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### Research Article

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# Comparative Responses of Tracheal Spirals and Parenchymal Strips to Histamine and Carbachol In Vitro

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**ABSTRACT** The responses of isolated guinea pig tracheal spirals and parenchymal strips to histamine and carbachol were compared. The parenchymal strip, a  $1.5 \times 1.5 \times 20$ -mm strip cut from the periphery of the lung, constricted at a lower dose and had a larger maximal response to histamine than to carbachol. In contrast, the response of the tracheal spiral to equimolar doses of histamine or carbachol was the same. The responsiveness of both muscle strips to histamine was decreased by treatment with the  $H_1$  receptor antagonist mepyramine ( $0.1 \mu\text{M}$ ), and the response to carbachol was blocked by treatment with atropine ( $0.1 \mu\text{M}$ ). Indomethacin ( $3 \mu\text{M}$ ), cimetidine ( $1 \mu\text{M}$ ), propranolol ( $10 \mu\text{M}$ ), and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) ( $4 \mu\text{M}$ ) did not alter the differential response of the two strips to histamine and carbachol. The differential response of parenchymal strips with many, few, or no conducting airways and blood vessels was identical, suggesting that the contractile element is alveolar duct smooth muscle or alveolar contractile elements. This differential pharmacologic response in vitro is consistent with the in vivo observation that histamine causes more peripheral airway constriction than does acetylcholine.

## INTRODUCTION

The broncho-active agents, histamine and acetylcholine, evoke different patterns of pulmonary response in vivo. For example, when these agents are infused intravenously in the anesthetized, vagotomized cat, histamine results in predominantly peripheral airway constriction as evidenced by a marked fall in dynamic compliance with only minor increases in pulmonary resistance (1). On the basis of these differential physiologic changes in pulmonary resistance and dynamic compliance, it was suggested that the peripheral airways were more responsive to histamine

than acetylcholine. These inferences were strengthened by the direct observation of preferential small airway constriction after histamine exposure in frozen lung sections (1). In comparison, acetylcholine in the same preparation had its major effects on the central airways as evidenced by an increase in pulmonary resistance at doses which did not alter static or dynamic compliance (1). On the basis of similar differential mechanical changes observed in the unanesthetized, atropinized guinea pig (2), we postulated a similar difference in the direct large and small airway effects in this animal. The differential effects of histamine and acetylcholine may result from differences in the uptake, distribution, and metabolism of these drugs, or there may be a difference in the sensitivity of smooth muscle from varying loci in the lung to the constrictive effects of these agents. To evaluate this latter possibility we have studied the comparative contractility of a tracheal spiral and an isolated parenchymal strip from the guinea pig.

## METHODS

Male Hartley-strain guinea pigs, 300–350 g body wt, were killed by cervical dislocation and exsanguination. The thorax was opened and the heart, lungs, and trachea removed en bloc. The trachea from the larynx to the carina was cut spirally (3) and suspended in a bath of Tyrode's solution (4) at  $37^\circ\text{C}$ . The solution was continuously gassed with 95% oxygen and 5% carbon dioxide. The lower end of the trachea was fixed to a support in the bath while the upper end was attached by a thread to a motion transducer (Harvard Apparatus, Millis, Mass., model 386) under a force of 2 g. A strip of subpleural parenchyma,  $\sim 1.5$  mm square and 20 mm long, was cut from the right lower lobe and suspended under a force of 200 mg in a bath similar to that used for the trachea. After 60 min, appropriate concentrations of drugs were added to the bath and allowed to contact the tissue for 1–3 min until a steady response was obtained. In initial experiments, it was determined that similar responses were obtained if the tissues were allowed to relax between addition of various concentrations of agonists or if the agonists were added cumulatively, the latter technique was adopted for routine use. After each dose-response curve, the tissues were allowed to relax until they returned to their initial length. All contractions are reported as a percent of the maximal contraction observed by that tissue

