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EFFECT OF CHEMICAL SYMPATHECTOMY ON THE DEVELOPMENT OF DOCA-SALT HYPERTENSION IN RATS

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The level of the arterial pressure (BP) depends mainly on the cardiac output (CO) and total peripheral vascular resistance (TPVR). During the development of DOCA-salt hypertension, which is sodium- and volume-dependent, CO rises initially, but this is followed by an increase in TPVR, which leads to stabilization of BP at a high level [11]. The mechanism of the rise in TPVR has not been finally established. In particular, there are conflicting data on the role of the sympathetic nervous system in this process [6, 9, 14]. According to Provoost [14] neonatal sympathectomy accelerates the development of DOCA-salt hypertension.

The object of this investigation was to study the role of the sympathetic nervous system in mechanisms of development of DOCA-salt hypertension and also to study the functional and structural changes taking place in the blood vessels in this condition.

EXPERIMENTAL METHOD

Experiments were carried out on four groups of Wistar rats: 1) normotensive rats (NR) with an intact sympathetic nervous system, 2) NR subjected to neonatal sympathectomy (NR_s), 3) rats with induced DOCA-salt hypertension with an intact sympathetic nervous system (DSR), 4) rats with DOCA-salt hypertension subjected to neonatal sympathectomy (DSR_s). Neonatal sympathectomy was simulated by subcutaneous injection of guanethidine (from "Pliva," Yugoslavia), starting with the first day after birth, and daily for 3 weeks in a dose of 25 mg/kg. Previous experiments [1] showed that as a result of de-sympathization under these conditions fewer than 1% of nerve cells remained in the stellate ganglion. At the age of 10-12 weeks unilateral nephrectomy was performed on all the animals. Arterial hypertension was induced by subcutaneous implantation of DOCA tablets in a dose of 40 mg per rat (the same operation was repeated 3 weeks later); instead of water, these animals were given 1.5% NaCl solution to drink. BP was measured in the caudal artery of the waking rats after 1, 3, 5, and 7 weeks by means of an automatic electroplethysmograph (Natsume KN 209, Japan). In the second week (prehypertensive stage) and seventh week, simultaneous perfusion of the blood vessels of the posterior part of the body with modified Tyrode solution, through a catheter introduced into the abdominal aorta [2, 10], was performed on the animals of all groups in pairs. The rate of perfusion was maintained at a constant level by means of a peristaltic pump (Harvard Model 1201, USA). The perfusion pressure, which under conditions of a constant blood flow,

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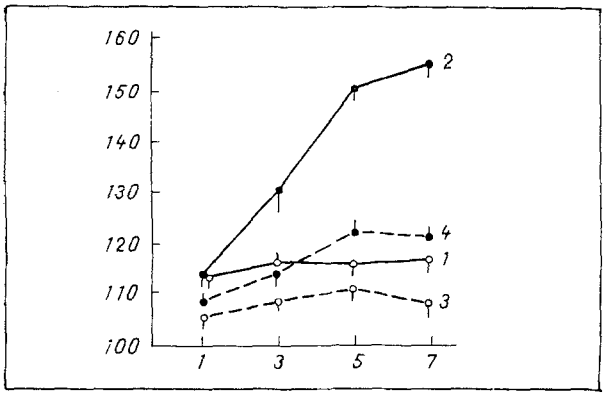

Fig. 1. Effect of neonatal chemical sympathectomy on development of DOCA-salt hypertension in rats. Abscissa, time of experiment (in weeks); ordinate, BP (in mm Hg). Here and in Figs. 2 and 3: 1) rats undergoing mock operation with intact sympathetic nervous system, 2) rats with intact sympathetic nervous system receiving DOCA + NaCl; 3) rats undergoing mock operation and neonatal sympathectomy, 4) rats undergoing neonatal sympathectomy and receiving DOCA + NaCl.

