Catecholamines, blood pressure, renin and myocardial function in the spontaneously hypertensive rat

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Summary

1. Neither nerve-growth-factor antiserum (NGFAS) administered subcutaneously nor 6-hydroxydopamine administered intraventricularly to immature spontaneously hypertensive rats (SHR) inhibited the development of the hypertensive syndrome. In contrast, NGFAS did not affect blood pressure in normotensive Kyoto/Wistar rats.

2. Peripheral vascular resistance was increased and cardiac index decreased in both NGFAS and 6-hydroxydopamine-treated SHR despite preservation of normal blood pressure.

3. NGFAS treatment did not influence the development of left ventricular hypertrophy in SHR, despite the lowering of blood pressure. In contrast, 6-hydroxydopamine caused an attenuation in the development of left ventricular hypertrophy.

4. Indices of left ventricular contractility were depressed by NGFAS treatment but not by 6-hydroxydopamine.

5. Plasma renin activity was unaffected by NGFAS treatment and increased by 6-hydroxydopamine.

Key words: blood pressure, catecholamines, 6-hydroxydopamine, hypertension, immunosympathectomy, myocardial hypertrophy, nerve growth factor antiserum.

Introduction

6-Hydroxydopamine administered intraventricularly (Haeusler, Finch & Thoenen, 1972; Erinoff, Heller & Oparil, 1975) or nerve-growth-factor antiserum administered subcutaneously (Low, Oparil, Erinoff & Sauls, 1975) to immature spontaneously hypertensive rats can prevent hypertension. Myocardial hypertrophy has been demonstrated in the SHR(1) (Takatsu & Kashii, 1972) before hypertension appears (Sen, Tarazi, Khairallah & Bumpus, 1974). Further, treatment with α-methyldopa, which lowers renin, but not with hydralazine, which raises renin, was effective in preventing left ventricular hypertrophy (Sen et al., 1974). This suggests that blood pressure may not be the sole factor contributing to myocardial hypertrophy in the SHR and that the renin-angiotensin system may play a permissive role. The present study was undertaken to evaluate further the influence of blood pressure, the sympathetic nervous system and the renin-angiotensin system on haemodynamics, myocardial function and the development of myocardial hypertrophy in the SHR.

Methods

Male SHR (Okamoto strain) (Taconic Farms Inc., Germantown, N.Y., U.S.A., or Laboratory Supply Co., Indianapolis, Ind., U.S.A.) were used. NGFAS (Burroughs Wellcome, Research Triangle Park, N.C., U.S.A.) was administered to neonatal SHR or normotensive Kyoto/Wistar rats. 6-Hydroxydopamine (6-OHDA HBr, Sigma, St Louis, Mo., U.S.A.) was injected into the right lateral ventricle of 32-days-old SHR as described previously (Erinoff et al., 1975). The procedure was repeated 6 days later except that the injection was made into the left lateral ventricle. Control rats received equal volumes of Merlis solution (Merlis, 1940) containing 0.1% ascorbic acid.

(1) Abbreviations: SHR, spontaneously hypertensive rats; NGFAS, nerve-growth-factor antiserum.
Systolic blood pressure of conscious rats was measured once a week by a tail-cuff method (Pfeffer, Pfeffer & Frohlich, 1971). Pulse rate was obtained from the pressure tracings.

At 80 days one group of SHR and Kyoto/Wistar rats was anaesthetized with sodium pentobarbitone (50 mg/kg, intraperitoneally) and subjected to haemodynamic study (Dowell, Cutilletta & Sodt, 1976). A catheter was inserted above the bifurcation of the abdominal aorta and attached to a Statham P23Db pressure transducer for arterial pressure measurements. A midline thoracotomy was performed and a square-wave electromagnetic flow probe (model 400, Carolina Medical Electronics, King, N.C., U.S.A.) placed on the ascending aorta. Left ventricular pressure was measured by puncturing the ventricle with a 3.8 cm 22 gauge needle attached directly to a Statham probe (model P23Db pressure transducer for arterial pressure measurements). The first derivative of left ventricular pressure (dp/dt) was obtained with a resistance-capacitance differentiating circuit (model RC-1, Electronics for Medicine, White Plains, N.Y., U.S.A.). Indices of left ventricular contractility, including peak cardiac output (pCO), stroke power (Sp), stroke work (SW), dp/dtmax and flow acceleration (dF/dt) were calculated from left ventricular pressure and aortic flow curves (Arcilla, Sodt & Replogle, 1974; Dowell et al., 1976).