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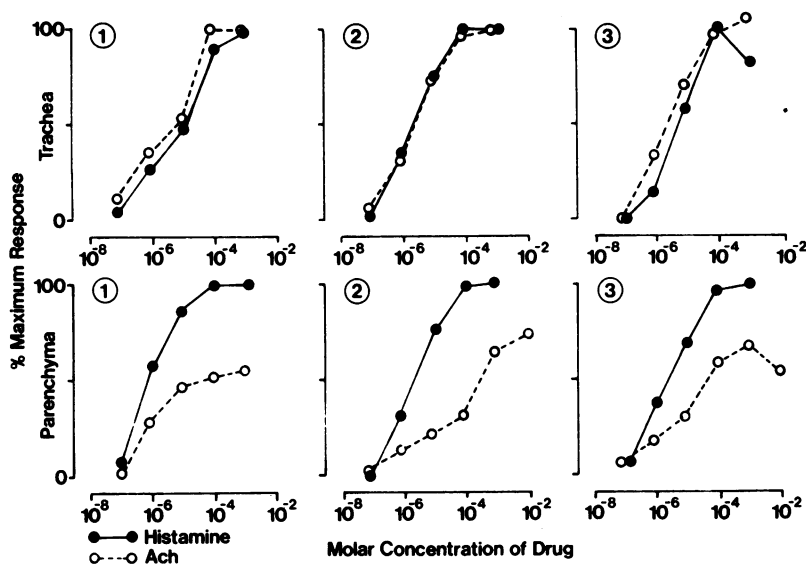


FIGURE 1 Effects of histamine and acetylcholine (Ach) on tracheal spirals (upper panels) and parenchymal strips (lower panels). The results of three separate experiments are presented. Responses are plotted as a percent of the maximum histamine response in a given tissue.

strip to the maximal concentration (1,000–100  $\mu\text{M}$ ) of histamine.

In some experiments, parenchymal strips were used which were  $\sim 0.5$  mm square and 20 mm in length, or 0.2 mm square and 10 mm in length. The 0.5 mm square strips were cut from the pleural edge of the thicker parenchymal strips described above and contracted in a fashion similar to the thicker parenchymal strips. The 0.2 mm square strips were also cut from the pleural edge of the thick strips. The 0.2 mm square strips were studied isometrically with an initial force of 150 mg. In these experiments, a force transducer (Grass Instrument Co., Quincy, Mass., model FT03 C) was used.

In some experiments, parenchymal strips were placed in 10% neutral buffered formalin immediately after completion of an experimental run and processed as outlined below. After fixation, the tissues were embedded in glycol methacrylate (5). Serial sections, 2  $\mu\text{m}$  thick, were cut on a microtome (Ivan Sorvall, Inc., Norwalk, Conn., model JB-4) with glass knives. Every 10th section was stained with hematoxylin/eosin-toluidine blue (6). These sections were examined by light microscopy with a 0.25 mm<sup>2</sup>-reticule, and serial reconstructions were made to scale.

The drugs used in this study were acetylcholine chloride, carbamylcholine (carbachol), histamine diphosphate, atropine sulphate, indomethacin, L-phenylephrine HCl, propranolol HCl (Sigma Chemical Co., St. Louis, Mo.), mepyramine maleate (K & K Laboratories, Plainview, N. Y.), *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)<sup>1</sup> (Aldrich Chemical Co., Inc., Milwaukee, Wis.), and cimetidine (kind gift of Mr. John Paul, Smith Kline & French Laboratories, Philadelphia, Pa.). Drugs were prepared freshly on the day of use and, except as noted, diluted in Tyrode's buffer to an appropriate concentration immediately before use. Indomethacin (10 mg/ml) was prepared in absolute ethanol, and EEDQ (3 mg/ml) was prepared in 10% ethanol-90% Propylene Glycol before dilution in Tyrode's buffer. The amounts of the solvents

<sup>1</sup>Abbreviation used in this paper: EEDQ, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.

carried over in the appropriate dilutions had no effect on the histamine or carbachol-induced contractions *in vitro*.

## RESULTS

The comparative responses of isolated tracheal spirals and parenchymal strips to histamine and acetylcholine are shown in Fig. 1. In each experiment the tracheal spiral showed a similar contractile response to equimolar doses of histamine or acetylcholine. In contrast, the parenchymal strip in each experiment responded at a lower molar dose and had a greater maximal response to histamine compared to acetylcholine. Because this difference in response may have been caused by acetylcholine degradation in the parenchymal strip, further experiments were carried out with carbamylcholine.

