DEVELOPMENT OF HYPERTENSION AND INCREASED AORTIC RELAXATION IN SPONTANEOUSLY HYPERTENSIVE RATS AFTER NEONATAL SYMPATHECTOMY

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One of the leading factors in the development of arterial hypertension is an increase in the resistance of resistive vessels. The increase in resistance of the vessels to the blood flow in arterial hypertension may be associated not only with increased reactivity of the smooth-muscle cells to vasoconstrictors, but also with a reduction of their relaxation under the influence of depressors. The discovery of a new, endothelially-dependent mechanism of vasodilatation in 1980 [7] led to the appearance of publications describing the study of vascular dilatation factors. It was shown that under the influence of certain agents on the vascular endothelium, a relaxing factor is synthesized in it and secreted, and by its action on the smooth-muscle cell it causes its relaxation through an increase in its cyclic GMP (cGMP) concentration [12]. However, the characteristics of vascular relaxation in arterial hypertension remain virtually unstudied.

The aim of this investigation was to compare relaxation of the aorta in spontaneously hypertensive (SHR) and normotensive (NR) rats in response to the endothelially dependent agent acetylcholine [7] and the endothelially independent vasodilator cAMP [12]. The study of the effect of neonatal sympathectomy on aortic relaxation in NR and SHR also is of definite interest, because sympathectomy lowers the total peripheral vascular resistance [2, 3].

EXPERIMENTAL METHOD

Intact and neonatally sympathectomized Wister-Kyoto rats (NR) and SHR of the Okamoto-Aoki strain aged 4 months were used. Sympathectomy was simulated by daily subcutaneous injections of guanethidine (Yugoslavia) in a dose of 25 mg/kg, starting 1 day after birth and continuing for 25 days [3]. Blood pressure (BP) was measured in the caudal artery by an electroplethysmographic method on a Narco Biosystems physiograph (USA). Reactivity of the aorta to noradrenalin (NA), acetylcholine (ACh), and 3,5-cAMP was studied on isolated rings of the thoracic aorta 2.5 mm wide. The preparations were incubated in a constant-temperature chamber (36°C), perfused with Krebs-bicarbonate solution (96% O_2 + 4% CO_2). After equilibration of the preparation for 40 min with a preload of 1.25 g, 6-hydroxydopamine was added to the solution in a concentration of 30 μg/ml. After incubation for 10 min in the solution of 6-hydroxydopamine the preparations were washed for 30 min, after which the tension developed in response to increasing doses of exogenous NA (10^{-9}-10^{-7} g/ml) was recorded by means of isometric transducers (Ugo Basile, Italy). The degree of relaxation of the aorta of the NR and SHR was investigated after addition of ACh in a dose of 10^{-8}-10^{-5} g/ml and cAMP in a dose of 10^{-8}-10^{-6} M to the solution after preliminary contraction induced by NA (amounting to 70% of maximal). The degree of relaxation was expressed as a percentage of the initial contraction, taken at 100. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Neonatal sympathectomy caused a fall of BP in SHR by 19% ($p < 0.01$) compared with its value in intact SHR. In intact SHR it was 179.1 ± 7.0 mm Hg, in sympathectomized SHR 145.0 ± 4.5 mm Hg; in intact NR it was 120.5 ± 2.8 mm Hg and in sympathectomized NR 118.3 ± 3.4 mm Hg. The effect of delayed development of spontaneous hypertension after neonatal sympathectomy

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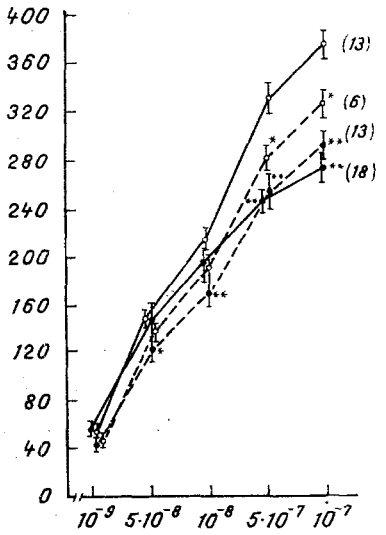

Fig. 1

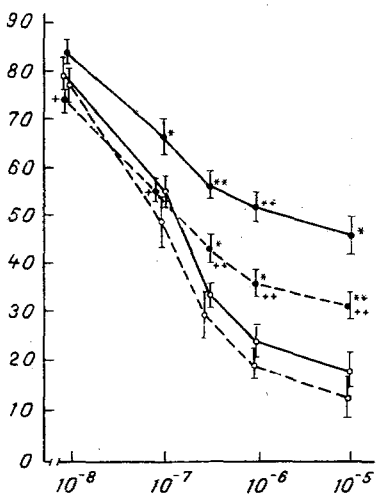

Fig. 2

Fig. 1. Contraction of aorta of intact and sympathectomized NR and SHR in response to NA. Abscissa, dose of NA (in g/ml); ordinate, developed tension (in mg). Empty circles — NR; filled circles — SHR; continuous line — rats with intact sympathetic systems; broken line — rats with neonatal sympathectomy. *p < 0.05 compared with intact NR; **p < 0.01. Number of animals given in parentheses.

