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CHANGES IN ACTIVITY OF THE HISTAMINE AND SEROTONIN SYSTEMS IN ACUTE MESENTERIC VASCULAR OBSTRUCTION

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Experiments on 24 dogs showed that acute occlusion of the cranial mesenteric artery, depending on its duration, leads to biphasic changes in the activity of the histamine and serotonin systems. In the stage of intestinal ischemia the liberation of histamine and serotonin from mast cells is increased, with activation of enzymes responsible for their inactivation (diamine and monoamine oxidases). In the state of intestinal infarction, the enzyme component of the histamine system is considerably inhibited and serotonin activity reduced as the result of progressive intoxication of the animal by substances of microbial and metabolic genesis.

KEY WORDS: mesenteric vessels; occlusion; histamine; serotonin.

Many investigators [4-6, 11] attach great importance to biologically active substances in the pathogenesis of irreversibility in the case of acute obstruction of the mesenteric vessels. Meanwhile data on the role of vasoactive amines such as histamine and serotonin are few in number and at times contradictory in nature [4, 7, 10]. A shortcoming of many investigations is the absence of information on the dynamics of changes in vasoactive substances in different stages of the disease (ischemia, necrosis of the intestine, peritonitis), and also on dependence of their blood levels on the state of inactivation enzymes.

EXPERIMENTAL METHOD

Considering the comparative rarity of the disease, activity of the histamine and serotonin systems was studied in experiments on 24 adult mongrel dogs of both sexes weighing 10-25 kg. Acute mesenteric vascular obstruction was produced by application of a tourniquet to the trunk of the cranial mesenteric artery (CMA) after laparotomy after intravenous hexobarbital (0.03 g/kg) anesthesia.

The animals were divided into four groups with six dogs in each group. In group 1 (control) the effect of anesthesia, operative trauma, and the prolonged enforced position of the animal on the operating table on indices of histamine and serotonin metabolism was studied. In the three main groups, giving rise to occlusion of CMA of different duration, three successive stages of acute mesenteric vascular obstruction were simulated: The stage of ischemia (3 h), infarction of the intestine (6 h), and peritonitis (12 h of occlusion). Blood for investigation was taken by cannulation of one femoral vein before the operation, 1, 3, 6, and 12 h after the beginning of occlusion, and 60 min after revascularization at each time of occlusion. Activity of the histamine and serotonin systems was judged from the blood concentrations of the amines and activity of their inactivation enzymes in the plasma. The histamine [8] and serotonin [9] levels in the blood were determined fluorometrically. Activity of diamine oxidase (DO) [2] and monoamine oxidase (MAO) [1] was determined from the decrease in the substrate concentration.

EXPERIMENTAL RESULTS

Data showing changes in the activity of the histamine and serotonin systems are given in Tables 1 and 2. No sharp changes in the histamine and serotonin concentration in the systemic blood stream could be found

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TABLE 1. Influence of CMA occlusion on histamine system (M ± m)

Experimental conditions	Histamine, ng/ml					DO, μg substrate/ml/h				
	initial	1 h	3 h	6 h	12 h	initial	1 h	3 h	6 h	12 h
Control	42,9±3,3	41,9±2,8	45,0±5,0	44,4±5,7	33,9±4,6	1,06±0,1	0,73±0,2	0,78±0,2	1,05±0,1	1,16±0,1
Occlusion CMA	37,9±2,8	43,0±4,0	34,3±3,5	39,8±5,5	28,8±3,8	1,34±0,2	1,62±0,2*	1,78±0,3*	0,54±0,1*	0,51±0,05*
Revascularization	—	—	31,7±6,2	37,3±4,7	39,9±7,2	—	—	1,90±0,3*	0,61±0,08	0,63±0,1*

Note. Here and in table 2 asterisk indicates $P < 0.05$ compared to control.

