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Role of Endogenous Histamine in Altered Lung Mechanics in Rabbits

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Background: **Unlike the effects of exogenous histamine, those of endogenous histamine on the lung mechanics have not yet been characterized. The site of endogenous histamine liberation by mivacurium was determined, as were the effects of this histamine on the airway and parenchymal mechanics in control rabbits (group C) and rabbits pretreated with H1 and H2 receptor blockers (group AH). The effectiveness of the receptor blockade was ensured by challenges with exogenous histamine.**

Methods: **Pulmonary input impedance at low frequencies (ZL) was measured in anesthetized mechanically ventilated open-chest rabbits under control conditions and every minute after administration of an intravenous bolus of mivacurium (2 mg/kg) and exogenous histamine (10 μg/kg). Histamine levels were determined in serum samples taken from the carotid artery and jugular vein before and 1, 3, and 6 min after mivacurium injection. Parameters of airway resistance (Raw) and inertance and parenchymal damping (G) and elastance (H) were extracted from ZL spectra.**

Results: **Mivacurium induced significant increases in plasma histamine levels, with the venous concentrations being significantly higher than those in the artery. The mivacurium-induced increase in Raw (28.7 ± 2.3%; mean ± SD) in group C was significantly higher than that in group AH (6.6 ± 3.4%), whereas the responses in G were not inhibited significantly (23.9 ± 6.9% *vs.* 15.5 ± 3.0%). The significant increases in Raw (70.6 ± 12.6%) and G (21.0 ± 4.9%) after exogenous histamine administration were virtually completely abolished by antihistamine pretreatment (3.6 ± 3.7% and 0.3 ± 2.6%).**

Conclusions: **After mivacurium administration, endogenous histamine is liberated at least partly in the systemic circulation, and it induces primarily a heterogeneous airway constriction with minor changes in the parenchymal properties. This response was considerably reduced but not abolished by antihistamine pretreatment, a circumstance suggesting that mivacurium may liberate other constrictor mediators that might also contribute to the airway and parenchymal constriction.**

COMPROMISED lung function and subsequent deterioration in gas exchange are frequently observed in the perioperative period. The resulting hypoxia can be observed during the induction and maintenance of anesthesia and also during recovery.[1,2] Various mechanisms are responsible for these adverse effects on the lung mechanics, such as the stimulation of irritant receptors by tracheal intubation[2] or histamine liberation induced by the administration of anesthetic agents.[3–8] Among the anesthetic agents, the myorelaxants are the most potent histamine-releasing drugs,[4–8] and mivacurium has been demonstrated to elevate the plasma histamine level significantly (more than threefold).[8]

Although the effects of exogenous histamine on the mechanical properties of the respiratory system have been well-established,[9–12] the consequences of the endogenous liberation of histamine on the lung mechanics have not been investigated. Estimating airway and parenchymal properties separately is important, as has been demonstrated by many previous investigations,[9–19] because the airway and parenchymal properties respond differently to a constrictor challenge.[9–13,15,16,18,19]

In the current study, therefore, we set out to investigate how endogenous histamine alters the mechanical properties of the airways and the parenchyma separately and to establish whether the histamine is released in the systemic or the pulmonary circulation. To confirm the primary role of endogenous histamine in the altered lung mechanics, the results obtained after the administration of histamine receptor–blocking agents were compared with those obtained with untreated animals. In this regard, the effectiveness of the receptor blockade was ensured by intravenous challenges with exogenous histamine.

Methods

Animal Preparation

After approval by the Animal Care Committee of the Canton of Geneva, 15 adult male Californian white rabbits (2.2–2.6 kg) in the supine position were studied. Anesthesia of the animals was induced by an intramuscular injection of xylazine (5 mg/kg), followed by an intravenous injection of midazolam (1 mg/kg) and xylazine (4 mg/kg) *via* an ear vein. The rabbits were then tracheotomized with a polyethylene cannula (3.5 mm ID; Portex, Hythe, UK) and mechanically ventilated (Model 900C; Siemens-Elema, Upsala, Sweden) with a tidal volume of 9–11 ml/kg at a frequency of 30/min and an inspired oxygen fraction of 0.3 in air. Continuous intravenous infusion of midazolam (1 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (40 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was then started *via* the ear vein and was maintained throughout the study. The femoral artery was prepared surgically in a sterile manner and then cannulated (28-gauge catheter; Braun, Melsungen, Germany) for blood sampling and continuous arterial blood pressure monitoring with a calibrated pres-

