A COMPARISON OF ANTIHYPERTENSIVE EFFECTS OF ATENOLOL AND PROPRANOLOL IN THE SPONTANEOUSLY HYPERTENSIVE, DOCA/SALINE HYPERTENSIVE AND RENAL HYPERTENSIVE RATS

Keisuke TAKEDA, Yoshito NAKAGAWA, Wan Pao CHIN and Shoichi IMAI

Department of Pharmacology, Niigata University School of Medicine, Asahimachi-dori 1, Niigata 951, Japan

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Abstract—Antihypertensive effects of a long-term oral regimen of atenolol were studied in SHR, DOCA/saline hypertensive and renal hypertensive rats (one kidney, one clip) in comparison with the effects of propranolol. Both the β-blockers prevented the development of hypertension in SHR but did not affect that in DOCA/saline and renal hypertensive rats. Both of the β-blockers produced no acute hypotensive effects on the established DOCA/saline and renal hypertension of the rat, although they produced a decrease in the heart rate.

Anti hypertensive effects of β-blockers having widely different pharmacological characteristics have been shown in SHR (1–5) and DOCA/saline hypertensive rats (6–9). As regards to atenolol, a cardio-selective β-blocker with no sympathomimetic (10–12) and membrane stabilizing activities (13–15) and poor penetrability through the blood-brain barrier (10, 16), retardation of the development of hypertension was observed in this laboratory in SHR with chronic regimen (2). Similar antihypertensive effects have been reported by Richer et al. (4).

In the present study the antihypertensive effects of a chronic oral regimen of atenolol was studied in DOCA/saline and renal hypertensive rats in comparison with those of propranolol. For comparison, the effects of these two blockers on the development of hypertension were studied in SHR.

Recently Buckingham et al. (7) and Tsukada et al. (9) have shown a lowering of the blood pressure of DOCA/saline hypertensive rats after acute oral administration of small doses of pindolol. Therefore, acute oral effects of a small dose of atenolol were examined in established DOCA/saline hypertensive and renal hypertensive rats.

MATERIALS AND METHODS

Animals were kept in group cages (5 to 6 rats per cage) with free access to tap water and to a rat pellet diet (Oriental MF). β-Blockers were administered by gavage in a volume of 0.5 ml/100 g twice daily (10 a.m. and 4 p.m.). Systolic blood pressure, heart rate and body weight were measured twice a week as described in a previous paper (1, 2). Systolic blood pressure and heart rate were measured at the tail using a photoelectric sphygmomanometer (Natsume KN-0090).

1) Chronic oral regimen with β-blockers in hypertensive animal models

A. SHR: SHRs used were bred from breeder rats kindly provided by Prof. Oka-moto of the Department of Pathology, Kinki
University School of Medicine. Daily administration of \( \beta \)-blockers was started at the age of 5 weeks after weaning and continued up to 12 weeks.

B. DOCA/saline hypertensive rats: Male Wistar-Imamichi rats (WI) weighing 330–370 g were used. The left kidney was removed under ether anesthesia. After nephrectomy, DOCA (10 mg/kg) was injected subcutaneously once a week as a 25 mg/ml suspension in 4% gum arabic. At the same time, drinking water was replaced by a 1% NaCl solution. Administration of \( \beta \)-blockers was initiated 3 days after operation and continued every day for 4 weeks.

C. Renal hypertensive rats (RHR): Male Wistar-Imamichi rats, weighing 150–200 g were used. Under ether anesthesia, the left renal artery was clamped by a silver ribbon (slit width, 0.2 mm).

II) Acute administration of atenolol in DOCA/saline hypertensive rats and RHR

DOCA/saline hypertensive rats and RHR were prepared by the above procedures. At 6 to 8 weeks after the operation, the systolic blood pressure and heart rate were 186.9±5.1 mmHg (mean±S.E.) and 419.6±9.1 beats/min (n=29) in DOCA/saline hypertensive rats and 212.0±4.0 mmHg and 458.6±15.9 beats/min (n=16) in RHR.

