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Functional and Structural Pattern of Arterial Responses in Hereditary Hypertriglyceridemic and Spontaneously Hypertensive Rats in Early Stage of Experimental Hypertension

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Summary

It has been shown that endothelium-derived nitric oxide (NO) plays an important role in regulation of vascular tone in the prenatal and early postnatal period. The aim of this paper was to determine the reactivity and accompanying structural changes in thoracic aorta from 4-week-old spontaneously hypertensive rats (SHR) and rats with hereditary hypertriglyceridemia (hHTG) in comparison with age-matched normotensive controls. For functional studies thoracic aorta was excised, cut into rings and mounted in organ baths for measurement of isometric contractile force. For morphological studies cardiovascular system of rats was perfused with glutaraldehyde fixative (at 100 mm Hg) via cannula placed in the left ventricle. Morphological changes of thoracic aorta were measured using light microscopy. Systolic blood pressure (SBP) in SHR (98±1 mm Hg) did not significantly differ from that of age-matched control rats (95±4 mm Hg), but was slightly increased in hHTG rats (110±2 mm Hg, $P<0.05$). Heart weight/body weight ratio was higher in SHR and hHTG rats than in control group indicating the hypertrophy of the heart in both models of hypertension. Endothelium-dependent relaxation of aorta induced by acetylcholine was preserved in all groups and did not differ from that in control normotensive rats. The maximal isometric contraction of thoracic aorta to noradrenaline (NA) was reduced in hypertensive groups and the concentration-response curves to NA were shifted to the right indicating increased sensitivity of smooth muscle to NA. The values of wall thickness and cross sectional area as well as inner diameter of thoracic aorta in SHR and hHTG rats were significantly decreased in comparison to control groups. Endothelial dysfunction seems to be absent in all young rats before development of hypertension. In conclusion, our observations indicate that in early stage of experimental hypertension NO-dependent relaxation is preserved so that putative impairment of this function provides no significant pathogenic contribution to the onset of hypertension in these two experimental models.

Key words

Prehypertensive period • Blood pressure • Thoracic aorta • Relaxation • Contraction • Vessel geometry

Introduction

Hypertension is a result of mutual interactions of genetic fond of the individual and risk factors, which can pass to pathological state. Adult rats with genetic hypertension are characterized by elevation of blood pressure and by important functional and morphological changes in cardiovascular system.

An impairment of endothelial function, as evaluated by the relaxant response to acetylcholine, has been detected in conduit and resistance arteries both in animal and human hypertension (Lüscher and Vanhoutte 1991). Structural abnormalities include cardiac hypertrophy and hypertrophy of the tunica media in conduit arteries, but prevailingly in resistance vessels are common accompaniments of chronic hypertension, and play an important role in the increase of vascular resistance, and therefore in the maintenance of high blood pressure (Folkow 1982, Mulvany and Aalkjaer 1980).

It has been shown that endothelium-derived nitric oxide (NO) plays an important role in regulation of vascular tone in prenatal and early postnatal period. But the data concerning the interrelationship between functional and structural properties of cardiovascular system in young rats in prehypertensive stage in these two models of genetic hypertension has not been performed.

There have been found structural changes in resistance vessels at prehypertensive phase in SHR. These changes may belong to factors contributing to the development of hypertension in the SHR (Lee 1985). The conduit arteries are apparently not involved in the development of hypertension at this stage of hypertension development. The structural alterations in the aorta from SHR was not evident in 4-week-old SHR, but become evident in rats 3 to 5-month-old (Owens *et al.* 1981), mainly due to hypertrophy of the vascular smooth muscle. On the other hand, Van Gorp *et al.* (2000) as well as Cebová and Török (2005) have found alterations in aortic wall properties, which proceed development of hypertension.

Endothelial dysfunction seems to be absent in SHR before development of hypertension, despite of presence of early structural alterations (Rizzoni *et al.* 1994). We have shown that in 6-week-old dog puppies with NO-dependent hypertension the endothelium-dependent relaxation of the aorta was fully preserved (Török and Gerová 1996, Gerová *et al.* 2005).