The comparative responses (mean of five experiments) of isolated tracheal spirals and parenchymal strips (1.5 mm square and 20 mm long) to carbachol and histamine are shown in Fig. 2. The maximal contraction of the parenchymal strip to carbachol was obtained at a bath concentration of 700  $\mu\text{M}$ ; at this concentration the contraction was only 65% of that achieved by the maximally effective dose of histamine, 90  $\mu\text{M}$ . The concentration of histamine required to produce a one-half maximal contraction was 1  $\mu\text{M}$ , 80-fold less than the molar concentration of carbachol to produce a one-half maximal contraction. The tracheal spirals did not demonstrate a differential response to histamine and carbachol. Maximal responses occurring at 100  $\mu\text{M}$  and one-half maximal responses at 3  $\mu\text{M}$  with both agonists (Fig. 2).

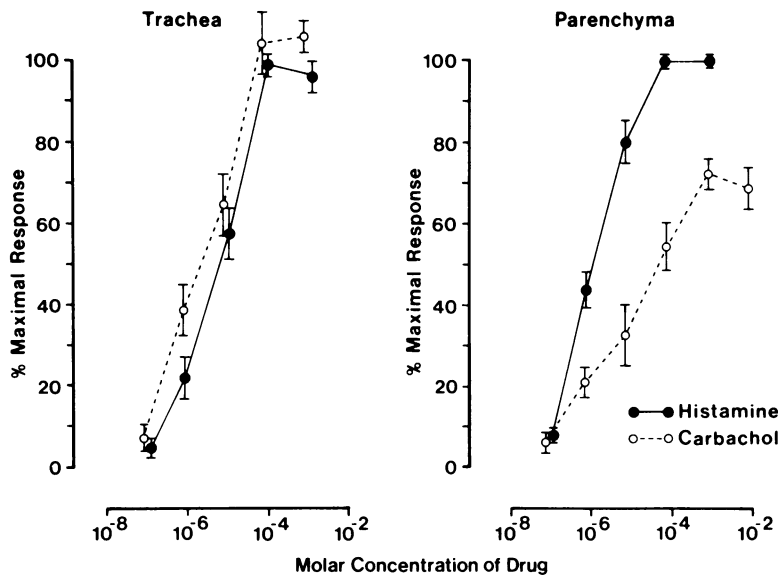


FIGURE 2 Mean ( $n = 5$ ) comparative response of guinea pig tracheal spirals and parenchymal strips to histamine and carbachol. Responses are plotted as a percent of the maximum histamine response in a given tissue. Vertical bars represent  $\pm 1$  SEM.

The pharmacologic specificity of the tracheal and parenchymal strip contraction was determined by testing the responses of both tissue strips to histamine and carbachol before and after addition of the  $H_1$  receptor antagonist, mepyramine maleate ( $0.1 \mu M$ ), and atropine ( $0.1 \mu M$ ). These antagonists had no effect on the resting tone of either strip. Mepyramine maleate ( $0.1 \mu M$ ) did not alter the response of the trachea or parenchyma to carbachol, although it shifted the dose-response curve of the tracheal spiral and parenchymal strip by 30- and 400-fold, respectively (Fig. 3). Atropine sulfate ( $0.1 \mu M$ ) shifted the dose-response curves of the trachea and parenchyma to carbachol 600- and 800-fold, respectively (Fig. 4). Atropine also had a minor antihistamine effect resulting in about an 8- to 10-fold shift of both the tracheal and parenchymal dose-response curves (Fig. 4).

The responses of the tracheal and parenchymal strips to histamine and carbachol were further evaluated to determine if secondarily released prostaglandins or catecholamines altered tissue responses, and for the absence of  $H_2$  receptors by treatment with indomethacin ( $3 \mu M$ ), propranolol ( $10 \mu M$ ), EEDQ (an alpha receptor antagonist) ( $4 \mu M$ ), and cimetidine ( $1 \mu M$ ). The concentrations of indomethacin and cimetidine were chosen on the basis of previously published reports (7, 8). The concentrations of propranolol and EEDQ used caused a 300- to 1,000-fold decrease in the sensitivity of the tracheal spirals or parenchymal strips to the effects of isoproterenol and phenylephrine, respectively.<sup>2</sup>

<sup>2</sup> Unpublished observations.

