8. G. A. Sevost'yanova, N. M. Mitrokhina, and G. I. Prozorov, Extrapyramidal Diseases of the Nervous System [in Russian], Moscow (1982), pp. 119-121.
9. H. Friemel (ed.), Immunologische Arbeitsmethoden, Fischer, Jean (1976).
10. R. O'Brien, M. Boublik, and S. Spector, J. Pharmacol. Exp. Ther., 194, 145 (1975).
11. E. S. Niesenbaum, E. M. Stricker, M. J. Zigmond, and T. W. Berger, Brain Res., 398, 221 (1986).
12. G. Paxinos and C. Watson, The Rat Brain in Stereotaxic Coordinates [in Russian], Sydney (1982).
13. B. Pescar and S. Spector, Science, 179, 1340 (1973).
14. A. Pouplard and J. Emile, Adv. Neurod., 40, 307 (1984).
15. U. Ungerstedt, Acta Physiol. Scand., Suppl. 361, 1 (1971).

DEPENDENCE OF HYPOXIC CHANGES IN MACRO- AND MICROCIRCULATION ON SKELETAL MUSCLE ADRENORECEPTOR ACTIVITY DURING HYPOTHERMIA

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It has been shown that hypoxia, superposed on hypothermia, causes changes in the macro- and microcirculation in skeletal muscle which differ qualitatively and quantitatively from changes taking place under the influence of a hypoxic stimulus during normothermia. The mechanisms of reduction of deviations or even reversal of the sign of parameters of the resistive and exchange (precapillary R_a- and postcapillary R_v-resistance, capillary filtration coefficient – CFC, and mean capillary hydrostatic pressure – P_m) functions of vessels of a skeletal muscle during exposure of an animal to hypoxic and hypothermic stimuli remain unchanged. According to data in the literature [5, 9] hypoxic hypoxia and acute hypothermia not only involve the direct action of oxygen deficiency in the blood and of cold on the contractile elements of the intramural vascular bed, but also cause various substances [13], including catecholamines [6], which together with other factors participate in changes in lumen of the arteries and veins, to enter the circulatory system. The intensity of the adrenergic component of the vascular changes during exposure to hypoxic and hypothermic stimuli differs: oxygen deficiency in the blood, if the duration of hypoxia is long enough, ultimately causes relaxation of vascular smooth muscles [12, 14], whereas hypothermia (to 30°C) causes their contraction [11] as a result of the action of catecholamines, the blood level of which rises considerably during cooling [6].

The aim of this investigation was to study the role of adrenergic mechanisms in changes in functional parameters of the vessels and transcapillary exchange of fluid in a skeletal muscle of an animal exposed to a combination of vascular factors induced by simultaneous hypoxia and hypothermia.

EXPERIMENTAL METHOD

Experiments were carried out on 22 cats of of both sexes (weighing 2.5-4.0 kg), anesthetized with urethane and chloralose (1.0 and 0.01 g/kg), receiving heparin (1500 U/kg). The gastrocnemius muscle (leg preparation) was isolated hemodynamically [2], the nerves were divided, and autologous perfusion was carried out with the animal's blood through the popliteal artery by means of a constant delivery pump [7]. Changes in R_a and R_v, P_m, and CFC were recorded by the method in [1]. Parameters of the macro- and microcirculation in the decentralized muscle were determined during hypoxia (inhalation of 10% oxygen in nitrogen, at the

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TABLE 1. Initial Characteristics of Hemodynamics in Muscle during Hypothermia, before Exposure to Hypoxic Stimulus (M ± m)

Experimental condition	R_a, mm Hg·100 g/ml·min	CFC, ml·100 g/min·mm Hg	P_m, mm Hg	R_v, mm Hg·100 g/ml·min
Intact α- and β-adrenoreceptors	16,7±3,2	0,0542±0,0056	16,1±0,74	0,94±0,26
α-Adrenoreceptor blockade				
by dihydroergotoxin	25,8±2,7	0,0180±0,0022	13,6±0,40	0,77±0,04
by phentolamine	10,0±0,85	0,040±0,0052	17,1±1,23	0,80±0,21
β-Adrenoreceptor blockade by propranolol	30,4±1,9	0,0228±0,0027	16,8±1,30	1,28±0,17

10th minute of exposure) of the animal (nine cats), cooled to 30 ± 0.3°C at the rate of 0.07 ± 0.02 deg/min; the results obtained in the first series of experiments were compared with those obtained during the action of the same stimuli, but after α-adrenoreceptor blockade by dihydroergotoxin (five cats) and phentolanine (three cats) and of β-adrenoreceptor blockade by propranolol [5]. For α-adrenoreceptor blockade dihydroergotoxin (DH-ergotoxin, from "Spofa") and phentolamine were given in doses of 1.0 and 1.2-1.5 mg/kg respectively, and for β-adrenoreceptor blockade propranolol (obsidan, East Germany) was given in a dose of 0.3 mg/kg. Completeness of α- and β-adrenoreceptor blockade was assessed on the basis of absence of corresponding (constrictor and dilator) vascular responses to a single injection of noradrenalin (10 μg) and isoprenaline (5 μg, novodrin, East Germany) into the blood vessels of the muscle.