Several studies have demonstrated functional changes in isolated blood vessels in prehypertensive animals, but these changes differ both quantitatively and qualitatively among the vascular beds (Zicha and Kuneš 1999). The data concerning the structural and functional alterations of the conduit arteries in prehypertensive phase of hHTG rats are completely missing.

The aim of this paper was to determine the reactivity and accompanying structural changes in thoracic aorta isolated from 4-week-old spontaneously hypertensive rats and rats with hereditary hypertriglyceridemia (hHTG) in comparison with age-matched Wistar rats.

Methods

Experiments were performed on young 4-week-old male rats. Rats were treated in accordance with the Guide for the Use of Laboratory Animals and the procedures were approved by the Local Institutional Ethics Committee. All rats were divided in three groups: 1) control (Wistar) rats, 2) spontaneously hypertensive rats (SHR) and 3) rats with hereditary hypertriglyceridemia (hHTG).

All rats were housed under a 12 h light – 12 h darkness cycle, at a constant humidity and temperature, with free access to standard laboratory rat chow and drinking water.

Systolic blood pressure was measured at the end of 4-week by the indirect tail-cuff technique. The animals were sacrificed by an overdose of anesthesia.

Functional study

The thoracic aorta was removed and immediately immersed in cold Krebs solution for isometric tension studies. After the connective tissue was carefully removed, aorta was cut into (3.0-3.5 mm width) rings. The rings were suspended between two stainless hooks in an organ bath (20 ml) filled with oxygenated (95 % O_2 + 5 % CO_2) modified Krebs solution maintained at 37 °C. Modified Krebs solution contained (mM): NaCl 118, KCl 5, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 11.0, $CaNa_2$.EDTA 0.03 and ascorbic acid 0.55. Isometric tension was monitored continuously using a force-displacement transducer Sanborn FT 10 connected to a line recorder TZ 4600 (Czech Republic). The rings were equilibrated under a resting tension of 10 mN for 60-90 min, and the buffer was changed every 15 min. To assess relaxation, cumulative concentration-response curves were obtained

with endothelium dependent vasodilator acetylcholine and endothelium-independent vasodilator sodium nitroprusside on preparations precontracted with submaximal concentration of phenylephrine (1 μM). The magnitude of relaxation response was expressed as a percentage of phenylephrine contraction. The cumulative contractile responses of the aortic ring to noradrenaline were studied also in the presence of endothelium. Contraction was expressed as percentage of the maximal contraction reached by noradrenaline.

Morphological study

The chest was opened and cardiovascular system was perfused via the left ventricle with 300 mM glutaraldehyde in 100 mM sodium phosphate buffer, pH 7.2-7.4, at a perfusion pressure 100 mm Hg for 10 min. After perfusion, middle part of the thoracic aorta was excised, cleaned, divided into segments of about 1 mm in length and fixed in the same fixative. After fixation, the segments were postfixed with 40 mM OsO_4 in 100 mM sodium phosphate buffer, washed in 100 mM sodium phosphate buffer, and stained en bloc with uranyl acetate. The blocks were dehydrated with increasing concentrations of alcohol, washed in propylene oxide am embedded in Durcupan ACM.

Two randomly selected blocks of aorta from each newborn were cut perpendicularly to the longitudinal axis. Both inner circumference and arterial wall thickness (tunica intima plus tunica media) were measured in semithin sections by light microscopy. The arterial wall thickness was measured at about 45 ° intervals around the vessel circumference. The cross-sectional area (tunica intima plus tunica media) of the arterial wall, the inner diameter, and wall thickness/inner diameter ratio of the vessels were then calculated from these data.

Substances used

The following substances were used: phenylephrine, acetylcholine chloride, sodium nitroprusside, glutaraldehyde (all from Sigma), Durcupan ACM (Fluka), and noradrenaline (Léčiva, Zentiva). All drugs were dissolved in distilled water.

Statistical analysis

All results are expressed as means ± S.E.M. ANOVA and Bonferroni test for unpaired variables were used for statistical evaluation. Results were considered to be significant when $P<0.05$.

