CONTROL OF DIFFERENT COMPONENTS OF THE MESENTERIC MICROCIRCULATION IN RATS

G. V. Leont'eva

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Research into the microcirculation, which has developed rapidly in recent years, has yielded much evidence of the heterogeneity of responses of the microcirculatory system (MCS) both within the same vascular region and in different organs [2, 4, 7, 8, 12]. Data have been obtained to show that tonic responses to neurohumoral, mechanical, chemical, and other stimuli differ in the arterioles, venules, and the nutritive and shunt divisions of MCS. No clear idea has yet been formed on differences in responses of the smooth-muscle cells of the different vascular segments and mechanisms controlling tone in each of them.

The aim of this investigation was to undertake a biomicroscopic and morphometric study of the reactivity of the mesenteric MCS of the small intestine during prolonged infusions of microdoses of noradrenalin (NA) and after their discontinuation. By an approach of this kind direct and quantitative data on simultaneously developing physiological reactions can be obtained in different components of the MCS in the same region, relations between them, and their time courses.

EXPERIMENTAL METHOD

Experiments were carried out on 20 male Wistar albino rats weighing 170-200 g, anesthetized with pentobarbital in a dose of 3-4 mg/100 g, in the course of which biomicroscopy and intravital morphometry of the different components of the mesenteric MCS of the small intestine were carried out initially, during intravenous drip infusions of NA (1-5 μg/kg/min) for 25 min, and for 25 min after the end of the NA infusions. The technique of the biomicroscopic and morphometric investigations was described previously [5].

EXPERIMENTAL RESULTS

The blood flow in the main arterioles and venules accelerates once the infusions of NA began. This was accompanied by constriction of muscular venules, but the diameter of the arterioles did not change appreciably. After 2-3 min the velocity of the blood flow in the arterioles, estimated visually, returned to its initial value, but in the venules it remained high until the end of NA infusion. The blood flow in many capillaries and postcapillaries changed from continuous into intermittent, evidence of increased vasomotor activity. In individual arteriolo-venular anastomoses (AVA) retrograde movement of blood was observed, followed by stopping of the flow, and at the same time the circulation along the main channels was activated [4]. After 7-8 min the blood flow in MCS stabilized; one-third of the length of the functioning capillary system was converted into purely plasmatic vessels, indicating increased tone of some of the precapillary sphincters (Figs. 1 and 2a, Table 1).

Stopping the infusion of NA led during the first minutes to acceleration of the blood flow in the venular portion, and after 5-7 min contraction of individual groups of smooth-muscle cells was observed, most frequently where the collecting venules empty into the muscular venules, although this was not observed in all experiments. In some parts of the vascular bed slowing of the blood flow took place, or even stasis, and the postcapillary and collecting venules became bead-like (Fig. 2b). Simultaneously a further increase in tone of those precapillary sphincters which had previously given a tonic response to infusion of NA was observed (Fig. 3). This led to exclusion of one-third of the capillary bed from the blood flow (Fig. 1; Table 1). In this microhemodynamic situation substantial structural changes were observed in the shunt blood flow: The flow stopped along some of the main channels, which appeared to be blocked, and true AVA were activated (Fig. 1). No significant changes were observed in the arteriolar bed at this stage of the experiment (Table 1).

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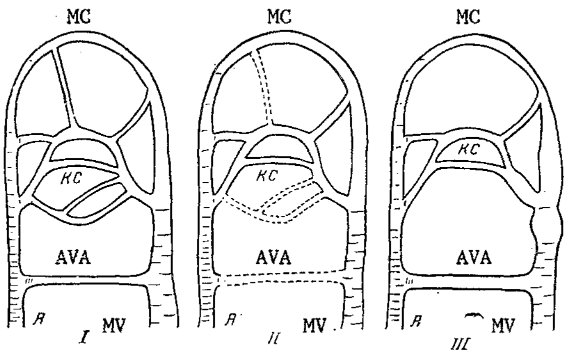

