Specific Features of Epithelium-Dependent Contractile Reactions of Smooth Muscles in Various Subdivisions of the Respiratory Tract

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Characteristic features of the endothelium-dependent smooth muscle contractile reactions to various physiologically active substances modulating adrenergic, cholinergic, and histaminergic regulatory systems are studied in rabbit trachea and in secondary and tertiary bronchi. The mechanical tension of the segments was recorded under quasi-isometric conditions. The epithelium was shown to participate in adrenergic regulation of the smooth muscles of the lower subdivisions of the respiratory tract and in the cholinergic regulation of its upper subdivisions. The histaminergic reactions of the smooth muscles in the airways had large amplitude at all levels, but the relaxing contribution of their epithelium was not detected.

Key Words: *epithelium; airways; smooth muscles; contractility; physiologically active substances*

There is ample evidence that respiratory epithelium participates in the control of smooth muscle (SM) contractile activity in the airways [4,6,10]. The state and functional activity of the epithelium strongly influences the contractile responses of SM-segments to catecholamines, cholinomimetic agents, histamine, and other physiologically active substances [5,8,11]. Interaction of these agents with the receptors in the epithelial cell membrane stimulates the synthesis of epithelium-derived relaxing factor which suppresses the contractile activity of SM cells due to activation of guanylate cyclase [3,12].

Although the differences between the epithelium-dependent reactions of SM in the trachea and bronchi have been documented [1], there are few data on participation of the epithelium in local regulation of the airway tone and possible contribution of the interactions between SM and epithelium to the regulation of various subdivisions of the respiratory tract and to the development of pathological reactions in the respiratory system.

Our aim was to study the epithelium-dependent contractile reactions in the SM of rabbit trachea and the 2nd-3rd-order bronchi to various physiologically active substances that modulate adrenergic, cholinergic, and histaminergic regulatory systems.

MATERIALS AND METHODS

Experiments were performed on 15 male Chinchilla rabbits weighing 2.5-3.0 kg. After isolation of the lungs, the trachea, secondary and tertiary bronchi were stripped off the adjacent tissues and cut into 2-3-mm wide ring segments. Epithelium was removed mechanically by rotation of a wooden spatula in the segment lumen.

The segments were placed in a thermostatically, controlled chamber perfused with oxygenated Krebs solution (in μM): NaCl, 120.4; KCl, 5.9; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; $C_2H_{12}O_6$, 11.5; $CaCl_2$, 2.8; $NaHCO_3$, 15.5; pH 7.35, 37°C. The conditional constriction solutions (acetylcholine, 1 μM, histamine, 50 μM) and test

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solutions (epinephrine, 0.01-10 μM, atropine, 0.1-10 μM, dimedrol, 0.01-10 μM) were prepared on the basis of Krebs' solution.

Mechanical tension (MT) of the segments was recorded in a quasi-isometric mode with the help of a 6MX1B mechanotron. Relaxation was evaluated in percentage of the amplitude of conditioning constriction. The data were statistically processed using the variation analysis methods.

RESULTS

In the first series of experiments we studied the cholinergic reactions of respiratory SM with intact or removed epithelium (Fig. 1). Tracheal and bronchial segments contracted conditionally by acetylcholine (1 μM) were relaxed by atropine in a dose-dependent manner. The degree of relaxation was the same in trachea and bronchi, while MT decreased to 9.5±2.6 and 9.0±3.1% of the conditioned contraction amplitude, respectively. The removal of epithelium led to strong inhibition of the relaxation of tracheal segments, MT being decreased only to 23±4%. The cholinergic reactions of bronchial segments did not change.

In the second series of experiments (Fig. 2), the segments were contracted conditionally by histamine (50 μM) and tested with dimedrol (0.01-10 μM). A dose-dependent relaxation was observed in all cases, MT being decreased to 15.4±4.7% and 42.8±3.9% of the initial value for the bronchi and trachea, respectively. The removal of epithelium had no effect on the relaxation of tracheal and bronchial segments.

In the third series of experiments we studied the adrenergic reactions of tracheal and bronchial SM segments. Epinephrine (0.01-10 μM) was applied after conditional contraction induced by histamine or acetylcholine (Fig. 3). Irrespective to the mode of conditional contraction, the segments slightly relaxed in a dose-dependent manner in response to epinephrine. Mechanical tension of intact tracheal segments conditioned by histamine decreased to 45.0±2.6% of the initial value, while in the acetylcholine-conditioned segments it accounted for 57.2±4.1%. The removal of epithelium did not change the adrenergic reactions of tracheal SM.

The segments prepared from the secondary and tertiary bronchi and conditioned by histamine reacted to epinephrine (10 μM) by MT decrease of 31.5±3.8% of the initial value; the corresponding value for acetylcholine-conditioned segments was 25.8±5.5%. In both cases the removal of epithelium inhibited the adrenergic reactions: MT decreased to 57.3±4.2 and 85.4±3.2%, respectively.

