STATE OF RESISTIVE LIMB VESSELS IN SPONTANEOUSLY HYPERTENSIVE RATS

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The increased peripheral resistance of the resistive vessels is a characteristic feature of any form of hypertension with a persistently raised arterial blood pressure (BP). Two possible mechanisms of the increased resistance to the blood flow in arterial hypertension are now known: 1) strengthening of contractile activity of the smooth muscles of the arterioles as a result of increased sensitivity to neurohumoral pressor factors [12]; 2) structural "functionally adaptive" changes in arteries: hypertrophy of the smooth-muscle layer and constriction of the lumen of the vessel [6] and (or) a decrease in the number of functioning arterioles (the rarefaction phenomenon [11]). Some workers consider that the increase in the resistance of the resistive vessels is due to the participation of both of these mechanisms [2].

In the present investigation the resistance and reactivity of resistive vessels of normotensive rats (NR) and of spontaneously hypertensive rats (SHR), which is one of the best models of essential hypertension in man, were studied under artificial perfusion conditions.

EXPERIMENTAL METHOD

SHR of two age groups were used in the experiments: young rats aged 7-8 weeks with normal BP (116 ± 2.6 mm Hg) and SHR aged 24-30 weeks, in a stage of persistent hypertension (168 ± 2.6 mm Hg). NR of the corresponding age (BP = 110 ± 4.7 mm Hg) served as the control. BP was measured before the experiments in waking animals by an electroplethysmographic method on the caudal artery by means of an attachment for the Narko Biosystems 4B four-channel polygraph (USA). A midline laparotomy was performed on rats anesthetized with pentobarbital (40 mg/kg) and massive ligatures were applied to the lumbar division* on both sides, the inferior vena cava was divided, and perfusion of the hind part of the body was carried out in vitro (with Tyrode solution containing dextran, 4% CO_2 + 96% O_2) through a cannula introduced into the abdominal aorta. The rate of perfusion (Q) was maintained constant by means of a Harvard Model 1201 peristaltic pump (USA). Changes in perfusion pressure (PP) at different rates of perfusion were estimated, and reactivity of the vessels was judged from the response of the limb vessels to gradually increasing doses of noradrenalin (NA), which was injected into the perfusion fluid by means of a Harvard automatic syringe (USA). The rate of perfusion was thereby kept constant (the NA concentration was expressed in μg/ml perfusion fluid). PP (when Q = const this adequately reflects the hydraulic resistance of the system) was recorded by Statham P23Db electromanometric transducers on an eight-channel RM-6000 polygraph (Nihon Kohden, Japan). The data were used to plot the rate of perfusion–PP and PP–dose of NA curves.

In each age group paired experiments were carried out, in which the limbs of normotensive and hypertensive animals were perfused simultaneously under identical conditions. The statistical significance of the data was estimated by Student's t test.

EXPERIMENTAL RESULTS

During perfusion of the preparations with Tyrode solution, injection of various vasodilators (1 mg/ml papaverine, 2 mg/ml sodium nitroprusside) into the perfusion fluid caused no additional fall in PP. Consequently, the vessels were in the maximally dilated state. In that case the resistance of the resistive vessels

*It is not stated in the text, nor is it clear from the context, exactly what was ligated – Translator.

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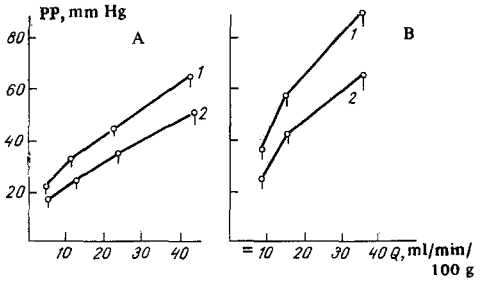

Fig. 1

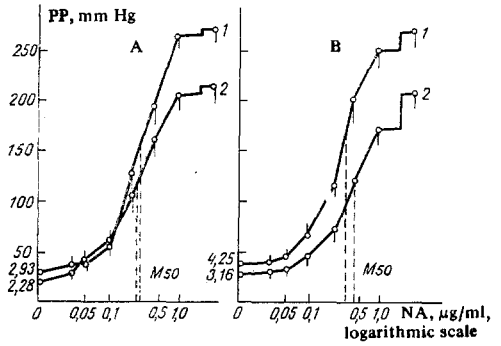

Fig. 2

Fig. 1. Dependence of PP on perfusion flow rate for resistive vessels of SHR and NR of different ages. A) Prehypertensive stage, B) persistent hypertension. 1) SHR, 2) NR. Abscissa, perfusion flow rate (in ml/min/100 g); ordinate, level of PP (in mm Hg).

