PARTICIPATION OF ADRENERGIC MECHANISMS IN MICROCIRCULATORY CHANGES DURING STRESS

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The writers showed previously that immobilizing rats for between 1 and 24 h disturbs their mesenteric microcirculation: The blood flow is slowed, aggregates of red cells form, plasmatized vessels appear, and arteriolo-venular shunts are opened [1]. Immobilization for 1 h daily for 5 days reduced the intensity of the microcirculatory disturbances, including aggregation of red cells, and led to an increase in the number of functioning microvessels in the mesentery. The development of erythrocytic aggregation in stress may be due to the action of various factors and of such physiologically active substances as ACTH, catecholamines, histamine, bradykinin, etc. [3, 10, 13].

The object of this investigation was to determine the degree of involvement of adrenergic mechanisms in the mechanism of erythrocyte aggregation and of the redistribution of the blood following a single exposure to stress, and also to study the role of adrenergic mechanisms in adaptation to stress at the level of the microcirculatory system.

EXPERIMENTAL METHOD

Experiments were carried out on 156 noninbred male rats weighing 200-300 g. As extraordinary stimulus the animals were immobilized (for 1 h once or daily for 5 days) or measured electrical stimulation was applied (for 3 h, once or daily for 5 days). The strength of the

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TABLE 1. Quantitative Evaluation of Degree of Development of Mesenteric Blood Vessels during Adaptation to Stress and Administration of Adrenoblockers (M±m)

Experimental conditions	K	P
1. Control	0,0492±0,0029	$P_{1-2}<0,001$
2. Immobilization for 1 h daily for 5 days	0,1088±0,0071	—
3. Phentolamine + immobilization for 1 h daily for 5 days	0,0398±0,0034	$P_{3-2}<0,001$
4. Control	0,0359±0,0032	$P_{4-5}<0,001$
5 Electrical stimulation for 3 h daily for 5 days	0,0887±0,0005	—
6. Pindolol + electrical stimulation for 3 h daily for 5 days	0,0398±0,0028	$P_{5-6}<0,001$

$$K = \frac{\text{Total length of blood vessels}}{\text{Area of surface of mesentery}}$$

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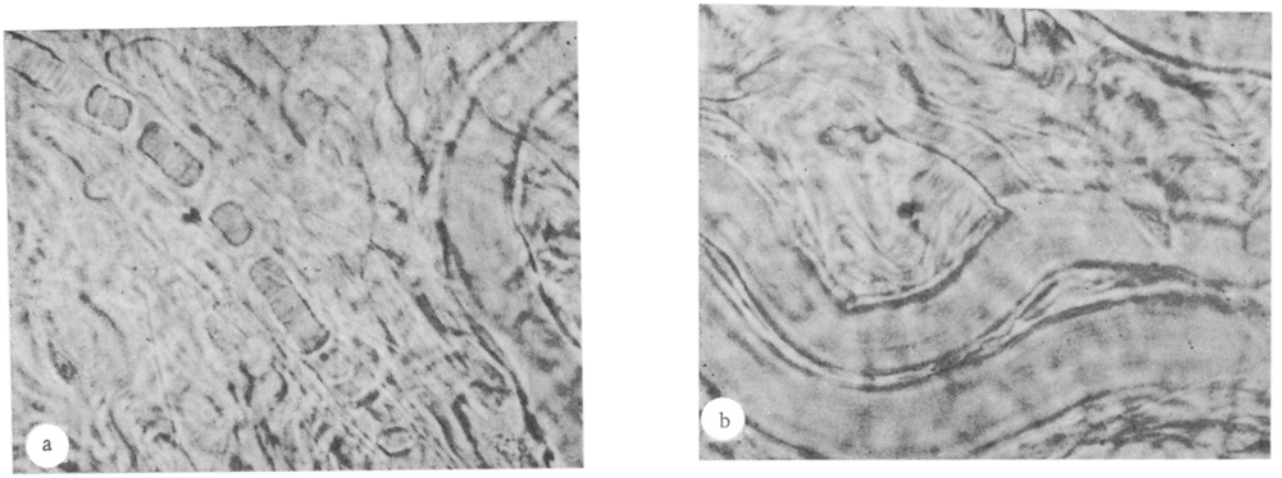

Fig. 1. State of microcirculation in mesentery of rat immobilized for 1 h: a) without phentolamine, b) after prophylactic administration of phentolamine, 180×.

