Hemodynamic effect and pharmacokinetics of semotiadil fumarate(SD-3211), a novel Ca channel blocker, in spontaneously hypertensive rats. Nobuaki Miyawaki, Toyokazu Takada, Chima Satoh, Kouichi Kawazu and Katsuhiko Nakata. Central Research Laboratories, Santen Pharmaceutical Co., Ltd., Osaka 533, Japan.

Semotiadil fumarate, a non-dihydropyridine type of Ca channel blocker, acts on vasculature selectively as compared with cardiac tissue and has a potent and long-lasting antihypertensive effect in spontaneously hypertensive rats (SHR).

In the present study, to make clear the details of its antihypertensive action, we studied hemodynamic effect of semotiadil using radio isotope-labeled microsphere techniques in male SHR. Semotiadil administered orally at 10 mg/kg produced a significant decrease in blood pressure with little influence on heart rate, accompanied with a reduction of total peripheral resistance and an increase in cardiac output. Thus, it is indicated that semotiadil shows antihypertensive effect through its peripheral vasodilation without cardiodepression.

Furthermore, in male SHR we determined antihypertensive effect of semotiadil administered orally at 30 mg/kg in relation to its concentrations in plasma and in resistance vessels (mesenteric artery), which was thought to be the target organ of this compound as described above. The analysis of the concentration-effect relationship for semotiadil in vivo revealed that a counterclockwise hysteresis was observed for the relation between plasma concentration and its antihypertensive effect, and indicated that the drug concentration in vascular tissue was more closely correlated with the effect than that in plasma. In addition, although the fashion of time courses for concentration of a major metabolite of semotiadil in plasma and vessels were coincident with the unchanged form of semotiadil, the level of the metabolite was clearly lower than that of the unchanged drug. According to the comparative study of Ca antagonistic activity between the unchanged form and the metabolite, in which the unchanged drug was shown to be 14 times more potent than the metabolite, it is suggested that the metabolite little contributes to the effect of semotiadil in vivo. Thus, semotiadil by itself existing in adequate level in peripheral arteries may relate to its long-lasting antihypertensive effect.