Hearts were excised, divided and weighed. The septum was included with the left ventricular wall. The left ventricles were homogenized and aliquots assayed for RNA, DNA (Maggio, Siekevitz & Palade, 1963) and hydroxyproline (Cutilletta, Dowell, Rudnick, Arcilla & Zak, 1975). The spleens were removed for determination of noradrenaline (Anton & Sayre, 1964).

A second group of rats was killed at 80 days by decapitation and exsanguinated. Blood was collected in iced tubes containing EDTA for determination of plasma renin activity (Haber, Koerner, Page, Kliman & Purnode, 1969) and heparin for determination of dopamine-β-hydroxylase activity (Molinoff, Weinshilboum & Axelrod, 1971). The brains were rapidly removed and dissected into the following regions: telencephalon without septum and corpus striatum, thalamus, diencephalon, midbrain and pons-medulla. The cervico-thoracic spinal cord, heart, spleen and kidneys were also removed. All organs except kidney were subjected to extraction and assayed for catecholamines (Anton & Sayre, 1964). Renal renin was extracted and quantified by a modification of the method of Boucher (1967), rat substrate prepared in our laboratory being used.

Results

From age 40 days, when it was first possible for us to measure blood pressure by the tail-cuff technique, 6-hydroxydopamine- and NGFAS-treated SHR had significantly lower systolic pressures than control rats. The treated animals showed an expected increase in pressure with age, but within the normal range for age-matched Kyoto/Wistar rats.

Fig. 1 summarizes the haemodynamic data for NGFAS-treated and untreated Kyoto/Wistar and SHR (Fig. 1a, b) and 6-hydroxydopamine-treated and control SHR (Fig. 1c, d). Fig. 1(a) shows that NGFAS treatment did not affect heart rate in any group, but did lower systolic blood pressure in the SHR to 117 mmHg, the range of the control rats. NGFAS did not lower blood pressure in the Kyoto/Wistar rats. Cardiac index in both untreated and NGFAS-treated SHR was significantly depressed when compared with the Kyoto/Wistar rats. NGFAS treatment per se did not lower cardiac index in either strain. Peripheral vascular resistance was higher in both untreated and NGFAS-treated SHR than in the Kyoto/Wistar rats. NGFAS lowered peripheral resistance in the SHR, but not to levels observed in normotensive Kyoto/Wistar rats because of the lower cardiac index in the hypertensive rat. The data show that abnormalities in peripheral resistance and cardiac output can appear in the SHR after peripheral sympathectomy with NGFAS, despite preservation of normal direct and indirect blood pressure. This suggests that haemodynamic abnormalities other than elevated blood pressure are present in the SHR.

Fig. 1(b) shows that the left ventricle/body weight ratio in both the untreated and treated SHR was significantly greater than that of the control rats. NGFAS treatment did not affect the left ventricle/body weight ratio in the SHR, despite the lowering of blood pressure. Myocardial RNA, DNA and hydroxyproline, expressed as mg/g of left ventricular wet weight, were also significantly greater in the SHR than in the Kyoto/Wistar rats and again were unaltered by NGFAS treatment. These data reflect the development of hypertrophy in the left ventricle of the SHR. Since NGFAS prevented hypertension but not left ventricular hypertrophy, this suggests
FIG. 1. Heart rate (HR), systolic blood pressure (SysP), cardiac index (CI) and peripheral vascular resistance (PVR) in NGFAS-treated and control SHR and Kyoto/Wistar rats (WKY) (a) and 6-hydroxydopamine (6-OHDA)-treated and control SHR (c). Body weight (BW), left ventricle to body weight ratio (LV/BW) and myocardial RNA, DNA and hydroxyproline (OH-Pro) in NGFAS-treated and control SHR and Kyoto/Wistar rats (WKY) (b) and 6-hydroxydopamine (6-OHDA)-treated and control SHR (d). NS = not significant.
that the development of myocardial hypertrophy in the SHR may be in part independent of blood pressure.

