FUNCTIONAL STATE OF THE HISTAMINE–HISTAMINASE SYSTEM IN THE COURSE OF EXPERIMENTAL ACUTE PANCREATITIS

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The role of neurohumoral factors and hormones in the pathogenesis of many diseases and, in particular, of inflammatory processes, is evident. When analyzing the role of serotoninergic structures [1], of the sympathicoadrenal complex [3], and of steroid hormones [2] in these processes, we were naturally interested in the degree of participation of the histamine–histaminase system in an inflammatory process in the pancreas. The role of histamine as the local mediator of inflammation has been a topic for discussion for a long time. Numerous investigations have shown that histamine may be one of the chief mediators in the early stages of inflammation. It activates the vascular endothelium locally for taking up colloidal particles. The neutralizing effect of antihistamines confirms the specific role of histamine in the inflammatory process.

The aim of this investigation was to study the state of the histamine–histaminase system in the course of experimental acute pancreatitis.

EXPERIMENTAL METHOD

Experiments were carried out on 150 male rats. The histamine concentration was determined by the method in [11] and histaminase activity by the method in [4]. Intact animals, undergoing a mock operation, and experimental animals, on the 1st, 3rd, 7th, 14th, and 28th-30th days of the disease served as test objects. Pancreatitis was produced by a modified method of Malkhasyan, et al. [5], by cooling the pancreas with ethyl chloride (under ether anesthesia), which was followed by the development of pancreatic necrosis. The data were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

Definite changes in the histamine concentration in the test tissues were found in experimental pancreatitis. In the acute period of the disease the severest metabolic disturbances took place in the organs (Table 1).

The early stages of the disease, associated with ether anesthesia and the after-effects of stress (fixation of the animals), are characterized by a disturbance of physiological equilibrium in the histamine–histaminase system in tissues of the brain and myocardium. For instance, the first day of the disease was characterized by a parallel fall in the histamine level in the brain by almost 1.7 times and of histaminase activity by 1.8 times compared with the initial value. By the 3rd day a tendency was observed for the ratios of the hormone concentration and enzyme activity to be restored, and this process continued throughout the inflammatory process (Table 2). Elevation of the free histamine level in tissues of the brain and myocardium, and restoration of its initial level in the liver are regular features of acute pancreatitis [7, 12]. Intensified histamine formation may be observed when histamine decarboxylase activity is raised and histaminase activity lowered.

On the basis of these results the pattern of changes in the system of histamine release and binding in experimental acute pancreatitis can be represented as follows. On the first days of development of pancreatitis humoral decompensation is accompanied by a fall in histamine concentration and a parallel fall in histaminase activity. In the course of development

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TABLE 1. Histamine Concentration in Tissues of Rats (in μg/g) with Experimental Pancreatitis

Tissue	Intact rats	Duration of pancreatitis, days							
		1		3		7		14	28
		mock operation	experiment	mock operation	experiment	mock operation	experiment	mock operation	experiment
Brain	0,306±0,026	0,163±0,08	0,175±0,009	0,33±0,023	0,254±0,006	0,27±0,02	0,166±0,008	0,186±0,007	0,93±0,06
p		<0,001	<0,001	<0,001	<0,001	<0,02	<0,001	<0,001	<0,001
Myocardium	2,86±0,15	2,3±0,21	1,41±0,06	4,31±0,11	3,581±0,25	1,96±0,03	1,584±0,04	2,14±0,21	3,498±0,11
p		<0,02	<0,001	<0,01	<0,02, but >0,05	<0,001	<0,001	0,02	<0,01, but >0,001
Liver	1,52±0,1	0,57±0,02	0,479±0,92	0,61±0,007	0,511±0,008	0,31±0,02	0,191±0,002	0,36±0,02	1,476±0,05
p		<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	>0,001, but <0,01

TABLE 2. Histaminase Activity in Tissues (in μg histamine/g tissue) of Animals with Experimental Pancreatitis