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sure transducer (model 156 PC 06-GW2; Honeywell, Zürich, Switzerland). The femoral vein was prepared in the same way as the femoral artery and cannulated for venous blood sampling and for drug delivery. The thorax was opened by means of a midline thoracotomy after an additional intravenous bolus of fentanyl (25 μg/kg), and the ribs were widely retracted. After the chest was opened, a positive end-expiratory pressure of 3 cm H_2O was maintained.

Airway pressure was measured continuously with a calibrated pressure transducer (model DP 45; Validyne, Northridge, CA). Rectal temperature was monitored with a temperature sensor (Thermalert, model TH-8; Physitemp, Clifton, NJ) and was maintained at 37 ± 0.5°C with a heating pad (Miostar, Zürich, Switzerland). Airway and arterial pressures, heart rate, and rectal temperature were displayed and stored at a sampling rate of 50 Hz *via* an analog/digital interface converter (Biopac, Santa Barbara, CA) on a microcomputer.

Arterial blood samples were analyzed radiometrically (model 505; Acid Base Laboratory, Copenhagen, Denmark), and the parameters of mechanical ventilation were adjusted to maintain normal gas exchange if necessary. The concentrations of O_2 and CO_2 were monitored throughout the study (Ultima; Datex/Instrumentarium, Helsinki, Finland).

Impedance Measurements

The measurement system for collection of the input impedance spectra of the rabbit pulmonary system (ZL) was similar to that used previously.[11–14,16] In brief, the tracheal cannula was detached from the respirator and was connected to a loudspeaker-in-box system at end-expiration. The pressure in the box chambers was set to 3 cm H_2O to keep the mean transpulmonary pressure constant during measurements. The loudspeaker delivered a computer-generated small-amplitude (<1 cm H_2O) pseudorandom signal (15 noninteger multiples between 0.5 and 21 Hz) through a screen pneumotachograph (11 mm ID), which was used to measure the tracheal flow ($\dot{V}$). The pressure drop across the screen was measured with a differential pressure transducer (model 33NA002D; ICSensors, Malpitas, CA). An identical pressure transducer was used to measure the tracheal pressure (Ptr) during oscillations *via* a side port of the endotracheal tube.

The signals Ptr and $\dot{V}$ were low-pass filtered (5th-order Butterworth, 25-Hz corner frequency) and sampled with an analog-digital board of another microcomputer at a rate of 256 Hz. Fast Fourier transformation with 4-s time windows and 95% overlapping was used to calculate ZL ($ZL = Ptr/\dot{V}$) from the 10-s recordings. The phase difference between the transducers and their connecting tubing to measure Ptr and $\dot{V}$ was not significant in the applied frequency range; therefore, no correction was necessary.

Separation of Airway and Parenchymal Parameters

To separate the mechanical properties of the airways and the parenchyma, the distinct difference in the frequency dependences of the two compartments at low oscillation frequencies was used.[11–14,16–19] It has been well-established that the airways can be described by a frequency-independent airway resistance (Raw) and inertance (Iaw).[11–14,16–19] In contrast, the parenchymal resistance and reactance have both been shown to decrease roughly inversely with increasing frequency. On the basis of these characteristics, the airway and parenchymal properties were separated by fitting a model incorporating an airway compartment containing Raw and Iaw, in series with a constant-phase tissue model[13] including damping (G) and elastance (H), to the ZL spectra by minimizing the differences between the measured and modeled impedance values:

$$ZL = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), and $\alpha = (2/\pi)\arctan(H/G)$. Impedance data at frequencies coinciding with the heart rate and its harmonics often exhibited poor reproducibility in subsequent measurements under identical experimental conditions and were therefore omitted from the model fitting. The reported Raw and Iaw values were corrected for the resistance and inertance, respectively, of the measurement set-up, including the tracheal cannula.

