EFFECTS OF ACUTE AND CHRONIC TREATMENTS WITH ATENOLOL AND PROPRANOLOL ON CARDIOVASCULAR RESPONSES TO HANDLING STRESS IN SPONTANEOUSLY HYPERTENSIVE RATS

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Although the mechanism of antihypertensive action of β-adrenergic blocking drugs (β-blockers) is not known, a theoretical advantage of cardioselective β-blockers over nonselective ones has been proposed in the treatment of hypertension. To study this hypothesis, we examined cardiovascular responses to handling stress in spontaneously hypertensive (SHR) rats after a single (100 mg/kg) and multiple oral treatments (100 mg/kg per day for 17 d) with either atenolol or propranolol. Atenolol and propranolol markedly suppressed the tachycardia induced by handling stress after acute and chronic administration. Resting mean arterial pressure (MAP) was reduced by acute and chronic atenolol treatment, but not by propranolol. Stress-induced increase in MAP was significantly reduced by chronic treatment with propranolol, whereas no consistent effects were observed with atenolol. Acute treatment with guanethidine (30 mg/kg) markedly reduced the rise in MAP induced by stress. These results suggest that suppression of cardiac function by β-blockers does not always attenuate the rise in MAP induced by stress, thus cardioselective β-blockers might not confer any further reduction of the blood pressure increase due to sympatho-adrenal excitation. Inhibition of stress-induced MAP rise by propranolol could be mediated by a modulation of the catecholamine release.

Keywords—handling stress; SHR rat; cardioselectivity; β-adrenergic blocking drug; antihypertensive action; atenolol; propranolol

INTRODUCTION
Various kinds of stressful stimuli activate cardiovascular functions and increase plasma catecholamine levels through sympahto-adrenal excitation.1,2) Since spontaneously hypertensive (SHR) rats have been reported to have enhanced sympahto-adrenal reactivity and cardiovascular responsiveness to stress compared to normotensive rats, SHR rats are useful tools to study the effects of drugs on cardiovascular responses to stress.3–6) One might expect that cardioselective β-adrenergic blocking drugs (β-blockers) would be more effective than nonselective β-blockers in reducing the rise in blood pressure due to stress, because the vasodilating action of catecholamines would be less blocked by cardioselective ones.

Weiss et al.7) and Weiss and Lundgren8) have reported that chronic treatment with metoprolol, a cardioselective β-blocker, is effective in reducing the increase in blood pressure due to environmental stress (sudden noise and vibration), but propranolol, a nonselective β-blocker, is not effective in young and old SHR rats. Recently, Kawashima9) has reported an attenuation of stress-induced increase in blood pressure after treatment with a nonselective β-blocker, oxprenolol, in SHR rats.

To study the mechanisms of antihypertensive action of atenolol and propranolol and test the theoretically proposed advantages of cardioselective β-blockers over nonselective ones in hypertension therapy, cardiovascular responses to handling stress were studied in SHR rats after acute...
and chronic treatments. In addition the acute effects of guanethidine were examined to determine the role of sympathetic nerve activity in cardiovascular responses to stress. Our results show that cardioselective \( \beta \)-blocker might have no advantage over nonselective one in reducing blood pressure increase induced by stress and that antihypertensive effects of atenolol might have different modes of action from those of propranolol.

MATERIALS AND METHODS

**Animals and Preparation** — Male SHR rats (F38) from the colony of the Department of Pharmacology, Jichi Medical School, 11–13 weeks of age were used. Animals were housed five per cage under controlled conditions: constant temperature (25 \( \pm \) 1°C) and humidity (60 \( \pm \) 5%), and 12 h light cycle (7 a.m.–7 p.m.). Food and water were given *an libitum*.

Rats were anesthetized with ether and indwelling cannulas were inserted into the lower abdominal aorta through the left femoral artery and into the inferior *vena cava* through the left femoral vein. Two electrodes were subcutaneously implanted in the chest and the right shoulder, and exteriorized at the back of the neck. After surgery rats were placed in individual plastic cages. Experiments were performed 3 d after the surgery to minimize the influence of injuries.

Mean arterial blood pressure (MAP) of a conscious and unrestrained rat in the home cage was recorded through an aortic cannula by an electronic system (CP-01, Century Technology RP-5 and RJG-4024, Nihon Kohden). Heart rate (HR) was monitored by connecting the implanted electrodes to a cardiotachometer system (RB-J5, RB-5, RT-5 and RJG-4024, Nihon Kohden).

