prevent disturbances of MC during AC, substances (antihypoxants, antioxidants) prolonging the period of reversible changes in the erythrocytes must be administered both before the operation and during perfusion.

LITERATURE CITED

1. A. A. Mozhina and S. N. Tereshchenko, Ultrastructural Principles of Pathology of the Heart and Vessles [in Russian], Tbilisi (1980), p. 145.
2. V. P. Osipov, Principles of Assisted Circulation [in Russian], Moscow (1976).
3. L. B. Shporova, Byull, Éksp. Biol. Med., No. 4, 406 (1980).
4. P. Gaehtgens, Arzneim.-Forsch., 31, 1995 (1981).
5. H. Neuhof, C. Mittermayer, and N. Freudenberg, Verh. Dtsch. Ges. Path., 62, 80 (1978).

FUNCTIONAL STATE OF PORTAL VEIN SMOOTH MUSCLES IN SPONTANEOUSLY HYPERTENSIVE RATS

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The important role of changes in the functional state of vascular smooth muscles in the regulation of vascular tone and of blood pressure is well known. Published data [6], including investigation in the authors' laboratory [2], have shown that the increase of vascular resistance in arterial hypertension arises as the result of disturbances of contractility of the smooth muscles of the arterioles and/or as a result of their structural and functional adaptation to high blood pressure (BP), caused by hypertrophy of the smooth-muscle layer of the arterioles. Changes in smooth muscles of the veins in arterial hypertension have received much less study, and the available data are very contradictory [4, 8-11, 13]. These changes are definitely interesting, considering the importance of venous tone in regulation of the cardiac output and the fact that in arterial hypertension the veins are not subjected to a pressure load. Changes in these smooth muscles, if present at all, may therefore reflect primary disturbances of the functional state of the vascular smooth muscles in arterial hypertension.

The aim of this investigation was to study some parameters of the functional state of smooth muscles of the portal vein and their response to noradrenalin in spontaneously hypertensive rats of different ages, i.e., in the course of the disease.

EXPERIMENTAL METHOD

Experiments were carried out on spontaneously hypertensive Kyoto-Wistar rats — SHR: group 1) young animals (4-6 weeks) with normal or slightly raised BP; group 2) rats aged 3 months with BP of 152 ± 4.3 mm Hg, group 3) rats with chronic hypertension (28 weeks, BP 166 ± 4.7 mm Hg). Normotensive Wistar-Kyoto rats (WKY) of the corresponding age (BP 100-118 mm Hg), also divided into three groups, were used as the control. BP was measured in the caudal artery of the conscious animals by an electroplethysmographic method, using an NK-709 apparatus (Natsume, Japan). The animals were killed by decapitation and the portal vein was removed and transferred into a thermostatically controlled working chamber filled with oxygenated Krebs' solution, at 35°C, and a load of 400 mg was attached. The portal vein preparation was kept under these conditions for 1 h before recording began in order to stabilize the spontaneous contractions, which were recorded on a two-channel (control—experimental) apparatus (Ugo Basile, Italy) under isometric conditions. Spontaneous activity with a load of 500 mg (opti-

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TABLE 1. Parameters of Contractility and Response to Noradrenalin of Portal Vein Smooth Muscles of Normotensive and Spontaneously Hypertensive Rats of Different Ages

Group of animals	Developed tension, mg	Frequency of contraction per minute	IFS, mg force/mg·min	Rate of contraction, mg force/sec	Rate of relaxation, mg force/sec	Reactivity to noradrenalin, ng/ml NA
1st WKY ($n = 12$)	200±24	5,1±0,7	346±7,2	87±17	146±31	370±50
1st SHR ($n = 12$)	90±35*	10±2,2*	198±24*	59±17	85±28	940±120*
2nd WKY ($n = 9$)	86±14	7,7±1,3	294±43	73±10	83±14	420±100
2nd SHR ($n = 9$)	148±23*	13±2,4*	445±58*	94±23	112±13*	180±30*
3rd WKY ($n = 8$)	152±24	4,7±0,5	273±50	57±12	79±19	530±90
3rd SHR ($n = 8$)	33±12	9,5±1,4*	103±21*	26±6,8*	32±14	1200±280*

Legend. *P < 0.05 compared with WKY.

