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EFFECT OF NEONATAL SYMPATHECTOMY ON SYSTEMIC HEMODYNAMICS AND MYOCARDIAL CONTRACTILITY IN SPONTANEOUSLY HYPERTENSIVE RATS

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A study of the role of the sympathetic nervous system in the genesis and development of spontaneous (hereditarily determined) hypertension in rats [13, 14] showed that at least one of the genetic defects responsible for the development of spontaneous hypertension consists of increased activity of the peripheral part of the sympathetic nervous system and a decrease in the inhibitory noradrenergic influences of the brain [14]. To study this problem more recently, besides determining catecholamines (CA), various methods of total sympathectomy also have been used, including immunologic and chemical methods [4, 6, 7, 9], with the aid of guanethidine and 6-hydroxydopamine (6-OH-DA) [5]. However, the results have been very contradictory. According to some workers, chemical or immunologic sympathectomy alone is insufficient to destroy sympathetic neurons and nervous pathways, and the two methods have to be combined for this to be done [7]. Morever, in most investigations the effect of sympathectomy was judged purely by changes in arterial pressure (BP) and heart rate (HR) [9, 11]. Changes in the systemic hemodynamics in spontaneously hypertensive rats (SHR) subjected to immunologic sympathectomy have been described in only a few publications [6]. The present writers showed previously that the early hypertensive stage in SHR is characterized by a hyperkinetic type of circulation. Activation of adrenergic influences on the heart plays an important role under these circumstances [2, 3].

In the investigation described below the effect of neonatal chemical sympathectomy by 6-OH-DA on the systemic hemodynamics and myocardial contractility in SHR was studied. Two problems were to be solved: 1) Is an intact sympathetic nervous system essential for the development of hypertension in SHR and also to maintain the normal BP level in normotensive animals? 2) What are the hemodynamic effects of sympathectomy due to 6-OH-DA in the rats of the above-mentioned two groups?

EXPERIMENTAL METHOD

Neonatal sympathectomy was induced in normotensive rats (NR) and SHR by means of 6-OH-DA-HCl. On the 1st and 2nd days after birth of the animals the compound was injected subcutaneously in a dose of 100 μg/g body weight per animal, and on the 8th and 15th days the injection of the compound was repeated, but this time in a dose of 250 μg/g. The rats were used in the experiments at the age of 10-12 weeks. NR and SHR with an intact sympathetic nervous system served as the control. Under pentobarbital anesthesia (50-60 mg/kg) and with artificial respiration by means of a "Harvard" respirator (model 860, USA), thoracotomy was performed and the transducer of an RT-400 electromagnetic flow meter (Narco Biosystems, USA) was applied to the ascending aorta to record the cardiac output (after deduction of the coronary blood flow). BP was measured through a catheter introduced into the common carotid artery by means of a Statham P23-1D electromagnetic transducer. Myocardial contractility was judged by analysis of the systolic ejection curve, using a special ED600G differentiator (Ni-

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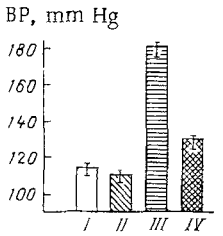

Fig. 1. BP of waking NR and SHR subjected to neonatal chemical sympathectomy by 6-OH-DA. Ordinate, systolic BP (in mm Hg). Here and in Fig. 2: I) intact NR, II) NR subjected to neonatal chemical sympathectomy; III) intact SHR, IV) SHR subjected to neonatal chemical sympathectomy.

