ROLE OF THE MAST CELLS IN DISTURBANCES OF VASCULAR PERMEABILITY IN RATS WITH STRESS DUE TO IMMOBILIZATION

M. P. Gorizontova, O. V. Alekseev, and Academician A. M. Chernukh*

UDC 616.46-001.1/.3-092.9-07:616.13-008.6-092:616.155.36

The role of the mast cells in the mechanism of disturbance of vascular permeability arising in rats immobilized for 24 h was studied. The antihistamine drug dimebolin was found to have a protective action and to reduce the depth and extent of the disturbances of vascular permeability. This effect appeared only if mast cells were present and it was combined with marked degranulation of these cells. The protective action of small doses of heparin indicates that it may play a mediator role in the mechanism of action of dimebolin. It is postulated that the mast cells may have both a damaging (through the liberation of histamine and serotonin) and a protective (through the liberation of heparin) action on vascular permeability during immobilization.

Key words: vascular permeability; mast cells; stress; heparin; histamine.

Exposure to extreme stimuli is followed by the liberation of histamine [6, 13, 19] and marked degranulation of the mast cells (MC) [18]. The writers showed previously [1] that an increase in degranulation of MC in the mesentery and a disturbance of permeability of the venules to particles of colloidal carbon take place in rats exposed to immobilization and measured electrical stimulation.

In this investigation the role of MC in the disturbance of vascular permeability associated with stress from immobilization was evaluated by a method of pharmacological analysis.

EXPERIMENTAL METHOD

Experiments were carried out on 49 noninbred male rats weighing 200-300 g. The animals were immobilized for 24 h in the supine position. Disturbances of vascular permeability were determined by the "labeled vessels" method. Purified black ink was injected intravenously into the rats in a dose of 0.2 ml /100 g body weight 30 min before sacrifice (15 ml of Carnoy's solution intraperitoneally). Cleared film preparations were made from the mesentery of the large intestine fixed in situ. The MC were stained with 0.5% toluidine blue. Disturbances of permeability were assessed from the number of labeled vessels in

*Academy of Medical Sciences of the USSR.

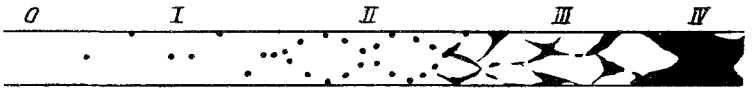

Fig. 1. Scheme showing degrees of disturbance of vascular permeability. I) diffuse punctate (dust-like) labeling; II) structural punctate (punctiform) labeling; III) speckled labeling; IV) confluent (sleeve-like) speckled labeling.

Laboratory of General Pathophysiology and Experimental Therapy, Institute of Normal and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 79, No. 3, pp. 22-25, March, 1975. Original article submitted May 28, 1974.

TABLE 1. Vascular Permeability and State of MC in Immobilized Rats during the Action of Drugs

Series No.	Experimental conditions	Number of animals	Number of mesenteric windows (in % of all examined)			Number of rats with different degrees of labeling (in % of total number of rats in experiment)					Mean number of MC in field of vision (135 x)	Percentage of degranulated MC
			Without label	1-10 labeled vessels	Over 10 labeled vessels	0	I	II	III	IV		
I	Dimebolin + immobilization	10	93	2	5	80	20	0	0	0	19,7± 1,21	29± 5,12
	Tipindole + immobilization	9	48	8	44	11	89	67	11	0	24,9± 0,7	0,22± 0,01
	Control: physiological saline (same program of injection as drugs) + immobilization	5	20	24	56	0	100	100	100	40	28,9± 0,11	0,28± 0,07
II	Substance 48/80 + immbolization	12	10	7	83	0	67	100	100	100	0	0
	Substance 48/80 + dimebolin + immobilization	5	10	3	87	0	60	60	60	60	0	0
	Control: physiological saline (injection by the same program as substance 48/80) + immobilization	5	48	20	32	0	100	60	60	40	24,6± 1,27	1,22± 0,57
III	Substance 48/80 + 10 units heparin + immobilization	6	68	17	15	33	66	33	0	0	0	0
	Substance 48/80 + 100 units heparin + immobilization	7	17	6	77	0	100	100	100	43	0	0
	Control: substance 48/80 + physiological saline (injected by the same program as heparin) + immobilization	5	16	0	84	0	100	100	100	80	0	0