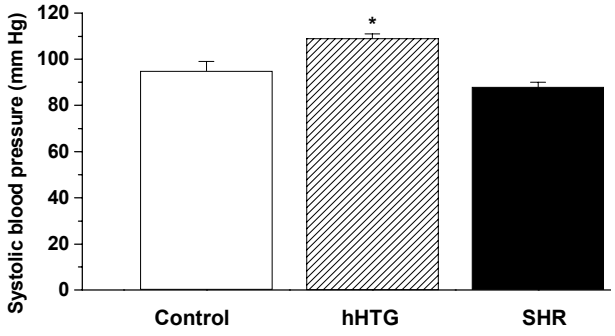

Fig. 1. Systolic blood pressure of control Wistar rats, hereditary hypertriglyceridemic (hHTG) and spontaneously hypertensive rats (SHR) at the end of 4th week. *P<0.05 compared with control

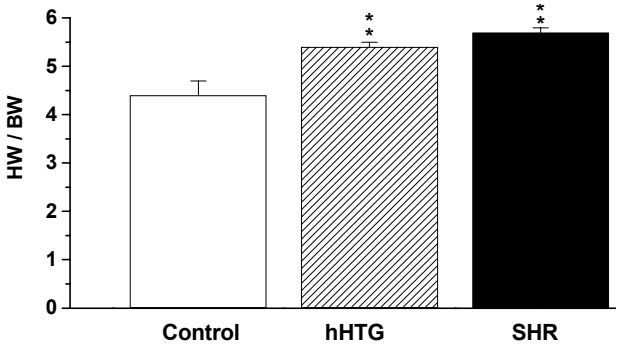

Fig. 2. Heart weight/body weight (HW/BW) ratio, expressed in mg/g, of control Wistar rats, hereditary hyperglyceridemic (hHTG) and spontaneously hypertensive rats (SHR) at the end of 4th week. **P<0.01 compared with control.

Results

Functional Studies

Systolic blood pressure in SHR (98±1 mm Hg) was not significantly different from age-matched control Wistar rats (95±4 mm Hg), but was slightly increased in hHTG rats (110±2 mm Hg, $P<0.05$) (Fig. 1). Body weight in control Wistar rats was 78±4 g. Body weight of hHTG (44±3 g, $P<0.01$) and SHR (56±2 g, $P<0.05$) were significantly smaller.

Heart weight/body weight ratio was higher in SHR (5.7±0.2) and hHTG rats (5.4±0.1) than in control groups (4.4+0.3) and indicates hypertrophy of the heart in both models of hypertension (Fig. 2).

Isolated thoracic aortas from SHR often developed phasic activity superimposed on a tonic contraction. Endothelium-dependent relaxation of thoracic aorta induced by acetylcholine was in all groups preserved and did not differ from that in control Wistar rats (Fig. 3).

Sodium nitroprusside elicited a dose-dependent

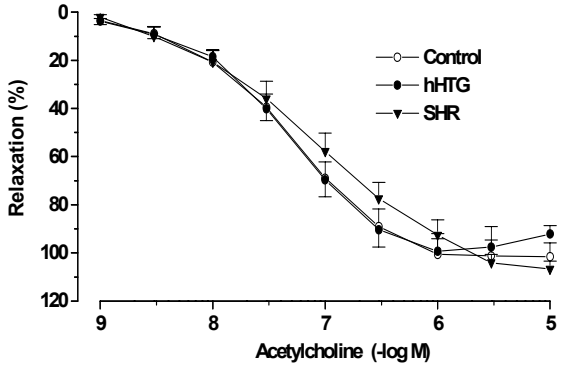

Fig. 3. Concentration–response curve for acetylcholine induced relaxation of aortic rings from control Wistar rats, hereditary hypertriglyceridemic hHTG) and spontaneously hypertensive rats (SHR).