Study Protocol

The rabbits were randomly assigned to one or other of the following two protocol groups. No pretreatment was performed in one group of rabbits (n = 8), whereas the animals in the second group received antihistamine pretreatment (n = 7) with both H1 (clemastine 1 mg) and H2 (ranitidine 10 mg) receptor blockers administered intravenously 1 h before the measurements. There was no significant difference in body weight between the study groups (2.38 ± 0.13 kg and 2.50 ± 0.09 kg for the rabbits without and with antihistamine pretreatment, respectively).

In both groups of rabbits, the lungs were hyperinflated by superimposing two inspiratory cycles to standardize the volume history. After 4–6 successive baseline ZL recordings, an intravenous bolus of mivacurium (2 mg/kg) was administered. ZL was measured in 1-min intervals until 10 min, followed by impedance measurements every 5 min, up to 25 min after the mivacurium injection.

After the last ZL recording, a recovery period of 30 min was allowed for the rabbits, and another set of baseline ZL recordings was collected. An intravenous bolus of histamine (10 μg/kg) was injected, and five ZL recordings, 1 min apart, were collected.

All technically acceptable ZL data under control con-

ditions were averaged and were fitted by the model. Model parameters obtained from the average of 4–8 ZL spectra during the peak response to mivacurium were used to characterize the lung mechanics under these conditions. Histamine responses were represented by model parameters identified from the peak responses in ZL after administration of the constrictor drug.

Measurement of Histamine Levels in Blood

Arterial and venous blood samples were taken 1, 3, and 6 min after mivacurium administration. Two milliliters of blood was placed into a cold container (EDTA) and immediately centrifuged (900*g* at 4°C for 10 min). Separated plasma was stored at −20°C until assay. Histamine levels in the serum were then determined by enzyme immunoassay (Immunotech, Marseille, France). Histamine concentrations were obtained from bound enzymatic activities and levels were calculated *via* a standard curve obtained with standards supplied with the measurement kit. Reference values were established from blood samples taken from another group of rabbits identical to those involved in the current study but receiving no anesthesia or treatment.

Statistical Analysis

Scatters in the parameters were expressed in SD values. The Kolmogorov-Smirnov test was used to test data for normality. Two-way repeated-measures ANOVA with antihistamine pretreatment as the first variable and administration of mivacurium as the second variable was used to estimate the effects of pretreatment and mivacurium on the mechanical conditions of the lungs. When the changes in the mechanical parameters were expressed as percentage changes from the baseline, the results from the two groups were compared with use of another two-way repeated-measures ANOVA, with the agent (mivacurium or histamine) as the first variable and antihistamine pretreatment as the second variable. A logarithmic transformation was necessary for the plasma histamine levels to comply with normality. Two-way repeated-measures ANOVA, with time as the first variable and either the vein or the artery as the second variable, was then applied to estimate the effects of mivacurium on the plasma histamine levels. The influence of antihistamine pretreatment on the plasma histamine levels was estimated by performance of one-way ANOVA on the relative changes of the log-transformed values. Pairwise comparisons were performed by means of Student-Newman-Keuls multiple-comparison procedures. Statistical tests were carried out with the significance level set at $P < 0.05$.

Results

Plasma histamine levels under control conditions and after mivacurium administration for the two groups of rabbits are demonstrated in figure 1. There was a significant increase in venous plasma histamine levels at 1, 3, and 6 min after mivacurium injection. In the vein, the increased endogenous histamine levels remained elevated throughout the sampling interval, whereas no change was observed in the artery. These levels proved significantly higher than those in the artery. With substantial interindividual variability, the plasma histamine levels of the control rabbits and of those under antihistamine pretreatment, respectively, were comparable with the venous peak levels at 1 min of 1.91 ± 0.2 and 1.66 ± 0.2 ($P = 0.39$) and the corresponding arterial levels of 1.70 ± 0.3 and 1.51 ± 0.2 ($P = 0.66$).

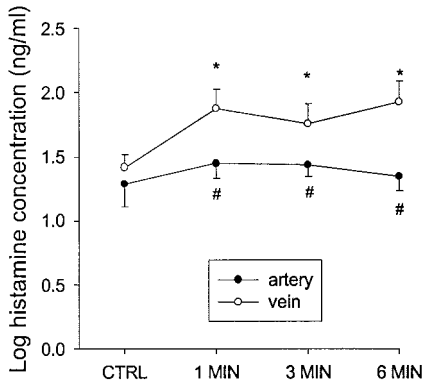

Fig. 1. Logarithms of plasma histamine levels before (CTRL), and 1, 3, and 6 min after the administration of mivacurium. * *P* < 0.05 *versus* CTRL. #*P* < 0.05 between histamine concentrations in the carotid artery and jugular vein.

