Is arterial media hypertrophy in spontaneously hypertensive rats a consequence of or a cause for hypertension?

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Summary

1. The increased peripheral resistance observed in established hypertension has been attributed to structural changes in the resistance vessels, which are considered to be due mainly to medial hypertrophy. This study was undertaken to examine the possibility that structural changes in the arterial bed are genetically determined and may be causative factors in the development of high blood pressure in the spontaneously hypertensive rat.

2. The wall dimensions of aorta, renal artery and intrarenal arteries down to a distended diameter of 35 μm were studied: (a) in 14-week-old spontaneously hypertensive rats; (b) in age- and sex-matched spontaneously hypertensive rats which had been treated with captopril for two generations and had been normotensive during their complete life span; (c) in normotensive Wistar-Kyoto control rats.

3. Cross-sectional areas of the media were increased in the hypertensive rats in comparison with 'normotensive spontaneously hypertensive rats' and Wistar-Kyoto rats. Increased numbers of smooth muscle cells were found in the major arteries of hypertensive animals.

4. These results indicate that hypertrophy of the media is a consequence of high blood pressure rather than a genetically determined pathogenetic factor for the development of hypertension in spontaneously hypertensive rats.

Key words: arterial media hypertrophy, hypertension.

Introduction

The mechanisms responsible for the development and maintenance of high blood pressure remain to be fully defined, but there is little doubt that the stable phase of arterial hypertension is characterized by an elevated peripheral vascular resistance (Pfeffer & Frohlich, 1973; Tobia, Walsh & Lee, 1974). Several mechanisms for this increased peripheral resistance have been suggested. Some authors have reviewed the evidence for an increased response to vasoactive stimulation in arterial hypertension (Collis & Alps, 1975, 1977; Lais, Schaffer & Brody, 1974).

Folkow, Hallbäck, Lundgren, Sivertson & Weiss (1975) explained the increased flow resistance by structural changes of resistance vessels in established hypertension. Their conclusions were based on the observation of an increased flow resistance at maximal vasodilatation and on an altered dose–response curve to noradrenaline in spontaneously hypertensive rats. The structural change is considered to be mainly a medial hypertrophy, which could be demonstrated in the caudal artery (Friedmann, Nakashima & Mar, 1971) and in intrarenal arteries (C. L. Berry & K. J. Henrichs, unpublished results) of deoxycorticosterone acetate hypertensive rats, in the mesenteric bed of spontaneously hypertensive rats (Mulvany, Hansen & Aalkjaer, 1978) and in the intrarenal arterial bed of patients with essential hypertension (Henrichs & Berry, 1979).

This study was undertaken to examine the possibility that structural changes of the arterial bed are genetically determined and are a causative factor in the development of high blood pressure in spontaneously hypertensive rats.

Methods

Studies were performed on male rats of the spontaneously hypertensive strain (SH rats). Male normotensive rats of the Wistar–Kyoto strain (WK rats) served as controls (n = 5). The SH rats consisted of two groups. The first group (n = 7) was treated with captopril (d-3-mercapto-
2-methylpropanoyl-L-proline; SQ 14 225) (50 mg day\(^{-1}\) g\(^{-1}\)); the parent generation of this group was treated with captopril during the complete gestational and lactational periods (100 mg day\(^{-1}\) g\(^{-1}\)). The experimental rats were weaned after 4–5 weeks of age and had remained normotensive. The second group was untreated SH rats (\(n = 9\)).

All animals were housed (two per cage) under controlled heating and lighting conditions and given laboratory rat chow and tap water ad libitum.

All animals were subject to weekly measurements of weight and blood pressure.

Systolic blood pressures were taken by the tail plethysmographic method with an automated cuff inflator–pulse reading system under light ether anaesthesia.

All rats were killed at the age of 14 weeks and a cannula was introduced into the aorta from the left ventricle and tied at the aortic valve. A second cannula for pressure control was inserted at the aortic bifurcation.

After flushing with warm sodium chloride solution (0.9%; 37°C) the arterial system was inflated with a warm barium sulphate (Micropaque)/gelatin mixture (37°C) at a pressure of 100 mmHg.

After cooling and fixation in neutral buffered formalin, aorta, right renal artery and right kidney were exised in toto and radiography was performed.

After identification of the intrarenal arteries by counting the number of divisions, tissue blocks were taken in which the arteries were cut at a right angle.

Rectangular sections of the aorta directly distal to the brachio-cephalic branch and directly proximal to the right renal artery were taken and are referred to as thoracic aorta and abdominal aorta. Histological sections were stained with haematoxylin and Miller's stains. Sections then underwent morphometry.