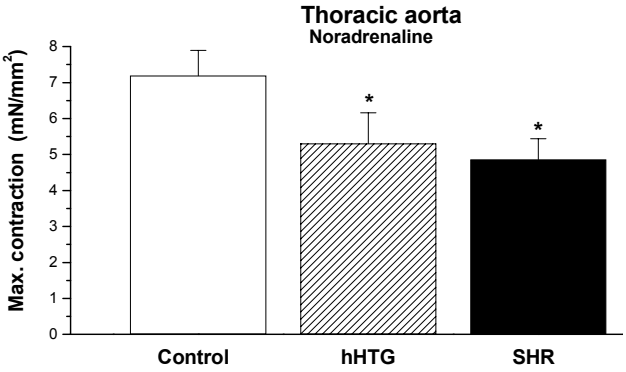

Fig. 5. Maximum contractile responses of the thoracic aorta induced by noradrenaline in control Wistar rats, hereditary hypertriglyceridemic (hHTG) and spontaneously hypertensive rats (SHR). *P<0.05 compared with control.

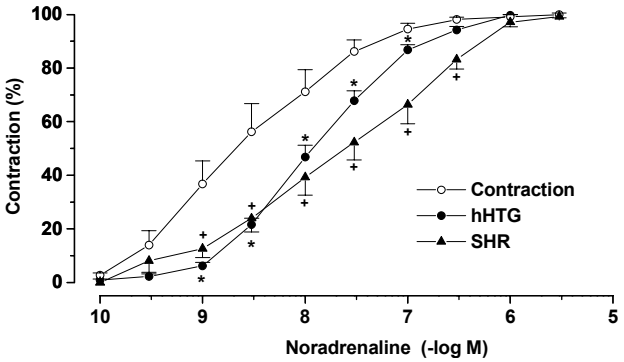

Fig. 4. Concentration–response curve for noradrenaline-induced contraction of the thoracic aorta from control Wistar rats, hereditary hypertriglyceridemic (hHTG) and spontaneously hypertensive rats (SHR). *P<0.05 compared with control, $^{+}$P<0.05 compared with control.

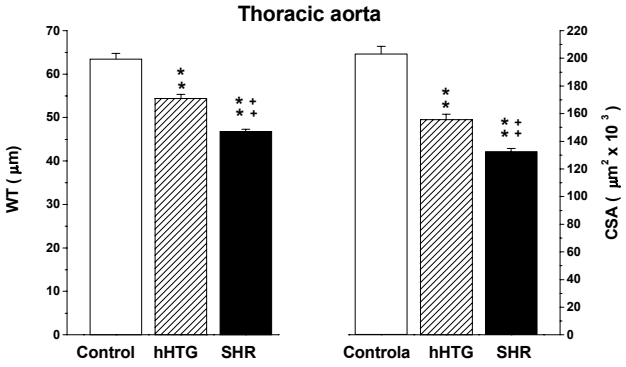

Fig. 6. Wall thickness (WT) and cross-sectional area (CSA) of the thoracic aorta in control Wistar rats, hereditary hypertriglyceridemic (hHTG) and spontaneously hypertensive rats (SHR) at the end of 4th week. **P<0.01 compared with corresponding control, $^{++}$P<0.01 compared with corresponding hHTG.

relaxation of phenylephrine-precontracted aortic rings. At concentration 0.3 μM sodium nitroprusside completely relaxed aortic preparations, the magnitude of this relaxation was not significantly different among these investigated groups of rats (not shown).

The maximal isometric contraction of the thoracic aorta to noradrenaline was in hypertensive groups reduced and the concentration-response curves to noradrenaline in hHTG as well as in SHR were shifted to the right indicating decreased sensitivity of smooth muscle to noradrenaline (Figs 4 and 5).

Morphological Studies

Wall thickness of aorta (65.5±1.3 μm) in 4-week-old control Wistar rats was significantly higher in comparing to wall thickness of aorta in age-matched hHTG rats (54.4±0.9 μm, P<0.01) and SHR (46.3±0.5 μm, P<0.01) (Fig. 6). Calculated cross sectional area of aortic wall, demonstrating changes in arterial wall mass, in control rats (203±50 μm^2 x 10^3) was significantly higher than those in hHTG (156±4 μm^2 x 10^3, P<0.01) and SHR (130±3 μm^2 x 10^3, P<0.01) (Fig. 6).

