BIOPHYSICS AND BIOCHEMISTRY

Mechanisms Responsible for the Resistance of Tracheal Smooth Muscle to Histamine in Rats

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A mechanographic study of contractile responses by tracheal smooth muscle segments of rats to a histaminergic agent showed that intact segments did not respond to histamine in the concentrations used (0.01-10 μM), whereas depolarized segments responded to histamine by dose-dependent contractions which were considerably enhanced following mechanical removal of the tracheal epithelium.

Key Words: *trachea; smooth muscle; histamine*

Heightened reactivity of the bronchi is an important pathogenic mechanism of obstructive lung disease [9-11]. Among the mediators of bronchospasm, a leading role is played by histamine. Activation of histamine receptors results in the exit of calcium to the cytosol and in muscular contraction. This is a characteristic feature of bronchial smooth muscle cells (SMC) in rabbits and guinea pigs [5,9], in which bronchospastic responses of allergic or inflammatory origin are readily inducible [6].

In rats, however, it is virtually impossible to produce bronchospasm by any means. This phenomenon has attracted the attention of many investigators, but has not received a uniquely interpretable explanation [6,9,11].

We focused on the observation that tracheal SMC do not respond by contraction to histamine in either physiological or supraphysiological concentrations [5], even though histamine receptors are abundant on the membranes of these cells.

The purpose of the present study was to examine the mechanisms responsible for the resistance of rat tracheal SMC to histaminergic agents.

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MATERIALS AND METHODS

Circular segments 3-4 mm wide prepared from the lower parts of tracheas of random-bred male rats were placed in a thermostatically controlled chamber containing a continuously aerated Krebs solution of the following composition (mM): 120.4 NaCl, 5.0 KCl, 1.2 $MgCl_2$, 2.5 $CaCl_2$, 1.2 NaH_2PO_4, 15.5 HEPES, and 11.5 glucose (pH 7.35, 37°C). This solution was changed every 10 min. In some rats, the tracheal epithelium was removed mechanically [12]. Contractile activity was recorded with a mechanotron under near-isometric conditions. Mechanical tension was estimated in percent of the contractile response to a hyperpotassic (40 mM KCl) Krebs solution.

RESULTS

The first series of tests was designed to assess the effect of histamine on the tracheal segments. As shown in Fig. 1, these segments failed to respond to histamine in concentrations of 0.01 to 10 μM, but did respond in a dose-dependent manner when 40 mM KCl were present in the solution. The

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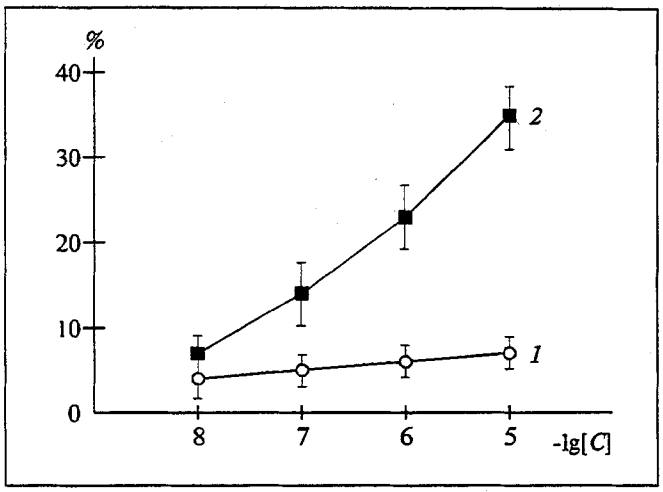

Fig. 1. Mechanical tension of rat tracheal segments plotted against histamine concentration in the bathing solution in the absence (*1*) and presence (*2*) of 40 mM KCl. Contractile responses of the segments were estimated in percent of the response to the hyperpotassic Krebs solution (40 mM KCl).

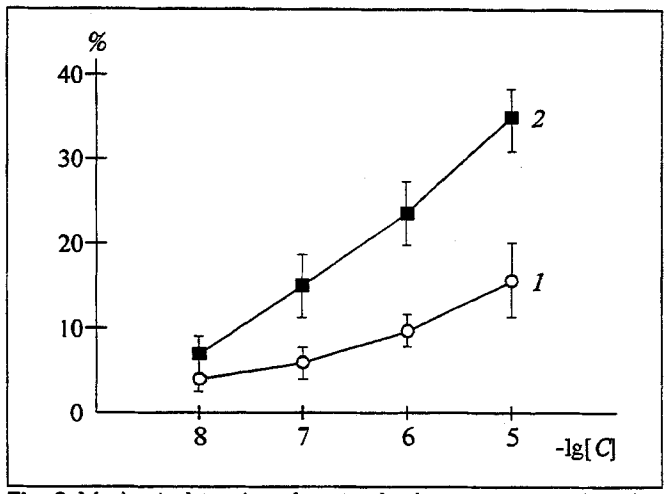

Fig. 2. Mechanical tension of rat tracheal segments as a function of histamine concentration in the bathing solution in the presence of 40 mM KCl before (*1*) and after (*2*) the removal of epithelium. Contractile responses were estimated in percent of the response to the hyperpotassic Krebs solution (40 mM KCl).

principal mechanism by which histamine elicits contraction of SMC is activation of the histamine receptor-operated sarcolemmic ion channels [5]. Presumably, the calcium channels coupled to the histamine receptors of rat tracheal SMC become capable of being activated only after the cell membranes have been depolarized. This hypothesis is supported by the reported effects of membrane potentials on the histamine receptor-operated calcium entry into SMC and on the magnitude of contractile responses by these cells to certain mediators [1,3,8].

In the second test series, we investigated the role of tracheal epithelium in histaminergic responses by SMC and found that their contractile responses to histamine (0.01-10 μM) were significantly increased after mechanical removal of the epithelium (Fig. 2).

Tracheal epithelium can produce a relaxing factor similar in nature to the endothelial factor of blood vessels [2,13,14], and this factor also appears to play a role in reducing the susceptibility of SMC to constricting agents.

The results of this study suggest, first, that two mechanisms are involved in making SMC of the rat trachea resistant to histaminergic agents. These mechanisms are closely associated with the dependence of the histamine receptor-operated calcium entry into these cells on the membrane potential. The smooth muscles of the airways are tonic muscles incapable of generating action potentials, which is why intact SMC do not respond to histaminergic agents. Second, the findings suggest that the tracheal epithelium exerts a relaxing influence on the SMC. The relaxing factor continuously produced by this epithelium inhibits the contractile responses of SMC to any agents.

The two mechanisms outlined above are probably responsible for the absence of bronchospastic reactions of allergic nature in rats.

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