Effect of β-receptor-blocking agents on cardiovascular structural changes in spontaneous and noradrenaline-induced hypertension in rats

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Summary

1. Continuous intravenous noradrenaline infusion for 1 week into rats by osmotic minipumps significantly increased blood pressure and left ventricular weight.

2. Concomitant α-receptor-blockade infusion significantly lowered blood pressure and the aortic weight without significant reduction in left ventricular weight.

3. Two β-receptor-blocking agents in noradrenaline-infused rats normalized left ventricular weight and significantly reduced the aortic weight, although blood pressure was still higher than control non-infused rats.

4. In 7-week-old spontaneously hypertensive rats, propranolol (perorally for 2 weeks) did not lower blood pressure but reduced significantly cardiovascular protein synthesis ([14C]lysine and [3H]uridine incorporation into non-collagen protein and RNA respectively) in both left ventricle and aorta. This effect was in contrast to hydralazine, which normalized blood pressure but did not reduce cardiovascular protein synthesis.

5. Results suggest that β-receptors play a modulating role in the structural cardiovascular response to blood pressure.

Key words: cardiac hypertrophy, hypertension, isoprenaline, noradrenaline, osmotic minipump, α- or β-receptor-blocking agents.

Introduction

Structural vascular changes are involved in the evolution of spontaneous and experimental hypertension (Folkow, Hallbäck, Lundgren, Sivertsson & Weiss, 1973). Especially in spontaneously hypertensive (SH) rats metabolic alterations of vascular walls (i.e., the acceleration of non-collagen and collagen protein synthesis) are induced at the early stage of hypertension and precede the medial hypertrophy or hyperplasia which is morphologically detectable at the age of 2–3 months (Yamori, 1974, 1976a,b,c,d; Yamabe & Lovenberg, 1974). Furthermore, vascular non-collagen synthesis is enhanced by blood pressure increase itself and also influenced by neurogenic innervation (Yamori, Nakada & Lovenberg, 1976). Thus the adrenergic system seems to modulate structural cardiovascular responses to blood pressure changes (Yamori, 1977; Tarazi & Sen, 1979; Lovenberg, Nakada & Yamori, 1979). In the present study, the relative role of β- and α-receptor components of the adrenergic system were therefore studied in rats with either spontaneous or noradrenaline-induced hypertension.

Methods

Experiment 1

Wistar–Kyoto (WK) rats obtained from National Institutes of Health (by the courtesy of Dr W. Lovenberg), 30 males at the age of 10 weeks, were divided into the following five groups: non-treated controls, WK rats infused with noradrenaline (NA; 0.04 μmol/h), WK rats infused with NA plus an α-receptor blocker (phentolamine, 20 μg/l) and WK rats infused with NA and perorally administered β-receptor blocker (propranolol, 30 mg/kg) or β-receptor blocker (atenolol, 15 mg/kg). Osmotic minipumps (Alzet, ALZA Corporation, California, U.S.A.; model 1702, infusion rate 0.5 μl/h) were implanted subcutaneously in the back
TABLE 1. Effect of continuous noradrenaline (NA) infusion with or without α- or β-receptor blocking agents on blood pressure and cardiovascular weights

Significance of differences from control (*P < 0.05; **P < 0.01) and from NA infusion (†P < 0.05; ††P < 0.01) are shown.

<table>
<thead>
<tr>
<th></th>
<th>Direct blood pressure (mmHg)</th>
<th>Heart rate</th>
<th>Ratio organ wt./body wt. (mg/g)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left ventricle</td>
</tr>
<tr>
<td>Control</td>
<td>132 ± 2</td>
<td>482 ± 15</td>
<td>2.10 ± 0.05</td>
</tr>
<tr>
<td>NA infusion</td>
<td>153 ± 4**</td>
<td>486 ± 14</td>
<td>2.33 ± 0.05*</td>
</tr>
<tr>
<td>NA infusion + α-receptor blocker (propranolol)</td>
<td>122 ± 4**</td>
<td>497 ± 15</td>
<td>2.19 ± 0.06</td>
</tr>
<tr>
<td>NA infusion + β-receptor blocker (atenolol)</td>
<td>143 ± 3*</td>
<td>417 ± 13**</td>
<td>2.12 ± 0.05†</td>
</tr>
</tbody>
</table>

