In vivo and in vitro Studies on Alpha-receptors in Human Airways; Potentiation with Bacterial Endotoxins*

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The increased responsiveness of the airway caliber-regulating system seen in asthmatics may be due to increased sensitivity of the afferent nerve endings, ie the irritant receptors, or of the smooth bronchial muscle receptors. Szentivanyi has proposed a theory of functional beta-receptor blockade as a cause of airway obstruction in disease. A possible alpha-receptor stimulation would then cause bronchoconstriction. Studies in animals have shown the presence of alpha-receptors in the airway muscles; in Groningen in 1969 we gave a preliminary report on the first simultaneous evidence in vivo and in vitro of the presence of bronchoconstricting alpha-receptors in human bronchial muscle.2

We have studied the effect in vivo of cholinergic blockade, adrenergic beta-blockade and alpha stimulation in 15 patients, most with airway ob-

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atropine. After blockade of the beta-receptors and the vagal reflex, metaoxedrine induced a decrease of Gaw in all but two subjects. The mean Gaw between the study after propranolol and the study after metaoxedrine was 0.17 (l/s)cm H₂O (P<0.01).

There was no difference in effect of metaoxedrine on Gaw at high and low lung volumes. The drug effects were identical in two subjects with reversed test sequence; both showed significant bronchoconstriction after inhalation of metaoxedrine, breaking an upward trend after atropine.

Results in vitro

The in vitro studies were performed on specimens of segmental bronchi of 3-5 mm diameter obtained from patients undergoing operation for lung tumor. Preparations with a breadth of 5-10 mm and length of about 15 mm were then mounted in plastic holders according to Lundholm and Mohme-Lundholm.° Tension changes of the circular muscle layer were measured with a Statham transducer on a Grass polygraph. The muscle was suspended in a buffer solution at 37° C and the various drugs were tested after adequate flushing of the preparations.

The alpha-mediated bronchoconstriction was studied after treatment with a lipo-poly saccharide-endotoxin from Escherichia coli (Difco). The method described by Kakiuchi and Rall was used to measure the effect of added endotoxin on the concentrations of cyclic 3'5' AMP.

Metaoxedrine alone did not cause any contraction, but when the muscle was pre-treated with the beta-blocker sotalol we obtained a slight contraction which increased with increasing doses of metaoxedrine. After the addition of bacterial endotoxin, the constricting effect of metaoxedrine increased two to ten times in muscles from nonobstructive patients. In preparation from a patient with chronic bronchitis, endotoxin potentiated the alpha-mediated constriction more than 1000 times (Fig 1). The endotoxin also increased sensitivity to histamine. The addition of endotoxin to the muscle preparations from three patients with normal bronchi decreased the amount of cyclic AMP more than 60 percent.

Endotoxin lowered the concentrations of CAMP in the bronchial muscles, which can explain the potentiation of the alpha-receptor mediated contraction. The lowering can be due to either a reduction of the adeny1 cyclase activity (decreased synthesis of CAMP) or to an activation of phosphodiesterase (increased breakdown of CAMP); both would potentiate the muscle-contracting effect. 6

If endotoxin can potentiate the 1-mediated bronchial contractility also in vivo, this might explain the increased tendency to airway constriction seen in connection with bronchial infections.

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