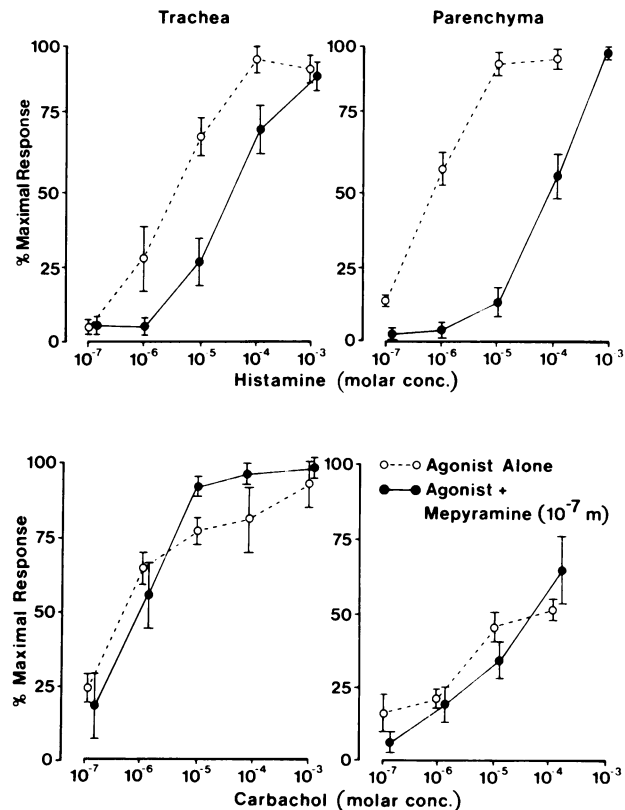


FIGURE 3 Mean ( $n = 4$ ) effects of mepyramine maleate ( $10^{-7} M$ ) on the response of the trachea and parenchyma to histamine and carbachol. Mepyramine blocked the response to histamine but did not significantly alter the response to carbachol. Vertical bars equal 1 SEM.

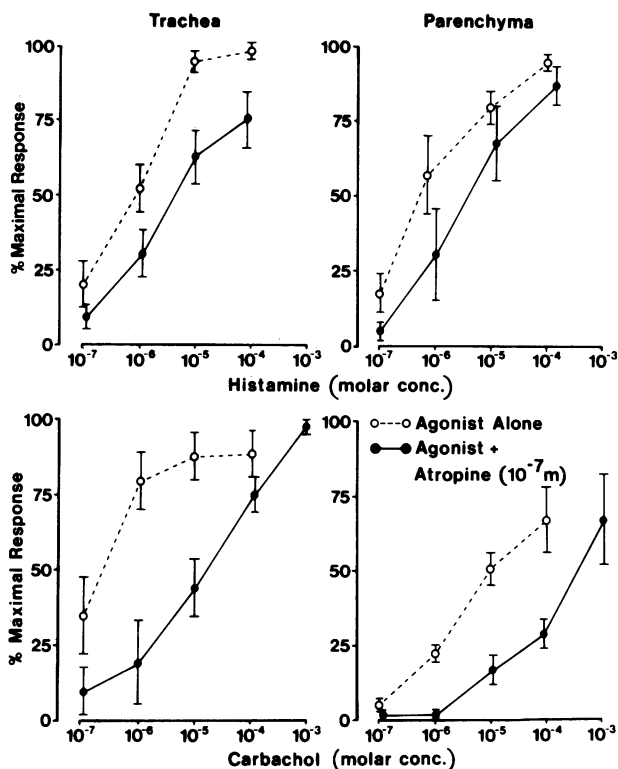


FIGURE 4 Mean ( $n = 4$ ) effects of atropine ( $10^{-7}M$ ) on the response of the trachea and parenchyma to histamine and carbachol. Atropine diminished the response to carbachol by 600–800-fold and the response to histamine 8–10-fold. Vertical bars equal 1 SEM.

Strips were allowed to incubate with the antagonists for at least 60 min before exposure to various agonists. In four experiments, indomethacin slightly enhanced the tracheal response to both histamine and carbachol but did not alter the parenchymal response to these agents. In four experiments with each of the antagonists, propranolol, EEDQ, and cimetidine, the response of both tissue strips to histamine and carbachol was not significantly altered, Table I.