Drugs used were propranolol hydrochloride (ICI Pharma) and atenolol (ICI Pharma).

Statistical analysis was performed using the Student's t-test for group comparison.

RESULTS

I) Chronic oral regimen with atenolol and propranolol in SHR, DOCA/saline hypertensive rats and RHR

A) Effects of atenolol and propranolol on the development of hypertension in SHR:

Atenolol was administered orally at doses of 15 mg/kg, 30 mg/kg and 45 mg/kg twice daily and propranolol at 1.5 mg/kg and 15 mg/kg twice daily. Administration of the \( \beta \)-blockers was started at the 5th week of age and continued for a period of 12 weeks. Significant antihypertensive effects were observed with 15, 30 and 45 mg/kg of atenolol and with 15 mg/kg of propranolol, 4 weeks after administration (Table 1). The blood pressure remained lower than that of the control SHR throughout the entire period of administration (Table 1). The heart rate was decreased immediately after administration of atenolol and propranolol and remained lower than that of the control SHR throughout the period of administration (Table 1). Figure 1 depicts the effects of 15 mg/kg of atenolol in comparison with that of propranolol (15 mg/kg). With 1.5 mg/kg of propranolol, there was no change in the blood pressure, although the heart rate was always lower in treated SHRs than in control SHRs (Table 1). The effects of \( \beta \)-blockers on the blood pressure and heart rate disappeared after withdrawal of the drugs. Both \( \beta \)-blockers had no effects on the body weight of SHRs as summarized in Table 1.

B) Effects of atenolol and propranolol on the development of hypertension in DOCA/saline hypertensive rats: Since the antihypertensive effects of propranolol in SHR were not demonstrated at a dose of 1.5 mg/kg, 15 mg/kg of propranolol was administered in the following experiments: The oral administrations of atenolol and propranolol were started at a time when the blood pressure still remained in a normal range. Atenolol (15, 30 and 45 mg/kg) and propranolol (15 mg/kg) did not lower the systolic blood pressure in DOCA/saline hypertensive rats. Rather, the hypertension developed faster than in the control groups. There was an immediate decrease in the heart rate at all doses of \( \beta \)-blockers. The effects of atenolol (15 mg/kg twice daily) and propranolol (15 mg/kg twice daily) on the systolic blood pressure and heart rate of the DOCA/saline hypertensive rats are depicted.
Table 1. Effects of chronic oral administration of atenolol and propranolol as assessed at 4, 8, 11 and 16 weeks after start of administration on the blood pressure, heart rate and body weight in SHR

|                  | Control (n=10) | Atenolol (n=10) | Propranolol (n=10) |
|------------------|---------------|-----------------|-------------------|
|                  | 15 mg/kg      | 30 mg/kg        | 45 mg/kg          |
| 4th. W.          | 168.2±3.8     | 152.3±2.5**     | 149.7±2.7**       |
| 8th. W.          | 174.8±1.4     | 152.5±3.4**     | 150.7±3.5**       |
| 11th. W.         | 186.1±3.2     | 161.0±3.9**     | 155.7±4.4**       |
| 18th. W.         | 187.1±2.2     | 184.6±3.7      | 177.4±4.6         |
|                  | 15 mg/kg      | 15 mg/kg        |                   |
| 4th. W.          | 446.0±3.4     | 378.0±8.4**     | 367.0±4.2**       |
| 8th. W.          | 436.0±10.5    | 379.0±6.6**     | 350.0±2.9**       |
| 11th. W.         | 426.0±20.8    | 360.0±7.1*      | 328.0±6.3*        |
| 16th. W.         | 396.0±13.0    | 427.0±9.8       | 385.0±12.4        |
|                  | 15 mg/kg      | 15 mg/kg        |                   |
| 4th. W.          | 136.5±6.6     | 143.7±8.3       | 129.4±6.1         |
| 8th. W.          | 179.2±9.2     | 175.9±7.8       | 172.0±10.6        |
| 11th. W.         | 209.3±13.5    | 208.3±12.8      | 198.8±14.7        |
| 16th. W.         | 232.6±16.3    | 224.4±16.4      | 221.6±17.1        |

in Fig. 2. Both β-blockers did not affect the body weight at any of the doses.