**Dose Determination** — We selected the dose of propranolol and atenolol which produce an approximately equipotent cardiac \( \beta \)-blocking effect. To determine the degree of \( \beta \)-receptor blockade, a submaximal dose (1 \( \mu \)g/kg) of isoproterenol was injected intravenously into conscious SHR rats through the venous cannula before and at various times after oral administration of atenolol (10, 30, 100 mg/kg) or propranolol (10, 30 and 100 mg/kg). The degree of cardiac \( \beta \)-receptor blockade was determined from the ratio between the area under the isoproterenol induced tachycardia/time curve for 1–5 h after the administration of \( \beta \)-blockers and that of saline. At doses of 30 and 100 mg/kg, *p.o.*, atenolol and propranolol produced almost the same degree of cardiac \( \beta \)-blocking effects. Since it has been reported that somewhat higher doses were required for atenolol and propranolol to produce antihypertensive effects in SHR rats, we selected the dose of 100 mg/kg, *p.o.*, for the following studies.

**Acute Study** — SHR rats of age 13 weeks were used. Resting MAP and HR were recorded in the home cage. Rats were considered to be in a resting condition when they were immobile with their eyes closed for at least 2 min. Handling stress was loaded by lifting the rat by the tail so that the front paws could barely touch the floor of the cage and holding in that position for 30 s. Isoproterenol (1 \( \mu \)g/kg) was then intravenously administered. These procedures were repeated 2–3 times intermittently until stable cardiovascular responses were observed. Thereafter, rats were orally administered with either atenolol (100 mg/kg), propranolol (100 mg/kg), or guanethidine (30 mg/kg), or saline. Handling stress and isoproterenol injection were performed before and 1, 2, 3 and 5 h after the administration of drugs.

**Chronic Study** — SHR rats (11 week-old) were orally administered with either atenolol (100 mg/kg per day), propranolol (100 mg/kg per day) or saline (5 ml/kg per day) for 17 consecutive days. At the 14th day of the experiment, rats were subjected to surgery as described in the acute study. Cardiovascular responses to handling stress and isoproterenol were determined at the 17th day of the experiment.

**Drugs** — Drugs used were: atenolol (I.C.I. Pharma), propranolol hydrochloride (I.C.I. Pharma), guanethidine sulfate (Tokyo Kasei), and
isoproterenol hydrochloride (Sigma).

**Statistical Analyses** — The significance of differences of the means between the treated and the control group was assessed with Scheffe's S-test or Dunnett's t-test. The significance of differences between before and after the administration of drugs was calculated by the paired t-test.

**RESULTS**

**Acute Study**

_a) β-Adrenergic Blocking Effects — Isoproterenol (1 μg/kg, i.v.) produced a marked increase in HR and a decrease in MAP. These responses were almost completely inhibited by propranolol (100 mg/kg, p.o.). While atenolol (100 mg/kg p.o.) suppressed isoproterenol-induced tachycardia, its inhibitory effect on hypotension was not so marked (Fig. 1). These results indicate that this dose of atenolol has a greater effect on heart than on blood vessels._

_b) Handling Stress — The resting MAP decreased after atenolol and guanethidine, whereas propranolol produced no effect. Resting HR decreased significantly after atenolol and propranolol, whereas guanethidine produced only a small degree of decrease (Fig. 2).

Handling stress induced marked increases in MAP (about 60 mmHg) and HR (about 120 beats/min). These responses to stress in the saline treated group were almost consistently observed throughout the experimental period of 5 h. Atenolol did not attenuate the increase in MAP due to the stress, but propranolol showed a tendency to suppress this response 1—2 h after administration. The increase in HR was almost

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**FIG. 1.** Changes in Heart Rate (HR) and Mean Arterial Pressure (MAP) Induced by Isoproterenol (1 μg/kg, i.v.) after a Single Oral Administration of Atenolol or Propranolol in SHR Rats

_Each point represents mean ± S.E. (n=7). a) significant difference from control value, p<0.05; ○ — ○ , saline; Δ — Δ , atenolol 100 mg/kg; ● — ● propranolol 100 mg/kg._

**FIG. 2.** Time Courses of Resting HR and MAP in SHR Rats after a Single Oral Administration of Atenolol, Propranolol, and Guanethidine

_Each point represents mean ± S.E. (n=5—7). a) significant difference from control value, p<0.05; b) significant difference from corresponding value at time zero, p<0.05: ○ — ○ , saline; Δ — Δ , atenolol 100 mg/kg; ● — ● propranolol 100 mg/kg; × — × , guanethidine 30 mg/kg._
completely suppressed by atenolol and propranolol over the period of 5 h.

Guanethidine significantly reduced the increase in MAP induced by stress, but its inhibitory effect on HR was not so pronounced as that of β-blockers (Fig. 3).

