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COMPARATIVE ANALYSIS OF EFFECTIVENESS OF SYNAPTIC INFLUENCES ON RESISTIVE VESSELS OF SPONTANEOUSLY HYPERTENSIVE AND NORMOTENSIVE RATS DURING CONSTANT-FLOW, CONSTANT-PRESSURE PERFUSION

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The development of all forms of arterial hypertension is linked with a change in the structure and function of the vascular system [1, 3, 10, 12]. One of the mechanisms of the structural changes in the vascular bed in hypertension is reduction of the internal diameter of the arteries, as a result of thickening of their wall [8]. Changes of this kind lead to an increase in the ratio of the thickness of the wall to the radius of the vessel and they are the main cause of the increase in reactivity to vasoconstrictor influences [10]. It was shown previously that during perfusion of vessels of the posterior part of the body of spontaneously hypertensive and normotensive rats, during constant-flow perfusion, injection of noradrenalin into the blood stream [8, 9] or stimulation of the sympathetic chains [1] induces a greater increase of resistance in hypertensive animals. However, when investigating vasomotor responses of hypertensive and normotensive animals, we discovered an interesting fact: The results obtained during constant-flow perfusion sometimes differed even qualitatively from those obtained under constant pressure conditions [15]. There is evidence that vasomotor responses in normotensive animals may differ qualitatively if different methods of perfusion are used [4], evidently on account of different conditions of contraction of the vascular smooth muscles [5]. The aim of this investigation was a comparative analysis of the reactivity of spontaneously hypertensive and normotensive rats perfused under the two different conditions.

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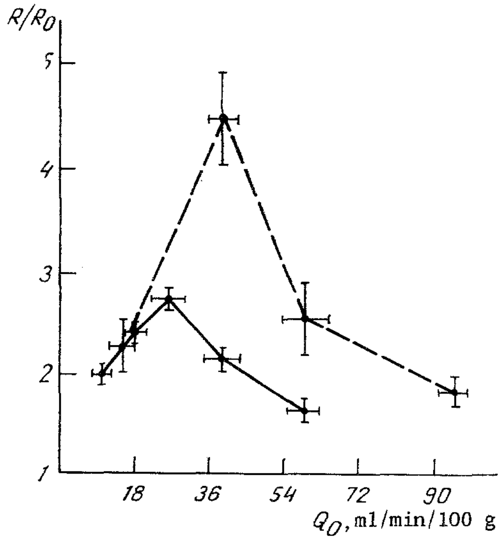

Fig. 1. Dependence of effectiveness of standard stimulation of sympathetic chains (ordinate) on initial rate of flow of perfusion fluid (abscissa). Perfusion under constant pressure (80 mm Hg), initial flow rate of perfusion fluid changed by noradrenalin; broken line indicates normotensive, continuous line — spontaneously hypertensive rats.

EXPERIMENTAL METHOD

Experiments were carried out on spontaneously hypertensive rats (SHR) and on normotensive Wistar—Kyoto (WKY) rats as the control. The age of the animals in both groups was 4-5 months. Only those SHR whose blood pressure exceeded 150 mm Hg were used in the experiments.

Blood vessels in the posterior half of the body of the anesthetized rats (urethane, 1 g/kg, intraperitoneally) were perfused with Tyrode solution at 37°C, through a catheter introduced into the abdominal aorta. During constant-pressure perfusion the volume velocity of outflow of perfusion fluid from the inferior vena cava was measured by means of a drop counter. Constant-flow perfusion was carried out by means of a peristaltic pump (LKB, Sweden). The perfusion pressure, which under these experimental conditions adequately reflects the resistance of the vessels, was measured at the inlet into the catheter by a DDA-2 electromanometer. The frequency of fall of the drops and the perfusion pressure were recorded on an N337/5 automatic recorder. Sympathetic chains were stimulated at the level of the fourth and fifth lumbar vertebrae with parameters: 6 V, 20 Hz, 0.5 msec, duration 10 sec. The effectiveness of the sympathetic influences was calculated as the ratio of the resistance of the vessels during stimulation to the initial resistance.

In the first series reactivity of the vessels of SHR and the control rats to sympathetic influences was studied during constant-pressure perfusion at 80 mm Hg. The effectiveness of sympathetic influences is strongly dependent on the initial vascular tone, and for that reason stimulation of the chains was carried out at various levels of vascular tones, which was changed by injecting various doses of noradrenalin (NA) into the perfusion fluid. A more detailed analysis of the graph of efficiency under constant pressure was given previously [14].

The effectiveness of sympathetic influences during perfusion by different methods was compared in experiments with rapid alternation of the conditions of perfusion of the same animal. In this way vasoconstrictor responses of the same vascular basin during perfusion under constant flow and under constant pressure could be adequately compared. During perfusion with Tyrode solution the blood vessels are maximally dilated [7], whereas in vivo they possess definite basal tone. To increase vascular tone, noradrenalin was added to the perfusion solution continuously in a concentration sufficient to increase vascular tone by 1.5-1.6 times relative to maximal vasodilatation. The increase in vascular tone was determined during constant pressure perfusion at 80 mm Hg by measuring the decrease in volume velocity of flow of the perfusion fluid. It must be pointed out that doses of NA giving rise to such an increase of tone differed in the control rats and in SHR; in the first case the effect was achieved with a concentration of 2×10^{-7} g/ml, in the second case — 4×10^{-7} g/ml. The effectiveness

