Calcium (Ca$^{2+}$) channel antagonists are currently used in the treatment of angina pectoris and systemic hypertension. Previous radioligand studies have shown that there exists specific receptor sites for Ca$^{2+}$ antagonists in the brain, heart, vascular smooth muscles and skeletal muscles in several species including human, and these drugs produce therapeutic effects by blocking Ca$^{2+}$ antagonist receptors mainly in cardiac and vascular smooth muscles (Godfraind et al: Pharmacol Rev 38: 321-416, 1986). Previously, the in vivo receptor blocking effects of Ca$^{2+}$ antagonists have not been investigated in relation to their pharmacokinetic parameters such as the plasma concentration. To clarify the relationship between the plasma concentration of Ca$^{2+}$ antagonists and their blocking effects (occupancy) of Ca$^{2+}$ antagonist receptors appears to be important for the analysis of the mode of action of these drugs in vivo. Thus, in the present study, we have measured simultaneously the plasma concentration, Ca$^{2+}$ antagonist receptors (ex vivo, in vivo) and systolic blood pressure in SHR (male, 15-17 weeks old) administered orally with mepirodipine, a novel long-lasting dihydropyridine Ca$^{2+}$ antagonist.

The dihydropyridine Ca$^{2+}$ antagonist receptors in membrane fractions of heart, brain and aorta of SHR, and the plasma concentration of mepirodipine were determined by a sensitive radioreceptor binding assay using (+)-[3H]PN 200-110 (PN) as a radioligand (Yamada et al: J Pharmacol Exp Ther 252: 327-332, 1990).

At 0.5, 3 and 6 hr after the oral administration of mepirodipine (3 mg/kg), there was a significant (69 %, 51 % and 41 % respectively) decrease in maximal (+)-[3H]PN binding sites (Bmax) of heart as well as prolonged hypotension (10-29 % decrease) compared to control values (Bmax: 207±7 fmol/mg protein, blood pressure: 173±3 mmHg). The Bmax for cardiac [3H]PN binding restored to control values at 12 hr following the oral mepirodipine administration. In the cerebral cortex, the mepirodipine administration produced a 34 % decrease in the Bmax for (+)-[3H]PN binding at 0.5 hr compared to control values (Bmax value: 119±3 fmol/mg protein), but no change at 3 hr. Specific (+)-[3H]PN binding in particulate fractions from aortic and cardiac tissues at 10 min after the intravenous administration of (+)-[3H]PN (15 μCi) to SHR was observed, and the in vivo specific binding of (+)-[3H]PN was markedly (40-90 %) inhibited in both tissues of SHR at 0.5 and 6 hr after the oral administration of mepirodipine. The plasma concentration of mepirodipine in SHR showed a maximum (66.7±11.4 ng/ml) at 0.5 hr after its oral administration, and then it decreased with time (3-12 hr). There was a statistically significant correlation (p<0.01) between plasma concentration, Ca$^{2+}$ antagonist receptor occupation and hypotensive effect following oral administration of mepirodipine in SHR. The plasma concentration of mepirodipine necessary for occupying 50 % of Ca$^{2+}$ antagonist receptors in the heart of SHR was approximately 8 ng/ml, while that in the cerebral cortex was approximately 150 ng/ml. There was 39 mmHg reduction of systolic blood pressure in the plasma concentration of mepirodipine at 8 ng/ml in SHR.

In conclusion, the present study has demonstrated that mepirodipine produces a selective and sustained occupation of cardiovascular Ca$^{2+}$ antagonist receptors in SHR, and there is an excellent correlation between the plasma concentration, the receptor occupation and hypotensive effect of mepirodipine. Accordingly, the simultaneous measurements of plasma concentration and receptor occupation of Ca$^{2+}$ antagonists in SHR may become a useful method to evaluate their pharmacokinetics in relation to the pharmacodynamic effects.