Histaminergic Regulation of Smooth Muscles in Rabbit Pulmonary Arteries

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Histaminergic contractile reactions of smooth muscles in rabbit lobar pulmonary arteries were studied using *in vitro* mechanographic technique. Histamine via activation of H-receptors induced a dose-dependent constriction of smooth muscle segments, while endothelium inhibited histamine-induced contractile reactions. Histamine increased sensitivity of smooth muscle cells in pulmonary artery to sodium nitroprusside.

Key Words: *pulmonary arteries; smooth muscles; histamine; endothelium*

Considerable attention is now focused on the regulation of vascular tone in pulmonary circulation [2,4,6]. Smooth muscle cells (SMC) in pulmonary arteries (PA) are responsible for the maintenance of adequate ventilation-perfusion ratio. Disturbances in the ventilation-perfusion relationships are the primary symptom of bronchial asthma and other respiratory pathologies [4,6,7]. It was previously reported that physiological reactions of blood vessels in the pulmonary and systemic circulation differ considerably [2,4].

Histamine, a mediator of immediate type hypersensitivity, plays a key role in the development of atopic bronchospasm episodes [6,7]. Histamine affects airway smooth muscles and simultaneously modulates the tone of pulmonary vessels. Histamine-induced contractile reactions in rabbit PA are of particular interest, because pulmonary vessels are considered as a "shock organ" of anaphylaxis in these animals [4].

Endothelium—smooth muscle interaction is an important mechanism of local regulation of vascular SMC tone [5,9]. Endothelium produces various constrictor and relaxing factors and modulates the contractile responses of SMC induced by various bioactive substances [1,5,8]. In the systemic circulation, the endothelium mediates relaxation of vascular SMC evoked by histaminergic agents [1]. An important role in the mechanisms of endothelium-dependent regulation is played by nitric oxide (NO) [3,8].

Our aim was to study the peculiarities of histaminergic regulation of contractile activity of smooth muscle in rabbit PA and the role of NO in these processes.

MATERIALS AND METHODS

Experiments were performed on ring segments isolated from lobar branches of rabbit PA. The animals were sacrificed by cervical dislocation, the lungs were isolated, and the lobar branches of PA were cut into 2-3-mm-wide rings. In some preparations the endothelium was mechanically removed. The segments were placed in a thermostatically controlled (37°C) chamber perfused with aerated Krebs solution containing (in mM): 120.4 NaCl, 5.9 KCl, 1.2 NaH_2PO_4, 1.2 $MgCl_2$, 11.5 $C_2H_{12}O_6$, 2.8 $CaCl_2$, and 15.5 $NaHCO_3$ (pH 7.35). Precontracting (40 mM KCl) and test solutions (1 nM-100 μM histamine, 10 μM diphenhydramine, 0.1-100 μM sodium nitroprusside) were prepared on the basis of Krebs solution. Mechanical tension (MT) of vascular segments was recorded in a near-isometric regimen on a 6MX1B mechanotron. Relaxation was evaluated as a percent of precontraction amplitude. The data were processed by methods of variation statistics.

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RESULTS

Histamine (10 nM-0.1 μM) induced a dose-dependent constriction of denuded segments of lobar PA branches (Fig. 1). This effect was abolished by H-receptor blocker diphenhydramine (10 μM).

Histamine-induced relaxation of segments isolated from systemic vessels is mediated by endothelium: histamine stimulates production of endothelium-derived relaxing factor (EDRF) [1]. Therefore, in the next experimental series we studied the effect of endothelium on histamine-induced contraction of vascular SMC in rabbit PA.

