Histamine-Dependent Changes in Free Radical Processes during Coronary Heart Disease

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Histamine is involved in the pathogenesis of coronary heart disease, intensifies generation of reactive oxygen species by blood leukocytes, and causes mobilization followed by exhaustion of antioxidant reserves. The prooxidant effect of histamine on free radical processes in patients with coronary heart disease determines the rate of recurrences and is associated with poorer prognosis and more severe course of the disease.

Key Words: *free radical processes; coronary heart disease; histamine*

General biological mechanisms, including free radical processes and antioxidant protection in the body, underlie the pathogenesis of various diseases. Reactive oxygen species (ROS) produced by leukocytes play a key role in the development of coronary heart disease (CHD) and other pathological processes [5, 6,15]. Histamine is a key inflammatory mediator released from basophils and mast cells in the myocardium and coronary arteries under the influence of ROS and involved in the pathogenesis of CHD [1, 10,12]. Histamine modulates cardiac conduction and coronary vascular tone and potentiates the release of catecholamines from the wall of coronary vessels [1, 7]. The count of histamine-sensitive blood cells increases with the rise in histamine concentration during CHD [2].

The effects of histamine on free radical processes in patients with CHD and other diseases are poorly understood. Some authors showed that histamine dose-dependently inhibits ROS generation by leukocytes under normal and pathological conditions [13,14], while others reported that this compound possesses considerable prooxidant activity [8].

MATERIALS AND METHODS

We examined 43 patients with CHD (23 men and 20 women). The age of patients was 41-79 years (average age 59.8±2.4 years). The diagnosis of CHD was made using standard criteria [3]. There were patients with stable angina pectoris of classes II (n=15, 35%), III (n= 12, 28%), and IV (n=11, 25%) and unstable angina pectoris (n=5, 12%). The control group included 42 healthy donors.

The intensity of ROS generation by leukocytes from heparinized venous blood was measured on a Wallak 1251 chemiluminometer. The leukocyte suspension (0.3 ml, 2500 cells/μl) was incubated with 0.04 ml histamine (final concentration 1.17×10^{-6} M), 0.04 ml saturated isosmotic aqueous solution of luminol (pH 7.35), and 0.2 ml 1% SiO_2. Control cells were incubated with 0.85% NaCl. The intensity of leukocyte chemiluminescence (ILC, mV/sec) and reaction of leukocytes to histamine (RL, %) were evaluated [4]. Plasma content of malonic dialdehyde (MDA) [9] and its total antioxidant state (TAS) were measured [11]. Some plasma samples (0.5 ml) were incubated with 0.02 ml histamine in a final concentration of 5×10^{-8} M for 15 min.

RESULTS

In CHD patients intensification of free radical processes was accompanied by inactivation of the plasma antioxidant system. In the acute stage of CHD, ILC 2.17-fold surpassed the control (p<0.001). In these patients plasma MDA content increased by 1.57 times (p<0.05), while TAS decreased by 1.17

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TABLE 1. Free Radical Processes in Patients with CHD (*M*±*m*)

Parameter	Healthy donors (*n*=42)	CHD patients	
		acute stage (*n*=43)	remission (*n*=29)
ILC, mV/sec	598.2±55.4	1296.0±152.0*	734.3±71.9+
MDA, μM	4.25±0.09	6.69±0.38**	4.50±0.31
TAS, μM	1.30±0.07	1.11±0.05**	1.24±0.05

Note. Here and in Table 2: *p<0.001 and **p<0.05 compared to healthy donors; +p<0.01 compared to the acute stage.

times (p<0.05). During remission these parameters tended to normal. ILC and MDA level decreased 1.76- (p<0.05) and 1.19-fold, respectively, while TAS increased 1.12-fold (Table 1).

In CHD patients and healthy donors histamine induced 2 types of chemiluminescence responses (Table 2). In the majority of donors and 60% patients with CHD histamine produced an antioxidant effect and inhibited ROS generation. In patients with CHD, RL was 2.08-fold lower than in healthy donors (p<0.01). In CHD patients ILC 2.12-fold surpassed the control (p<0.001). The prooxidant effect of histamine was observed in 40% CHD patients. In these patients RL 1.46-fold surpassed that in healthy donors, while ILC after incubation with histamine increased by 1.51 times (p<0.01).