each of the 10 "windows" examined in the mesentery of each animal and from the intensity of labeling (Fig. 1). The antihistamine drug dimebolin (1 mg/100 g, in 5 ml physiological saline, intraperitoneally) and the antiserotonin drug tipindole (2 μg/ml physiological saline, intraperitoneally in a volume of 5 ml) were injected twice – 30 min before the rats were immobilized and 30 min before injection of the ink. The substance 48/80, a liberator of histamine and serotonin, was injected by the scheme described by Riley and West [16]. Heparin (Richter) was injected intraperitoneally (10 and 100 units per animal) in 5 ml physiological saline.

EXPERIMENTAL RESULTS AND DISCUSSION

In the experiments of series I (Table 1) a protective action of dimebolin and tipindole on vascular permeability was discovered. Dimebolin was particularly effective for it significantly reduced the number of labeled venules and also the intensity of labeling. The protective effect of dimebolin was combined with a decrease in the number of MC in the mesentery (by more than 33%) and with an increase in the number of degranulated MC (by 100×). A similar action of antihistamine drugs on MC was observed previously [15, 20]. Meanwhile tipindole, with much weaker protective activity, had no significant effect on the number of MC or on their degranulation. The attempt to explain these facts led to the suggestion that the protective action of dimebolin is somehow mediated through MC.

This hypothesis was tested in the next series (II) of experiments with intraperitoneal injection of substance 48/80. The experiments showed that in the absence of MC in the mesentery immobilization caused more marked disturbances of vascular permeability (Fig. 2), whereas dimebolin under these conditions had

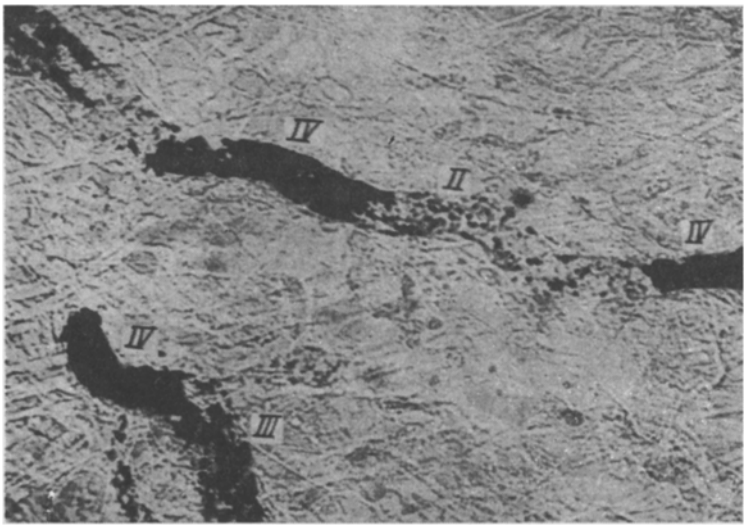

Fig. 2. Deposition of ink in venules of rat mesentery after intraperitoneal injection of substance 48/80 and immobilization for 24 h. Disturbance of vascular permeability of various degrees (I, II, III, IV) can be seen, magnification 20 × 5.7.

no protective action (Table 1). It was concluded from these results that the MC play a protective role on vascular permeability in immobilized animals and that the positive effect of dimebolin under these circumstances is mediated through degranulation of the MC. The MC evidently contain a substance that prevents the disturbance of vascular permeability and which is liberated during degranulation. This substance could be heparin.