The results obtained show that SM cholinergic reactions are pronounced along the entire length of the respiratory tract. However, the epithelium is involved in the cholinergic regulation only in the upper airways. The adrenergic reactions occur predominantly in the lower parts of the respiratory tract. The contribution of epithelium to adrenergic relaxation is pronounced, since its removal decreased relaxation 2-fold. In the trachea the epithelium-dependent adrenergic reactions were observed only in acetylcholine-contracted segments, where the removal of epithelium decreased relaxation by 15%. The histaminergic SM reactions were characterized by high amplitude at all the levels, although they did not demonstrate the epithelium-dependent contribution to relaxation. Presumably, the epithelium participates in the adrenergic regulation of SM in the lower subdivisions of the respiratory tract and in the cholinergic regulation of its upper subdivisions.

Our findings suggest that the specificity of pharmacological sensitivity of the airway SM at various levels of the respiratory tract under normal and pathological [2,6,7] conditions is associated with epithelium-dependent factors. The respiratory epithelium

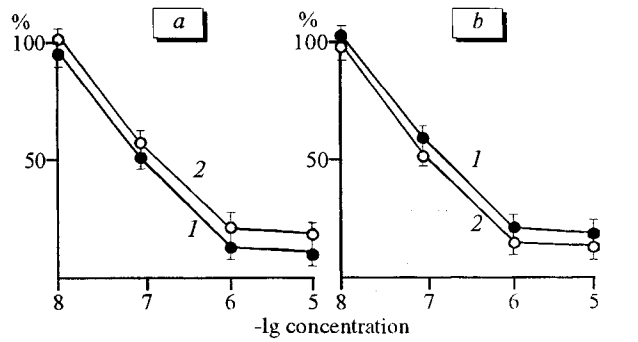

Fig. 1. Dependence of mechanical tension of tracheal (*a*) and bronchial (*b*) segments in rabbits on atropine concentration in the presence of epithelium (*1*) and after its removal (*2*). Conditional contraction by acetylcholine (1 μM). Here and in Figs. 2 and 3: amplitude of the response is shown as percentage of the conditional contraction value.

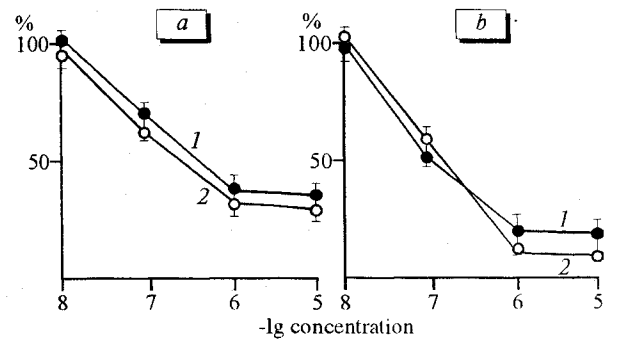

Fig. 2. Dependence of mechanical tension of tracheal (*a*) and bronchial (*b*) segments in rabbits on dimedrolum concentration in the presence of epithelium (*1*) and after its removal (*2*). Conditional contraction by histamine (50 μM).

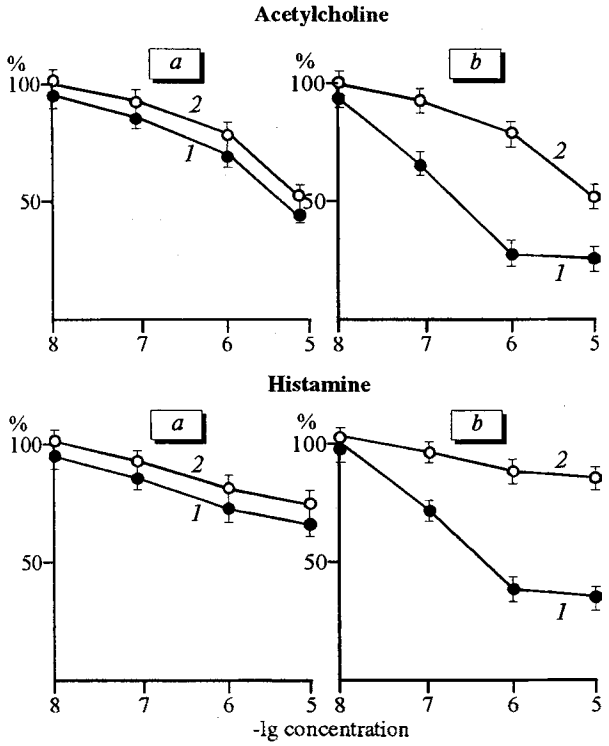

Fig. 3. Dependence of mechanical tension of (*a*) tracheal and (*b*) bronchial segments in rabbits on epinephrine concentration (*1*) in the presence of epithelium and (*2*) after its removal. Conditional contraction by acetylcholine (1 μM) and histamine (50 μM).

may play a key role in the local regulation of the airway tone, while its inflammatory-allergic disturbances may lead to the imbalance of the regulatory processes and to inadequate SM reactions to hormones, transmitters, and pharmacological agents.

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