of rats under pentabarbital anaesthesia (45 mg/kg intraperitoneally). The tip of the silastic tube connected with the pump was inserted into the superior vena cava through the jugular vein and its position was confirmed at death. Indirect blood pressure was measured at the tail before and after the implantation. Direct blood pressure was also determined by a pressor transducer through a cannula implanted into the femoral artery. Rats were killed by decapitation 7 days after the implantation and the heart and aorta were excised immediately after decapitation. The free wall of the right ventricle was carefully removed and the left ventricle, including septum, and both atriums were dissected out. For the determination of the aortic weight, perivascular adipose and connective tissues were carefully removed and the thoracic plus abdominal portion from the right common carotid artery to iliac bifurcation was carefully trimmed. Weights of these parts were measured after organs were carefully blotted on the paper.

Experiment 2

Young stroke-prone SH rats were obtained from National Institutes of Health (by the courtesy of Dr W. Lovenberg), 15 males in total, and were divided into the following three groups: non-treated rats, β-receptor blocker (propranolol 50 mg/kg orally) and hydralazine (8 mg/kg orally) -treated groups. Five age-matched WK rats were also used as a non-treated control group. Indirect blood pressures were repeatedly checked during 2 weeks of treatment. Rats were killed by decapitation 2 h after L-[U-¹⁴C]lysine (0.08 μCi/g) and [³H]uridine (0.14 μCi/g) were injected intravenously. Organs were dissected out, weighed as described in experiment 1, and were kept frozen until DNA, RNA, collagen and non-collagen protein were extracted with cold ethanol by a modification of Ogur & Rosen’s (1950) method for respective assays (Schneider, 1957; Lowry, Rosebrough, Farr & Randall, 1951). Radioactive lysine and uridine incorporations into collagen and non-collagen proteins, and RNA, respectively, were determined as indices for protein and RNA synthesis.

Results

Experiment 1

Sustained hypertension of around 150 mmHg was noted after the NA infusion. Because of the difficulty in detecting tail-blood pressure in NA-infused rats, direct blood pressure was checked in unanaesthetized rats with an implanted femoral artery catheter and blood pressure rises were confirmed. As shown in Table 1, the sustained hypertension for 1 week was also confirmed at autopsy by its morphological effect on cardiovascular structure; the weights of the left ventricle and aorta were significantly increased in the NA-infused groups.

Concomitant α-receptor-blocker infusion completely abolished the development of NA-induced hypertension, and therefore reduced the aortic weight significantly. However, α-receptor-blockade failed to decrease the heart weight significantly (P > 0.05).

The two β-receptor blockers significantly slowed down the heart rate. Although blood pressure in these groups was maintained at a significantly higher level than the control group, left ventricle weights were normalized and the aortic weights were significantly decreased compared with those of the NA-infused group. The reduction of aortic weights was nearly equivalent to that produced by α-receptor blockade although the differences in blood
pressure between the two types of blockers were highly significant.

**Experiment 2**

Treatment with the $\beta$-receptor blocker for 2 weeks did not block the quick development of severe hypertension in stroke-prone SH rats; rises in blood pressure during this period in the non-treated group of stroke-prone SH rats (163 ± 4 to 212 ± 3 mmHg) were not significantly different from those in the treated group (163 ± 7 to 199 ± 10 mmHg). However, propranolol significantly decreased the protein/DNA ratio (88.5 ± 2.2 vs 103.7 ± 1.9), lysine incorporation into non-collagen protein (91.2 ± 10.4 vs 128.2 ± 7.7 d.p.m./mg) and collagen (23.2 ± 1.1 vs 28.8 ± 1.8 d.p.m./mg), and also uridine incorporation into RNA (6.8 ± 0.6 vs 9.7 ± 0.8 d.p.m./mg) in the left ventricle compared with those in the non-treated group. A similar reduction was noted in the aorta of the treated group compared with non-treated group; non-collagen protein (63.7 ± 1.9 vs 95.5 ± 8.0 d.p.m./mg), collagen (22.5 ± 2.8 vs 45.4 ± 4.6 d.p.m./mg) and RNA (4.1 ± 0.5 vs 6.3 ± 0.2 d.p.m./mg).

