DISTURBANCE OF VASCULAR PERMEABILITY AND THE MICRO-CIRCULATION DURING SHORT-TERM IMMOBILIZATION STRESS

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Immobilization of rats for 1 or 3 h leads to an increase in vascular permeability for ink particles and disturbances of the microcirculation in the mesenteric microvessels (formation of aggregates, appearance of "plasmatic vessels," closure of arteriolar-venular shunts). An important role in the pathogeneis of these changes is played by histamine liberated from the mast cells without their undergoing degranulation. Liberation of histamine may be the trigger mechanism in the development of disturbances of vascular permeability during prolonged immobilization stress.

KEY WORDS: vascular permeability; microcirculation; stress; histamine; mast cells.

Previous experiments [2] showed that histamine liberated during degranulation of mast cells plays an important role in the disturbances of vascular permeability accompanying immobilization of animals. However, it has been shown in respect of carrageen inflammation that the duration of the histamine phase of edema does not exceed 60-90 min [5].

In the investigation described below the permeability of the microvessels and microcirculation was studied during short-term immobilization of rats and the role of histamine in the mechanisms of the disturbance of permeability and of the microcirculation was evaluated.

EXPERIMENTAL METHOD

Experiments were carried out on 115 noninbred male rats weighing 200-250 g. The animals were immobilized for 1 or 3 h. The rats received an intravenous injection of 0.2 ml of purified ink. Disturbances of vascular permeability were estimated for extent and depth in mesenteric preparations by the method suggested previously [2]. The microcirculation in the mesentery of the rats was studied biomicroscopically, using an apparatus constructed in the laboratory on the basis of the MBI-6 microscope. The histamine content in the mast cells was measured by the fluorometric method [8] as modified by Aleksandrov [1]. Measurements were made with the ML-2 microscope, using FS 1-2 and FS 1-4 filters; the histamine content was expressed in relative units of fluorescence. The following drugs were given: dimeboline (1 mg/100 g, intraperitoneally), Tavegyl (Sandoz; 4 mg/kg, by mouth), and tipindole (10 µg per rat, intraperitoneally). Dimeboline and tipindole were injected 30 min before the rats were immobilized and 30 min before injection of the ink. Tavegyl was given as a single dose 1 h before immobilization of the animals. The results were subjected to statistical analysis [3].

EXPERIMENTAL RESULTS AND DISCUSSION

The state of permeability of the microvessels in rats immobilized for 1 and 3 h was studied in the experiments of series I. Particles of colloidal carbon were deposited in their venules 7-50 µ in diameter (Fig. 1a); the depth and spread of the disturbances were greater in the case of immobilization for 3 h.

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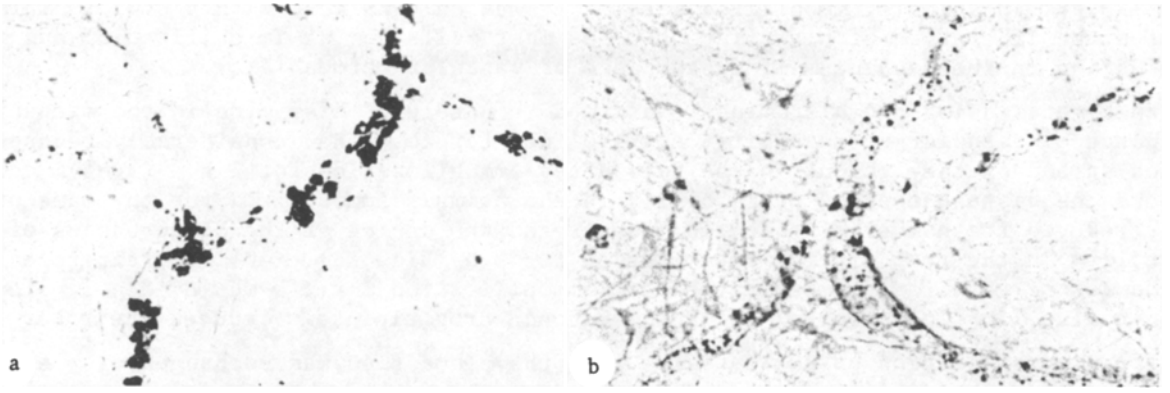

Fig. 1. Deposition of particles of colloidal carbon in venules of the rat mesentery: a) after immobilization for 3 h; b) after immobilization for 3 h preceded by administration of Tavegyl; magnification 20 × 5.7.