The cross-sectional area of the media and the circumference of the internal elastic lamina were measured. Cross-sectional area of the media was defined as that area which is between internal elastic lamina and outermost concentric elastic lamina (external elastic lamina) including both laminae.

From the circumference of the internal elastic lamina, the diameter of the vessel was calculated. Medial smooth muscle cell nuclei were counted.

Results

The SH rats that had been treated with captopril were normotensive during their complete life span. At the end of the experiment, this group of rats had a mean systolic blood pressure of 125 ± 4.3 mmHg. The untreated SH rats had a mean systolic blood pressure of 189.4 ± 4.9 mmHg, and the WK rats had a mean systolic blood pressure of 135 ± 6.7 mmHg. All pressure values are means of the last two readings before death.

The body weights of the treated SH rats (193.3 ± 12.4 g) and the untreated SH rats (217.2 ± 7.1 g) were lower than those of the WK rats (250.4 ± 23.3 g). The heart weights were greater in hypertensive rats (1.28 g) when compared with captopril-treated rats (0.77 g) and WK rats (0.81 g), (\(P < 0.05\)). The microscopic appearance of arteries of all three groups of rats was similar. The aortic media consisted of eight to ten concentric fibromuscular and elastic lamellae; there was no difference in quantity of lamellar units between the groups.

In the renal arteries typically the numbers of lamellar units were lower and thick internal and external elastic laminae were found. Apart from external and internal elastic laminae complete concentric elastic lamellar units were not found in the intrarenal arterial tree. The intima was inconspicuous in all three groups. The endothelial layer was regularly destroyed in the procedure. Cross-sectional areas of the media at different sites of the arterial tree of the groups of animals are shown in Table 1. At both sites in the aorta the untreated SH rats displayed significantly greater medial areas than the treated SH rats and the WK rats (\(P < 0.01\)). The increase in medial mass was around 50% when compared with those of the normotensive animals (\(P < 0.001\)). This increase in medial mass in the hypertensive animals proved to be even more pronounced in the intrarenal arteries (a twofold increase, \(P < 0.001\)), when compared with the results obtained from the treated SH rats. In the fourth intrarenal divisional arteries medial substance was more than doubled in the untreated SH rats compared with the normotensive SH rats (\(P < 0.001\)). No significant difference in cross-sectional areas of the media was found in the treated SH and WK rats.

Cross-sectional areas of the media in peripheral intrarenal arteries with diameters between 35 and 80 \(\mu\)m were also greater in the hypertensive animals (\(P < 0.05\)); these arteries could not be identified by the number of divisions. Numbers of smooth muscle cell nuclei in both aortic sections were similar in all three groups of rats, but in the renal arteries the untreated SH rats (271 ± 58 nuclei) displayed an increased number of smooth muscle cell nuclei when compared with the treated SH rats (158 ± 25...
nuclei) and the WK rats (172 ± 32 nuclei) (P < 0.01). In the first intrarenal divisional artery there were increased counts of smooth muscle cell nuclei in the hypertensive (112 ± 22) compared with the treated SH rats (70 ± 12) and the WK rats (75 ± 8) (P < 0.05). In the second to fourth divisional arteries no significant differences were found in any group of rats.

Discussion

These experiments were performed to determine whether structural changes in the arterial tree found in SH rats are genetically determined and are pathogenetic factors in arterial hypertension.

The morphometric data presented confirm that arterial hypertension induces medial hypertrophy both in the major arteries and in the peripheral intrarenal arteries. The cross-sectional areas of the media in fourth divisional intrarenal arteries (diameters between 75 and 120 μm) were more than doubled in the hypertensive animals in comparison with normotensive animals.

Increased quantities of smooth muscle cell nuclei were found in the major arteries but not in the peripheral arteries. It is of interest that a so-called hyperplasia and a hypertrophy may contribute to the haemodynamic alterations in arterial hypertension (Mulvany et al., 1978).

In contrast those SH rats that were kept normotensive by treatment with captopril displayed arterial wall dimensions similar to those of the normotensive WK rats. To exclude the possibility that the differences observed were due to captopril-induced changes of the arterial wall composition unrelated to blood pressure development, control experiments were performed in adult WK rats which had been treated orally with converting enzyme inhibitors for 3 months. Upon morphometric examination, the treated WK rats revealed no alteration in arterial wall dimensions when compared with untreated WK rats (K. J. Henrichs, unpublished work). These results suggest that the structural change of the vasculature in SH rats is an adaptive change rather than a genetically determined phenomenon acting as a causative factor in hypertension.

References