TABLE 1. Effect of Neonatal Sympathectomy on Parameters of Hemodynamics and Myocardial Contractility in NR and SHR (M ± m)

Parameter studied	NR (n=32)	Sympathectomized NR (n = 10)	SHR (n=30)	Sympathectomized SHR (n = 8)
BP (mean), mm Hg	83,7±3,2	97,1±5,9	136,8±3,2*	112,3±2,9**
HR, beats/min	291,1±13,4	424,0±22,7*	341,1±10,2*	404,8±17,8**
Cardiac index, ml/min/kg	158,0±10,4	268,0±20,7*	283,0±10,9*	264,1±27,2
TPVR, conventional units	0,56±0,04	0,38±0,05*	0,50±0,03	0,45±0,02
External work, g·m/min	49,8±2,7	71,5±4,9*	140,5±9,5	96,6±76,4**
Stroke work, g·m/stroke	0,18±0,01	0,18±0,01	0,42±0,02	0,24±0,03**
Peak flow rate, ml/sec	2,99±0,1	2,35±0,23	4,10±0,4*	1,90±0,2**
Maximal acceleration of blood flow, ml/sec^2	96,6±6,3	131,0±21,3*	136,2±6,8*	99,4±10,5**
Body weight, g	290,0±5,3	207,5±10,8	300,0±5,4	248,6±20,5**
Relative weight of left ventricle, mg/100 g	257,4±10,3	268,2±7,4	328,2±9,3*	335,2±4,6*

Legend. *P < 0.05 compared with NR; **P < 0.05 compared with SHR.

hon Kohden, Japan), which can give data on the peak blood flow rate (df) and its first derivative (df/dt) — maximal acceleration of the blood flow. All hemodynamic parameters were recorded on an RM-6000 8-channel polygraph (Nihon Kohden, Japan). The numerical results were subjected to statistical analysis by Student's test. On the day of the experiment BP of all the animals was measured in the waking state in the caudal artery by a plethysmographic method, using an NK-709 automatic electromanometer (Natsume, Japan), with a device printing out the values of the systolic BP and HR.

EXPERIMENTAL RESULTS

Neonatal sympathectomy on NR caused no significant changes in BP. Arterial hypertension did not develop in SHR subjected to the sympatholytic action of 6-OH-DA: At the 10th-11th week BP of these animals in the waking state was about 130 mm Hg, whereas in intact SHR during this period BP rose to 160-170 mm Hg (Fig. 1). Similar differences also were observed in rats anesthetized with pentobarbital (Table 1). A substantial increase in cardiac output and, in particular, in the cardiac index took place in sympathectomized NR. In this connection it must be pointed out that the sympathectomized animals were retarded in their development (body weight) compared with control rats with an intact sympathetic nervous system (Table 1). The total peripheral vascular resistance (TPVR) of the sympathectomized NR was about the same as that of the control NR, but the relative peripheral vascular resistance (RPVR) was significantly reduced ($P < 0.05$). In other words, the arterial system was adequately dilated when compared with the increased cardiac output, so that the normal BP could be maintained. Because of the considerable tachycardia the systolic volume and its (systolic) index were virtually unchanged.

The external work of the heart and its index were significantly increased mainly on account of the increased cardiac output. The stroke work of the heart and its index remained unchanged.

The parameters of myocardial contractility also remained unchanged in the sympathectomized NR. Only some tendency was observed for the value of "the maximal increase in blood

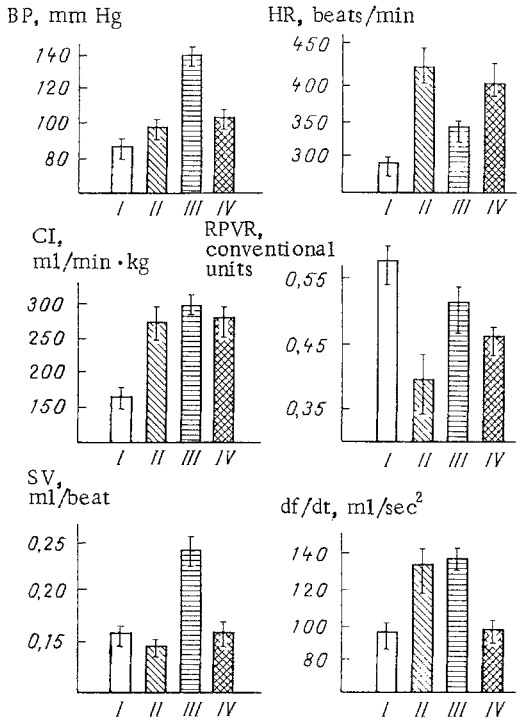

Fig. 2. Parameters of hemodynamics and myocardial contractility in NR and SHR subjected to neonatal chemical sympathectomy. Ordinate, BP (mean) of anesthetized animals (in mm Hg), HR) heart rate, beats/min; CI) cardiac index (in ml/min•kg); RPVR) relative peripheral vascular resistance (in conventional units); SV) systolic volume (in ml/beat); df/dt) maximal acceleration of blood flow (in ml/sec^2).