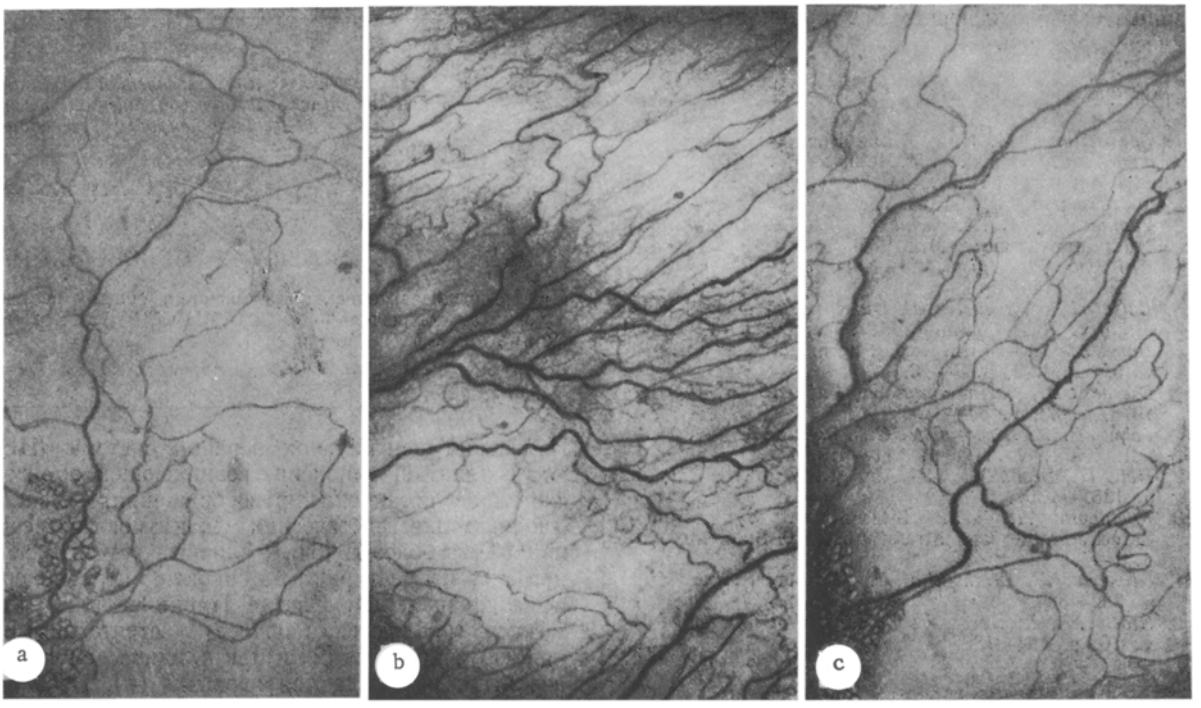

Fig. 2. State of microcirculation in rat mesentery: a) intact rat, b) electrical stimulation for 3 h daily for 5 days, c) treatment with pindolol after electrical stimulation for 3 h daily for 5 days, 6.4×.

current applied to the cage was 2 mA, pulse duration 3 sec, and interval between pulses, 1.5 min.

The microcirculation in the mesentery was studied biomicroscopically on an apparatus for intravital investigation mounted on a "Docuval" microscope (from Carl Zeiss, East Germany). many).

In some experiments the degree of development of the vascular system in the mesentery was assessed quantitatively. For this purpose an image of the microvessels was transferred from the photographic negative to standard sheets of paper, using a photographic enlarger. The total length of the blood vessels was then measured by means of the macroscopic equipment of the TAS texture analysis system (from Leitz, West Germany). The results were subjected to statistical analysis.*

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Adrenalectomy was carried out transdorsally under ether anesthesia. Animals undergoing a mock operation formed the control group. The rats were used in the experiments 7 days after the operation.

The α-adrenoblocker phentolamine (1 mg/kg, intramuscularly) and the β-adrenoblocker pindolol (visken, 0.5 mg/kg, subcutaneously, 1 h before stress) were used in the experiments.

EXPERIMENTAL RESULTS

Adrenalectomy had no significant effect on the state of the mesenteric microcirculation. However, the block flow in the venules was slowed, in agreement with data in the literature [14]. Immobilization of the rats for 1 h after adrenalectomy led to slowing of the blood flow, pavementing of the leukocytes in the venules, prestatis, and statis. Aggregation of erythrocytes in the animals of this group was about equal in degree to that in rats immobilized after mock adrenalectomy. Daily immobilization of adrenalectomized rats for 1 h or electrical stimulation of these rats for 3 h led to the development of adaptive changes in the microcirculatory system in 75-80% of cases: The number of functioning vessels was increased, the blood flow was accelerated, and the number of erythrocytic aggregates and of plasmatized vessels was reduced.