The animals were cooled by placing them in a special bath, in which the coolant (water) made contact with the animal's skin through polyethylene tubes. The temperature of the blood entering the vessels of the muscle corresponded to the animal's body temperature. The assigned temperature of the blood entering the organ was maintained by means of a heat exchanger and ultrathermostat (U 15°, East Germany). The temperature in the esophagus and in the blood entering the muscle was measured by transducers of a type TPEM-1 electrothermometer.

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

EXPERIMENTAL RESULTS

Changes in parameters of the vascular functions of the muscle during exposure to the stimuli chosen for investigation are presented in this paper as percentages of background values. The background values are shown in absolute terms in Table 1.

The hypoxic stimulus against the background of hypothermia caused a small decrease (by 2.9 ± 1.2%) of R_a in the decentralized skeletal muscle and a small (not statistically signifcant, $p > 0.05$) decrease (by 12.3 ± 5.9%) is CFC; the values of R_v and P_m were reduced by 12.2 ± 4.2 and 6.2 ± 1.2% respectively ($p < 0.05$). These results as a whole agree with those obtained previously [4] in experiments on an analogous preparation, under similar technical conditions, but with nervous connections of the muscle with the rest of the body intact. During α-adrenoreceptor blockade by dihydroergotoxin, hypoxia superposed on hypothermia induced a marked decrease (by 12.2 ± 1.4%; $p < 0.01$) in R_a compared with the previous background value of this parameter, which differed significantly from the dilating effect of hypoxia on the contractile elements of the arterial bed of the muscle when the adrenoreceptors were intact (Fig. 1). A qualitatively similar effect was obtained by α-adrenoreceptor blockade with phentolamine. The deviation of R_a was smaller than in the case of α-adrenoreceptor blockade by dihydroergotoxin, but the recorded change was statistically significant ($p < 0.05$), which was not observed when oxygen deficiency acted directly on the arteries of the muscle, also during hypothermia, but when activity of the adrenergic vascular structures was preserved.

As a result of the action of hypoxia, CFC in muscles with intact vascular adrenoreceptors was increased by 12.3 ± 5.8% ($p > 0.05$) compared with the initial level obtained as a result of preceding hypothermia (Fig. 1). This parameter, reflecting changes in the number of functioning capillaries, depends in the existing view [10] on the activity of "precapillary sphincters," which, as a result of dilatation induced by oxygen deficiency in the blood, led evidently to an increase in area of the microvascular surface, unless there had been a considerable increase in vascular permeability [15]. During α-adrenoreceptor blockade by dihydroergotoxin the combined action of hypoxia and hypothermia led to a sharp (more than threefold) increase in CFC compared with the deviation of this same parameter during exposure to the same conditions but without adrenoreceptor blockade (Fig. 1). α-Adrenoreceptor

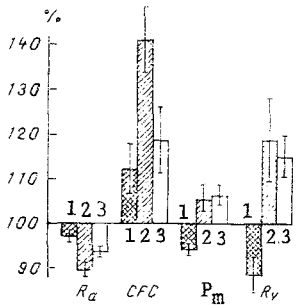

Fig. 1

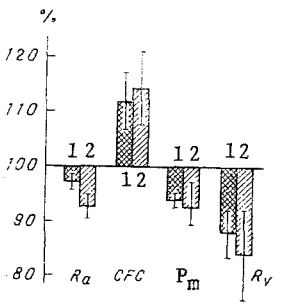

Fig. 2

Fig. 1. Changes (in %; M ± m) of R_a and R_v, CFC, and P_m in gastrocnemius muscle during combined exposure to hypoxia and acute hypothermia (to 30°C) before and during α-adrenoreceptor blockade. 1) Combined action of hypoxia and hypothermia before adrenoreceptor blockade (here and in Fig. 2); 2) during α-adrenoreceptor blockade by dihydroergotoxin, and 3) during α-adrenoreceptor blockade by phentolamine.

Fig. 2. Changes (in %; M ± m) in R_a, R_v, P_m, and CFC during exposure to hypoxia and hypothermia, before and after β-adrenoreceptor blockade. 2) During β-adrenoreceptor blockade.

blockade by phentolamine caused a smaller deviation of the coefficient (CFC) from its initial level, but the change in this parameter of the exchange function of the microvessels which was recorded was statistically significant ($p < 0.05$; Fig. 1).

Another parameter of the exchange function of the vessels, reflecting the direction and intensity of transcapillary movement of fluid (P_m), increased after α-adrenoreceptor blockade in response to the action of the hypoxic stimulus against the background of hypothermia (in the series of experiments with α-adrenoreceptor blockade by phentolamine deviations from the background level were statistically significant, $p < 0.05$), whereas before blockade a combination of hypoxia and hypothermia led to a decrease in its value. Differences in the changes in P_m in response to the hypoxic stimulus, recorded when activity of the α-adrenoreceptors was preserved and when it was blocked pharmacologically, are due to changes in R_v which, in the absence of adrenoreceptor blockade, decreased during hypoxia, and increased after their blockade (Fig. 1). This state of affairs is based on the previously established fact that during perfusion of the vessels of an organ with a constant volume of blood the level of P_c is determined by changes in R_v [1].