Fig. 1

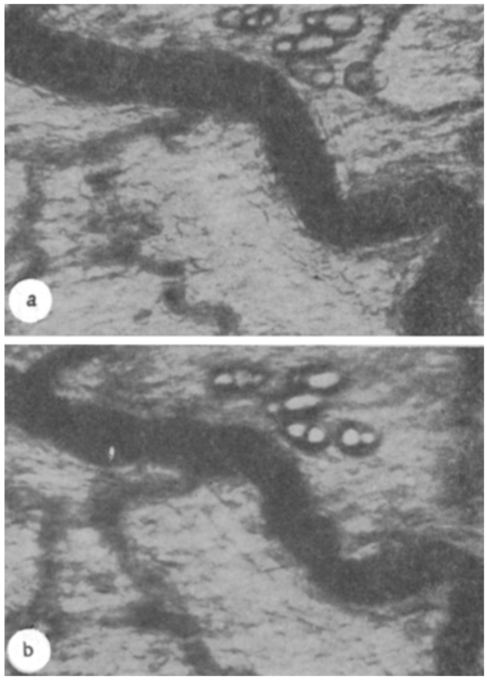

Fig. 2

Fig. 1. Scheme of functioning mesenteric microculatory bed, before (I), during (II), and after end of infusion of NA (III).

Fig. 2. Dynamics of changes in a venule: a) during infusion of NA; b) constriction, bead-shaped outlines of venule after infusion of NA. 260×.

In response to small doses of NA, the constrictor reaction of the muscular venules was thus the most distinct and constant. It was observed during infusion of NA and was often intensified after the end of infusion, possibly due to reflex intensification of the vasoconstrictor impulsation in response to changes in the central hemodynamics. Measurement of the systemic arterial pressure at intervals during the experiment revealed moderate fluctuations: initially 120 mm Hg, during infusion of NA 140-145 mm Hg, and after infusion a fall to 130 mm Hg (data of V. P. Nosova). Increased constriction of individual groups of myocytes in the postcapillary component, leading to stasis in different parts of MCS, was evidently the morphologic manifestation of active blood deposition in the venular bed. Ultimately the combination of passive dilatation of the nonmuscular venules, congested with blood, above the point of narrowing and the active uniform constriction of the muscular venules led to an increase in the total capacity of the venular bed, which was revealed by morphometry (Table 1). Other investigators, using indirect methods, also have suggested the possibility of similar responses of the intestinal venular system to adrenergic stimulation [3, 7]. Our own data, based on visual observation, confirm this conclusion and suggest that the two opposite responses of the mesenteric capacitive vessels, namely mobilization and deposition of blood, may be based on a constrictor mechanism.

The venoconstrictor action of NA is now regarded as a firmly established fact. High sensitivity of veins in the splanchnic region to NA is explained by their active participation in deposition of blood and an increase in its venous return to the heart [7, 17]. Measurement of the inflow of blood from the veins to the heart is a very important factor in self-regulation of the cardiovascular system. The opinion is held that a chain of biochemical processes leading to an increase in stroke volume and systolic pressure in the left ventricle, i.e., ultimately to an increase in the hydraulic power of the flow in the high pressure region, is initiated by nervous impulses increasing the rigidity of the veins [8].

Constriction of the arterioles was not increased, either visually or morphometrically, during or after infusion of NA. The response of the arteriolar component could be judged only by brief acceleration of the blood flow. The transient character of the arteriolar response can be explained by "self-regulatory escape" of the resistive vessels of the abdominal organs from adrenergic influences [7]. The absence of tonic responses of the mesenteric arterioles has been observed in a number of situations leading to strengthening of sympathetic

TABLE 1. Morphometric Parameters of Mesenteric Microcirculatory System during Experiment

Parameter studied	Initial value (n = 15)	Infusion of NA (n = 15)	Discontinuing infusion of NA (n = 15)
Diameter, μ, of Terminal			
arterioles	35,6±0,7	36.4±0,6	36,5±0,6
Metarterioles	13,9±0,3	15,9±0,4**	16,3±0,4**
Muscular venules	43,3±0,8	36,7±0,7***	38,8±0,6***
Collecting venules	19,1±0,4	18,8±0,4	30,5±0.7***
Postcapillaries	9,4±0,6	10,1±0,2*	14,4±0,8***
Capillaries	7,2±0,4	7,1±0,2	7,2±0,3
Length of capillaries, relative units			
Functioning	29,6±1,4	19,7±1,5***	18,6±1,1***
Plasmatic	0	9,9±0,9***	3,6±1,3
Empty	0	0	9,9±1,1***