Adrenalectomy in rats thus did not affect the onset of microcirculatory disturbances following a single exposure to stress, nor did it prevent the development of adaptive changes in the microcirculatory system after repeated exposure to extraordinary stimuli.

Prophylactic administration of phentolamine before immobilization for 1 h or electrical stimulation for 3 h improved the state of the blood flow in the mesentery: The blood flow was accelerated and the number of erythrocytic aggregates and plasmatized blood vessels was reduced (Fig. 1a, b). The use of phentolamine before repeated immobilization or electrical stimulation had the effect that, in the first case, improvement of the blood flow and increased vascularization in the mesentery occurred in only 14% of cases, and in 20% in the second case, i.e., adaptation in the microcirculatory system virtually did not develop (Table 1).

Administration of the β-adrenoblocker pindolol in experiments with a single application of the extraordinary stimulus was even more effective as regards improving the blood flow than pehntolamine, and injection of pindolol in the experiments with daily exposure to the stressors also prevented the development of adaptive reactions (Fig. 2a-c; Table 1).

A rapid physiological response to extraordinary stimulation is an increase in activity of the sympathetic nervous system and of the adrenal medulla. Investigation on medullectomized and sympathectomized rats have shown [11] that during intensive stress 70% of the circulating noradrenalin is liberated from sympathetic endings and only 30% from the adrenal medulla. The results of the present experiments, indicating that the role of catecholamines of the adrenals in the development of microcirculatory disturbances following a single exposure to stress and during adaptation to stress in the microcirculatory system is unimportant, are in agreement with the results of the investigation cited above. The positive effect noted from the use of adrenoblockers after a single exposure to the stressor indicates that catacholamines liberated from nerve endings play a much important role in the microcirculatory changes associated with stress. When discussing the results we shall examine only the possible points of application of adrenoblockers at the level of the functional unit of the organ and tissue. For instance, the presence of α- and β-adrenoreceptors in the walls of microvessels is well known [6]. Investigations showing the presence of β-adrenoreceptors in the erythrocyte membrane have recently been published [4, 5]. Much research has yielded indirect evidence of the presence of α-adrenoreceptors [9,]2] and β-adrenoreceptors [7, 8] on the mast cell membrane. Consequently, the positive effect of adrenoblockers on the microcirculation may be due to direct blockade of adrenergic structures at the level of the microcirculatory system, namely in the walls of the microvessels and on the erythrocyte and mast cell membranes.

Abolition of adaptation to stress at the level of the microcirculatory system as a result of administration of adrenoblockers can be explained perfectly well, for the important role of adrenergic mechanisms in adaptation of the cardiovascular system to physical exertion or to extraordinary stimuli is well known [2].

It must also be noted that administration of β-adrenoblocker pindolol blocks the adenylate cyclase mechanism of the increase in cyclic AMP content in cells. This mechanism, under

stress conditions, may have its advantages and disadvantages. For instance, a decrease in the cyclic AMP content in erythrocytes may lead to changes in slow ability of the membranes and in other biophysical characteristics [4], whereas in the mast cells it may lead to an increase in histamine liberation. Both these factors, in turn, facilitate erythrocyte aggregation.

The experiments thus showed that an essential role in the mechanism of the microcirculatory disturbances following a single exposure to stressors and in the development of adaptation at the level of the microcirculatory system is played by catecholamines liberated from adrenergic nerve terminals.

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STUDY OF THE PURKINJE CELL POPULATION IN THE CEREBELLAR CORTEX OF DOGS AFTER SYSTEMIC CIRCULATORY ARREST

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Changes in the CNS after severe hypoxia resulting from systemic circulatory arrest are among the main pathogenetic mechanisms of postresuscitation sickness [5]. Different components of the nervous system respond unequally and at different times to hypoxia. The Purkinje cells (PC) of the cerebellar cortex are the most sensitive of the neurons to ischemia [2], and they are probably the first cells to be damaged in clinical death [4]. The need to study processes taking place in the cerebellar cortex after systemic circulatory arrest is also confirmed by the data of clinical observations on the role of cerebellar damage in the formation of delayed encephalopathy in patients surviving after clinical death [1].

In the investigation described below a morphological study was undertaken of the composition of the PC population in the medial, intermediate, and lateral zones of the cerebellum in dogs surviving systemic circulatory arrest (electric shock) for 12 min. The content of nucleic acid in pale and dark PC of intact animals and of animals surviving clinical death also was determined cytophotometrically, since the PC population is heterogeneous [14].

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