The real and imaginary parts of ZL and the corresponding model fits under control conditions and after mivacurium and histamine administration in a representative rabbit are illustrated in figure 2. The quasihyperbolic decrease in RL at low frequencies is a consequence of the decreasing contribution of the tissue resistance ($Rti = G/\omega^{\alpha}$), whereas the plateaus at higher frequencies correspond to the flow resistances of the airways. The decreases in RL are mirrored in the increases in XL, reflecting the elastic properties of the parenchyma ($XL_E = EL/j\omega$, where EL is the lung elastance). The linearly increasing inertive component ($XL_I = j\omega Iaw$) dominates the XL data at high frequencies. Mivacurium injection increased RL at all frequencies. The parallel increases in RL indicate marked elevations in Raw, whereas the smaller changes in the frequency dependence of RL suggest an elevated Rti. The smaller changes in low-frequency XL indicate increases in the lung elastance. In general, the administration of exogenous histamine caused qualitatively similar but larger responses in both RL and XL.

Figure 3 depicts the endogenous and exogenous histamine-induced changes in the airway and parenchymal mechanical parameters and the effects of antihistamine pretreatment. Significant increases in Raw and G were observed after administration of both mivacurium and histamine, as confirmed by two-way repeated-measures

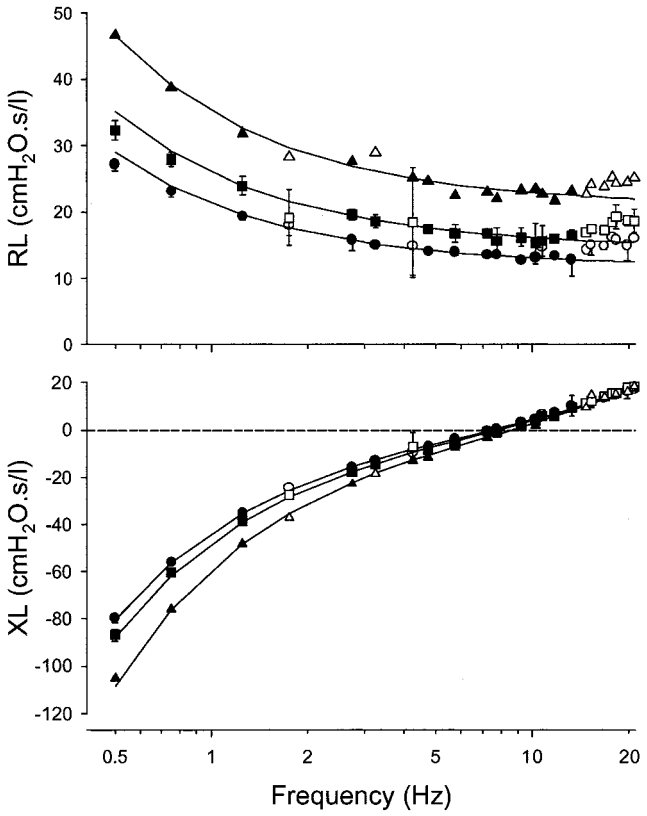

Fig. 2. Real (RL) and imaginary parts (XL) of pulmonary input impedance in a representative rabbit under baseline conditions (circles) and after intravenous administration of mivacurium (squares) and histamine (triangles). Symbols with bars indicate mean ± SD values from 4–6 consecutive measurements. Lines indicate the corresponding model fits. Hollow symbols: data points that were excluded from model fits because of corruption by cardiac artifacts.

ANOVA. The increases in H were statistically significant only after exogenous histamine challenges. Although there was a general tendency toward lower values for lung mechanical parameters for the rabbits participating in antihistamine pretreatment, there was no statistically significant difference between the two groups in the parameters under control conditions. Two-way ANOVA also demonstrated that there was a highly significant interaction between both the mivacurium-induced and histamine-induced responses in Raw and antihistamine pretreatment ($P < 0.00005$ and $P < 0.001$), *i.e.*, the increase in Raw induced by either mivacurium or histamine was significantly inhibited by antihistamine pretreatment. However, antihistamine pretreatment significantly diminished only the increases in G in response to exogenous histamine ($P < 0.005$). Antihistamine pretreatment did not affect the increases induced in Iaw and H by either mivacurium or histamine, and it had no effect on the mivacurium-induced changes in G.