flow" to rise. Neonatal sympathectomy in NR thus did not lead to a fall in BP; it actually rose a little (but not statistically significantly). However, these animals developed a hyperkinetic type of circulation. In sympathectomized NR under the influence of guanethidine this was also found by Rodionov et al. [5].

It must be borne in mind that neonatal sympathectomy due to 6-OH-DA leads to destruction of both peripheral and central portions of the sympathetic nervous system in rats [11]. The absence of any significant changes in the BP level of such rats is evidence that an intact sympathetic nervous system is probably not the only factor maintaining its normal level. Under these conditions activation of other mechanisms of BP regulation takes place, compensating for the absence of sympathetic influences on the cardiovascular system in NR. In particular, a sharply increased sensitivity of the cardiovascular system to adrenalin and noradrenalin has been found after sympathectomy [11]. If it is recalled in this connection that the adrenal medulla is resistant to 6-OH-DA and is not destroyed by it [11], it can be postulated that adrenalin secreted from the adrenals, on entering the blood stream, has a more powerful cardiostimulating action in sympathectomized rats. Evidence in support of this is given by our data showing an increase in cardiac output and cardiac index, as well as the development of tachycardia. A no less important compensatory mechanism maintaining the normal BP level in sympathectomized NR may be an increase in the blood volume of these animals. The sympathetic nervous system is known to be an important determinant of the total blood volume [1]. Injection of 6-OH-DA thus causes an increase in blood volume of normotensive animals [10], thereby leading to an increase in their cardiac output. This increase, together with the increased sensitivity of the heart and blood vessels to CA of adrenal origin [11], maintain the normal BP level.

The SHR did not develop arterial hypertension. All types of BP were significantly lower than in intact SHR (Fig.1). The indices of the cardiac output in sympathectomized SHR were reduced to the values obtained in sympathectomized NR. Tachycardia was characteristic of the sympathectomized SHR, just as for the corresponding NR. Accordingly the systolic volume and its index were considerably reduced (Fig. 2). The external work of the heart and its index were significantly lower in the sympathectomized rats.

The vascular resistance (RPVR and TPVR) was practically unchanged, but parameters of myocardial contractility were reduced in these animals. Analysis of the data on changes in BP and the systemic hemodynamics in the sympathectomized SHR shows that an intact sympathetic nervous system and, in particular, its central portions, is essential for the development of spontaneous hypertension (it must be borne in mind that 6-OH-DA passes through the blood-brain barrier [11]). It can be postulated that in SHR there is increased (as a result of genetic disturbances) sensitivity of certain brain regions (the medulla) and of the descending noradrenergic pathways to 6-OH-DA, injection of which causes their destruction and a fall in BP. According to data in the literature [12], destruction of descending noradrenergic pathways from the nuclei of the tractus solitarius (NTS) by 6-OH-DA prevents the development of hypertension in rats with a lesion of NTS.

The fact discovered by ourselves (Table 1) and also by Cutilletta et al. [6] deserves particular attention: sympathectomy in SHR, despite the fall in BP, does not lead to regression of myocardial hypertrophy found in intact SHR. This hypertrophy probably also maintains myocardial contractility (the pumping function of the heart) at an adequate, although slightly reduced, level, as is shown by the data we obtained for the external work of the heart and the maximal acceleration of the blood flow in desympathized SHR. Most probably the development of myocardial hypertrophy is connected with a genetic defect of development of the heart muscle in SHR, for it may be manifested even in the absence of a raised BP. An intact sympathetic nervous system is essential for the development of arterial hypertension, however, and for its maintenance at a high level in SHR.

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