**Chronic Study**

a) **β-Adrenergic Blocking Effects** — Isoproterenol-induced tachycardia was markedly reduced even 24 h (i.e. 0 h in Fig. 4) after the repeated administration of propranolol for 16 d. The response was almost completely inhibited after the dose on the 17th day. Reduction of isoproterenol-induced tachycardia by atenolol 24 h after the repeated administration was smaller than the reduction induced by propranolol. After the dose of atenolol on the 17th day, this tachycardia was almost completely inhibited.

Hypotensive response to isoproterenol was significantly reduced by atenolol and propranolol, but the degree of the inhibition was greater by propranolol.

b) **Handling Stress** — SHR rats treated with atenolol showed a somewhat lower level of resting MAP than saline treated rats at 0 h on the 17th day (Fig. 5). After the last dose, atenolol produced a significant reduction of resting MAP, whereas propranolol did not show any effect on resting MAP.

No significant changes in resting HR were observed in animals treated with β-blockers and saline at 0 h on the 17th day. After the last dose of β-blockers resting HR was significantly reduced when compared to the values at 0 h (Fig. 5).

The increase in MAP during handling stress was significantly reduced 1—5 h after the dose of

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**FIG. 3. Time Courses of HR and MAP in SHR Rats during Handling Stress after a Single Oral Administration of Atenolol, Propranolol and Guanethidine**

Each point represents mean ± S.E. (n=5—7). a), b) same as in Fig. 2; ○ — ○, saline; △ — △, atenolol 100 mg/kg; ⋄ — ⋄, propranolol 100 mg/kg; × — ×, guanethidine 30 mg/kg.

**FIG. 4. Changes in HR and MAP Induced by Isoproterenol (1 μg/kg, i.v.) after Repeated Oral Administration of Atenolol or Propranolol for 17 d in SHR Rats**

Each point represents mean ± S.E. (n=7). a) same as in Fig. 2; ○ — ○, saline; △ — △, atenolol 100 mg/kg per day; ⋄ — ⋄, propranolol 100 mg/kg per day.
propranolol on the 17th day. Although atenolol significantly reduced the response at 0 and 5 h, it produced a significant enhancement at 1 and 2 h when compared to the response at 0 h (Fig. 6).

The increase in HR during handling stress was markedly reduced even 24 h after the administration of atenolol and propranolol for 16 d (at 0 h in Fig. 6). Stress-induced tachycardia was significantly reduced after the dose of atenolol and propranolol on the 17th day of the experiment.

DISCUSSION

In the present study, handling stress was used to study the mechanism of antihypertensive action of atenolol, a cardioselective β-blocker, and propranolol, a nonselective one, in SHR rats. The results of our experiments have demonstrated that the resting MAP is effectively reduced by acute and chronic oral treatment for 17 d with atenolol but not with propranolol, and that stress-induced rise in MAP is reduced by chronic treatment with propranolol but not consistently with atenolol. Tachycardic response to stress is significantly reduced by these β-blockers.

The increases in blood pressure and heart rate induced by stress have been ascribed to the results of the sequence of events involving activation of the central nervous system, increased sympathetic nerve activity and release of catecholamines at the sympathetic nerve endings, and the stimulation of the release of catecholamines from the adrenal medulla.2,6 The released catecholamines produce stimulation of both constrictor α-receptor and dilator β-receptor in the vascular bed, and cardiac stimulation through β-receptor in the heart. Theoretically, cardioselective β-blockers are

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**FIG. 5. Time Courses of Resting HR and MAP in SHR Rats after Repeated Oral Doses of Atenolol and Propranolol for 17 d**

Each point represents mean ± S.E. (n = 7). a), b) same as in Fig. 2; ○ — ○, saline; △ — △, atenolol 100 mg/kg per day; ● — ●, propranolol 100 mg/kg per day.

**FIG. 6. Time Courses of HR and MAP During Handling Stress in SHR Rats after Repeated Oral Doses of Atenolol and Propranolol for 17 d**

Each point represents mean ± S.E. (n = 7). a), b) same as in Fig. 2; ○ — ○, saline; △ — △, atenolol 100 mg/kg per day; ● — ●, propranolol 100 mg/kg per day.
expected to be more effective in reducing stress-induced rise in blood pressure than nonselective ones, because cardioselective β-blockers should specifically inhibit the increase in cardiac output and have a less effect on the vasodilating action of catecholamine released by the stress. However, no such expected results were observed with atenolol in the present study. We have recently confirmed the cardioselectivity of atenolol against vessels in Donryu rats in vivo and in SHR rats. Atenolol at the dose of 100 mg/kg, p.o., used in this study exhibited a relatively cardioselective β-blockade in SHR rats (see Fig. 1 and 4).

