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MAST CELL – LEUKOCYTE INTERACTION IN INCREASED VASCULAR PERMEABILITY OF AN INFLAMMATORY FOCUS

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KEY WORDS: inflammation, vascular permeability; mast cells; leukocytes

The results of in vitro studies of modulation of the functions of different kinds of leukocytes (neutrophils, eosinophils, monocytes, lymphocytes) by biologically active substances of mast cells (MC), on the one hand [6, 11], and the degranulating effect of products of leukocytes (lysosomal enzymes and nonenzymic cationic proteins, cytokines, free radicals, lymphokines) on MC, on the other hand [3, 8-10, 12], point to possible interaction between MC and leukocytes in the pathogenesis of inflammation.

The aim of this investigation was to study the kinetics of peritoneal MC during the exudative phase of infectious peritonitis in rats under natural conditions of inflammation and during its development against a background of isolated and combined removal of MC and leukocytes.

EXPERIMENTAL METHOD

Experiments were carried out on 317 male Wistar rats weighing 180-200 g. Peritonitis was produced by intraperitoneal injection of $2 \cdot 10^9$ ($0.5LD_{50}$) cell bodies of a 24-h culture of *E. coli*, isolated from a patient with peritonitis, in 1 ml of isotonic sodium chloride solution. Vascular permeability in the peritoneal cavity at different times after reproduction of peritonitis was judged from the concentration of 1% trypan blue (5 ml/kg) in isotonic sodium chloride solution [1], injected intravenously 5 min before decapitation, in the peritoneal washings. The washings were obtained by irrigating the peritoneal cavity with 5 ml of isotonic sodium chloride solution containing 5 U/ml heparin. The concentration of the dye in the washings was determined on a KFK-2 photoelectric colorimeter at a wavelength of 590 nm (after deduction of a figure for turbidity of the exudate, determined at 400 nm). The peritoneal MC were disintegrated 10 days before reproduction of peritonitis by intraperitoneal injection of 10 ml/100 g body weight of sterile distilled water [1, 4]. Leukopenia was induced by a single intravenous injection of 0.75 mg/kg of vinblastine sulfate (Richter, Hungary) 4 days before reproduction of peritonitis [15].

EXPERIMENTAL RESULTS

The increase in vascular permeability (VP) of the peritoneal cavity in rats during the natural development of inflammation was phasic in character and included immediate and delayed phases (Fig. 1). The immediate phase was observed in the first 15 min after reproduction of peritonitis. Toward the 30th minute VP was appreciably reduced, but was nevertheless higher than initially. The delayed phase reached a peak toward 5 h, and VP returned to normal by the 5th day.

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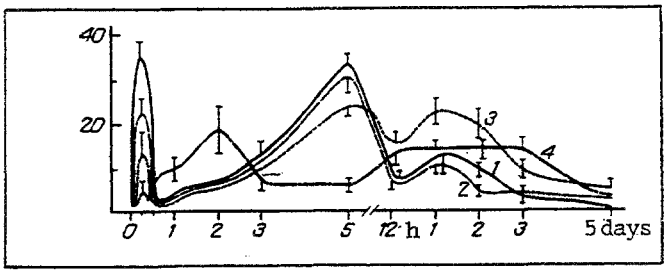

Fig. 1. Permeability of peritoneal vessels of rats during development of acute infectious peritonitis under natural conditions of inflammation (1) and during its development against the background of isolated removal of mast cells (2) and leukocytes (3), and their combined removal (4). Abscissa, time after reproduction of inflammation; ordinate: concentration of trypan blue in peritoneal washings $\cdot 10^{-6}$ g/ml.

