1) Acute Tolerance to the Hypotensive Effect of Pindolol in Conscious SHR. Kazuki Matsunaga and Motohiko Ueda. Department of Pharmacology, Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553.

The antihypertensive effect of pindolol, a potent nonselective β -blocking agent with intrinsic β -sympathomimetic activity, is well documented in man as well as in experimental animals, but its mechanism of action is still obscure. In our previous study, pindolol at doses of 0.03-10 mg/kg i.p. caused sustained acute hypotension in conscious SHR which was apparently related to reduction of total peripheral resistance and inhibited by 1-propranolol but not by d-propranolol. Therefore, acute hypotension produced by pindolol in SHR was suggested to be due to partial agonistic activity at the vascular β -adrenoceptors.

In this study, we examined the development and mechanism of acute tolerance to the hypotension produced by pindolol in conscious SHR. Although pindolol at doses larger than 1 mg/kg i.p. produced a marked hypotensive effect on the first day, its hypotensive effects gradually decreased after the second day. At a daily dose of 3 mg/kg i.p., the hypotensive effect (50 ± 4 mmHg) on first day was attenuated to 12 ± 2 mmHg on the fourth day. The development of this acute tolerance to pindolol was slightly reduced by bilateral adrenalectomy but not by the combined administration with captopril 100 mg/kg p.o. or trichlor-methiazide 3 mg/kg p.o. The hypotensive effect of pindolol was not reduced by the repeated administration of isoproterenol 1 mg/kg i.p. Thus, compensatory activation of the renin-angiotensin system, fluid retention and β -adrenoceptor subsensitivity seemed to be ruled out from the mechanism of this acute tolerance to pindolol.

In conscious SHR tolerant to pindolol, prazosin 3 mg/kg i.p., clonidine 0.1 mg/kg i.p., hydralazine 3 mg/kg i.p., nifedipine 3 mg/kg i.p. and captopril 100 mg/kg i.p. produced marked hypotensive effects similar to those in saline-treated SHR. The depressor response to isoproterenol (0.1-0.3 μ g/kg i.v.) was markedly reduced in conscious SHR tolerant to pindolol. The correlation between both hypotensive responses to isoproterenol(x) and pindolol(y) in these SHR could be expressed by the following equation: $y = 1.00x + 0.56$ $r = 0.837$ ($p < 0.001$).

Therefore, the main mechanism of this acute tolerance to pindolol seemed to be an "autoblockade," by which the effect of pindolol was inhibited by the pindolol remaining from a previous administration. In other words, intrinsic β -sympathomimetic activity, which produced a hypotensive effect, was inhibited by a β -blocking effect.

Since pindolol even at low dose (about 0.1 mg/kg i.p.) possesses a sufficiently hypotensive effect, an inadequate high dose should be avoided to prevent the tolerance.