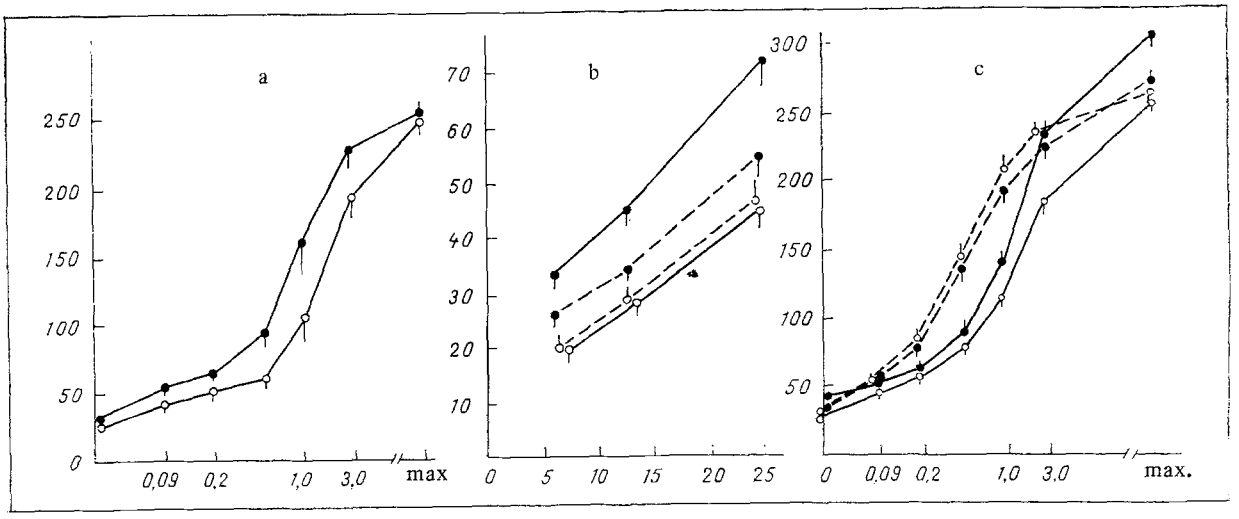

Fig. 2. Role of the sympathetic nervous system in adaptive structural changes in resistive vessels of posterior part of body in rats during development of DOPA-salt hypertension. a) Reactivity of vessels to exogenous NA in 2nd week of development of DOCA-salt hypertension; b) reactivity of vessels to exogenous NA in 7th week of development of DOCA-salt hypertension. Abscissa, logarithm of dose of NA (in μg/ml perfusate); ordinate, perfusion pressure (in mm Hg); c) dependence of perfusion pressure on perfusion rate in rats in 7th week of DOCA-salt hypertension. Abscissa, perfusion rate (in ml/min·100 g); ordinate, perfusion pressure (in mm Hg).

adequately reflects the resistance of the vascular network, was measured at the entrance to the catheter by means of a "Statham P 231 D" electromagnetic transducer and recorded on an RM-6000 polygraph (Nihon Kohden, Japan). At the beginning of the experiment responses of the limb vessels of the anesthetized animals to stimulation of the sympathetic chains at the level of the lumbar division of the spinal cord were determined (parameters of stimulation: voltage 12 V, pulse duration 3 msec, frequency 2-20 Hz, duration of stimulation 15 sec). The response of the vessels of the sympathectomized rats under these conditions was a

physiological test of the effectiveness of desympathization. In the second part of the experiment the animals were killed and changes in perfusion pressure (P) for different rates of perfusion (Q) and during injection of gradually increasing doses of noradrenalin (NA) by means of an automatic syringe (Sage Instruments, Model 341, USA) were recorded *in vitro*. Perfusion of the vessels with Tyrode solution *in vitro* dilates them to the maximal degree and the resistance of the vessels to the blood flow is due entirely to structural features of the vascular network and, in particular, the ratio of the thickness of the wall of the vessels to their internal radius [2, 10]. On the basis of these results graphs of P and Q as functions of the dose of NA (dose — effect) were plotted. The results were subjected to statistical analysis by Student's t test in paired experiments.

EXPERIMENTAL RESULTS

In animals with an intact sympathetic nervous system into which DOCA tablets were implanted, and which subsequently drank NaCl solution (group 3), arterial hypertension developed gradually: in the 7th week of the experiment the BP level rose by 35% (Fig. 1). In the sympathectomized rats (group 4) DOCA-salt loading did not lead to the development of any marked degree of hypertension.