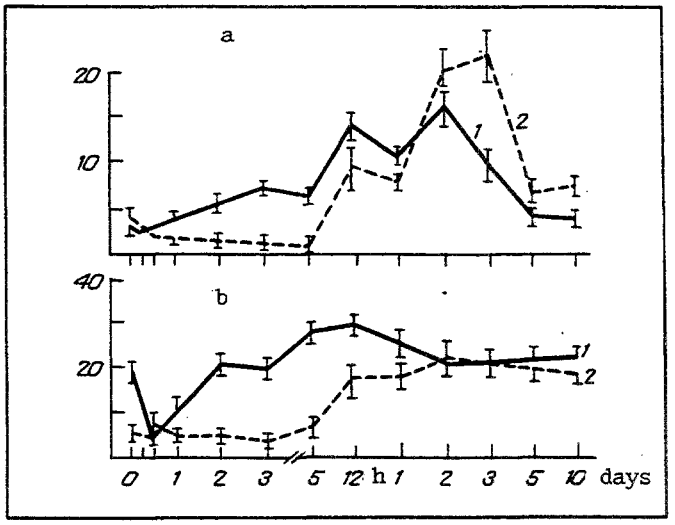

Fig. 2. Number of leukocytes in peritoneal cavity (a) and peripheral blood (b) of rats in course of acute infectious peritonitis under natural conditions of inflammation (1) and during its development against the background of leukopenia (2). Abscissa: time after reproduction of inflammation; ordinate: total number of leukocytes in peritoneal cavity, $\cdot 10^7$ (a) and in peripheral blood, $\cdot 10^9$/liter (b).

Removal of MC considerably inhibited the growth of VP in the intermediate phase. At the 15th minute VP was 37.7% lower than under natural conditions of inflammation. Removal of MC had a weaker effect in the delayed phase, delaying the end of exudation. At the 5th day VP still remained higher than during the ordinary course of inflammation (by almost 4 times).

Leukopenia also significantly inhibited the increase of VP in the immediate phase: VP increased only fourfold compared with initially, and was 2.6 times less than during the natural course of inflammation. In addition, leukopenia disturbed VP in the delayed phase. For instance, in the period of its peak in this phase (5 h) VP was 27.6% lower than in the ordinary course of inflammation. Meanwhile, in subsequent periods of peritonitis it exceeded values observed during the natural development of inflammation. This predominance of VP coincided with an excess of the usual number of leukocytes in the focus found in inflammation and a considerable increase in their number in the blood (Fig. 2), probably as a result of double stimulation of hematopoiesis in connection with inflammation and with the action of vinblastine, which is characterized by leukocytosis (Fig. 3) on the 6th day (corresponding to the 2nd day of peritonitis). On the 5th day VP did not differ significantly from the initial value, although it remained higher (by 11 times) than normal.

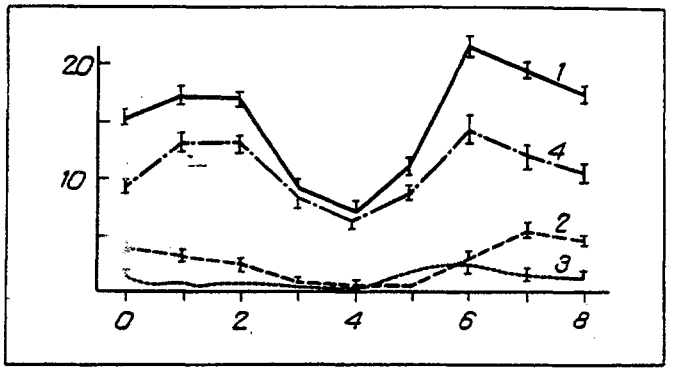

Fig. 3. Leukocyte count in peripheral blood of rats at different times after single intravenous injection of vinblastine sulfate (0.75 mg/kg). Abscissa: time after injection of vinblastine (in days); ordinate: total leukocyte count (1), number of polymorphonuclear leukocytes (2), monocytes (3), and lymphocytes (4) – $\cdot 10^9$/liter.

Combined removal of MC and leukocytes had the greatest effect on VP. It not only inhibited the degree of excess of VP, but also sharply disturbed its kinetics throughout the period of the exudative phase of inflammation. Two unusual peaks of VP were observed – with maxima at 2 h and 12 h — 3 days, probably reflecting changes in the immediate and delayed phases. On the 5th day VP had virtually returned to its initial level, although it still remained higher than normal (by 7 times).