To test this hypothesis an attempt was made to study the possible protective role of heparin. Experiments showed that in the absence of MC in the mesentery (preliminary injection of substance 48/80; series III), heparin injected by the same program as dimebolin largely simulated the protective effect of dimebolin as shown in series I. It is important to note that the protective action of heparin was manifested only if given in small doses.

These results are in harmony with others showing that injection of small doses of heparin into rats prevents the increased vascular permeability arising under the influence of exogenous or endogenous histamine [4]. A beneficial effect has also been obtained by the use of heparin in the treatment of various infectious-allergic diseases in which the disturbances of permeability are one of the essential pathogenetic components [2, 8, 9]. The ability of heparin to form complexes with histamine [9, 12, 17], with serotonin [3, 11], and with the cationic proteins of lysosomes of polymorphonuclear leukocytes [7] has been described in the literature. Heparin has been shown to inhibit the activity of the plasma kallikrein and plasma permeability [5, 14]. An increase in the activity of diamine oxidase (an enzyme similar in many respects to histaminase) has been described after the injection of heparin [10].

The existing data, however, are insufficient to allow any of these effects of heparin to be regarded as the sole cause of its protective action on vascular permeability. The "antihistamine" or "antiserotonin" effect of heparin can hardly be the basis of this action, for histamine and serotonin mediate only acute and comparatively short-lasting disturbances of vascular permeability.

The results indicate that the MC play a dual role in the mechanisms of the change in vascular permeability during immobilization: on the one hand they increase it (through the liberation of histamine and serotonin), whereas on the other hand they prevent its disturbance (by the liberation of heparin). The corresponding beneficial effect of the drugs can also be explained not only by their direct antihistamine action but also by their influence on other factors regulating vascular permeability and, in particular, the liberation of heparin.

LITERATURE CITED

1. M. P. Gorizontova and A. M. Chernukh, Pat. Fiziol., No. 2, 73 (1974).
2. V. P. Kaznacheev, Fundamental Enzymic Processes in the Pathology and Clinical Picture of Rheumatic Fever [in Russian], Novosibirsk (1960).

3. B. A. Kudryashov, T. M. Kalishevskaya, and L. A. Lyapina, Vopr. Med. Khimii, No. 3, 269 (1973).
4. G. F. Nazarov and N.N. Petrishchev, Byull. Éksperim. Biol. i Med., 65, No. 2, 58 (1968).
5. N. Back and R. Steger, Proc. Soc. Exp. Biol. (New York), 133, 740 (1970).
6. R. Cass and P. B. Marshall, Arch. Internat. Pharmacodyn., 136, 311 (1962).
7. J. M. Clark and R. D. Higginbotham, J. Immunol., 101, 488 (1968).
8. D. A. Dolowitz and T. F. Dougherty, Laryngoscope, 70, 873 (1960).
9. T. F. Dougherty and D. A. Dolowitz, Am. J. Cardiol., 14, 18 (1964).
10. R. Hansson and H. Thysell, Acta Physiol. Scand., 88, 346 (1973).
11. R. D. Higginbotham, Fed. Proc., 18, 572 (1959).
12. Y. Kobajaschi, Arch. Biochem., 96, 20 (1962).
13. J. Le Blanc, Proc. Soc. Exp. Biol. (New York), 112, 25 (1963).
14. D. Y. McConnell, L. Y. Kagen, and E. L. Backer, Proc. Soc. Exp. Biol. (New York), 119, 652 (1965).
15. J. Mota and W. Dias da Silva, Brit. J. Pharmacol., 15, 396 (1960).
16. J. F. Riley and G. B. West, J. Path. Bact., 69, 269 (1955).
17. R. K. Sanyal and G. B. West, Nature, 178, 1293 (1956).
18. H. Selye, The Mast Cells, Washington (1965).
19. H. Selye, P. Jean, and M. Cantin, Proc. Soc. Exp. Biol. (New York), 103, 444 (1960).
20. D. E. Smith, Proc. Soc. Exp. Biol. (New York), 97, 872 (1958).