To determine if the conducting blood vessels and airways in the parenchymal strip significantly effected the contractile response of the strip as a whole, the responses of three different thicknesses of parenchymal strips (five experiments with each type) were compared (Fig. 5). Regardless of whether the tissue strips were 1.5 mm square and 20 mm long, 0.5 mm square and 20 mm long, or 0.2 mm square and 10 mm long, all strips demonstrated the same relative responsiveness to histamine and carbachol. The relative content of conducting airways and blood vessels in each of the different types of strips was determined from examination of histological sections. Representative reconstructions of the various tissue strips from serial sections are shown in Fig. 6. The relative density of conducting

airways and blood vessels in each of the three tissue strips was markedly different. In the 1.5 mm-square strip, conducting airways and blood vessels were numerous; in the 0.5 mm-square strip, there were few, and in the 0.2 mm-square strips, no such structures could be found.

## DISCUSSION

We have demonstrated that an *in vitro* parenchymal strip from the guinea pig is more sensitive (responds at a lower dose) and has a greater maximum response to histamine than to acetylcholine or carbachol. In contrast, a central airway strip (tracheal spiral) from this animal responded similarly to equimolar concentrations of both of these agents. These findings provide *in vitro* support for interpretations made by analysis of differential changes in pulmonary resistance and dynamic compliance in the unanesthetized guinea pig (2), and suggest that comparison of responses of tracheal and parenchymal contractility may be a useful *in vitro* technique to determine the relative pharmacologic sensitivity of the peripheral airways and air spaces as compared to central airways.

To compare the relative responses of tracheal and parenchymal strips, we normalized the contractions obtained with each agent to the maximal contraction obtained by each strip to histamine. In this manner, the assessment of responsiveness was not influenced by the amount or orientation of the contractile elements, but rather by the differential activity of the contractile elements to pharmacologic agents. The pharmacologic nature of the parenchymal and tracheal histamine receptors was demonstrated to be  $H_1$  by selective blockade of the histamine response with an  $H_1$  class antihistamine, mepyramine maleate, and the carbachol response with atropine (Figs. 3 and 4). Mepyramine had no significant anticholinergic effects, whereas atropine had minor antihistamine effects on both the trachea and parenchyma as shown in Fig. 4. The dose ratios for the antihistaminic effects of atropine were 40–150-fold smaller than the effects of the antagonists in blocking their primary receptors. These antihistaminic effects of atropine are of similar magnitude as have been reported by previous investigators with other tissue preparations (9, 10).

A possible explanation of the diminished response to carbachol compared to histamine in the parenchymal strip is that during processing the parenchymal strip is exposed to endogenous acetylcholine and thus becomes tachyphylactic to muscarinic stimulation. This seems unlikely because the parenchymal strips do not demonstrate tachyphylaxis to acetylcholine or histamine in our experimental protocol, and do not have resting histaminergic or cholinergic tone as evidenced by the lack of initial relaxation with atropine or mepyramine.

TABLE I  
Effects of Antagonists on the Contractile Response of Tracheal Spirals and Parenchymal Strips to Histamine and Carbachol

Concentration	Cimetidine		Propranolol		EEDQ		Indomethacin	
	Control	Drug	Control	Drug	Control	Drug	Control	Drug
$\mu\text{M}$								
Trachea								
Histamine								
0.1	2/1	1/1	6/5	3/1	5/4	7/4	3/1	2/3
1	23/10	15/10	36/14	26/10	34/11	42/21	21/9	21/12
10	70/12	80/30	74/5	74/2	75/7	90/24	75/15	93/9
100	100/—	114/14	99/1	103/4	100/—	109/15	100/—	118/15
Carbachol								
0.1	18/15	11/7	20/7	10/4	18/11	25/10	15/8	33/17
1	63/18	65/12	71/7	52/8	64/20	85/5	64/12	66/14
10	82/16	89/7	96/9	81/18	90/22	111/11	87/8	108/4
100	88/14	98/3	114/10	102/22	105/19	131/12	92/12	115/3
Parenchyma								
Histamine								
0.1	10/5	10/6	7/7	3/1	11/5	13/5	8/7	16/9
1	42/16	59/18	41/29	25/16	46/11	46/11	43/14	31/11
10	72/8	205/79	71/18	61/18	74/10	72/15	76/16	63/7
100	100/—	260/119	99/2	91/13	100/—	84/14	100/—	97/7
Carbachol								
0.1	3/1	1/1	8/10	8/8	14/6	11/5	5/3	12/14
1	8/2	6/3	18/20	18/16	40/5	36/14	15/6	23/12
10	28/8	30/10	31/20	43/27	59/5	54/18	32/12	25/9
100	58/21	56/9	47/17	54/19	74/4	66/19	64/8	55/15

The maximal response of each tissue strip to histamine before the addition of antagonists was assigned a value of 100 and other responses scored on that basis. Values shown are the mean/SE for four experiments done with each agent.