The antioxidant effect of histamine was most typical of patients with angina pectoris functional class II and III (57 and 23% patients with histamine-induced antioxidant changes, respectively). However, antioxidant activity of histamine was observed only in 5 and 15% patients with unstable angina and class IV angina pectoris, respectively. By contrast, histamine produced a prooxidant effect in most patients with unstable angina and class IV angina pectoris (25 and 50% patients with histamine-induced prooxidant changes, respectively). Prooxidant activity of histamine was observed only in 8 and 17% patients with angina pectoris functional class II and III, respectively. These results indicate that the prooxidant effect of histamine and suppression of ROS generation by leukocytes were more often observed in patients with severe CHD.

During remission parameters of chemiluminescence tended to normal. Antioxidant activity of histamine was observed in 64% patients with CHD. ILC and RL decreased by 1.92 (p<0.01) and 1.73 times (p<0.05), respectively. Histamine produced a prooxidant effect in 36% CHD patients in remission. ILC decreased by 1.33 times.

In all healthy donors histamine decreased TAS from 1.30±0.07 to 1.13±0.05 μM (p=0.064). However, in 31% patients with CHD histamine increased TAS from 1.05±0.05 to 1.34±0.06 μM (p<0.01). Probably, under pathological conditions histamine activates the antioxidant system due to mobilization of its reserve capacities.

Previous studies showed that in CHD patients various factors intensify free radical processes even under ischemic and hypoxic conditions. This is associated with accumulation of NADPH and xanthine oxidase in ischemic cells and tissues (intensification of ATP catabolism), accumulation of catecholamines and epinephrine oxidation into adrenochrome. These changes promote superoxide anion formation and intensify generation of other ROS [6]. Initiation of free radical processes is related to intensive ROS generation by activated leukocytes, particularly, during suppression of the antioxidant system [5].

Our results and published data indicate that histamine is involved in the pathogenesis of CHD. Histamine produces the direct effect on the myocardium and coronary vessels, intensifies ROS generation by blood leukocytes, and causes mobilization followed by exhaustion of antioxidant reserves. This

TABLE 2. Antioxidant (A) and Prooxidant (P) Effects of Histamine on ROS Generation by Leukocytes from Patients with CHD (*M*±*m*)

Parameter	Healthy donors		CHD patients	
	A (*n*=23, 72%)	P (*n*=9, 28%)	A (*n*=18, 60%)	P (*n*=12, 40%)
ILC, mV/sec				
control	556.9±63.3	652.6±29.8	1182.0±117.3*	839.1±109.1
histamine	478.1±66.6	701.2±26.2	1044.0±110.4**	1061.0±108.2**
RL, %	18.7±2.5	5.8±1.1	9.0±1.8**	8.5±2.3

is manifested not only in decreased antioxidant effect of histamine due to desensitization of specific receptors on leukocytes [13], but also in more potent ROS generation by these cells. The prooxidant effect of histamine is probably associated with activation of chemotaxis in neutrophils and eosinophils, which intensively generate ROS and promote the release of histamine [12]. This closes the vicious circle. Moreover, histamine increases catecholamine content, which is followed by oxidation of epinephrine into adrenochrome and production of superoxide anions [6]. Against the background of antioxidant system insufficiency ROS intensify lipid peroxidation. Moreover, ROS attack cell membrane, increase their permeability, play an important role in tissue injuries produced by immune complexes, and potentiate and prolong inflammation [5,15]. The prooxidant effect of histamine on ROS generation by blood leukocytes in CHD patients in remission probably determines the rate of recurrences and is associated with poorer prognosis and more severe course of the disease.

Our results show the effects of histamine on free radical processes and antioxidant system in the body and illustrate new aspects of its pathogenic activity during CHD. These data indicate that chemiluminescence assays should be used to estimate the severity, prognosis, and efficiency of therapy of chronic cardiovascular diseases.

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