The inner diameter of aorta in control Wistar rats was 954±14 μm. In age-matched hHTG rats (849±19μm, P<0.01) and SHR (855±12 μm, P<0.01) was significantly smaller. Wall thickness/inner diameter ratio was decreased only in SHR group (6.68±0.16 x 10^{-2} in control vs. 5.50±0.14 x 10^{-2} in SHR, P<0.01) (Fig. 7).

Discussion

Sustained genetic hypertension in adult rats is usually associated with the presence of structural abnormalities in conduit (Kristek *et al.* 2003, Török and Kristek 2001, Török *et al.* 2002) as well in resistance vessels (Folkow 1982, Mulvany and Aalkjaer 1980). Previous investigations have demonstrated that in adult SHR arterial pressure usually overcomes value of 180

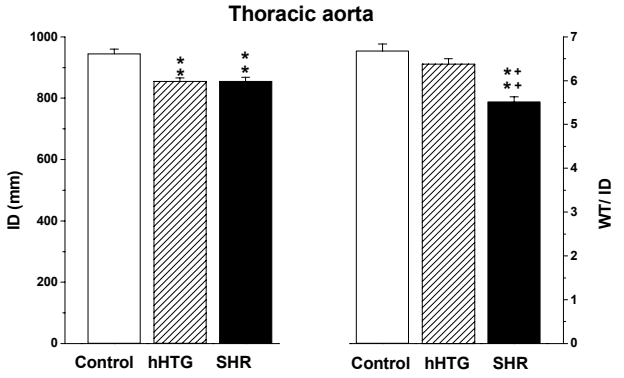

Fig. 7. Inner diameter (ID) and wall thickness/inner diameter ratio (WT/ID) of the thoracic aorta in control Wistar rats, hereditary hypertriglyceridemic (hHTG) and spontaneously hypertensive rats (SHR) at the end of 4th week. **P<0.01 compared with corresponding control, $^{++}$P<0.01 compared with corresponding hHTG.

mmHg while hypertension in hHTG rats is characterized as a mild hypertension with values 140-150 mm Hg. In spite of differences in magnitude of blood pressure in both animal models of hypertension, an increase of arterial pressure is accompanied by hypertrophy of tunica media of thoracic aorta (Török and Kristek 2001, Török *et al.* 2002).

The mayor finding of the present study was that reactivity of thoracic aorta to noradrenaline was in 4-week-old SHR and hHTG rats smaller than in age-matched control Wistar rats. At the same time morphological studies showed that wall thickness of thoracic aorta of SHR and hHTG rats were thinner as that in control thoracic aorta. There were no significant differences between blood pressure values from control Wistar and SHR. This is consistent with measurements of other investigators in prehypertensive stage in the development of spontaneous hypertension (Gray 1984a,b, Lee 1985). Aortic hypotrophy and reduction of contractile responses in aorta are similar in hHTG and SHR in spite of higher basal values of arterial pressure in hHTG.

Our experiments showed that acetylcholine elicited marked relaxation of thoracic aorta from all investigated groups. It has been shown that nitric oxide in blood vessels is operative close to birth, but this feature seemed to be specific for pulmonary vessels (Shaul *et al.* 1996). In previous experiments (Török and Gerová 1996) we have found that after 6-week administration of N^G-nitro-L-arginine methyl ester to 5-day-old dog puppies, the thoracic aorta was capable of pronounced relaxation. Pronounced endothelium-dependent relaxation of aorta was observed in thoracic aorta from 4-week-old rats with NO-dependent hypertension – with mean blood pressure of 150 mm Hg (Gerová *et al.* 2002). Also Rizzoni *et al.* (1994) and Dickhout and Lee (1997) found that endothelial dysfunction of small arteries was absent in young SHR before development of hypertension, despite the presence of early vascular structural alterations. These findings are in consent with statement that in the postnatal period endothelial cells of vessels contain probably high level of nitric oxide synthase. This statement was supported also by Arnal *et al.* (1994) who found in cultured endothelial cells that growing cells had a higher concentration of NO synthase than mature quiescent ones.