To test the hypothesis that the differential responses to histamine and carbachol might be in part a result of prostaglandins synthesized and released during contraction of the strips (7, 11), to local adrenergic mechanisms (12), or differential populations of  $H_1$  and  $H_2$  receptors (13, 14), the strips were contracted with histamine and carbachol before and after addition of indomethacin, propranolol, EEDQ, or cimetidine. Indomethacin had no effect on the differential response of the two strips, suggesting that prostaglandins (synthesized by prostaglandin synthetase during contraction) are not responsible for the differential activity to histamine and carbachol. The  $\alpha$  and  $\beta$  receptor antagonists, EEDQ and propranolol, did not alter the responses of the trachea or the parenchymal strip to histamine and carbachol, suggesting that local catecholamine release, as demonstrated in the chick intestine (12), does not account for the observed differential response. The  $H_2$  receptor antagonist cimetidine had no significant effect on the response of

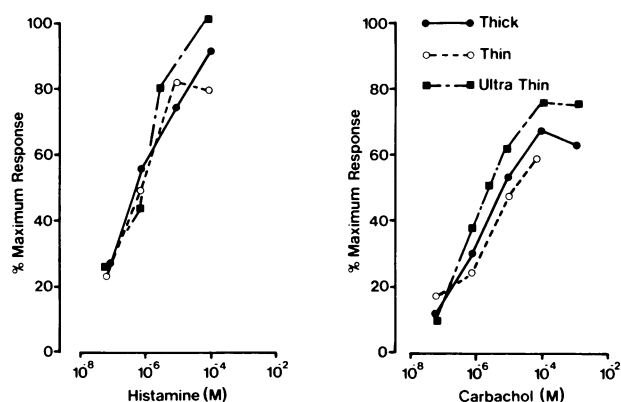


FIGURE 5 Comparative responses of parenchymal strips of varying dimensions and composition. Thick strips (1.5 mm square and 20 mm in length), thin strips (0.5 mm square and 20 mm in length), and ultra thin strips (0.2 mm square and 10 mm in length), had similar responses to histamine and carbachol. Each curve represents the mean of five experiments with each type of strip.

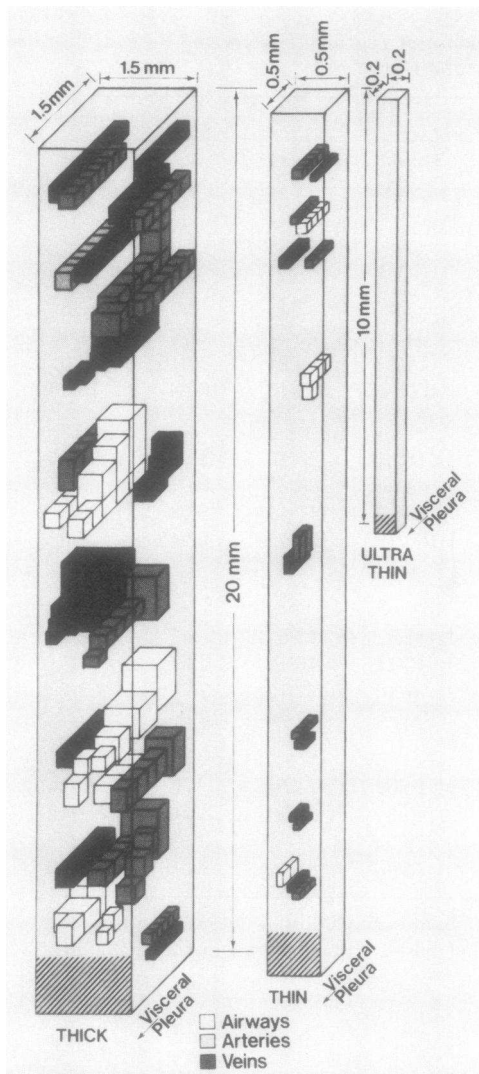


FIGURE 6 Representative reconstructions of thick, thin, and ultra thin strips from histological sections. The thin strips were cut from the pleural surface of a thick strip. See text for details.

the tissues to histamine and carbachol, suggesting the  $H_2$  receptors present in the two tissues in differing amounts cannot account for the observed responses. Thus, the greater sensitivity to histamine, as compared to carbachol, of the parenchymal strip most probably represents an intrinsic property of the contractile tissue itself rather than a response to local adrenergic modulating factors to locally synthesized prostaglandins, or to different populations of  $H_1$  and  $H_2$  receptors.