In the prehypertensive stage of the disease in the 2nd week after the beginning of the action of DOCA and NaCl, BP in the animals of group 3 was the same as in those of group 1. Nevertheless, in the rats of group 3 sensitivity of exogenous NA was much greater than in the rats of group 1: A parallel shift of the dose—effect curve to the left was observed (Fig. 2a). In the sympathectomized rats of group 4 the resistance of the vessels under conditions of maximal vasodilatation, the maximal response to NA, and also sensitivity to NA were the same as in the rats of group 2 (NR_s). Desympathization itself is known to lead to a compensatory increase in sensitivity of the blood vessels to NA. It was thus evidently impossible to detect any difference in sensitivity of the vessels between the animals of groups 2 and 4.

Structural changes in the vessels (meaning an increase in the ratio of the thickness of the wall to the lumen of the vessel as a result of hypertrophy of the vascular smooth muscles [2, 10], were discovered only in the stage of stable hypertension (7th week) in animals with an intact sympathetic nervous system (group 3). Evidence of structural changes observed in the vessels was given by the following observations: At all values of Q tested the resistance of the vessels of these rats at maximal vasodilatation was 1.5 times higher (Fig. 2b), the angle of slope of the dose—effect curve was 35% higher, and the maximal response of NA was 20% higher than the corresponding values in NR (Fig. 2c). No structural changes in the vessels were found at this period in sympathectomized rats which also received DOCA and NaCl, and which did not develop arterial hypertension, by contrast with the NR and NR_s groups (Fig. 2b, c).

The effectiveness of synaptic influences on the vessels, assessed as the increase in perfusion pressure in response to stimulation of the sympathetic chains, by the 7th week was 1.8 times higher in hypertensive animals with an intact sympathetic nervous system than in NR (Fig. 3). Responses of the vascular smooth muscles to stimulation of the sympathetic chains were substantially depressed in the sympathectomized rats of groups 2 and 4 and did not exceed 10 mm Hg, evidence of the high degree of desympathization of the vessels.

In the prehypertensive stage of loading with DOCA and NaCl the sensitivity of the vascular smooth muscles to NA thus increased, in agreement with data obtained by other workers on vessels of the limbs [7, 15] and kidneys [8]. This increase in sensitivity was evidently due to the effect of NaCl on smooth-muscle cells [12] and was probably one of the factors initiating the development of hypertension. The structural changes were the result of the developing hypertension, i.e., of pressure loading [2, 10, 15].

The second important conclusion from this investigation is that stable elevation of BP due to administration of DOCA and NaCl is accompanied by an increase in vasoconstriction in response to stimulation of the sympathetic chains, i.e., by a disturbance of the neurogenic mechanisms regulating vascular tone (Fig. 3). This latter disturbance is evidently associated with increased release of NA by sympathetic endings into the synaptic chain and (or) a decrease in its neuronal reuptake [3, 5], but not with structural changes in the vessels discovered at this stage. Possible confirmation of this view is provided by the fact that no

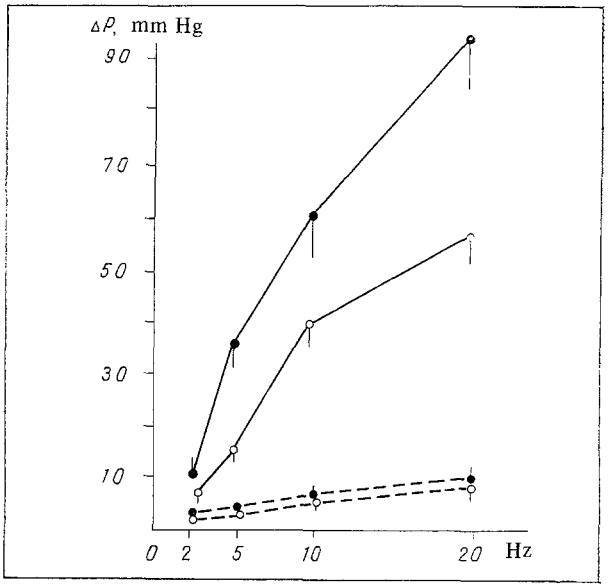

Fig. 3. Dependence of perfusion pressure in vessels of posterior part of body on frequency of stimulation of sympathetic chains in rats. Abscissa, frequency of stimulation of sympathetic chains (in Hz); ordinate, changes (P) in perfusion pressure (in mm Hg).