We have shown that after 6-week-lasting inhibition of nitric oxide (NO) synthase in dog puppies, which were hypertensive (mean blood pressure 168 mm Hg), the endothelial function is fully preserved (Török and Gerová 1996). Also results in this paper demonstrate that in hHTG rats, with increased blood pressure, the endothelium-dependent relaxation is not impaired. On the base of similar studies performed in SHR by other investigators (Rizzoni *et al.* 1998) it is suggested that neither a hemodynamic nor structural factors are involved in the genesis of endothelial dysfunction in prehypertensive stage in SHR and hHTG rats.

Our experiments showed that magnitude of noradrenaline-induced contraction of aorta from 4-week-old SHR and hHTG rats was smaller than in age-matched Wistar rats. This is in good consent with findings of Mizutani *et al.* (1999) which demonstrated that maximum mechanical strength in the 4-week-old SHRSP were lower than those in the age-matched WKY rats. Morphometric analysis suggests that our results may be explained by a smaller wall thickness, arterial wall mass (cross sectional area) as well as a smaller inner diameter of investigated aortic rings. The finding of remodelled wall of thoracic aorta (inward hypotrophic remodelling) cannot be generalized because the reduction in reactivity of aortic rings to noradrenaline in SHR is associated with increased reactivity in mesenteric vascular beds (Criscione *et al.* 1992). In thoracic aorta from 4-week-old hHTG rats and SHR the concentration-response curves to noradrenaline were shifted to the right indicating decreased sensitivity of smooth muscle to noadrenaline.

In hypertension, the postsynaptic α_1-adrenergic functions in resistant vessels become dominant, whereas β-adrenergic functions are attenuated. Enhancement of vasoconstriction in young SHR might be not only due to

a greater NA release from sympathetic nerves of SHR (Westfall *et al.* 1984), but also due to the hyperactivity of vessels or their supersensitivity to α_1-adrenergic stimuli. Beside this, the diminished feedback inhibition and increased feedback facilitation, which enhance NA release to nerve stimulation, seem to be augmented in genetic hypertension. This reduced negative feedback of NA is characteristic for young SHR aged 4 to10 weeks (Szemeredi *et al.* 1988, Tsuda *et al.* 1987). Information concerning the function of sympathetic nerve system in blood vessels of young rats with hereditary hypertriglyceridemia is missing.

The elevation of peripheral vascular resistance in primary hypertension is partially caused by the decrease of arteriolar lumen diameter due to media thickening or remodelling. In animals with genetic hypertension, the hypertrophy of blood vessel wall parallels the developmental rise in blood pressure and systemic resistance, which is maximal at about 36-week of age (Marque *et al.* 1999).

Phenotypic abnormalities of the cytoplasmic free calcium in vascular smooth muscle have been associated with the predisposition to high blood pressure. Sugiyama *et al.* (1990) found an increase in cytoplasmic free calcium in rat aortic medial vascular smooth muscle cells of 8- and 12-weeek-old SHR with concomitant elevation in blood pressure in comparison to Wistar-Kyoto rats. Blood pressure and basal cytoplasmic free calcium levels are not yet elevated in 4-week-old SHR, but there was already abnormal calcium handling in vascular smooth muscle cells in response to stimulation with caffeine or angiotensin II (Sugiyama *et al.* 1990).

The relative importance of NO in endothelium-dependent relaxation of vascular system is dependent on vessel size. In large conduit arteries, NO is a major component of the acetylcholine-dependent relaxation, whereas hyperpolarizing factor may play an important role in relaxation of resistance arteries (Hwa *et al.* 1994). Basal release of NO does not appear to be impaired in SHR, at least in conduit arteries. Nava and Lüscher (1994) reported that basal NO synthase activity in aorta from SHR was twice of that from the normotensive control rats. Therefore, one could speculate that in thoracic aorta and other conduit arteries the increase of NO formation represents a major counterregulatory mechanism for the increased vascular resistance in genetic model of arterial hypertension.

Our observations indicate that in early stage of experimental hypertension endothelium-dependent relaxation of aorta to acetylcholine is not impaired. Preservation of endothelial function provides no significant pathogenic contribution to the onset of hypertension in these two experimental models.

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Reprint requests

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