mum), changes in calcium concentration in solution surrounding the vein, and the action of various concentrations of noradrenalin were studied in each experiment. On the basis of the recording of spontaneous contractions of the portal vein the following parameters of its contractile function were calculated: the developed phasic tension (mg force), the frequency of spontaneous contractions per minute, the intensity of functioning of structures (IFS), calculated as the product of developed tension and frequency of contraction, per unit weight of portal vein (mg force/mg·min), the rate of development of tension (mg force/sec) and the rate of fall of tension (relaxation) (mg force/sec). The response of the portal vein to noradrenalin was assessed as the value of the "apparent" dissociation constant (K) of the noradrenalin–receptor complex, which was determined graphically in a system of double coordinates: the reciprocal of the noradrenalin concentration versus the reciprocal of phasic tension [1]. The significance of the results was determined by Student's t test.

EXPERIMENTAL RESULTS

Data characterizing the contractile function of smooth muscles of the portal vein of SHR and WKY and its response to noradrenalin are given in Table 1. The principal parameters of contractility in SHR of groups 1 and 3 were reduced on average by 1.7 and 3 times, respectively, whereas in SHR aged 12 weeks (group 2) these parameters were 1.5 times higher than in WKY. The response of SHR of groups 1 and 3 to noradrenalin also was depressed by 2.5 and 2.3 times, respectively, compared with the control, but in group 2, on the other hand, it was more than doubled, in agreement with the age dynamics of the principal parameters of spontaneous contractile activity.

The threshold of sensitivity to calcium in the solution surrounding the vein was depressed in all SHR (Fig. 1). With an increase in age of the experimental animals this threshold fell still more. For instance, whereas spontaneous activity was absent in all preparations when the calcium concentration was 0.35 mM, spontaneous activity appeared in 25% of veins studied in SHR of group 1 in this same concentration, in 50% of veins in group 2, and in 63% in group 3.

The study of the contractile function of smooth muscles of the portal vein in SHR depending on the stage of development of arterial hypertension thus showed that an increase of contractility took place in SHR only in the early hypertensive stage, and that in the prehypertensive stage and the stage of permanent hypertension, contractility was depressed. Meanwhile Greenberg and Bohr [8] and Sutter and Ljung [13] found an increase in contractility of the portal vein of SHR in the stage of permanent hypertension. However, the authors cited used Wistar rats as their control animals, and not Wistar–Kyoto (WKY) rats, as in the present investigation, for the latter are known to be a more adequate control for SHR. The increase in contractility discovered by the present writers in the early hypertensive stage in SHR, as a result of increased contractility of the smooth muscles, may evidently lie at the basis of the increased venous return and the increased cardiac output for which this is to a certain extent responsible. In fact, as the authors' previous investigations on anesthetized and conscious rats [1] and data obtained by other workers [7] have shown, in SHR in this period the circulation was of hyperkinetic type, characterized by increased cardiac output

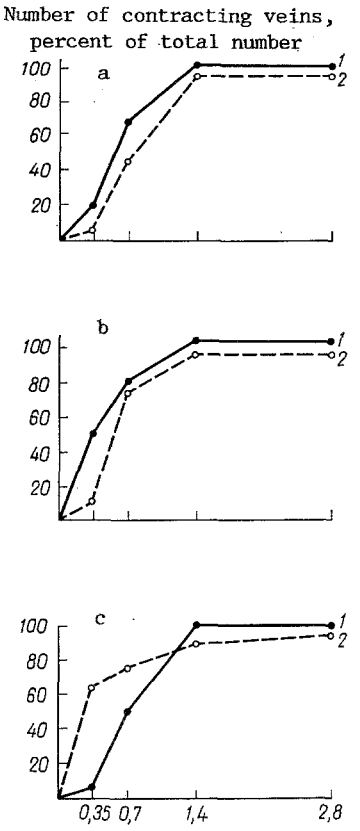

Fig. 1. Effect of various calcium concentrations in solution surrounding vein on number of contracting veins (in percent of total number of SHR of different ages). Abscissa, calcium concentration (in mM); ordinate, number of contracting veins (in percent of total number). 1) SHR; 2) WKY. a) Age 4-6 weeks, b) 12 weeks, c) 28 weeks.