TABLE 2. Influence of CMA occlusion on Serotonin system (M ± m)

Experimental conditions	Serotonin ng/ml					MAO, μg substrate/ml/h				
	initial	1 h	3 h	6 h	12 h	initial	1 h	3 h	6 h	12 h
Control	76,2±14,9	51,6±6,0	59,9±7,1	78,0±8,9	96,5±5,9	1,88±0,3	2,00±0,4	1,99±0,2	1,97±0,4	2,36±0,3
Occlusion CMA	84,4±8,0	73,5±7,3*	89,2±2,2*	69,2±5,7	57,2±6,3*	1,93±0,3	2,75±0,3	4,00±0,3*	2,43±0,3	0,76±0,1*
Revascularization	—	—	76,9±4,3	68,9±8,2	22,6±2,3*	—	—	4,36±0,1*	1,63±0,3	0,33±0,04*

in the control group during the 12 h of the experiment. In experimental animals with acute occlusion of CMA changes in the histamine – DO system of the blood took place mainly on account of DO activity, which increased considerably 3 h after occlusion, and fell sharply later, 6 and 12 h after the beginning of occlusion. It is the enzyme systems of the body which are most sensitive to hypoxia and which are the first to respond to a change in the internal milieu. The fact that an increase in DO activity was not accompanied by a change in the histamine concentration in the systemic blood stream confirms the view that vasoactive amines (histamine, serotonin, bradykinin) act mainly locally, at the site of their formation [3].

At the same time, the possibility likewise cannot be ruled out that the increase in DO activity may have arisen in response to an increase in the blood concentration of putresceine and cadaverine, which also are substrates for oxidative deamination by DO [5]. The progressive fall in activity of the enzyme 6 and 12 h after occlusion of CMA may be an indication of inactivation of enzyme systems. The poor prognostic significance of a fall in DO activity was demonstrated by experiments using aminoguanidine, an inhibitor of DO [5], which led to a considerable decrease in the survival period of animals with acute occlusion of CMA.

Changes in activity of the serotonin system were more marked than those of histamine metabolism. After occlusion of CMA for 3 h an increase was observed both in the serotonin level in the peripheral blood and in the MAO activity compared with the control. Serotonin, like histamine, is known to be contained in mast cells. In response to injury, inflammation, and hypoxia of tissue the process of degranulation of mast cells with liberation of vasoactive substances is intensified [3]. The greater increase in the blood serotonin level in the experimental animals after occlusion of CBA at this period compared with the control, in the writers' opinion, can be attributed more to the effect of progressive hypoxia of the exsanguinated cat than to stimulation of the vagus nerve [10], for exposure to the latter factor also was present in the control. The increase in MAO activity was most probably an adaptive reaction of the animal in response to an increase in substrate concentration.

The gradual fall in the blood serotonin level between the 6th and 12th hour of occlusion evidently took place in connection with ischemic necrosis of the intestine and weakening of the function of the serotonin-forming enterochromaffin cells. Changes in enzyme structure under the influence of ischemic toxemia could have been the cause of the decrease in activity of MAO and also of DO at this period.

During revascularization changes were observed only in the serotonin system after occlusion of CMA for 12 h. They were manifested as a fall in the blood concentration of the amine itself and of its inactivation enzyme. Death of the experimental animals began to occur 10-15 min after restoration of the mesenteric arterial blood flow, in the presence of signs of severe hypotension and progressive cardiovascular weakness.

As a result of analysis of these data two phases could be distinguished in the dynamics of the changes in activity of the histamine and serotonin systems: initial (occlusion of CMA for 1-3 h) and later (6-12 h). In the first phase, parallel with progression of intestinal ischemia there was an increase in the liberation of histamine and serotonin from the mast cells, with activation of their inactivated enzyme (DO and MAO), resembling a defensive reaction of the animal. The development of irreversible changes (infarction of the intestine) led to considerable inhibition of the enzymic component of the histamine system and to a decrease in the activity of the serotonin system, caused by progressive intoxication of the animal by substances of microbial and metabolic genesis.

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