64) Mechanisms of the Acute Hypotensive Effect of β -Adrenergic Blocking Drugs with α -Blocking Activity in Conscious SHR. Hajime Nakahara, Mikio Nakazawa, Keisuke Takeda, and Shoichi Imai. Department of Pharmacology, Niigata University School of Medicine, Niigata 951

Like labetalol, arotinolol (S-596) and nipradilol (K-351) have been reported to possess the α -adrenergic blocking effect besides the β -adrenergic blocking effect and to exhibit the acute hypotensive effect in experimental animals. The potency ratio of α - and β -adrenergic blocking effects of the three compounds as assessed in the isolated smooth muscle preparations of the rat aorta and the isolated atrial muscle preparations of the guinea pig was 0.5 for labetalol, 0.006 for arotinolol and 0.013 for nipradilol. In the present study we attempted to investigate the role of α -adrenergic blocking effect in the acute hypotensive effect of the above three β -adrenergic blocking drugs with α -blocking activity in conscious SHR. For comparison, the effects of prazosin and hydralazine were also studied.

According to the method of Weeks and Jones, male SHR (12W) were anesthetized with ether and catheters were implanted into the right femoral artery and vein to measure blood pressure and to administer adrenergic agonists, respectively. After the recovery period of four days, animals were treated orally with either vehicle (0.5% CMC) or drugs as mentioned below. The resting blood pressure and the heart rate were recorded under conscious and unrestrained condition before and 1, 4, 8 and 24 hours after the administration of the drugs. At the same time α - and β -adrenergic blocking effects were assessed by determining the extent of the blockade against the responses induced by phenylephrine (1 and 3 μ g/kg), noradrenaline (1 μ g/kg) and isoproterenol (0.3 μ g/kg) injected via the venous cannula.

The resting blood pressure fell about 20 to 30 mmHg at 1 to 4 hours after oral administration of labetalol (30mg/kg), arotinolol (100mg/kg), nipradilol (100mg/kg) or prazosin (0.3mg/kg). Hydralazine (3mg/kg) and lower doses of arotinolol (30mg/kg) and nipradilol (10, 30mg/kg) elicited a slight fall of the blood pressure but propranolol (100mg/kg) did not. The changes in the heart rate were varied: a decrease (β -blockers), an increase (hydralazine) and no change (prazosin) were noted. Prazosin abolished (80-100%), and labetalol clearly diminished (45%) the pressor response to phenylephrine (1 μ g/kg, i.v.), while the diminishment of the pressor response to phenylephrine was slight (15-20%) with arotinolol (100mg/kg) and nipradilol (100mg/kg). Hydralazine did not alter the pressor response to phenylephrine. The depressor response to isoproterenol was suppressed by nipradilol (3mg/kg) or propranolol (100mg/kg). The analysis of the relationship between the changes in the resting blood pressure and the changes observed in the pressor response to phenylephrine revealed that the hypotensive effect of prazosin was in proportion to the degree of the α -blockade. The same holds true for the hypotensive effects of higher doses of the three β -blockers with α -blocking activity, but not for those of lower doses. Combined administration of propranolol (100mg/kg) with prazosin (0.01 mg/kg) did not result in a definite hypotensive effect. The dose of prazosin was so chosen as to produce an α -blockade of a similar magnitude to those produced by either arotinolol or nipradilol. This dose of prazosin, when given alone, produced a definite fall of the blood pressure. These results suggest that unlike prazosin the hypotensive effects of lower doses of 3 β -blockers with α -blocking activities were not related with the α -blocking activities and that the hypotensive effects at lower doses could not be explained on the basis of combined effects of β - and α -blocking activities.