Legend. *P < 0.05; **P < 0.01; ***P < 0.001.

influences, when constriction only of muscular arteries 200-400 μ in diameter was observed [10]. Physiological and histological investigations have shown that the sympathetic innervation in the rat mesentery reaches the terminal arterioles but does not extend to metarterioles or precapillaries [14]. Data in recent years have conclusively shown that the resistive function in the mesenteric vascular bed is performed not by arterioles, but by muscular arteries [19]. The possibility cannot be ruled out that constriction of arterioles can be induced by more powerful influences than those indicated above.

An increase in tone of the muscular venules led to an increase in the intravascular pressure within them, as was shown indirectly by the retrograde blood flow in certain AVA. This was accompanied by tonic reactions of the precapillary sphincters with conversion of one-third of the length of the functioning capillary bed into plasmatic vessels which, in the modern view, are mainly reabsorptive [1]. Attention is drawn to the striking agreement between our own data, obtained by visual observation and intravital morphometry, and results of other workers [6], who judged the area of the functioning capillary bed by the value of the coefficient of capillary filtration, and after injecting similar doses of NA, found a reduction of this parameter in the small intestine by 33% also. The increase in tone of the precapillary sphincters could be explained by their high sensitivity to NA [2, 9, 13, 14, 20]. However, the absence of constriction of the arterioles which, like precapillaries, have myocytes of visceral type, under these circumstances suggests an autoregulatory mechanism of the tonic responses of the precapillaries, linked with an increase of postcapillary resistance and of intracapillary pressure. This hypothesis is in agreement with data showing their extreme sensitivity to changes in intravascular pressure [11, 15-18].

The relationship between pre- and postcapillary resistance is a key factor in the microcirculation, for it determines filtration and reabsorption processes, i.e., transcapillary exchange. Mobilization and deposition of blood, like a change in extravascular fluid volume, are adaptive reactions ensuring an adequate supply of blood to the heart. The autoregulatory dependence of precapillary resistance on postcapillary is thus an essential condition for the coordinated activation of these mechanisms regulating the venous return of blood.

Injection of small doses of NA into the bloodstream thus activates physiological reactions of the mesenteric microvessels leading to acceleration of the venous return of blood and reabsorption of tissue fluid into the bloodstream. Stopping the infusion of NA causes deposition of blood in the venular bed, and this process is based on intensification of venoconstrictor responses. Development of constriction of the postcapillary segment is coordina-

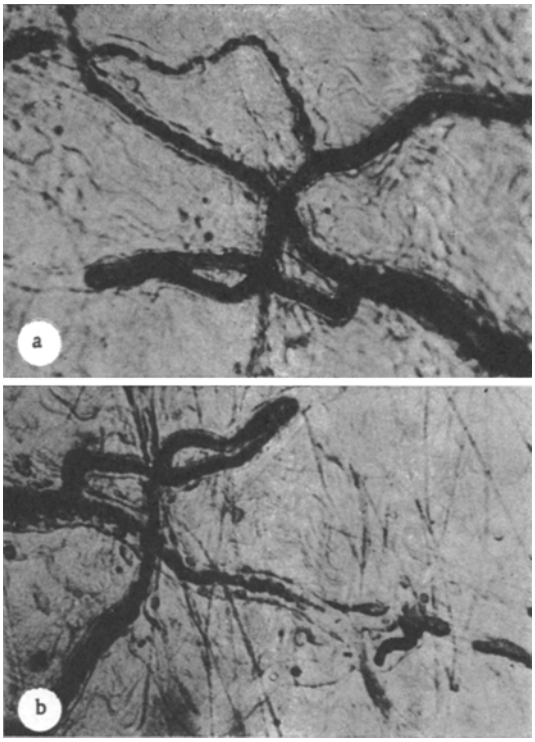

Fig. 3. Tonic reactions of precapillary sphincters: a) beginning of formation of plasmatic capillary; b) empty capillary. 250×.