To demonstrate more clearly how the pretreatment of the rabbits with antihistamine inhibited the constrictor response of the lungs, we expressed the parameter changes induced by mivacurium and exogenous histamine as percentage changes from the control values (fig. 4). Two-way ANOVA confirmed that the increase in Raw induced by either mivacurium (28.7 ± 2.3%) or histamine (70.6 ± 12.6%) was markedly and statistically significantly reduced by antihistamine pretreatment (6.6 ± 3.4% and 3.6 ± 3.7%), with increases being statistically significantly different from zero ($P < 0.05$) after mivacurium-induced changes only. In the control group, greater increases in Raw were induced by exogenous histamine than by mivacurium, whereas the changes in Raw after histamine or mivacurium administration were not significantly different for the rabbits that took part in antihistamine pretreatment. The relatively small mivacurium-induced increases in G (23.9 ± 6.9%) and H (7.6 ± 4.4%) were not inhibited significantly by antihistamine pretreatment (15.5 ± 3.0% and 3.6 ± 2.1%); in contrast, the increases in these parameters in response to histamine (21.0 ± 4.9 and 15.6 ± 4.5%) were significantly smaller for the rabbits that received histamine receptor blockers (0.3 ± 2.6% and 6.3 ± 1.0%). Although the increases in G after mivacurium and histamine administration were almost the same in the control rabbits, the mivacurium-induced increases in G were significantly greater than those obtained after exogenous histamine administration in the rabbits pretreated with antihistamine, *i.e.*, antihistamine completely prevented the histamine response of the lungs, whereas a small but statistically significant response in G remained after mivacurium administration.

Discussion

The results of the current study demonstrated that mivacurium induced significant increases in plasma histamine levels in rabbits, with the venous concentrations being significantly higher than those in the artery. This endogenously released histamine was shown to induce a significant increase in the airway resistance and in the viscoelastic parameters of the lung parenchyma. Furthermore, exogenous histamine caused qualitatively similar changes in the mechanical properties of the airways and the parenchyma. Antihistamine pretreatment in another group of rabbits lowered the airway and parenchymal responses to endogenous histamine, but the elevations in the mechanical parameters were still statistically significant. In contrast, pretreatment of the rabbits with antihistamine completely prevented lung responses to the exogenous administration of histamine.

Methodological Considerations

We applied a measurement technique that permits separation of the airway resistance from the parenchymal components. This approach allows an estimation of

