CHANGES IN VASCULAR PERMEABILITY AND STATE OF THE MESENTERIC MAST CELLS OF RATS WITH ACUTE EXPERIMENTAL PANCREATITIS TREATED WITH SODIUM THIOSULFATE

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UDC 616.37-002.1-092.9-07:616.16-031:611.383]-008.6+616.383.4-008.953.6]-02:546.33'.224'.223.2

KEY WORDS: mesentery; mast cells; pancreatitis.

Features directly or indirectly indicating increased vascular permeability — edema and hemmorhages — are observed in pancreatitis [4, 7]. The opinion is held that under the influence of circulating pancreatic enzymes and other vasoactive substances, causing capillary leakage and generalized vasodilation [12], systemic lesions arise in the blood vessels.

The object of the present investigation was to establish the role of mast cells in disturbances of vascular permeability in the mesentery of the small intestine and also to discover the effect of sodium thiosulfate on microvascular permeability in this region in acute experimental pancreatitis. It was shown previously that under similar experimental conditions, sodium thiosulfate significantly prevented the development of edema and damage to blood vessels in the pancreas itself [3].

EXPERIMENTAL METHOD

Experiments were carried out on 49 noninbred male albino rats weighing 150-180 g, divided into two groups. The splenic segment of the pancreas was cooled with ethyl chloride in the animals of group 1 [6]. Histological controls confirmed the presence of pancreatic necrosis with a hemorrhagic component 24 h after injury to the organ. Rats of group 2 were given a single intraperitoneal injection of a 30% aqueous solution of sodium thiosulfate in a dose of 50 mg/100 g body weight 4 h after cooling of the pancreas. Rats undergoing a mock operation served as the control. The animals of all groups were decapitated 24 h after the beginning of the experiment. A disturbance of vascular permeability was detected in the mesentery of the small intestine [2]. The mast cells and eosinophilic leukocytes were counted in film preparations of the mesentery stained by the Jenner–Giemsa method, in 10 fields of vision under magnification by a × 20 objective. The mean histamine and serotonin content per mast cell was determined fluorometrically [1, 10, 13] by means of the FMÉL-1A photometric attachment. The content of biogenic amines was expressed in relative units of intensity of fluorescence (FU).

EXPERIMENTAL RESULTS

At autopsy on the animals of group 1 about 5-6 ml of transparent fluid was found in the peritoneal cavity. The mesentery, retroperitoneal cellular tissue, and the duodenal segments of the pancreas were in a state of marked edema. The number of blood vessels 921 μ in diameter, labeled with ink, was considerably increased (Table 1). All four stages of labeling were observed whereas in the control there were only one-ninth as many "labeled" vessels ($P < 0.001$) and only the first two stages of retroperitoneal cellular tissue were not seen and there were 2.3 times fewer "labeled" vessels ($P < 0.05$) than in the animals of group 1. The degree of permeability observed corresponded to the first three stages of labeling. The serotonin content per mast cell in the animals of group 1 was 36.5 times less than in the intact rats ($P < 0.001$) and the histamine content was 35.8% less ($P < 0.02$). The mean content of serotonin and histamine per mesenteric mast cell in the animals of group 2 did not differ significantly from the corresponding data in intact and control rats (Table 2). The number

Central Research Laboratory, Erevan Postgraduate Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR P. N. Veselkin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 3, pp. 288-290, March, 1981. Original article submitted May 27, 1980.

0007-4888/81/9103-0291$07.50

TABLE 1. State of Vascular Permeability in Mesentery of Small Intestine of Rats (M ± m)

Group and number of animals	Number of labeled vessels in 10 mesenteric windows	Distribution of vessels by degree of permeability			
		I	II	III	IV
Intact (6)	0	—	—	—	—
Control (6)	1,5±0,3	0,2±0,1	1,3±0,6	—	—
Experimental:					
group 1 (7)	13,6±2,6	1,1±0,4	10,0±1,9	2,3±0,8	0,2±0,1
P_1	<0,001	>0,05	<0,01	—	—
group 2 (6)	6,0±1,6	0,8±0,3	3,5±1,0	1,7±0,8	—
P_1	<0,05	>0,1	>0,05	—	—
P_2	<0,05	>0,5	<0,05	>0,5	—

Legend. P_1) Relative to control group; P_2) relative to group 1.