ted with contraction of the myocytes of the precapillary sphincters. No tonic reactions of the arterioles were discovered under these circumstances. Consequently, venules are able to carry out active correction of the capillary blood flow by autoregulation. These vascular reactions are due to the higher sensitivity of the venules than of the arterioles to adrenalin. Variability of the shunt blood flow during and after infusion of NA can evidently also be interpreted as adaptation of the juxtacapillary hemodynamics to the changing conditions of the venous outflow. The leading role of the postcapillary component in local changes in the mesenteric microcirculation is explained, evidently, by the predominant physiological function of the splanchnic vascular region, namely to ensure an adequate supply of blood to the heart.

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SUBSTANCE P IN CENTRAL MECHANISMS OF THE AVOIDANCE REACTION

V. G. Zilov, A. P. Patyshakuliev,
L. I. Ivanova, and S. K. Rogacheva

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KEY WORDS: substance P; avoidance reaction; ventromedial hypothalamus; dorsal hippocampus; mesencephalic reticular formation.

The contradictory results of investigations into the effect of substance P (SP) on the formation of active and passive avoidance in animals [10, 11, 14] served to motivate the present experiments in which an attempt was made to assess the role of SP in the development of the avoidance reaction (AR) in rabbits. Most attention was paid to the effect of SP on excitability of the ventromedial hypothalamus, and also on reticulo-hippocampal-hypothalamic interrelations during the formation of defensive motivation, which forms the basis of AR, in animals.

EXPEPIMENTAL METHOD

Experiments were carried out on 16 unanesthetized rabbits weighing 2.7-3 kg. The animals were fed before the experiments. Thin (0.1 mm) bipolar nichrome electrodes were implanted in accordance with Sawyer's atlas into the ventromedial hypothalamus of the scalped rabbit. Threshold electrical stimulation of the center for "affective reactions" (1.5-4 V, frequency 50 Hz, pulse duration 1 msec) was applied. Bipolar electrodes were also implanted into the dorsal region of the hippocampus (DH) and mesencephalic reticular formation (MRF). Conditioning stimulation of DH and MRF in experiments to study both the threshold of stimulation of the ventromedial hypothalamus and changes in the latent period of evoked AR had a strength of 5-7 V at a frequency of 50 Hz, with pulse duration of 1 msec for the dorsal hippocampus and 2-4 msec with the same frequency and pulse duration for MRF. The duration of conditioning stimulation of the limbico-mesencephalic formations was 15 sec. The EEG was recorded from various regions of the cortex by means of needle electrodes on an eight-channel EEG-80 electroencephalograph (Medicor, Hungary). The power of the principal EEG rhythms within the range from 1.5 to 70 Hz was recorded and studied on a type ANIEG-8 wide-band EEG analyzer-integrator (Medicor). The ECG was recorded in standard lead II. SP (from Sigma, USA) in a dose of 30 μg/kg, diluted in 5 ml of physiological saline, was injected slowly (1 ml/min) into the marginal vein of the rabbit's ear. Excitability of the ventromedial hypothalamus and the character of reticulo-hippocampal influences were determined at the end of intravenous injection of SP and at 15-min intervals thereafter for 1.5 h. The location of the subcortical electrodes was determined by an express method, in brain sections cut to a thickness of 50-100 μ.

EXPERIMENTAL RESULTS

Threshold stimulation of the ventromedial hypothalamus (the center for "affective reactions"), after a short latent period, evoked AR in the animals. This reaction, based on defensive motivation, was accompanied by specific patterns of powers of the principal EEG rhythms in the frontal and occipital regions of the cortex.

The character of hippocampal and reticular influences on excitability of hypothalamic motivational centers was established previously [4]. In the present experiments conditioning stimulation of DH significantly impeded the formation of AR in the animals, as was shown both by elevation of the threshold of stimulation of the ventromedial hypothalamus ($P < 0.05$) and

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