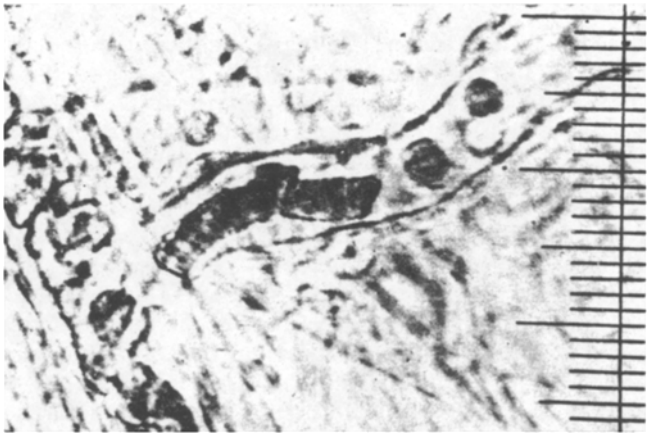

Fig. 2. Formation of aggregates of different shapes in mesenteric venules of rats after immobilization for 1 h. Magnification 58 × 5.7.

TABLE 1. Number and Percentage of Degranulated Mast Cells in Mesentery of Immobilized Rats (M ± m)

Conditions	Number of animals	Mean number of mast cells per field of vision (135 ×)	Percentage of degranulated mast cells
Control	5	25,2± 1,6	0,09± 0,06
Immobilization			
1 h	5	30,9± 1,2*	0,16± 0,01
3 h	5	21,5± 4,7	0,25± 0,08

*Difference from control statistically significant (P = 0.12).

Considering that the disturbance of vascular permeability in these experiments was connected with the liberation of histamine, which takes place during exposure to extremal stimuli [4, 7], the state of the mast cells in the mesentery of the experimental rats was investigated. It was found that after immobilization for 1 h the number of cells was increased, but after immobilization for 3 h their number was somewhat reduced. The same number of degranulated cells was found in the control and experimental animals (Table 1).

However, liberation of histamine and other biologically active substances contained in the granules of mast cells is known to take place even without their degranulation [6, 9]. Whereas in the control rats the histamine content in the mast cells (in conventional units)

was 60 ± 3.48, in animals immobilized for 1 h it was only 29 ± 2.32 ($P < 0.05$). This fact indicates the liberation of histamine from the mast cells during immobilization and their participation in the mechanism of disturbance of vascular permeability.

Experiments using antihistamines confirmed this role of histamine in the mechanism of disturbance of vascular permeability. Dimeboline, for instance, considerably reduced the extent and spread of the lesions in the rats after immobilization for 1 h. Tavegyl completely abolished the disturbances of permeability in the animals immobilized for the same period and greatly reduced the number of affected vessels and the degree of the disturbances of vascular permeability in the rats after immobilization for 3 h (Fig. 1b). An important role in the disturbances of vascular permeability after immobilization for 1 h was evidently played by serotonin also, for injection of the antiserotonin drug tipindole reduced their severity.

After immobilization of the rats for 1 h, the blood flow was unchanged over a large area of the mesentery, but in some places definite disturbances of the microcirculation were observed: granular blood flow, the formation of aggregates of different shapes and sizes, leading to occlusion of some microvessels, and the formation of "plasmatic" vessels (Fig. 2). Opening of arteriolo-venular shunts also was observed. The disturbances of the microcirculation were less severe in the mesentery of rats receiving the antihistamine Tavegyl. In particular, the number of aggregates was reduced.

Assuming that the normalizing action of Tavegyl was connected with its deaggregating action, the ESR was determined. During immobilization for 1 h a marked increase in the ESR was observed: 2.2 ± 0.28 compared with the normal level of 1.4 ± 0.19; $P = 0.2$) . After Tavegyl the ESR was slowed to 1.8 ± 0.3. Similar results were observed after immobilization for 3 h: the ESR in the experimental rats was 2.7 ± 0.41 but in rats previously receiving Tavegyl it was 1.4 ± 0.24 ($P = 0.001$).

The results show that during short-term immobilization stress disturbances of the microcirculation and of permeability of the microvessels are observed, and an important role in the mechanism of their development is played by histamine which is liberated from the mast cells without their degranulation. Histamine evidently plays the role of trigger mechanism in the development of disturbances of vascular permeability. For instance, after immobilization of rats for 24 h, Tavegyl, used to diminish the disturbances of vascular permeability, was more effective if given 1 h before immobilization of the animals than if given 8 h before the end of the experiment.

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