity injected

Tissue blood flow (ml/min/kg) = reference flow rate x radioactivity in the tissue/radioactivity in reference blood sample/weight of tissue

All values were expressed as the mean±S.E. The comparison among 3 groups was assessed by Dunnet's $t$-test.

**Results**

Figure 1 shows the time course of changes in SBP during CS-905 dosing. In the control SHR, SBP was 213±5 mmHg before drug administration; it rose to 222±5 mmHg at the 3rd week of dosing period; and then it remained at the same level during the rest of the observation period. Chronic treatment with CS-905 (1 and 3 mg/kg/day) lowered SBP in a dose-dependent manner during the 15-week dosing period. The degree of the decrease in SBP at week 15 was 19 and 43 mmHg in the low and high dose groups, respectively.

As shown in Table 1, mean blood pressure was decreased, cardiac output (CO) increased, and thus total peripheral resistance decreased after a 15-week treatment with CS-905. HR was decreased significantly only in the low dose group, compared with the vehicle group.

Figure 2 shows the distribution of cardiac output after long-term treatment with CS-905. CS-905 produced little change in the distribution of cardiac output; it tended to decrease in the heart and testes, tended to increase in the kidney and liver and remained unchanged in the brain, spleen and gastrointestinal organs. Long-term administration
of CS-905 produced an increase of regional blood flows in the brain, spleen and kidney, while it hardly altered blood flows in other organs (Fig. 3).

The relative heart weight divided by the body weight was significantly decreased after long term treatment with CS-905, although there were no differences in the body weight and relative weights of other organs including the kidney among the 3 groups (Table 2).

**Discussion**

The present study demonstrated that CS-905 had antihypertensive action in SHR without inducing tolerance throughout the 15-week dosing period (Fig. 1). It is well-known that many antihypertensive drugs become less effective on chronic administration. The tolerance in the antihypertensive effect has primarily been attributed to fluid expansion due to salt and water retention (5). We have already reported that CS-905 causes natriuresis and diuresis after chronic administration as well as after acute administration (6). These natriuretic effects may account for the lack of tolerance development with CS-905.
The antihypertensive effect by chronic treatment with CS-905 is attributed to a decrease of total peripheral resistance (Table 1). After long-term administration, CS-905 increased cardiac output in a dose-dependent manner (Table 1): the result coincides with that after an intravenous administration in anesthetized dogs (S. Miyake, unpublished observation). The increase of cardiac output is most probably due to the decrease of cardiac afterload, because CS-905 has no cardiac stimulant action. The long lasting decrease of cardiac afterload leads to a decrease of the heart/body weight ratio (Table 2): a beneficial effect on the cardiac hypertrophy shared by other agents as well (7–9).

Unlike nicardipine, CS-905 causes neither tachycardia nor bradycardia after a single oral administration in SHR (1). In the present study, however, the heart rate was decreased after 15 weeks of consecutive administrations in the low dose group (Table 1). This decrease of heart rate might have been incidental in view of the lack of dose-dependency.

CS-905 did not decrease blood flows in any organ in spite of lowered systemic blood pressure (Fig. 3), suggesting that the agent dilated blood vessels in the whole body. The vasodilation seemed particularly marked in the kidney because blood flow in this organ was increased in the face of decreased blood pressure. Dihydropyridine calcium blockers in general increase cerebral blood flow after a single administration (10). However, the increase of cerebral blood flow was so small in the present study that its functional significance is not certain. Rather, it can be stated that long-term treatment with CS-905 does
not deteriorate the autoregulation of cerebral blood flow.

The chronic treatment with CS-905 produced a significant increase of renal blood flow: 36 and 51%, respectively, in the 1 and 3 mg/kg/day group as compared with control SHR (Fig. 4). There are two possible mechanisms that can account for the increased renal blood flow. It is well-known that intrarenal injection of Ca blockers increase renal blood flow (11, 12). However, conflicting results have been reported on the changes of renal blood flow after intravenous or oral administration of Ca blockers (10, 13, 14). Nievelstein et al. reported that nifedipine did not increase renal blood flow in intact SHR, but increased it in SHR with sinoaortic denervation (15). These findings suggest that a dihydropyridine Ca blocker has a direct renal vasodilating effect, but the effect is masked by the increased sympathetic activity due to baroreceptor reflexes. Since the onset of blood pressure lowering effect is slow after CS-905, the agent activates the sympathetic nervous system to a much lesser degree compared with fast-acting calcium blockers such as nicardipine and nifedipine (1, 2). The marked increase of renal blood flow by CS-905 in the present study may be at least partly related to the lack or a lesser degree of sympathetic activation.

The second possibility is as follows: Glomeruli of SHR are protected from systemic hypertension by relative afferent arteriolar vasoconstriction (16), so that the renal blood flow of old SHR is decreased compared with that of age-matched WKY (17). Chronic treatment with CS-905 produced a sustained reduction of blood pressure in SHR, which in turn may abolish or lessen the afferent arteriolar vasoconstriction. We have already reported that chronic treatment with CS-905 decreases urinary protein excretion and improves renal histopathological changes in SHR (6). These beneficial changes may be attributed to the elimination of afferent arteriolar vasoconstriction.

We previously reported that chronic treatment with CS-905 decreased PRA in SHR (6). Stasch et al. reported a similar effect and suggested that high renin levels in old SHR were due to renal ischemia-stimulated renin release (8). It is therefore possible that the increase of renal blood flow, hence improvement of renal ischemia underlies the decrease of PRA following chronic treatment with CS-905.

It is well-established that dihydropyridine Ca blockers increase coronary blood flow (18–20). CS-905 also increases coronary blood flow when administered intravenously in anesthetized dogs (S. Miyake, unpublished observation). However, there was no significant change in regional blood flow in the heart among the three groups in the present study (Fig. 4). A possible explanation for this difference is that the decrease of myocardial O₂ consumption due to decreased afterload and decreased heart mass may counteract the increase of coronary blood flow induced by the direct vasodilator action of CS-905.

In conclusion, long-term administration of CS-905 produced a sustained reduction of blood pressure during the 15-week dosing period without inducing tolerance. The agent prevented cardiac hypertrophy, and it increased cardiac output and regional blood flow in the kidney. These beneficial effects of CS-905 are important in the long-term therapy of hypertension, particularly in relation to cardiac and renal functions that are impaired in this disease.

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