Fig. 2. Dependence of PP on dose of NA in perfusion fluid for resistive vessels of SHR and NR of different ages. Abscissa, dose of NA (in μg/ml). Numbers at beginning of curves indicate values of resistance (conventional units) during maximal vasodilatation. Remainder of legend as to Fig. 1.

to the blood flow was due entirely to the structural features of the vascular network [6]. As Fig. 1 shows, PP and, consequently, the resistance of the arterial vessels was raised under these circumstances in both adult and young SHR (by 35 and 27% respectively). When the rate of perfusion was increased PP rose; at all values of PP tested, it exceeded PP in the control significantly ($P < 0.01$) in both groups of SHR, i.e., the PP–perfusion flow rate curves were shifted to the left. The value of the change in PP (in per cent) in young SHR compared with NR of the same age, incidentally, remained about the same for all perfusion flow rates: 27% at Q = 5.5 ml/min and 29% at Q = 45 ml/min (Fig. 1a). Meanwhile in SHR aged 24 weeks the PP–perfusion flow rate curve not only was shifted to the left, but it lay within the slope of the corresponding curve for NR: with an increase in the perfusion flow rate from 7.5 to 37 ml/min the degree of increase in PP was more marked in SHR than in NR (Fig. 1B).

Values of the internal radii (r_i) of "equivalent" vessels of SHR and NR, and also the extensibility of these vessels for different values of extensile pressure (EP = PP/2), calculated from the experimental data, are given in Table 1. In both adult and young SHR the internal radius of the resistive vessels was reduced. However, whereas the extensibility of the vessel walls of SHR in the prehypertensive stage was the same as in NR of the corresponding age, in adult SHR extensibility was much less than in the control rats. With an increase in EP from 15 to 35 mm Hg the extensibility of the vessels of SHR in a stage of persistent hypertension was 31% below that of NR (Table 1).

According to data in the literature [6] the chronically raised BP leads to constriction of the lumen of resistive vessels because of adaptive hypertrophy of their wall. Numerous observations on patients with arterial hypertension and also investigations on SHR have in fact demonstrated thickening of the arterial walls [3, 13]. The ratio of the thickness of the wall (w) to the internal radius (w/r_i) is increased under these circumstances and the extensibility of the wall is reduced [8]. The results of the present investigation demonstrate (Table 1)

TABLE 1. Internal Radius and Extensibility of Equivalent Vessels in NR and SHR of Different Ages

Group of animals	Internal radius (r_i) when			Extensibility $\Delta r_i/\Delta_{EP}$, %, within the range 15-35 mm Hg
	EP = 15 mm Hg	EP = 25 mm Hg	EP = 35 mm Hg	
NR (8 weeks)	0,859±0,014	0,979±0,008	1,022±0,010	0,795±0,08
SHR (8 weeks)	0,761±0,013	0,853±0,010	0,909±0,010	0,815±0,07
$\frac{SHR - NR}{NR} \cdot 100$	−11,40	−12,90	−11,10	+2,5
P	<0,001	<0,001	<0,001	>0,5
NR (24 weeks)	0,76±0,014	0,79±0,012	0,86±0,016	0,570±0,076
SHR (24 weeks)	0,70±0,010	0,72±0,006	0,76±0,009	0,495±0,040
$\frac{SHR - NR}{NR} \cdot 100$	−7,9	−8,9	−11,6	−30,7
P	<0,01	<0,01	<0,01	<0,05

that the internal radius and extensibility of the vessels of SHR in a stage of lasting hypertension are significantly lower than in NR. However, in the present experiments the peripheral resistance during maximal vasodilatation was increased not only in SHR with a high BP, but also in young SHR with a normal BP (Fig. 1A). Under these circumstances a reduction in extensibility, which would be evidence of hypertrophy of the arterial walls, was not present (Table 1). The data can be explained on the grounds that the total number of resistive vessels is reduced in such SHR. We know [1, 14] that in SHR in the early stage of hypertension a hyperkinetic type of circulation due to activation of the sympathetic nervous system is present. Resistive vessels in this case respond to an increase in regional blood flow unmotivated by energy demands by spasm (what Guyton [5] calls "total body autoregulation"). Functional occlusion of some of the arterioles may develop as an autoregulatory reaction to an increased blood flow in the initial stage of development of hypertension. In fact, according to data in the literature [4], the number of open arterioles in SHR 40 days old was 62% less, and the total number of arterioles 32% less than in NR. An increase in the number of arterioles was found in the cremaster muscle and mesentery of SHR [10, 11], in the brain of rats with vasorenal and DOCA-salt hypertension, in the ocular conjunctiva of patients with essential hypertension [9], etc. The diameter of the functioning arterioles (of the 3rd and 4th order, which make the main contribution to resistance to the blood flow) not only was not less under these circumstances, but was actually greater than normally [10]. In the stage of lasting hypertension, however, the shift and steepness of the BP–perfusion flow rate curve and also the lowered extensibility were probably due mainly to hypertrophy of the vascular smooth muscles [8].