difference was found in the response of the vessels in NR and hypertensive animals (groups 1 and 3) to exogenous NA within the same range of perfusion pressure as in experiments with stimulation of the sympathetic chains (up to 100 mm Hg; Fig. 2c). Further evidence of the participation of the sympathetic nervous system in the development of DOCA-salt hypertension also is given by data [3, 4] obtained by different techniques. Neonatal desympathization also prevented the development of experimental DOCA-salt hypertension [6, 9].

According to Guyton et al. [11], in the early stage of DOCA-salt hypertension the rise in BP is due to the increasing CO as a result of an increase in blood volume. This latter increase leads to autoregulatory (myogenic in character) constriction of the arterioles and an increase in peripheral vascular resistance to the blood flow. Subsequent pressure loading causes structural changes in the vessels. However, Guyton did not consider the role of the sympathetic nervous system in the development of this particular form of hypertension in his scheme. As was shown above, after neonatal sympathectomy DOCA-salt hypertension did not develop; BP did not exceed the normotensive level (Fig. 1). Consequently, not only an increase in the circulating blood volume, but also the pressure of an intact sympathetic system are essential for a stable rise of BP in response to administration of DOCA and NaCl.

The following scheme is suggested for the sequence of activation of the various mechanisms of BP regulation in the pathogenesis of DOCA-salt hypertension. DOCA and NaCl increase CO, and in response to this, constriction and spasm of some vessels develop as a result of an autoregulatory reaction [11] and (or) an increase in sensitivity of the smooth muscles to NA (Fig. 2a). As a result a small transient rise of BP develops, and is observable also in desympathized animals receiving DOCA and NaCl. A stable rise of BP in response to DOCA and salt loading is evidently impossible without some increase in activity of the sympathetic nervous system, as is shown by prevention of this form of hypertension after neonatal sympathectomy, the increased spike discharge in cervical sympathetic fibers [4], and the increased NA turnover as a result of disturbance of Na^+ metabolism in the body [3, 5].

Activation of the sympathetic nervous system leads to an increase in general vasoconstriction, including in the kidneys, which brings about a more rapid and more marked reorganization of their excretory function under hypertensive conditions; this is evidently one of the general and principal mechanisms of development of arterial hypertension of varied genesis [11]. From this point of view it is a demonstrative fact that denervation of the single remaining kidney after unilateral nephrectomy prevents the development of DOCA-salt

hypertension in rats and leads to an increase in the Na^+ excretion of these animals compared with its corresponding value in rats with an intact sympathetic innervation of the kidney and receiving DOCA and NaCl [13].

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PREVENTION OF DISTURBANCES OF CARDIAC CONTRACTILITY DURING LONG-TERM STRESS BY PRELIMINARY ADAPTATION TO SHORT-TERM STRESS

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KEY WORDS: atrium; myocardium; stress; adaptation.

As a result of prolonged exposure to stress, damage to heart muscle may arise under the influence of an excess of catecholamines [3, 11], its contractile function may be disturbed, and its resistance to hypoxia and to excess of calcium may be lowered [4, 6]. When the ways of preventing stress injuries of this kind are studied it must be remembered that during repeated exposure to stress of limited duration and, in particular, during repeated immobilization of animals, the response to stress gradually diminishes: Excitation of the adrenergic and pituitary–adrenal systems becomes weaker [10].

The object of the present investigation was to study the possibility of using adaptation of animals to repeated short-term stress in order to prevent disturbances of cardiac contractility during long-term immobilization stress.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 160-240 g. The animals were divided into four groups: 1) control, 2) long-term immobilization stress, 3) adaptation to repeated short-term immobilization stress, 4) adaptation to short-term immobilization stress

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