The indices of left ventricular contractility including peak cardiac output (pCO), stroke power (Sp), stroke work (SW), dP/dt max, and flow acceleration (dF/dt), were significantly depressed by NGFAS treatment in the SHR. NGFAS did not affect these indices in the Kyoto/Wistar rats. The data indicate that peripheral sympathectomy with NGFAS depressed myocardial contractility in the SHR but not in the Kyoto/Wistar rats. These data suggest that myocardial function at this age in the SHR is in part dependent on peripheral sympathetic activity.

6-Hydroxydopamine treatment tended to lower heart rate in the SHR but the difference did not attain statistical significance (Fig. 1c). Similarly, systolic blood pressure of 6-hydroxydopamine-treated animals was not significantly lower than control after Nembutal anaesthesia. 6-Hydroxydopamine did not alter cardiac index or peripheral vascular resistance.

The left ventricle/body weight ratios of 6-hydroxydopamine-treated SHR were significantly lower than those of vehicle-treated hypertensive control rats but greater than those of normotensive Kyoto/Wistar rats (Fig. 1d). Left ventricular RNA, DNA and hydroxyproline were similar in 6-hydroxydopamine-treated and vehicle-treated control SHR. Thus centrally administered 6-hydroxydopamine caused an attenuation in the development of left ventricular hypertrophy that was not seen with NGFAS, despite comparable blood pressure lowering in both groups of conscious rats.

The indices of left ventricular contractility were unchanged by treatment with 6-hydroxydopamine. This is consistent with maintenance of peripheral sympathetic function in similarly treated SHR.

Plasma renin activity in the NGFAS-treated SHR (1.5 ± 0.3 ng h⁻¹ ml⁻¹) was unchanged from control (1.9 ± 1.1 ng h⁻¹ ml⁻¹) but was significantly elevated (5.3 ± 1.9 ng h⁻¹ ml⁻¹) (P < 0.01) in 6-hydroxydopamine-treated SHR. Kidney renin activity was elevated (2.2 ± 0.1 i.u./g vs. control 1.6 ± 0.1 i.u./g) (P < 0.005) in the NGFAS-treated SHR, probably reflecting failure to mobilize renin stores from the sympathetically denervated kidney. Dopamine-β-hydroxylation activity tended to be lower in NGFAS-treated animals (0.69 ± 0.05 μmol min⁻¹ 1⁻¹ vs. control 0.81 ± 0.04 μmol min⁻¹ 1⁻¹), but the difference from normal did not attain statistical significance. Plasma dopamine-β-hydroxylase activity in 6-hydroxydopamine-treated rats was normal (0.69 ± 0.05 μmol min⁻¹ 1⁻¹).

NGFAS treatment completely depleted myocardial and spleen noradrenaline, compatible with nearly complete sympathetic denervation of these organs. Regional brain and spinal cord noradrenaline concentrations were normal in the NGFAS-treated SHR. In contrast, the 6-hydroxydopamine-treated animals showed a complete loss of telencephalic noradrenaline and significant depletions in midbrain and pons-medulla. Spinal cord noradrenaline was more than 90% depleted. Myocardial and spleen noradrenaline concentration in the 6-hydroxydopamine-treated rats was unchanged from the control value. This is one indicator of the integrity of sympathetic innervation of these organs.

Discussion

This study has shown that either extensive destruction of noradrenergic structures in brain and spinal cord by 6-hydroxydopamine administered into the lateral ventricles, or peripheral sympathectomy resulting from NGFAS treatment, can inhibit the development of the hypertensive syndrome in the SHR. In contrast NGFAS treatment does not change blood pressure or haemodynamic function in the normotensive Kyoto/Wistar rat. Although both interventions lower the arterial pressure of the SHR into the normal range, neither prevents entirely the development of haemodynamic abnormalities such as increased peripheral vascular resistance and depressed cardiac index nor protects against left ventricular hypertrophy. These observations suggest that the haemodynamic abnormalities and pattern of myocardial growth may be characteristic of the SHR and in part independent of blood pressure. The differential effects of NGFAS and central 6-hydroxydopamine on peripheral vascular resistance, myocardial contractility, left ventricular hypertrophy and plasma and renal renin activity in the developing SHR support the concepts that (1) destruction of central and peripheral noradrenergic structures have different effects on cardiovascular homeostasis in the young SHR, (2) myocardial contractility is in part dependent on peripheral sympathetic activity at this stage and (3) hypertension in the SHR can be prevented by a number of pro-
Sympathectomy in hypertensive rats

References