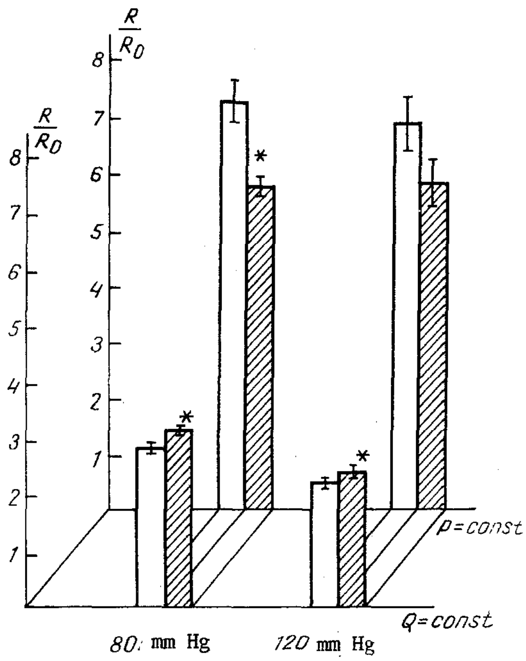

Fig. 2. Comparison of effectiveness of sympathetic influences (R/R_0) in normotensive (unshaded columns) and spontaneously hypertensive rats (shaded columns) during perfusion under two conditions with initial perfusion pressures of 80 and 120 mm Hg.

of sympathetic influences was studied at pressures of 80 and 120 mm Hg; at each of these pressures recordings were made first at constant pressure, and next at constant flow.

The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Comparison of the effectiveness of sympathetic influences in SHR (blood pressure — BP — 165 ± 5.0 mm Hg, n = 10) and the control rats (BP 112.2 ± 7.0 mm Hg, n = 13) was carried out during perfusion of the system of blood vessels under constant pressure (80 mm Hg). It will be clear from Fig. 1 that with all initial values of resistance of the system of blood vessels in the posterior half of the body the effectiveness of sympathetic influences was lower in SHR than in the control animals.

In the main series of experiments the same vascular bed of the posterior half of the body was perfused alternately under stabilized pressure conditions and under constant flow conditions. In this series of experiments nine SHR and nine control rats were used. Stimulation of the sympathetic chains was repeated four times in each animal — at a pressure of 80 and 120 mm Hg under the two different conditions of perfusion. It will be clear from Fig. 2 that during constant-flow perfusion the magnitude of the vasoconstrictor response was greater in SHR, whereas during stabilized pressure perfusion the opposite situation was found.

High reactivity of the vessels of SHR to constrictor influences under constant flow conditions has been observed by many workers, who link this phenomenon with an increase in the ratio of the thickness of the wall to the lumen of the vessel in hypertension [10, 12]. However, under conditions of constant pressure perfusion, we obtained a diametrically opposite result: The effectiveness of sympathetic influences in SHR was found to be less than in the control rats. This phenomenon evidently cannot be attributed to lower secretion of noradrenalin or a change in the receptor apparatus of SHR, for the ratio between vascular reactivity in the same preparations of SHR and WKY rats showed a qualitative change during alternation of the method of perfusion.

How do these two different conditions of perfusion differ? During constant-flow perfusion the increase in perfusion pressure is proportional to the increase in resistance of the vascular bed [5]. Consequently, as the constrictor response develops, contraction of the smooth-muscle cells of the vessel walls is prevented by the increasing pressure in the system, for the flow remains unchanged. It is this fact which explains the well known fact of lower reactivity of vessels perfused with stabilized flow compared with constant pressure (2.5; Fig. 2). It can be stated with only a small error that under stabilized flow conditions the levels of contraction of the vascular smooth muscles are close to isometric. Conversely, during constant pressure perfusion contraction of the vascular media is accompanied by considerable shortening of the smooth muscles. This schedule of contraction is close to isotonic. The facts given above suggest that smooth-muscle cells of vessels in SHR can develop considerable "force" of contraction under isometric conditions, however, the amplitude of their contraction under isotonic conditions is limited. To explain the phenomenon discovered, two hypotheses, not mutually exclusive, can be put forward. First, an increase in the "force" of contraction under near-isometric conditions, whereas under isotonic conditions there is a simultaneous reduction in the amplitude of contraction, can occur if the smooth-muscle cells become shorter but thicker. Such a change in shape of the smooth-muscle cells has been described in the late stages of development of doca—salt hypertension [11]. We also know that the degree of shortening of strips of caudal arteries of SHR aged 28-31 weeks is less than in control rats of the same age [13]. However, some morphological investigations revealed no shortening of the smooth-muscle cells of the vessels in spontaneous hypertension [6]. There is therefore another possible explanation of the phenomenon observed: Thickening of the walls of the arteries in hypertension gives rise to a change in their mechanical properties — their rigidity is increased. It has been calculated theoretically that a more rigid vessel can respond more strongly during intensive vasoconstriction when under constant flow conditions and, conversely, it changes its lumen by a lesser degree under constant pressure by comparison with a less rigid vessel [2]. It is therefore possible that sympathetic influences in spontaneously hypertensive rats during perfusion under constant pressure are less effective because of the greater resistance of the more rigid vessels of SHR to deformation.

Further investigations will shed light on the problem of which of these factors is responsible, and to what extent, for the phenomenon observed.

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