CARDIOVASCULAR RESPONSES TO ACUTE AND SUBCHRONIC TREATMENT WITH OXPRENOLOL IN SPONTANEOUSLY HYPERTENSIVE RATS AT REST AND AT STRESS

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To further examine the mechanism of antihypertensive action, effects of a single (50 mg/kg) and repeated oral administration (50 mg/kg per day, for 14 days) of oxprenolol on mean arterial pressure (MAP) and heart rate (HR) were studied in spontaneously hypertensive (SHR) rats at rest and during handling stress. MAP was measured through a indwelling aortic cannula and HR was determined via chronically implanted electrodes. A single oral dose of oxprenolol produced a gradual fall in resting MAP. Although repeated dose of oxprenolol did not alter the developmental course of hypertension in SHR rats, a prompt and significant fall in MAP at rest was observed after the dose on the 14th day of the experiment. A single and repeated dose of oxprenolol attenuated the increase in MAP during handling stress, but these effects were less apparent when compared to the fall in resting MAP. Significant reductions in stress-induced tachycardia were observed both after a single and repeated dose, whereas resting HR tended to increase. These results indicate that some of the postulated antihypertensive mechanisms such as central inhibition of sympathetic outflow, peripheral inhibition of sympathetic nerve functions and suppression of cardiac output are not directly related to a fall in MAP observed in SHR rats after oxprenolol treatment. Time courses of the hypotensive effect of a single and repeated doses suggest that the accumulation of oxprenolol in active sites which appear to be located in deep compartments is required to develop hypotensive effect.

Keywords — oxprenolol; SHR rats; hypotension; mean arterial pressure; heart rate

INTRODUCTION

A number of hypotheses has been proposed to explain the antihypertensive action of beta adrenoceptor blocking agents. These are (1) a central inhibition of sympathetic activity, (2) suppression of cardiac output, (3) suppression of renin release, (4) inhibition of peripheral adrenergic nerve function, (5) resetting of baroreceptors, and others.1–6) Because of the difficulties of demonstrating the antihypertensive effects of beta adrenoceptor blocking agents in experimental hypertensive animals,3,4) these hypotheses are left to be confirmed. Especially in spontaneously hypertensive (SHR) rats, various results have been reported on the antihypertensive effect of these drugs6–12) (see a review by Buckingham and Hamilton3) for the early reports).

Since SHR rats are reported to have hyperactive cardiovascular responsiveness to various forms of stress,13–16) evaluation of antihypertensive drugs may be influenced by methods used for measurement of blood pressure.

The purpose of this study was to further examine the mechanism of antihypertensive action of oxprenolol, a non-selective beta adrenoceptor blocking agent with membrane stabilizing17) and intrinsic sympathomimetic activities (ISA).18) Thus, oxprenolol was acutely and subchronically administered to SHR rats and blood pressure and heart rate (HR) were determined at rest and during handling stress. The results of this study confirm hypotensive action of resting blood pressure, but do not appear to support the central and cardiac mecha-
nisms of antihypertensive action of oxprenolol in SHR rats.

MATERIALS AND METHODS
Male SHR rats (F 38) were used for the study. Rats were housed in wire mesh cages five to six per cage with constant temperature (25 ± 1°C) and humidity (55 ± 5%), and with an automatic lighting cycle (7 A.M. to 7 P.M.). Food and water were provided ad lib.

Acute Study — Two days before the experiments, SHR rats of 14 to 15 weeks of age were anesthetized with ether and a cannulation into lower abdominal aorta through the left femoral artery was done as described previously. Two electrodes were subcutaneously implanted for HR determination (Kudo and Sokabe, in preparation). After surgery, each rat was isolated in a clear plastic cage.

In the morning of the experimental day, MAP of conscious and unrestrained rat was recorded in the home cage through the aortic cannula using an electronic system (CP-01, Century Technology; RP-5, and RTG-4008, Nihon Kohden). HR was monitored by attaching the implanted electrodes to a cardiotachometer system (RB-5j, RB-5, RF-5, and KJG-4008, Nihon Kohden) (Kudo and Sokabe, in preparation). Resting MAP and HR were determined after the accommodation of SHR rats to experimental condition. Rats were considered to be in resting condition when they were immobile having had 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. A marked rise in MAP along with tachycardia was induced by this procedure. Handling stress was repeated intermittently until stable cardiovascular responses were observed. Then rats were orally administered with either 50 mg/kg of oxprenolol hydrochloride or vehicle (distilled water, 2.5 ml/kg). At 0.5, 1, 2 and 4 h after the administration of oxprenolol, MAP and HR were recorded at rest and at stress. Blood samples (0.5 ml) were drawn from the arterial cannula at the designated time intervals. The same volume of saline was infused through the cannula to minimize the possible activation of renin-angiotensin system. Plasma samples were obtained by centrifugation of blood and stored at -20°C until determination for oxprenolol concentrations by an enzyme immunoassay.

