22) Hypotensive Effect and Cerebral Blood Flow Increasing Action of OPC-13340, a New Long Acting Ca antagonist, in Aged SHR. Natsuki Nakayama, Goro Miyakoda, Mika Otsuka and Youichi Yabuuchi. 2nd Tokushima Institute of New Drug Research, Otsuka Pharmaceutical Co., Ltd. Tokushima 771-01.

Recently, the number of aged people is increasing year by year, and it is getting a very important subject to treat properly the aged hypertensive patients. It is well known that cerebral blood flow is auto-regulated and maintained at constant level independent of the perfusion pressure (blood pressure). However, the lower break point of pressure-blood flow curve shifts to the right (high blood pressure side) in hypertensive patients, and sometimes drastic hypotension causes decrease of cerebral blood flow and results in cerebral ischemia. So that anti-hypertensive agents which have mild hypotensive action and do not decrease cerebral blood flow are preferable in these application.

OPC-13340 (methyl 3-phenyl-2(E)-propyl 1,4-dihydro-2,6-dimethyl 4-(3-nitrophenyl)-3,5-pyridine dicarboxylate) is a new long acting Ca antagonist (J CARDIOVASC PHARMACOL 15: 836, 1990) now undergoing clinical trials as an anti-hypertensive as well as an anti-anginal agent with once daily treatment. In this study, the hypotensive action and effects on the cerebral blood flow (CBF) of OPC-13340 were examined in normotensive Wistar rats (NTR) and aged spontaneously hypertensive rats (SHR) comparing with those of nicardipine and nimodipine.

Materials and Methods (1) Measurement of blood pressure: Male Wistar rats (15 weeks old) or SHR (52 weeks old) were anesthetized with sodium pentobarbital and cannulated into the abdominal aorta, and the blood pressure was measured in conscious state after 2 days of the surgery. (2) Measurement of CBF: Male Wistar rats (10 weeks old) or SHR (50 weeks old) were anesthetized and hydrogen electrodes were implanted stereotactically into deep cerebrum and cortex. After more than 2 weeks, the CBF was measured in conscious state using hydrogen clearance method.

(3) Drugs: Drugs were dissolved in 90% polyethylene glycol 400, and orally administered in the volume of 1ml/kg. The control experiments using solvent were carried out for both measurement. (4) Statistics: Multiple group comparisons were done by analysis of variance (ANOVA), followed by Turkey's test using SAS program.

Results and Discussion: In NTR, OPC-13340 (10mg/kg) significantly decreased systolic blood pressure (sBP) about 25mmHg, and increased CBF 50-60% in both cortex and deep cerebrum from 1hr to 8hr after administration ($P<0.01$). Nicardipine or nimodipine (30mg/kg) caused same extent of hypotension as OPC-13340, but increased CBF only 20-30%. On the other hand, in the case of aged SHR, OPC-13340 (1mg/kg) decreased sBP about 36mmHg and tended to increase CBF 10-15%. OPC-13340 (3mg/kg) decreased sBP about 50mmHg, and in this case CBF did not increase. In contrast to this, nicardipine (3 and 10 mg/kg) dropped the sBP about 35 and 50mmHg, respectively, and significantly decreased the CBF by 10-20% compared to prevalue. These data suggest following findings. (1) OPC-13340 has more potent CBF increasing action compared with nicardipine or nimodipine at the dose of same hypotensive action in NTR. (2) In aged SHR, moderate hypotensive treatment does not drop CBF, but drastic hypotension causes decrease of CBF in the case of nicardipine. The administration of OPC-13340 does not cause deterioration of CBF even at the dose which causes drastic hypotension.

In conclusion, the anti-hypertensive treatment of elderly patients with OPC-13340 might be safer than that with nicardipine with respect to the cerebral blood flow.