Dissociation of cardiac suppression from the blood pressure lowering effect during stress was observed in SHR rats. While atenolol strongly inhibited tachycardia due to stress, the rise in MAP was not reduced by the drug. Similar results have been reported with oxprenolol. To further evaluate the contribution of cardiac function to the stress-induced increase in MAP, guanethidine was used for the study. After acute guanethidine treatment, we found a marked reduction of the stress-induced increase in MAP, but only a slight inhibition of tachycardiac response to stress (Fig. 3). These data suggest that the increase in MAP during handling stress is mainly induced by the increased peripheral resistance rather than by activation of cardiac function.

Although acute and chronic treatment with propranolol did not attenuate resting MAP in SHR rats, stress-induced increase in MAP tended to decrease after acute treatment and was significantly reduced after chronic treatment with propranolol. On the other hand, acute treatment with atenolol produced no discernible effects on the stress-induced increase in MAP and no consistent effects were observed after chronic treatment (Fig. 3 and 6). These results suggest that propranolol might attenuate sympathetic nervous reactivity to stress and modulate the release of endogeneous catecholamine through its action on the central nervous system, as indicated also by other investigators. A similar mechanism has been proposed for antihypertensive action of long-term treatment with propranolol in SHR rats. Accumulation of propranolol in the brain is well confirmed in rats, while atenolol is reported to penetrate poorly into the brain in rats. These differences in disposition between atenolol and propranolol may partly explain the observed changes in pharmacological actions in SHR rats.

Our observations are inconsistent with those reported by Weiss et al. and Weiss and Lundgren, who found that the pressure rises induced by environmental stress in SHR rats were effectively reduced by chronic treatment with metoprolol (a cardioselective β-blocker), but not with propranolol. The different patterns of elevation of plasma catecholamine concentrations in response to various types of stress have been observed in rats. It is suggested that mild stress mainly induces elevation of plasma epinephrine concentration through activation of adrenomedullary discharge while severe stress stimulates the release of norepinephrine from sympathetic nerve endings. Thus cardiovascular responses to stress may differ depending on the nature of stress. Judging from the blood pressure response of control SHR rats, handling stress resulting in MAP rise by 60 to 70 mmHg (Fig. 3 and 6) can be considered to be more potent than environmental stress resulting in MAP rise by about 25 mmHg. In addition, cardioselective β-blocker will not attenuate the vasodilator effects of epinephrine from the adrenal medulla. Thus, the difference in severity of stress loaded to SHR rats could produce the different cardiovascular effects between cardioselective and nonselective β-blockers.

We observed a significant reduction in resting MAP in SHR rats after acute and chronic treatment with atenolol. However, no correlation was observed between the reduction of resting MAP and HR. Although the mechanism of hypotensive action of atenolol is not known, cardiac function may play an important role in the maintenance of resting blood pressure during the developmental phase of hypertension in SHR rats, and cardioselective blockade by atenolol may lead to a reduction in resting MAP.
hand, acute and chronic treatment with propranolol significantly reduced resting HR but not resting MAP. Similar results have been reported by other investigators.\textsuperscript{28,30–33} This may be partly explained by the facts that propranolol can inhibit both $\beta$-receptor-mediated cardiac stimulation and peripheral vasodilation. Thus, contribution of cardiac suppression to the reduction of resting MAP could be masked by the peripheral vascular constriction in SHR rats treated with propranolol.

Excretion rate of propranolol in rats is reported to be slower than that of atenolol.\textsuperscript{28,34} Although we did not determine plasma concentrations of atenolol and propranolol, tachycardiac response to isoproterenol was significantly reduced by these $\beta$-blockers for at least 5 h after the oral doses in both acute and chronic studies (Fig. 1 and 4). Furthermore, isoproterenol-induced tachycardia was significantly reduced even 24 h after the repeated administration of these $\beta$-blockers for 16 d (0 h in Fig. 4). These data indicate the persistence of $\beta$-blocking activity of these drugs for more than 24 h after the oral dose of 100 mg/kg per day in SHR rats.

In summary, atenolol reduced the resting MAP in SHR rats after acute and chronic treatments, while propranolol reduced the stress-induced increase in MAP after chronic treatment. Our results suggest that the antihypertensive action of atenolol might be different from that of propranolol. Cardioselective $\beta$-blockers might have no advantage over nonselective $\beta$-blockers in reducing blood pressure increase induced by the excitation of sympatho-adrenal system due to stress.

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REFERENCES
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