In contrast, hydrallazine effectively blocked the development of hypertension in stroke-prone SH rats; no significant rises were noted in blood pressure during 2 weeks (158 ± 7 to 150 ± 4 mmHg). However, no significant reduction in indices of protein and RNA synthesis was noted either in the left ventricle; non-collagen protein (115.0 ± 2.1 d.p.m./mg), collagen (27.8 ± 1.3 d.p.m./mg) and RNA (8.7 ± 0.9 d.p.m./mg), or in the aorta; non-collagen protein (78.6 ± 6.7 d.p.m./mg), collagen (36.8 ± 9.8 d.p.m./mg) and RNA (6.2 ± 1.0 d.p.m./mg).

In comparison with untreated normotensive WK rats (132 ± 3 mmHg), stroke-prone SH rats showed significant increases in the protein/DNA ratio, non-collagen protein and collagen in left ventricles as well as in the aorta; these were proved to be good indices for cardiovascular hypertrophy.

**Discussion**

Cardiac hypertrophy and medial hypertrophy of blood vessels are structural changes in hypertension which are generally regarded as being secondary to hypertension and are therefore called adaptive structural changes (Folkow et al., 1973). However, the early development of structural changes in spontaneous hypertension suggests that factors other than the rise in pressure can accelerate cardiovascular structural changes (Sen, Tarazi, Khairallah & Bumpus, 1974; Yamori, 1974, 1976a,b,c,d; Frohlich & Tarazi, 1979). These factors include increased neural vasomotor tone and adrenergic drive which have already been noted in the early stages of spontaneous hypertension. The same conclusions were also suggested from studies of the effects of various antihypertensive drugs or of surgical denervation on vascular protein synthesis (Yamori, 1976a,b,c,d) as well as on cardiac weight in SH rats (Sen et al., 1974; Tarazi & Sen, 1979). Cardiac hypertrophy has been experimentally induced by noradrenaline infusion (Gans & Carter, 1970; Laks, Morady & Swan, 1973) or isoprenaline administration (Stanton, Brenner & Mayfield, 1969; Alderman & Harrison, 1971; Szabo, Csaky & Szegi, 1975; Pagano & Inchiosa, 1977). We induced hypertension as well as cardiac hypertrophy by continuous noradrenaline infusion with osmotic minipumps and produced more marked cardiac hypertrophy without hypertension by isoprenaline infusion (Yamori, Ooshima & Tarazi, 1980). These previous observations indicate that $\beta$-adrenoreceptor stimulation induces cardiac hypertrophy more potently than noradrenaline despite the absence of significant pressor effect. The effective inhibition of noradrenaline-induced cardiac hypertrophy by $\beta$-receptor blockers observed in this study appears to confirm the involvement of $\beta$-receptor stimulation in the development of cardiac hypertrophy. Moreover, $\beta$-receptor blockers, although less effective in attenuating both noradrenaline-induced and spontaneous hypertension, yet significantly decreased the aortic weight in noradrenaline-induced hypertension and clearly reduced non-collagen, collagen and RNA synthesis in the left ventricle and aorta of stroke-prone SH rats. These results contrasted with the failure of hydralazine to suppress cardiovascular hypertrophy or protein synthesis despite its marked antihypertensive effect (Sen et al., 1974; Yamori, 1976a,b,c,d). These observations suggest that $\beta$-receptors may modulate cardiovascular structural changes in hypertension. Therefore $\beta$-receptor blockers may be important for preventing the hypertensive cardiovascular structural changes in hypertension, provided that adequate doses are used in relation to the prevailing level of sympathetic tone.

**References**

Alderman, E.L. & Harrison, D.C. (1971) Myocardial hypertrophy resulting from low dosage isoproterenol