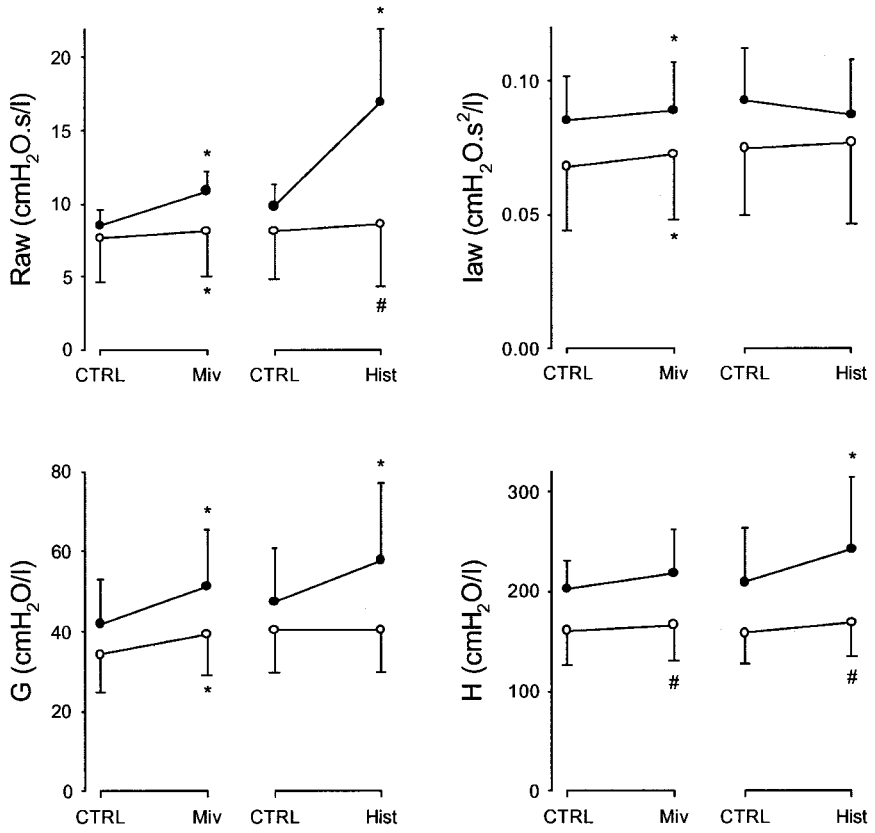

Fig. 3. Values of airway resistance (Raw) and inertance (Iaw) and tissue damping (G) and elastance (H) under control conditions (CTRL) and after mivacurium (Miv) or exogenous histamine (Hist) administration in rabbits with no pretreatment (*closed symbols*) and in rabbits pretreated with H1 and H2 receptor blockers (*open symbols*). *$P < 0.05$ *versus* previous control; #$P < 0.05$ between protocol groups.

the specific effects of different constrictor stimuli and also the effectiveness of the blockade of the lung response to induced constriction by assessment of the airway and parenchymal properties separately. The efficacy of a particular bronchodilator therapy depends on whether the airway or the parenchymal contractile elements are involved in the lung constriction.[18] Therefore, when anesthesiologists are faced with lung constriction after the administration of highly histamine-releasing anesthetic drugs, it is important for them to understand whether the airways or the viscoelastic properties of the parenchyma are responsible for the deteriorated lung function. The ZL data obtained in the current study are comparable with those reported from previous studies of rabbits[14] and are qualitatively similar to those obtained for other mammals.[11–13,16,18,19] Likewise, in agreement with previous findings, the model involving an airway and a constant-phase tissue compartment was consistent with the frequency dependence of ZL.

Mivacurium, previously demonstrated to be one of the most potent histamine-releasing drugs among myorelaxants,[8] was chosen in the current study to investigate the effects of endogenous histamine on the airway and parenchymal properties. A larger dose was applied here than in clinical practice in consequence of the substantially higher clearance and enhanced metabolism of anesthetic drugs in rabbits.[20] With this dose, the increases in plasma histamine levels in our rabbits were comparable to those observed earlier in humans after a lower dose of mivacurium.[8]

Site of Histamine Release

Myorelaxants induce histamine release either *via* an immunoglobulin E–mediated (anaphylactic) reaction or *via* a direct effect on mast cells present in most tissues and on basophils located in the blood (anaphylactoid reaction).[4,6,7] Furthermore, it has been demonstrated that the anatomic site of mast cell degranulation depends on the specific myorelaxant administered.[6] In the current study, the significant elevation in plasma histamine levels after mivacurium administration was observed only in the central venous blood from the systemic peripheral circulation, whereas the arterial blood leaving the pulmonary capillaries was essentially free of endogenous histamine. Although we cannot exclude that histamine released in the pulmonary system was completely bound to the histamine receptors in the lungs, endogenous histamine appears to be at least partly systemic in origin. In addition, the lack of an increase in histamine level in the carotid artery suggests that all histamine liberated in the systemic circulation was cleared from the circulation after lung passage. Since the half-life of histamine is longer than the circulatory time,[7] we can hypothesize that the histamine may not have been metabolized yet, but most of the drug was bound