Tissue	Intact rats	Duration of pancreatitis, days							
		1		3		7		14	28
		mock operation	experiment	mock operation	experiment	mock operation	experiment	mock operation	experiment
Brain	24,8±1,104	11,2±0,6	13,9±0,044	19,1±0	13,4±0,95	18,2±0	29,5±1,776	24,8±0,8	10,7±1,1
p		<0,01	<0,001	0,02	<0,001	0,05	0,02	<0,001	<0,001
Myocardium	32,7±0,43	25,0±0	18,7±4,5	23,0±0	11,5±0,56	16,25±2,61	27,7±2,15	14,2±1,2	20,31±2,2
p		<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001
Liver	22,6±1,72	30,0±0	37,5±1,25	28,0±0	30,02±1,07	28,0±0	32,01±2,28	28,76±1,04	11,9±1,8
p		>0,001, but <0,01	>0,001, but <0,01	0,02	<0,001	<0,05	<0,001	<0,01	<0,01

of the process, the disturbed relationships between histamine concentration and histaminase activity are restored. According to data in the literature, bound histamine is found in the myocardium, and in the presence of a high noradrenalin level, its concentration falls until it disappears completely through breakdown of the inactive histamine–protein complex with conversion into the active state [6, 8]. Data obtained previously on experimental pancreatitis showed that the noradrenalin concentration in the myocardial tissue by the 30th day exceeds the adrenalin concentration by almost 18 times. This fact is in agreement with data in the literature and proves the existence of a definite relationship between the noradrenalin and histamine concentrations and it confirms functional antagonism between histamine and adrenalin in experimental acute pancreatitis.

We know that under the influence of inflammatory stimuli on tissues, permeability factors are released (histamine, serotonin, kinins). In research in recent years the role of biologically active substances in pancreatitis has been revealed. These substances can induce pain, can disturb vascular permeability, and give rise to hemodynamic changes and so on, at different stages of acute pancreatitis; disturbance of permeability, moreover, is induced by definite concentrations of histamine. Concentrations of histamine and serotonin in the blood of patients with cholecystopancreatitis depend on the severity of the pathological process. Investigations in this field have led to the practical conclusion that antihistamine drugs must be given. No clear data on the blood histamine and serotonin levels in patients with pancreatitis are available, for they depend on the form and phase of the pathological process. The increase in the histamine concentration in the acute period aggravates the circulatory disturbance and thereby contributes to the development of the pathological process in the pancreas and in the body as a whole.

The mechanism of histamine release from the mast cells is similar to the mechanism of secretion of mediators and hormones, for like noradrenalin and serotonin, histamine can be regarded as a specific mediator. We know that cell membrane depolarization is the trigger mechanism for mediator release from nerve endings. However, these mechanism have not been studied in mast cells. It has been suggested that histamine release is caused by an antigen or by other degranulating agents as a result of cation exchange [9]. So far as the increase in the histamine concentration in the brain is concerned, the presence of histidine decarboxylase and histamine has been demonstrated in certain nuclei of the rat hypothalamus. By studying the action of compound 48/80 on histamine release, some workers have proved the presence of mast cells in some hypothalamic nuclei, for this compound induces histamine release by 47% [10].

The first day of the disease was thus characterized by the disturbance of equilibrium in the histamine–histaminase system in the brain and myocardial tissues, probably as a result of compensatory and adaptive mechanisms in the inflammatory process. The state of the histamine–histaminase system in experimental acute pancreatitis justifies agreement with recommendations of the use of antihistamine drugs in the treatment of patients, especially in the acute stage of the disease.

LITERATURE CITED

1. B. E. Bagratuni, Zh. Éksp. Klin. Med., No. 2, 30 (1975).
2. B. E. Bagratuni, S. A. Manukyan, and A. V. Tingilyan, Zh. Éksp. Klin. Med., No. 3, 23 (1975).
3. B. E. Bagratuni, Zh. Éksp. Klin. Med., No. 3, 288 (1980).
4. E. E. Goryachenkova, Biokhimiya, 21, No. 2, 247 (1956).
5. V. A. Malkhasyan and P. S. Simavoryan, Éksp. Khir., No. 3, 30 (1972).
6. E. Amundsen, Ann. Chir. Gynaecol. Fenn., 61, No. 5, 251 (1972).
7. M. J. Hughes and I. A. Coret, Am. J. Physiol., 223, No. 5, 1257 (1972).
8. H. Pollard, S. Bischoff, C. Llorens-Cortes, et al., Brain Res., 118, No. 3, 509 (1976).
9. S. M. Rosenthal and H. Tabor, J. Pharmacol. Exp. Ther., 92, No. 1, 425 (1948).
10. T. White, Br. J. Pharmacol., 26, No. 2, 494 (1966).