Effects of MPC-1304, a Novel Calcium Antagonist, on Stroke-Prone Spontaneously Hypertensive Rats. Kazuto Shigematsu2, Masami Niwa1, Kimihiro Yamashita1, Yasufumi Kataoka1, Hisashi Taguchi2, and Kohtaro Taniyama1. Departments of 1Pharmacology 2, and 2Pathology 2, Nagasaki University School of Medicine, Nagasaki 852.

When stroke-prone spontaneously hypertensive rats (SHRSP) are fed a high-salt diet, severe hypertension occurred and their life span is short because of complications of end-organ damage. We and others obtained data that remedies with antihypertensives such as angiotensin I converting enzyme inhibitor, angiotensin II receptor antagonist and β-adrenoceptor antagonist were effective in controlling high blood pressure and also protected against secondary untoward events related to hypertension in the SHRSP. In this study, effects of MPC-1304, a newly developed calcium antagonist of 1,4-dihydropyridine derivative, on blood pressure and hypertensive complications in SHRSP fed a high-salt diet (SP diet, Funabashi Farm Co., 0.8% NaCl) were investigated. The antihypertensive effectiveness of nicardipine was used for purpose of comparison.

MCP-1304 and nicardipine were added to the diet, in doses of 0.01% (wt/wt) (0.01% MPC-1304 diet), 0.03% (0.03% MPC-1304 diet) and 0.1% (0.1% nicardipine diet), respectively, throughout the experimental period (8-30 weeks of age). Systolic blood pressure and heart rate were measured once in the morning every other week throughout the experimental period, indirectly using an electrosphygmomanometer. One day after measuring systolic blood pressure in the 30-week-old animals, the rats were fasted overnight and decapitated. Blood sampling and serum biochemical analysis, organ weight measurement and histological examination were carried out.

The mean values of the amount of the drugs daily ingested calculated from the daily intake of 0.01% and 0.03% MPC-1304 diets, and 0.1% nicardipine diet were 5.5 mg/kg, 16.2 mg/kg, and 46.9 mg/kg, respectively. Between 8 and 12 weeks of age, the systolic blood pressure of control SHRSP increased rapidly. At 10 weeks of age, the systolic blood pressure of control SHRSP reached 200 mmHg and exceeded 200 mmHg at 12 weeks of age. The systolic blood pressure level maintained over 230 mmHg between 16 and 30 weeks of age. The 1,4-dihydropyridine derivatives ingested by the SHRSP maintained systolic blood pressure to be below 210 mmHg throughout the experimental period. The chronic ingestion of MPC-1304 reduced the concentration of blood urea nitrogen, creatinine, triglyceride and total cholesterol in the serum. Treatment with MPC-1304 inhibited the incidence of cerebral stroke, cardiac fibrosis, proliferative and fibrinoid arteriolitis and malignant nephrosclerosis. There was no significant difference in the antihypertensive effectiveness between 0.01% MPC-1304 and 0.1% nicardipine diets.

Treatment with MPC-1304 significantly reduced the blood pressure during 22-week study. There were no lesions in the brains of the SHRSP treated with MPC-1304. Histological examinations confirmed that MPC-1304 had appreciable and beneficial effects in preventing or reducing the incidence of secondary hypertensive lesions. Among the protective effects of long-term administration of MPC-1304 and nicardipine on secondary lesions detected histopathologically, we noted a dramatic improvement of renal lesions such as glomerular sclerosis, proliferative and fibrinoid arteriolitis. Thus, MPC-1304 had antihypertensive effects in the SHRSP. The present study showed that the SHRSP are an useful experimental model which can be used to evaluate the potency of therapeutic value of antihypertensives.