TABLE 2. State of Mast Cells and Eosinophils in Mesentery of Small Intestine of Rats (M ± m)

Group and number of animals	Number of mast cells	Degranulation of mast cells, %	Serotonin, FU	Histamine, FU	Number of eosinophils
Intact (6)	50,3±2,9	9,4±2,6	54,0±2,6	28,2±2,4	213,0±15,8
Control (6)	51,6±6,7	10,2±1,6	43,7±5,2	23,1±1,1	115,0±5,5
P_1	>0,5	>0,5	>0,1	>0,05	<0,001
Experimental					
group 1 (6)	50,6±6,3	4,9±1,7	19,7±4,4	18,1±2,5	77,4±7,0
P_1	>0,5	>0,1	<0,001	<0,02	<0,001
P_2	>0,5	>0,05	<0,01	>0,05	<0,01
group 2 (6)	53,6±9,2	5,4±1,7	54,7±4,6	26,9±4,1	170,5±29,5
P_1	>0,5	>0,2	>0,5	>0,5	>0,2
P_2	>0,5	>0,05	>0,1	>0,5	>0,05
P_3	>0,5	>0,5	<0,001	>0,05	<0,01

Legend. P_1 relative to intact animals; P_2) relative to controls; P_3) relative to animals of group 1.

of mast cells and percentage of their degranulation were identical in the animals of all groups, evidence of secretion of biogenic amines by the mast cells by a process of granulolysis without degranulation. Counting the number of tissue eosinophils (Table 2) revealed a decrease in their number in the mesentery of the rats of group 1 by 68.4% ($P < 0.001$), whereas in the animals of group 2 the eosinophil count did not differ significantly from that in the intact rats.

An important role in the increase in vascular permeability and disturbance of the hemodynamics in the mesenteric microcirculation of the small intestine may be played by trypsin, elastase, phospholipase A, kinins, and other substances present in blood and peritoneal exudate in particularly high quantities in the acute stage of pancreatitis [5, 15]. These products may act on mesenteric microvessels indirectly or through direct contact. In the writers' view, mast cells, whose population in the rat mesentery is particularly rich in biogenic amines [9], could be among the mediators concerned. Under the influence of tissue proteases and as a result of the local chemical action on the mast cells, they actively secrete histamine and serotonin [11, 14], which evidently also took place under the present experimental conditions. Besides an increased output of biogenic amines, a sharp decrease also was found in the number of tissue eosinophils, which are known to possess histaminase activity [8].

The results of this investigation thus indicate a marked increase in vascular permeability in the acute phase of experimental pancreatitis, with a corresponding increase in the output of serotonin and histamine from the mast cells and a decrease in the number of tissue eosinophils. Sodium thiosulfate, which inhibits the development of inflammatory and necrotic processes in the pancreas [3], prevents the liberation of biogenic amines from the mast cells and has a protective action on the vessel wall.

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EXPERIMENTAL STUDY OF THE USE OF D-PENICILLIAMINE IN CIRRHOSIS OF THE LIVER

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UDC 616.36-004-092.9-085.015.25

KEY WORDS: experimental cirrhosis of the liver; D-penicillamine.

D-penicillamine (D-PA) is known to be an effective remedy for systemic diseases of connective tissue. In recent years the beneficial effect of D-PA in chronic hepatitis and cirrhosis of the liver has been reported [3, 9, 15]. However, there are no reports in the literature on experimental research into the use of D-PA in this pathology, although one or two communications have dealt with the biochemical study of the effect of D-PA on collagen synthesis [10, 14].

The object of the present investigation was a combined study of the action of a therapeutic dose of D-PA on different manifestations of the pathological process during the development of experimental cirrhosis and also a comparative study of the action of D-PA and prednisolone, a drug widely used in clinical practice for the treatment of chronic liver diseases.

EXPERIMENTAL METHOD

Experiments were carried out on a model of metatoxic cirrhosis of the liver of the writers' own design, using a cyclic combination of hepatotoxic agent and hepatogenous antigen [8]. In this particular model experimental cirrhosis of the liver is accompanied by more marked autoimmune manifestations and it bears a closer resemblance to active human cirrhosis of the liver than models described previously [2, 5, 6].

Experiments lasting 7.5 months were set up on 97 male chinchilla rabbits, and comprised two series of chronic experiments. In series I (37 animals) the effect of D-PA on the

I. M. Sechenov First Moscow Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR F. N. Komarov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 3, pp. 290-293, March, 1981. Original article submitted July 14, 1980.