These results are evidence of the important role of α-adrenergic structures in changes of smooth muscle tone of the vascular bed of a skeletal muscle during exposure to a combination of hypoxic stimulation and preliminary hypothermia. Meanwhile β-adrenoreceptor blockade did not change deviations of the parameters of resistance (R_a and R_v) and exchange (CFC and P_m) coupled vascular functions [8] of the skeletal muscle, either qualitatively or quantitatively, taking place during exposure of the hypothermic animal to a hypoxic stimulus before the corresponding pharmacological blockade (Fig. 2). When α-adrenoreceptors were blocked by dihydroergotoxin the hypoxic stimulus had no significant effect on the value of R_a, but against the background of β-adrenoreceptor blockade it caused a decrease of 11.0 ± 3.9% in R_a ($p < 0.05$). In both cases CFC was increased – by 42.0 ± 6.7 and 23.6 ± 8.3% respectively ($p = 0.05$), whereas P_m and R_v were reduced by 6.4 ± 2.0 and 17.7 ± 4.4% respectively (α-block), but were increased by 12.4 ± 2.1 and 23.1 ± 7.3% (β-block) respectively. Hence it follows that the action of hypoxia against the background of adrenoreceptor blockade may modify the parameters of the macro- and microcirculation of an organ considerably; these differences, moreover, may be not just quantitative, but qualitative in character (P_m and R_v) also. On the other hand, during exposure to the hypoxic stimulus against a background of hypothermia, with vascular α-adrenoreceptor activity intact (Fig. 2), there were virtually no deviations of CFC, P_m, and R_v relative to the background values. Meanwhile the manifestation of the phenomenon depended only a little on fluctuations in background values of the vascular functions (Table 1, Fig. 2), due to previous β-adrenoreceptor blockade, and to other

factors which are difficult to take into account at the present time (age, sex, depth of anesthesia, duration of the acute experiment, etc.).

The facts described above suggest that an adrenergic constrictor mechanism participates in the "protective action" of artificial hypothermia used in medicine [3], and which, as the present investigation showed, leads to qualitative and quantitative changes in the responses of the macro- and microcirculation of the muscle to hypoxia, compared with the effect of hypoxia on the vessels under normothermic conditions. The dilator effect of oxygen deficiency on smooth-muscle formations of the vessels, which is well marked in normothermia, is altered in hypothermia. In fact, when the α-adrenoreceptors are intact, hypoxia against the background of hypothermia causes only a very small increase in CFC and a decrease in P_m in the microvessels of the muscle. During α-adrenoreceptor blockade of the vessels of the muscle, however, the number of functioning capillaries (and their permeability also, perhaps), is sharply increased (more than threefold) and P_m also rises considerably, which must lead to intensification of filtration of fluid into the interstitial space and to the development of edema of the muscle tissue.

LITERATURE CITED

1. B. I. Tkachenko (ed.), Integration of Vascular Functions [in Russian], Leningrad (1984), p. 158.
2. Yu. A. Kudryashov, Fiziol. Zh. SSSR, 62, No. 5, 711 (1976).
3. E. N. Meshalkin, I. P. Vereshchagin, and Yu. A. Vlasov, Nonstationary Blood Flow in Man under Artificial Conditions [in Russian], Moscow (1984).
4. A. A. Nurmatov and V. A. Kul'chitskii, Abstracts of Proceedings of the 4th All-Union Symposium on the Circulation in Skeletal Muscles [in Russian], Riga (1986), pp. 83-84.
5. S. A. Polenov, Physiology of the Circulation: Regulation of the Circulation [in Russian], Leningrad (1986), pp. 384-408.
6. B. A. Saakov, Pathological Physiology of Extremal States, ed. by P. D. Gorizontov and N. N. Sirotinin [in Russian], Moscow (1973), pp. 237-266.
7. B. I. Tkachenko, The Venous Circulation [in Russian], Leningrad (1979).
8. B. I. Tkachenko, Fiziol. Zh. SSSR, 72, No. 9, 1161 (1986).
9. B. I. Tkachenko and G. F. Sultanov, Physiology of the Circulation: Regulation of the Circulation [in Russian], Leningrad (1986), pp. 428-457.
10. B. Folkow and E. Neil, The Circulation [Russian translation], Moscow (1976).
11. R. R. Shabaev and Yu. A. Kudryashov, Fiziol. Zh. SSSR, 71, No. 7, 882 (1985).
12. D. D. Heistad and F. M. Abboud, Circulation, 61, No. 3, 463 (1980).
13. L. Laszt, Angiologica (Basel), 8, No. 3-5, 202 (1971).
14. G. M. Pohost, J. B. Newell, N. P. Hamlim, and M. J. Powell, Cadiovasc. Res., 10, No. 4, 405 (1976).
15. B. Rippe, A. Kamiya, and B. Folkow, Acta Physiol. Scand., 105, No. 2, 171 (1979).