Bunitrolol (BNT) (1, 2) and pindolol (PDL) (3) are β-adrenergic blocking drugs with intrinsic sympathomimetic activity. We determined the antihypertensive effect of BNT in hypertensive rats using PDL as the reference drug. The previous reports indicated that PDL is effective in spontaneously hypertensive rats (SHR) (4-6), but not effective in deoxycorticosterone and salt (DOC) hypertensive rats nor in two kidney, one clip hypertensive (CLIP) rats (4, 7).

BNT and PDL were given orally at 50 and 30 mg/kg, per day, respectively, every day for 10 weeks in SHR, DOC, and CLIP rats. Tail blood pressure (BP) and heart rate (HR) were determined every week. At the end of the experiment, the mean BP was determined directly through a cannula inserted into the abdominal aorta. Plasma renin activity (PRA) was measured. Vascular lesions in the renal, cardiac, and mesenteric areas were examined. No antihypertensive effects of BNT and PDL were demonstrated in the three models of hypertensive rats except in the DOC hypertensive rats treated with PDL.

SHR rats were female, 6 weeks of age, weighing 160-190 g, as reported previously (8). The drug treatments were started 6 weeks after the surgery or initiation of DOC treatment. A total of 9 experimental groups with 9-10 rats in each were studied. Tail BP and HR were determined as reported previously (8) once a week immediately before and for 9 weeks after the drug treatments had started. The intervals between the drug administration and the determination were 5–8 hr, and they were randomized in each rat. At the end of the drug treatments, during the 10th week, mean BP values were determined directly without anesthesia or restraint as reported previously (9). The drugs were administered orally by a gastric tube twice (10:00–12:00 hr) daily for 10 weeks. Administration frequency was changed from twice to once at the 3rd, 4th, and 6th week after the treatment had started in SHR, DOC, and CLIP hypertensive rats, respectively. Bunitrolol hydrochloride (C.H. Boehringer Sohn) and pindolol (Sandoz) were used. BNT and PDL were dissolved with H2O and 0.24% of tartaric acid, respectively, at a volume of 5 ml/kg body weight. The doses of BNT and PDL were 50 and 30 mg/kg, respectively, and referred to the free bases. For the control rats, H2O was given by the same schedule. After the direct BP determination, 0.5 ml of blood sample was obtained from the aortic cannula, and it was used for determination of PRA by the modified
method of Carvalho et al. (9). The rat was then sacrificed with ether and inspected macroscopically.

The body weight of each of the three groups of differently treated SHR and CLIP rats increased gradually at almost an equal rate. In DOC hypertension, PDL treatment increased body weight more markedly from the 3rd week as compared to the other groups when PDL decreased BP in this group.

The control groups of the three types of hypertensive rats that were given H_2O showed fairly constant HR values during the experiment. In SHR rats, PDL and BNT treatments slightly decreased HR against the control group, but the differences were statistically not significant. In DOC hypertension, PDL and BNT treatments decreased HR gradually from the initiation of treatment. The differences were statistically significant against the control. In CLIP hypertension, PDL and BNT treatments decreased HR after the 3rd and 2nd week, respectively, against the control group.

In SHR rats given H_2O, BP elevated to over 150 mmHg at the 3rd week of the experiment, 9 weeks of age; and BP continued to increase until the 10th week. PDL and BNT treatments did not change the BP curves from that of the control group. In DOC hypertension (Fig. 1), PDL treatment increased BP for the first 2 weeks and decreased after the 3rd week when compared with the control group. The difference at the 3rd week was statistically significant (P<0.025). BNT treatment increased BP over the H_2O group, but the difference at either week was statistically not significant. In CLIP hypertension (Fig. 2), PDL treatment increased BP during the experiment except at the 6th week. The reason of this marked BP decrease at the 6th week was not known. However, it might be due to the change of administration frequency of the drug. The same was observed in the BNT treated group. BNT treatment also increased BP for the first 5 weeks and for the 7–9th weeks.

PRA was decreased in SHR rats treated with PDL and BNT. The difference of PDL treated group was statistically significant.
against the H2O group. In DOC hypertension, the treatments with PDL and BNT also decreased PRA, although the differences were statistically not significant. In CLIP hypertension, PRA was increased with PDL and decreased with BNT, but neither difference was significant.

The vascular lesions were not evident in the SHR rats. The treatment with PDL or BNT did not change the severity of vascular lesions in DOC and CLIP hypertension.

In DOC hypertension, BNT treatment rather increased BP, whereas PDL decreased BP after the 3rd week. This antihypertensive effect of PDL was substantiated by the observed increase in body weight. As reported previously, a simultaneous decrease in BP and increase in body weight are seen after the treatment with hydralazine and related drugs (10). The increase in body weight is probably due to the improved general condition caused by BP depression with the drugs.

We gave BNT and PDL twice daily at first to the rats because the plasma half-life of BNT in rats given this drug at a dose of 50 mg/kg, p.o., is known to be 45 min (11). However, irritable symptom and general weakness were frequently seen after twice daily administration. The incidence of death was also increased. Therefore, we had to change the administration frequency from twice to once daily.

As BNT and PDL have an intrinsic sympathomimetic activity, only a minor effect on HR is seen by the acute treatment. However, chronic treatments with these drugs decreased HR in the three models of hypertensive rats. The effect in SHR rats is in accord with the previous report (5). It took several weeks before HR decreased significantly after daily administration of BNT or PDL in DOC and CLIP hypertensive rats.

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