Subchronic Study — SHR rats of 12 to 13 weeks of age were orally administered with either oxprenolol hydrochloride (50 mg/kg per day) or distilled water (2.5 ml/kg per day) for 14 consecutive days. Systolic blood pressure and HR were determined indirectly by a tail cuff method (KN-0090, Natsume Seisakusho).

![Graph showing mean arterial pressure over time](image)

**FIG. 1. Time Courses of Mean Arterial Pressure at Rest and during Handling Stress in SHR Rats after a Single Oral Dose of Oxprenolol (50 mg/kg)**

Each point represents the mean ± S.E.M. for 6 rats. Significant difference from vehicle treated control group: "p < 0.05.
before the start of the study, and 4 h after the administration of oxprenolol or distilled water on the 7th and 12th day of experiment. On the 12th day rats were subjected to surgical procedures as described in the acute study. On the 14th day MAP and HR at rest and at stress were recorded before and after the dose of oxprenolol. Blood samples were collected at the designated times.

Drug — Oxprenolol hydrochloride was provided from Chiba-Geigy (Japan), Takarazuka.

Statistical Analysis of Data — Mean and S.E.M. are presented in figures. Statistical significance was calculated according to the Student's t-test for the comparison of the means between oxprenolol and vehicle treated group.

RESULTS

Acute Study

Handling stress induced a sharp rise in MAP along with a tachycardia. Resting MAP and HR, and peak values of MAP and HR associated with stress are shown in the figures.

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**FIG. 2.** Time Courses of Heart Rate at Rest and during Handling Stress in SHR Rats after a Single Oral Dose of Oxprenolol (50 mg/kg)

Each point represents the mean ± S.E.M. for 6 rats. Significant difference from control values: **p < 0.01.

**FIG. 3.** Effects of Repeated Doses of Oxprenolol (50 mg/kg per day) on Blood Pressure and Heart Rate in SHR Rats as determined by the Tail Cuff Method

Each point represents the mean ± S.E.M. for 7 rats. Significant difference from control values: *p < 0.05.
A single oral administration of oxprenolol (50 mg/kg) produced a slight and gradual fall in resting MAP (Fig. 1). At 4 h after the administration, resting MAP in oxprenolol treated rats was significantly lower than that in vehicle treated rats ($p < 0.05$). A stress-induced rise in MAP in the oxprenolol treated rat was slightly reduced compared with the control rat. However, the difference between the two groups was not statistically significant.

A tendency to increase in resting HR was observed after a single oral oxprenolol administration, whereas a tachycardia associated with handling stress was significantly reduced throughout the experiment ($p < 0.01$) (Fig. 2).

**Subchronic Study**

There was no significant difference in growth between oxprenolol and vehicle treated SHR rats during the experimental period of 14 days.

Systolic blood pressure and HR before the treatment and at 4 h after the dose of oxprenolol or water on the 7th and 12th day are shown in Fig. 3. Consecutive administrations of oxprenolol

**FIG. 4. Time Courses of Mean Arterial Pressure at Rest and during Handling Stress in SHR Rats after Repeated Doses of Oxprenolol (50 mg/kg per day) for 14 Consecutive Days**

Each point represents the mean ± S.E.M. for 7 rats. Significant difference from control values: *$p < 0.05$; **$p < 0.01$.

**FIG. 5. Time Courses of Heart Rate at Rest and during Handling Stress in SHR Rats after Repeated Doses of Oxprenolol (50 mg/kg per day) for 14 Consecutive Days**

Each point represents the means ± S.E.M. for 7 rats. Significant difference from control values: **$p < 0.01$.**
(50 mg/kg per day) did not alter developmental course of hypertension in the SHR rat. However, HR on the 7th and 12th day were significantly reduced in the oxprenolol treated group when compared with those in the control (p < 0.05).

Before the administration of oxprenolol on day 14, that is, 24 h after the dose on the 13th day, no differences in resting MAP and HR, and cardiovascular responsiveness to handling stress were observed between the two groups (at 0 time in Fig. 4 and 5). A prompt and significant fall in resting MAP was observed after the administration of oxprenolol on the 14th day. A significant reduction in resting MAP lasted throughout the experimental period of 4 h (Fig. 4). Resting HR in the oxprenolol treated rat showed a tendency to increase (Fig. 5). The dose of oxprenolol on the 14th day caused a reduction in MAP during handling stress, and a significant reduction was observed at 30 min after the administration (Fig. 4). Stress-induced tachycardia in the oxprenolol treated group was significantly reduced when compared with those in the vehicle treated control group (Fig. 5).