Removal of MC was thus reflected chiefly as inhibition of the degree of elevation of VP in the immediate phase, evidence of the role of MC in the disturbance of VP mainly during this period. Leukopenia affected both the immediate and the delayed phases, indicating that leukocytes have an influence on the rise of VP throughout the exudative phase of inflammation. Meanwhile, after isolated removal of MC or of leukocytes the general principles of the change in VP, characteristic of the natural course of inflammation, were preserved. At the same time, the combined removal of these cells radically altered the whole kinetics of VP, by delaying the development of the immediate and delayed phases of the increase in VP.

These results are evidence that under natural conditions of inflammation MC interact with leukocytes against VP. The experiments showed that histamine and serotonin, in vitro, acting through their specific receptors on the surface of the leukocytes and a change in relations between cyclic nucleotides in the cells, can modulate different functions (chemotaxis, chemokinesis, degranulation, free radical formation) of the leukocytes and, in turn, leukocytic factors can control degranulation of MC and release of mediator-modulators. Considering that both types of cells release biologically active substances, capable of directly raising VP, and independent of one another in their action on the endothelium [3], it can be tentatively suggested that interaction of MC with leukocytes is based mainly on mutual regulation of the formation of their products. It seems that the MC – leukocytes tandem may play an essential role in the cooperative regulation of VP under normal conditions and may behave as a relatively autonomous and self-regulated component of the mediator system, also characterized as a whole by self-regulation [2], during inflammation.

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PLASMA ALDOSTERONE AND ELECTROLYTE LEVELS IN THE MYOCARDIUM OF RATS WITH ACUTE ALCOHOL INTOXICATION AFTER A SINGLE PHYSICAL LOADING TEST (SPLT)

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KEY WORDS: acute alcohol intoxication; single physical loading test; mineralocorticoid function of the adrenals

The modifying effect of ethanol on neuroendocrine regulation and on ionic homeostasis in vivo is confirmed by many investigations [2, 9]. Meanwhile information on the trend of these changes is extremely contradictory. This applies also to the mineralocorticoid function of the adrenals, especially in the late period after acute alcohol intoxication. To assess the functional reserves of these systems physical loading tests have been used [4, 5, 8], but there have been only solitary studies of electrolyte metabolism [3] and the aldosterone concentration in the recovery period [11]. This aspect, nevertheless, is particularly important for a comprehensive analysis both of endocrine-metabolic reactions and of the state of the cardiovascular system in response to loading tests in the late period after alcoholic excess.

The aim of this investigation was to study the time course of the plasma aldosterone and electrolyte concentrations in response to SPLT 14 days after acute alcohol intoxication, and also the coefficient of distribution of Na^+, K^+, Ca^{2+}, and Mg^{2+} between the plasma and myocardium, and the ECG parameters under experimental conditions.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-210 g, receiving 40° ethanol intraperitoneally in a dose of LD_{25}. Intact rats (IR) served as the control. On the 14th day an SPLT was carried out, involving running on a treadmill with free choice of load. The speed of movement of the treadmill was 16 m/min. Blood plasma and myocardium were sampled before and 1, 3, 6, 12, and 24 h after SPLT. The plasma aldosterone concentration (PAC) was measured by radioimmunoassay using commercial kits from the firm "Sorin" (France). Concentrations of K^+, Na^+, Ca^{2+}, and Mg^{2+} in blood plasma and myocardium were determined on a Hitachi 180-80 atomic absorption spectrophotometer. The coefficient of distribution K^+pl/K^+m, Na^+pl/Na^+m, $Ca^{2+}pl/Ca^{2+}m$, and $Mg^{2+}pl/Mg^{2+}m$ represented the ratios of plasma and myocardial concentrations of the electrolytes. The ECG was recorded in six standard leads on a "Kardiolux-300T" electrocardiograph (Yugoslavia), after which HR and the durations of the PQ, QRS, and QT intervals were measured. The results were subjected to analysis by standard statistical programs, using Student's test.

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