C) Effects of atenolol and propranolol on the development of hypertension in renal hypertensive rats: Both β-blockers (15, 30 and 45 mg/kg of atenolol and 15 mg/kg of propranolol) were ineffective on the development of renal hypertension: the systolic blood pressure tended to be slightly higher with 30 mg/kg and 45 mg/kg of atenolol as well as with 15 mg/kg of propranolol. The heart rate was significantly suppressed soon after oral administration of β-blockers. 15 mg/kg of atenolol and 15 mg/kg of propranolol, as shown in Fig. 3. Atenolol as well as propranolol did not affect the daily growth of the animals at any of the doses.

II) Acute effects of atenolol and propranolol in established DOCA/saline hypertensive rats and RHR

To examine whether the smaller doses of atenolol were effective in DOCA/saline hypertensive rats, the effects of 150 μg/kg of this compound were studied in comparison with
Fig. 1. Antihypertensive effects of chronic oral administration of atenolol and propranolol in SHR. β-Blockers were administered twice a day. Ordinate: the systolic blood pressure (BP) or the heart rate (HR). Abscissa: weeks after start of the administration of β-blockers. White column indicates the administration period. Each point represents the mean±S.E.

Fig. 2. Effects of chronic oral administration of atenolol and propranolol on the development of hypertension in DOCA/saline hypertensive rats. White column indicates the oral administration period. Abscissa: days after the administration of β-blockers. Abbreviations are as in Fig. 1.
those of 15 and 30 mg/kg. It was found that the smaller dose as well as the two higher doses of this compound were without effects on the blood pressure or on the heart rate, although the two higher doses (15 mg/kg and 30 mg/kg) induced significant decreases in the heart rate.

The effects of 30 mg/kg of atenolol are shown in Fig. 4. Propranolol (15 mg/kg) decreased the heart rate but raised the blood pressure.

In established RHRs, even a higher dose of atenolol 30 mg/kg p.o., did not produce any effects on either the blood pressure or the heart rate. Propranolol (15 mg/kg p.o.) also had no effects.

**DISCUSSION**

In the present study, the antihypertensive effect was observed with atenolol in SHR. Atenolol is a $\beta$-blocker which penetrates poorly into the brain (10, 16). Thus, it is necessary to take into consideration some peripheral mechanism to explain the observed
antihypertensive effect of the compound in addition to the central mechanism proposed for propranolol (17, 18). A definite decrease in the heart rate was observed soon after administration of atenolol (as well as of propranolol) in all the hypertensive models used. However, the antihypertensive effects in SHR appeared 4 weeks later corresponding to the findings in humans (19). One possible mechanism is, therefore, the long-term auto-regulatory process as proposed by Coleman and Guyton (20), which comes into operation in response to a long-standing reduction of the cardiac output and leads to a decrease in the peripheral vascular resistance. Lack of antihypertensive effects in atenolol in DOCA/saline hypertensive rats and renal hypertensive rats were in agreement with previous reports obtained in this laboratory (1) or elsewhere with many other β-blockers (21–23).

Recently it was found that smaller doses of several β-blockers could produce hypotensive effects on the DOCA/saline hypertensive rats, while higher doses failed to induce antihypertensive effects (24). In view of these recent findings, acute experiments were conducted with a smaller dose of atenolol using the established DOCA/saline hypertensive rats. No antihypertensive effects were observed. Furthermore, higher doses of atenolol were without effects, as was propranolol. Thus, the effectiveness of smaller doses seems to be limited to pindolol. A higher dose of propranolol (15 mg/kg) produced even pressor effects. It may probably be due to the liberation of catecholamines from the adrenal medulla (21, 25) or elevation of the vascular tone of skeletal muscle due to blockade of β-receptor (26, 27).

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