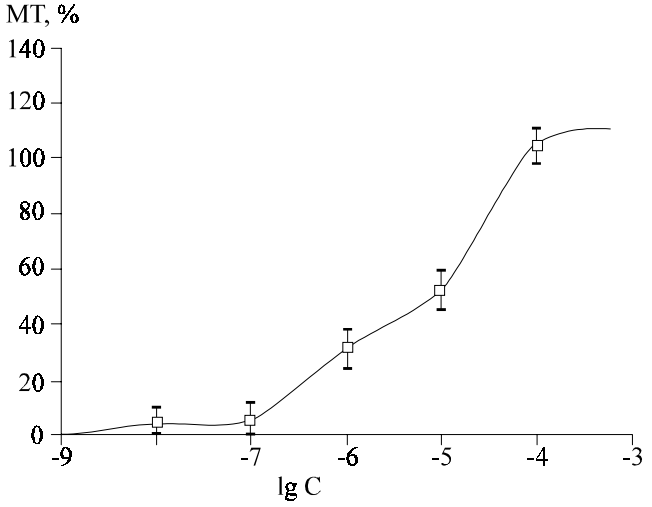

Fig. 1. Mechanical tension (MT) of denuded segments from rabbit pulmonary artery in the presence of various concentration of histamine. Precontraction with high-potassium Krebs solution (40 mM KCl). Here and in Fig. 2: abscissa: logarithm of histamine concentration; ordinate: MT, percent of precontraction amplitude.

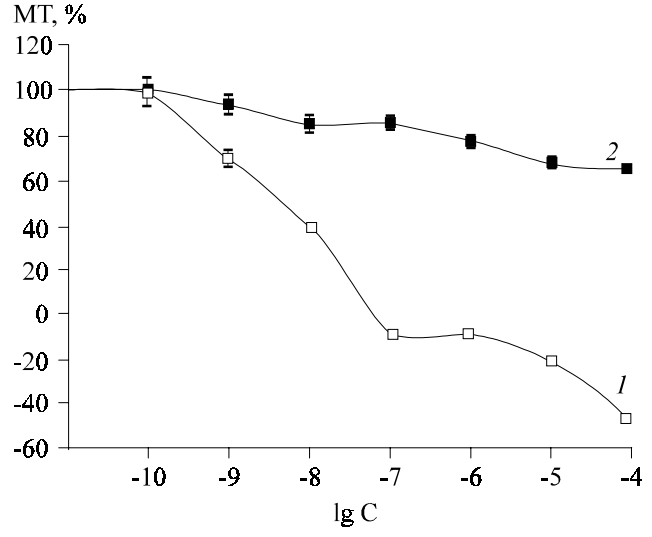

Fig. 2. Mechanical tension (MT) of denuded segments from rabbit pulmonary artery in the presence of various sodium nitroprusside concentrations. Precontraction with (*1*) histamine (45 μM) and (*2*) high-potassium Krebs solution (40 mM KCl).

The amplitude of maximum response of intact PA segments to histamine (10 μM) was 65.2±2.9% (n=21) of potassium-induced contracture (40 mM KCl). After denudation, the maximum contraction amplitude increased to 109.3±3.8% (n=24, p<0.05); EC_{50} decreased from 13.4 to 7.58 μM (p<0.05). Hence, the effect of histamine on pulmonary vessels, similarly to that in systemic vessels is also mediated via enhanced production of endothelium-derived relaxing factor (NO), but the direct contractile effect of histamine on SMC in pulmonary vessels prevails.

The effects of EDRF can be simulated by NO-producing agents activating cytoplasmic guanylate cyclase, *e.g.* sodium nitroprusside. In the next experimental series we studied the effect of sodium nitroprusside on MT of PA segments precontracted with high-potassium Krebs solution (40 mM KCl) and histamine (50 μM).

Sodium nitroprusside produced a more potent relaxing effect on denuded vascular segments precontracted with histamine (Fig. 2). It can be assumed that histamine potentiates the relaxing effect of nitric compounds on SMC in pulmonary vessels. This can be related to a modulating effect of histamine on the guanylate cyclase — cGMP system [10].

Our experiments demonstrated that direct contractile effect of histamine is a specific feature of histaminergic regulation of contractile activity in rabbit PA. The endothelium inhibits histamine-induced contraction of rabbit PA. On the other hand, histamine increases the sensitivity of SMC in rabbit PA to sodium nitroprusside.

The revealed peculiarities of histaminergic regulation of pulmonary vessels are of crucial therapeutic and physiologic importance. Histamine induces bronchial constriction and simultaneously increases the tone of pulmonary vessels, thereby maintaining the ventilation/perfusion ratio [5,9]. However, in severe cases of bronchial asthma, hyperproduction of NO can exert different effects on vascular and bronchial tone [6,7]. This regulatory imbalance can aggravate the course of the disease.

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