Another possible explanation of the differential response to histamine and carbachol is that histamine may contract the alveolar duct smooth muscle and vascular smooth muscle in the parenchymal strip, whereas carbachol may contract the alveolar duct smooth muscle but relax vascular smooth muscle, thus

resulting in the observed response in the strip as a whole. To test this hypothesis and to obtain a better idea of the tissue type actually responsible for the contraction of the parenchymal strip, the contractile responses of strips with varying amounts of identifiable conducting airways and blood vessels were compared (Figs. 5 and 6). In each of the tissue strips, the differential sensitivity to carbachol and histamine was evident (Fig. 5) even though the strips contained markedly different quantities of identifiable conducting airways and blood vessels (Fig. 6). All of the strips contained large quantities of alveolar duct smooth muscle, which is abundant in the guinea pig (15). Because of the similar response to pharmacologic agents observed with the markedly different composition of the parenchymal strips, it seems reasonable to assume that alveolar duct smooth muscle or alveolar contractile elements (16) were responsible for the parenchymal strip contraction.

Previous investigators have noted different responses to pharmacologic agents in smooth muscle obtained from large and small airways of a variety of species. Golla and Symes (17) demonstrated that tracheal and bronchiolar smooth muscle from the cat had different responses to adrenaline, tyramine, and nicotine. Somlyo and Somlyo (18) demonstrated that tracheal smooth muscle from the rabbit was more responsive to acetylcholine than to histamine, although bronchiolar smooth muscle strips were equally responsive. Fleish and Calkins (19) confirmed Somlyo and Somlyo's (18) finding and also examined the effects of a variety of agonists including prostaglandins, bradykinin, and serotonin. In the guinea pig, Persson and Eckman (20) demonstrated that tracheal spirals and 1 mm-diameter airways had similar responses to histamine and acetylcholine. Although the authors did not specifically state the location and airway type examined, comparison with the morphometric data presented by Kliment (21) suggest that this probably represented a second or third generation bronchus (lobar or segmental). According to Kliment (21), in the guinea pig there is a mean of 12 airway branchings to the periphery. Thus, although the airways studied by Persson and Eckman were physically small compared to the trachea, they probably represented central rather than peripheral airways. Thus, Persson and Eckman's data (20) demonstrate the similarity of responses of tracheal and second or third generation airway smooth muscle to histamine and acetylcholine. In this study the differences found between tracheal and parenchymal strips suggest that there is an intrinsic difference in the pharmacologic response between central airway (trachea and first two to three generations) smooth muscle and parenchymal contractile elements to histamine and carbachol.

Other investigators have studied the properties of parenchymal strips. Kapaneci et al. (16) demonstrated

cells in alveolar septa which contracted when epinephrine was placed in the bathing fluid. Their studies demonstrated that the parenchyma may contain contractile elements which are not simple smooth muscle. Lulich, et al. (22) used a cat lung strip similar to the guinea pig parenchymal strip described in this report. They noted different responses of the parenchymal strip and trachea to histamine but did not compare the differential effects of carbachol and histamine. Although they postulated that the contractile elements were in the parenchyma and not in conducting airways or blood vessels, they did not attempt to validate this by histologic techniques. Thus, the present results are consonant with their findings but extend them by virtue of the histologic demonstration that conducting airways and blood vessels are not responsible for the contractions and by demonstrating the differential sensitivity to carbachol and histamine.

Currently, peripheral airway function can only be assessed *in vivo* by inference through the comparison of differential changes in various tests of pulmonary function. On the basis of such an analysis, it has been suggested that the peripheral airways are more sensitive to histamine than to acetylcholine (1). In this report we provide evidence *in vitro* which supports this *in vivo* prediction by comparing the relative responses of tracheal spirals and parenchymal strips to histamine and carbachol. These results suggest that the parenchymal strip *in vitro* reflects peripheral airway function *in vivo* and may be a useful preparation in which to directly examine the effects of various bronchoactive agents on the lung periphery.

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