Fig. 2. Relaxation of aorta of intact and sympathectomized NR and SHR in response to ACh. Abscissa, cumulative dose of ACH (in g/ml); ordinate, % of initial contraction induced by NA. *p < 0.05 Compared with intact NR; **p < 0.001; p < 0.05 compared with intact SHR; $^{++}$p < 0.01. Remainder of legend as to Fig. 1.

is well known [1, 14]. It is connected with reduction of the increased sympathetic nervous activity in SHR and with lowering of the total peripheral vascular resistance [2]. In previous investigations using the method of perfusion of the vascular bed of the posterior part of the body, the present writers found reduction of the increased vascular reactivity of SHR to NA after sympathectomy [1]. Unlike the resistive vessels of the hind limbs, which were investigated *in situ*, reactivity of the aortic rings of SHR to NA was 27% less than that of NR, with doses of NA higher than 10^{-8} g/ml (Fig. 1). Reactivity of the aorta to NA was reduced after neonatal sympathectomy only in NR, and in SHR it was almost unchanged. The difference which was found in NA reuptake by sympathetic endings between sympathectomized and intact rats (data not given) did not affect the results, for all preparations were preincubated in 6-hydroxydopamine solution. Reduction of contractility of the aortic smooth muscles in SHR also was found by other workers [4]. Hypertrophy of the large elastic vessels, including the aorta, by contrast with hypertrophy of the small arteries of muscular type [11], evidently takes place mainly through an increase in the number of noncontractile cells in the vascular wall [8].

Relaxation of the aorta in response to ACh (Fig. 2) was significantly less in SHR than in NR, and the difference was more marked if ACh was added when vascular tone was higher. Similar results were obtained in previous investigations [9, 15]. Since ACH is an endothelially dependent agent of vascular relaxation [7], reduction of aortic relaxation in SHR may be due to changes in the structural-functional organization of its endothelial layer in SHR [10] and reduced secretion of the endothelial relaxing factor. The possibility of a decrease in the sensitivity of the smooth-muscle cells of SHR to this factor [15] and (or) disturbance of the cGMP-dependent mechanism of removal of cytoplasmic calcium [13] likewise cannot be ruled out. The suggestion that relaxation of the smooth-muscle cell itself is disturbed in SHR is also confirmed by data showing that aortic relaxation in SHR is reduced in response to the endothelially independent agent 3,5-cAMP also (Fig. 3). Fujimoto and co-workers [6] found reduction of relaxation of the femoral artery in SHR in response to cAMP, and to the β-agonist isoproterenol, already in the prehypertensive stage, at the age of 4 weeks.

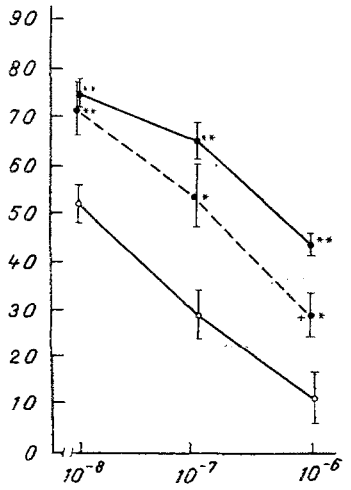

Fig. 3. Relaxation of aorta of intact and sympathectomized NR and SHR in response to cAMP. Abscissa, cumulative dose of cAMP (in M); ordinate, % of initial contraction induced by NA. *$p < 0.05$ Compared with intact NR; **$p < 0.01$; $^{+}p < 0.05$ compared with intact SHR. No data for group of sympathectomized NR. Remainder of legend as to Fig. 1.

Reduction of vasodilatation is evidently characteristic of all forms of experimental arterial hypertension. The fact is thus all the more interesting that after neonatal sympathectomy, relaxation of the aorta of SHR was significantly increased (Figs. 2 and 3). Relaxation of the aorta of sympathectomized SHR in response to ACh was increased by 20-35% (for a dose of ACh of over 10^{-8} g/ml), and in response to cAMP by 36% (dose of cAMP 10^{-6} M) compared with that of intact SHR ($p < 0.01$), although the values found in NR were not reached. This last fact may perhaps be due to the increased resistance of SHR to guanethidine sympathectomy [1], as a result of which, the procedure was incomplete. In the present experiments this conclusion is supported by the fact that despite a fall of BP in the sympathectomized SHR, its level was still higher than in NR. However, even incomplete sympathectomy led to increased vasodilatation in SHR. Relaxation of the aorta to ACh in NR after neonatal sympathectomy was not significantly changed (Fig. 2). The question whether increased relaxation of the aorta in sympathectomized SHR is the result of the fall of pressure on the vessel wall and reduction of its hypertrophy or the result of functional biochemical changes in the smooth-muscle cells, induced by reduction of their sympathetic innervation, cannot yet be answered. The second hypothesis seems very probable if data showing that even acute short-term sympathectomy by reserpine causes an increase in the dilator properties of the vessels in SHR are taken into consideration [5].

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