21) Antihypertensive Effect of YM730, A New Calcium Antagonist, in Stroke-prone Spontaneously Hypertensive Rats. Hamao Toda, Hisayo Oohata, Kazuko Fujimoto, Takeshi Suzuki, Koichiro Kawashima, and Osamu Inagaki*. Department of Pharmacology, Kyoritsu College of Pharmacy, Tokyo 105 and Institute for Pharmacology*, Yamanouchi Pharmaceuticals Co., Ltd., Ibaraki-ken 305.

(3S)-1-Benzyl-3-pyrrolidinylmethyl(4S)-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride (YM730), is a new dihydropyridine type calcium antagonist with a longer duration of action. Antihypertensive effect of YM730 was investigated during its long-term administration in stroke-prone spontaneously hypertensive (SHRSP) rats.

Materials and Methods. Male SHRSP rats aged 10-weeks at the beginning of the experiment were divided into groups and administered orally either 1 or 3 mg/kg per day of YM730 for 9 weeks. Nicardipine (15 mg/kg per day) was used as a standard antihypertensive drug. Control rats received a gavage of distilled water (5 ml/kg per day). Blood pressure and heart rate were determined once every week for 8 weeks by the tail-cuff method. In the 9th week of the experiment, mean blood pressure was determined through a catheter inserted into the abdominal aorta in unanesthetized and freely moving rats. Blood samples (0.3 ml) for the determination of plasma renin concentration (PRC) were obtained from the aortic catheter soon after the determination of blood pressure. In weeks 1, 4 and 8 of the experiments, rats were fasted overnight and loaded with 30 ml/kg of saline together with drug solutions and placed in individual metabolism cages. Urine was collected for 6 hours. At the end of the experiment, rats were sacrificed by decapitation, the brain, heart, and kidney were dissected out and weighed, and examined histologically.

Results. YM730 at each dose did not affect the growth of SHRSP rats. Consistent and dose-dependent antihypertensive effect of YM730 in the SHRSP was observed throughout the experiment. Blood pressure in SHRSP rats treated with YM730 at a dose of 3 mg/kg per day was almost the same with that in animals treated with nicardipine at a dose of 15 mg/kg per day. At the early stage of the experiment, slight tachycardia was observed in rats treated with the higher dose of YM730 and nicardipine. Increases in urine volume, and urinary excretion of sodium and chloride were produced by YM730 and nicardipine throughout the experiment. YM730 and nicardipine did not significantly affect PRC. Administration of YM730 and nicardipine for 9 weeks did not attenuate weights of the brain, heart and kidney.

Discussion. The results of the present study demonstrate that YM730 has consistent antihypertensive action in the SHRSP. The fact that YM730 at a dose of 3 mg/kg per day produced almost the same degree of reduction in blood pressure with that produced by nicardipine at a dose of 15 mg/kg per day suggests that YM730 is three times as potent as nicardipine in antihypertensive effect in SHRSP rats. Diuretic action of YM730 appears to contribute to its antihypertensive effect at least in part. Although administration of YM730 for 9 weeks reduced blood pressure significantly in SHRSP rats, the weight of the heart was not reduced significantly. Administration of the drug for longer period of time may be required to observe any effect on the heart size. In conclusion, YM730 produced sustained antihypertensive and diuretic effects in SHRSP rats.