30) Antihypertensive Effects of Arotinolol (S-596) in Spontaneously Hypertensive Rats. Koichiro Kishi*, Koichiro Kawashima** and Hirofumi Sokabe*.

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INTRODUCTION

Arotinolol (ARL) is a β -adrenoceptive blocking agent which possesses α -adrenoceptive blocking property (Miyagishi et al.: ARCH INT PHARMACODYN 261:222, 1983). ARL (10 mg/kg per day, p.o.) showed significant antihypertensive effects in spontaneously hypertensive (SHR) rats during 2 weeks (Hara et al.: FOLIA PHARMACOL JAPON 82:103, 1983). They determined blood pressure (BP) directly by the aortic cannulation. We examined antihypertensive effects of ARL in SHR for 12 weeks, using propranolol (PPL) as the reference drug. Effects on plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) were determined.

MATERIALS AND METHODS

Ten-week-old male SHR rats of F40 from the colony of the Department of Pharmacology, Jichi Medical School were used. A total of 4 experimental groups, with 9-11 rats in each, were studied. ARL and PPL were suspended with 0.5 % methyl cellulose at a volume of 5 ml/kg body weight. ARL (20 and 100 mg/kg) and PPL (100 mg/kg) were administered orally by a gastric tube once a day for 12 weeks. Tail BP and heart rate (HR) were determined every week, using a rat tail manometer-tachometer system (KN-210, Natsume) after prewarming the rats at 50 °C for 3 min. The interval between the drug administration and the BP determination was 20 hr. At the end of the experiment, mean BP was determined directly without anesthesia or restraint through a cannula inserted into the abdominal aorta. Blood sample (0.8 ml) were obtained from the same cannula. Then, the rats were sacrificed and inspected macroscopically. PRC and PAC were determined by the modified method of Carvalho et al., and the direct radio-immuno-assay, respectively.

RESULTS

The increases in body weights of two ARL treated groups were slightly faster than that of the control group. It was slightly slower in PPL group. ARL and PPL treatments significantly decreased HR compared to the control from the first week. Tail BP values were slightly larger in two ARL treated groups than in the control, whereas they were slightly smaller in PPL group than in the control. However, differences were not statistically significant. Mean BP determined directly at the 12th week were lower in two ARL and PPL groups than in the control. The differences were more than 20 mmHg.

ARL and PPL treatments significantly affected the organ weights. Kidney weights were larger in higher dose of ARL and PPL groups than in the control. Liver weights were larger in two ARL groups than in the control.

Both PRC and PAC values were smaller in higher dose of ARL and PPL groups than in the control. There were no significant correlation between mean BP and PRC or PAC value.

DISCUSSIONS

Discrepancy between mean and tail BP values became apparent after administration of β -adrenoceptive blocking drugs. Mean BP determined directly without anesthesia or restraint must be more reliable than tail BP determined indirectly after prewarming at 50 °C for 3 min. Therefore, ARL (20 mg/kg, p.o.) may have almost the same chronic antihypertensive activity in SHR rats as PPL (100 mg/kg, p.o.) does.

The reason of increases in kidney and liver weights in ARL and PPL treated groups is unknown, but may be related to their toxicity.

The fact that no significant correlation existed between mean BP and PRC or PAC value suggests that participation of the renin-angiotensin-aldosterone system in the pathogenesis of hypertension and antihypertensive effect of ARL or PPL in SHR rats is limited.