DISCUSSION

Subchronic treatment of SHR rats with oxprenolol did not alter the developmental course of hypertension by the dosage schedule used in this study (50 mg/kg once daily for 14 consecutive days, Fig. 3 and 4). However, Takeda et al. have reported an attenuation of developmental course of hypertension in SHR rats treated with oxprenolol for longer period of time (12 weeks) with divided doses (15, 30 and 45 mg/kg twice daily). Considering a short half-life of oxprenolol in SHR rats, a regimen of dosage of at least twice daily would be necessary to expect a sustained hypertensive effect.

A significant fall in resting MAP was observed at 4 h after a single and repeated dose of oxprenolol. However, the hypotensive effect was somewhat blunted when blood pressure was determined under stressful conditions such as tail cuff method and during handling (Figs. 1, 3 and 4). The results indicate that evaluation of antihypertensive effect of oxprenolol in SHR rats varies with methods used for measurement of blood pressure. Because SHR rats are reported to have hyperreactivity of sympathoadrenal system to various kinds of stress, stressful stimuli associated with blood pressure determination might exaggerate the degree of blood pressure elevation and mask the hypotensive action of oxprenolol as suggested by Chiueh and Kopin.

If a drug lowers blood pressure by interference with sympathetic nerve function through acting on the central nervous system, on the presynaptic beta receptors, or by direct neuron blocking activity, accentuation of hypotensive effect should be observed when blood pressure is measured under stressful conditions. A single oral administration of guanethidine (30 mg/kg), a neuron blocking drug, produced a significant and greater fall in MAP during handling stress than that at rest (Kudo and Sokabe, in preparation). On the other hand, the reverse was observed with oxprenolol and also with other beta adrenoceptor blocking agent such as atenolol (Kudo and Sokabe, in preparation). Thus, involvement of central nervous system and peripheral nerve function in hypotensive effect of beta adrenoceptor blocking agents in SHR rats seems less likely. In addition, Smits et al. have recently presented the data which do not support a central mechanism of antihypertensive action for propranolol, because the dose required to produce an equal level of hypotension is the same between intracerebroventricular and subcutaneous injections in conscious SHR rats.

Suppression of cardiac function is not likely related to the hypotensive action of oxprenolol in SHR rats because resting HR tended to increase both after acute and subchronic treatments, whereas resting MAP fell with time. In addition, elevation of MAP during handling stress was not attenuated in spite of a significant reduction of stress-induced tachycardia. Moreover, dissociation of cardiac suppression with blood pressure lowering effect was also reported on other beta adrenoceptor blocking
Hypotensive Effect of Oxprenolol in SHR Rats

agents, \(3,8,11,12\)

ISA and suggested alpha adrenoceptor blocking action of oxprenolol\(^{23,24}\) may be partially responsible for a slight increase in resting HR and a fall in MAP. The possibility that oxprenolol produces hypotension by direct vasodilation has been reported by Naylor and Chang.\(^{25}\) Further studies on this property of oxprenolol is imperative to clarify the possible mechanism of hypotensive action.

Although effect of oxprenolol on plasma renin activity was not determined in this study, Weber \textit{et al.}\(^{26}\) have reported that oxprenolol has a suppressing effect on resting plasma renin activity in rabbits. However, it is less probable that oxprenolol causes a hypotension in SHR rats by reducing plasma renin activity since there is no evidence that high blood pressure of the SHR is dependent on plasma renin activity.\(^{19}\)

Almost the same plasma levels of oxprenolol were observed after a single and repeated dose in SHR rats.\(^{21}\) However, a difference in the time course of hypotensive responses to oxprenolol was observed between acute and subchronic treatment. After repeated dose of oxprenolol, a rapid and sustained fall in MAP was observed, whereas a hypotension developed gradually after a single dose. These results indicate that accumulation of oxprenolol to active sites which may exist in deep compartments is required to develop a hypotensive action. After repeated doses, subthreshold levels of oxprenolol may be deposited in the active sites and a prompt hypotensive effect could be elicited upon the dose on the next day.

In summary, oxprenolol produced a significant fall in resting MAP in SHR rats both after a single and repeated oral administration. No positive evidence was found for the involvement of the central nervous system, peripheral neuronal functions or cardiac output in the antihypertensive action of oxprenolol in the SHR.

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**REFERENCES**

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