Reactivity of the vascular smooth muscles of normotensive and hypertensive SHR was investigated by Folkow's method [6] in which the response of vessels dilated beforehand to the maximal extent to gradually increasing doses of exogenous NA is assessed. On the basis of the results BP–dose of NA curves were plotted (Fig. 2) and their analysis gave the following results: 1) resistance is significantly increased ($P < 0.05$) at maximal vasodilatation in young SHR by 17%, and in adult SHR by 35%; 2) the threshold dose of NA causing an increase in BP by 25% of its level at maximal vasodilatation is the same in both groups of SHR and in the corresponding control; 3) the tangent of the angle of slope of the curve is increased by 40% in young and twofold in adult SHR ($P < 0.05$); 4) the magnitude of the response to injection of a maximal dose of NA in young SHR was 57 mm Hg higher, and in adult SHR 75 mm Hg higher than in NR of the corresponding age; 5) the dose of NA inducing half of the maximal response (M_{50}) was significantly lower in SHR at the age of 24 weeks than in NR at the same age.

In both adult and young normotensive SHR, besides an increase in the structural component of resistance, an increase also was observed in the angle of slope and in the maximal constrictor response to NA. Changes observed in the curve in SHR in the stage of lasting hypertension are in good agreement with data obtained by Folkow [6] and, in his opinion, they are evidence of increased reactivity of the vessels on account of thickening of their wall. The increase in the ratio w/r_i has the result that the same degree of contraction of the smooth muscles as under normal conditions causes a much greater decrease in the radius and increase in resistance. However, changes in the BP–dose of NA relationship may evidently reflect not only an increase in w/r_i, but also a decrease in the number of functioning arterioles (an increase in the maximal pressor response to NA and in the angle of slope of the curve compared with the control was observed in the present experiments in young SHR also, in which, to judge from the BP–perfusion flow rate curve, hypertrophy of the vascular smooth muscles was absent). It can thus be postulated on the basis of these results that the increase in the structural component of resistance in SHR is to some extent genetically determined and is not due to elevation of BP [7].

Later, as the hypertension becomes stabilized (24 weeks), the leading mechanism in the increase in peripheral resistance, in the writers' opinion, is no longer a decrease in the number of arterioles, but adaptive hypertrophy of the smooth muscles of the resistive vessels. In adult SHR the structural component of resistance (by 35% compared with 17% in young SHR) and the angle of slope of the BP–dose of NA curve (by 100% compared with 40% in young SHR) increases even more in adult SHR.

The experiments thus showed that two mechanisms may evidently participate in the increase in the structural component of resistance of the resistive vessels: a decrease in the density of the network of arterioles and hypertrophy of the vessel walls; moreover these are two interconnected processes, causing an increase in the systemic resistance in SHR in the course of development of hypertension.

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TIME COURSE OF CHANGES IN THE HEPATIC MICRO- AND MACROCIRCULATION FOLLOWING ACUTE BLOOD LOSS IN RATS

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Many investigations of the hepatic circulation in acute blood loss have been published [1, 3, 4, 7-9]. However, the question of what changes arise under these circumstances at the level of the terminal microvessels of the liver, how they are connected with hemodynamic disturbances in the liver and the hepatic system, and what their role is in the pathogenesis of the posthemorrhagic syndrome still remains insufficiently explained.

In the investigation described below the hepatic micro- and macrocirculation and the systemic arterial blood pressure (BP) were studied in rats after acute blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on 56 male Wistar albino rats weighing 250-300 g. The microcirculation in the liver was studied by contact luminescence biomicroscopy under general urethane anesthesia [5]. Simultaneously with visual observation of the hepatic microcirculation, measurements were made of the volume

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