accompanied by an inappropriately normal peripheral resistance. In the stage of permanent hypertension the caridac output of SHR was reduced. The possibility cannot be ruled out that this takes place to a certain extent on account of a fall in the central blood volume [12], as a result of a decrease in venous tone, demonstrated in the present investigation and in those of other workers [4, 10, 11]. Our own data on the increased response of the venous smooth muscles to noradrenalin as a result of the considerably increased sensitivity of the smooth-muscle adrenoreceptors to noradrenalin are further proof of the increased contractility of the veins in SHR in the early hypertensive stage (K for SHR during this period was less than half its value for WKY of the same age). It can be tentatively suggested that activation of the sympathetic nervous system, which takes place in SHR in the early hypertensive stage (1), extends not only to the heart and resistive vessels (arterioles), but also to smooth muscle of the veins. Catecholamines, which cause constriction not only of venules, but of large venous trunks (the portal vein, for example) and raise the venous pressure, increase the venous return to the heart under these circumstances and the central blood volume. In the prehypertensive stage and the stage of permanent hypertension, as the authors showed previously [1, 2], activity of the sympathetic nervous system was either unchanged or depressed. The similar changes in reactivity of the smooth muscles of the portal vein to noradrenalin and their contractility, found in the present investigation, may probably be connected with this fact.

The results of a study of contractility of venous smooth muscles in SHR depending on changes in the calcium concentraion in the medium surrounding the preparations are of definite interest. The lowering of the threshold of sensitivity to calcium found in SHR points to a disturbance of the functioning of membrane mechanisms responsible for regulation of the calcium concentration in the cytoplasm during coupling of excitation and contraction. Bohr et al.

[5], who studied contractility and reactivity of vascular smooth muscles in rats with arterial hypertension (SHR and rats with renovasal hypertension) with different calcium concentrations in the solution surrounding the vessels, concluded that membrane permeability of the vascular smooth muscles of hypertertensive animals to calcium is increased. For that reason vascular smooth muscles can exhibit their activity in a calcium-free medium or a medium with a minimal calcium concentration. This mechanism may possibly lie at the basis of changes found in SHR in the present investigation, for it was shown that the portal vein smooth muscle in SHR, unlike that of the control animals, contracted when low concentrations of calcium were present in the surrounding medium. It can be tentatively suggested that this membrane defect is hereditary in character, for increased membrane permeability of the portal vein smooth muscles to calcium was found in all SHR irrespective of the stage of the disease. However, this defect is evidently not the only one necessary for hypertension to develop in SHR, as some workers consider [3], for contractility of the smooth muscles or, more exactly, changes in their contractility, depended on the stage of the disease (as follows from the results of the present investigation). In the early hypertensive stage increased reactivity to noradrenalin and activation of the sympathetic nervous system as a whole, together with increased membrane permeability of the smooth muscles to calcium, leads to increased contractility of the large vein, which we found, and which is one cause of the hyperkinetic type of circulation observed in SHR during this period.

LITERATURE CITED

1. Kh. M. Markov, V. G. Pinelis, V. S. Poleshchuk, et al., Patol. Fiziol., No. 5, 35 (1984).
2. V. G. Pinelis, A. V. Kozlov, T. P. Vakulina, and Kh. M. Markov, Kardiologiya, No. 5, 66 (1983).
3. Yu. V. Postnov, Kardiologiya, No. 7, 5 (1981).
4. A. Arner, Acta Physiol. Scand., Suppl. 505, 1 (1982).
5. D. Bohr, A. Harris, C. Guthe, and R. Webb, Topics in the Pathophysiology of Hypertension, New York (1984), pp. 100-111.
6. B. Folkow, Clin. Sci. Mol. Med., 55, 3 (1978).
7. E. Frohlich, Postgrad. Med., 2, 62 (1972).
8. S. Greenberg and D. Bohr, Circulat. Res., 36/37, Suppl. 1, 208 (1975).
9. M. Hallbak, Y. Lundgren, and L. Weiss, Acta Physiol. Scand., 81, 176 (1971).
10. M. Mulvany, B. Ljung, M. Stoltze, et al., Blood Vessels, 17, 202 (1980).
11. U. Peiper, P. Klemt, and R. Popov, Basic Res. Cardiol., 74, 21 (1979).
12. B. Rippe, S. Lundin, and B. Folkow, Clin. Exp. Hypertens., 1, 39 (1978).
13. M. Sutter and B. Ljung, Acta Physiol. Scand., 99, 484 (1977).