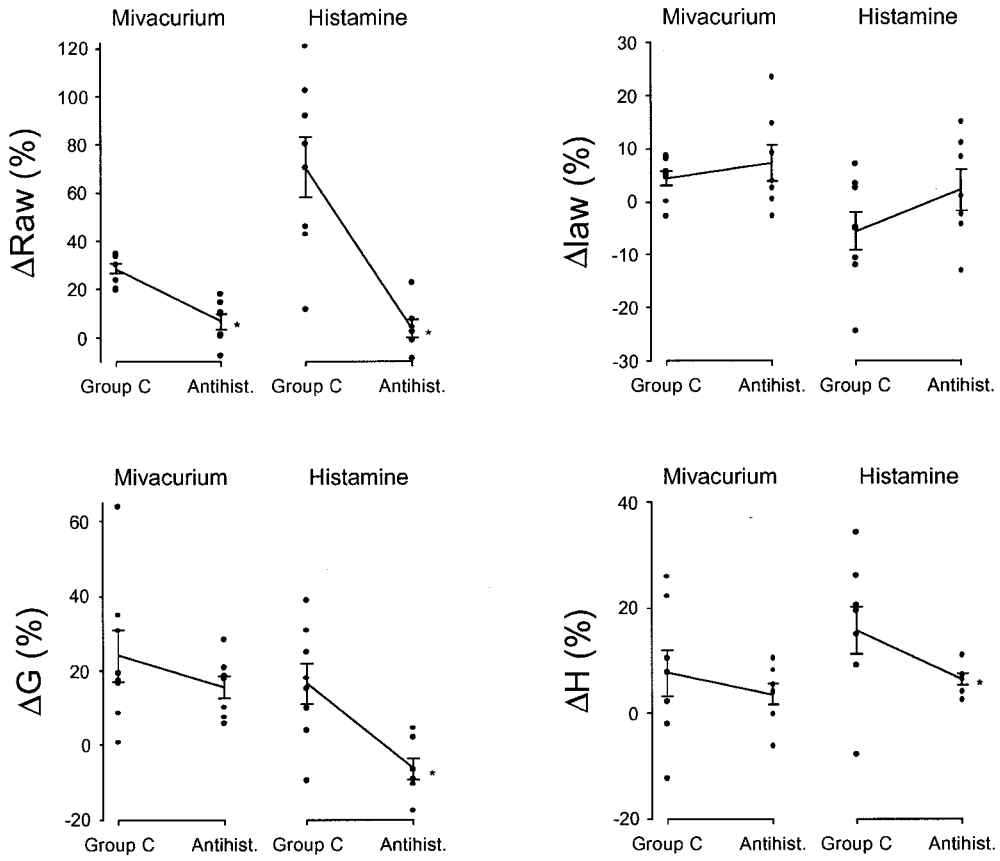

Fig. 4. Changes relative to baseline in airway resistance (Raw) and inertance (Iaw) and tissue damping (G) and elastance (H) in response to the administration of mivacurium or exogenous histamine in the control group of rabbits (group C) and in rabbits pretreated with H1 and H2 receptor blockers (Antihist). *$P < 0.05$ between protocol groups.

to the H1 receptors in the bronchial tree, leading to contraction of the bronchial smooth muscles.

Effects of Endogenous and Exogenous Histamine

Both endogenous and exogenous histamine induced significant elevations in the airway and the parenchymal mechanical parameters. Although there were marked increases in endogenous histamine level after mivacurium administration (530% in the jugular vein at 1 min), the responses in the airways and in the lung tissue were greater after administration of an exogenous histamine bolus, presumably because of the larger dose of exogenous histamine administered than that released by mivacurium. As concerns the interpretation of such a lung response, Lutchen *et al.*[16] demonstrated that increases in Raw associated with smaller elevations in G with no significant change in H are due to a heterogeneous constriction of the peripheral airways. Therefore, ventilation heterogeneities were likely to contribute to the increases in G after both mivacurium and histamine administrations, although the contribution of this phenomenon depends on the agent administered.

The changes in Raw, G, and H were associated after the administration of exogenous histamine, which suggests the dominant role of heterogenous constriction of the airways in the lung response. In this regard, the statistically significant increase in H after exogenous histamine can be attributed to the marked increase in Raw, which might have led to inhomogeneous airway obstructions, with subsequent loss in lung volume.[17] These findings agree with the results of previous investigations of rabbits in which airway narrowings were found to be responsible for the altered lung mechanical properties after an exogenous histamine challenge.[15] The dominant role of inhomogeneities and peripheral closures in the increases in the parenchymal mechanical parameters in the current study is further confirmed by the finding of Shardonofsky *et al.*[10] that the elevations in Rti in response to histamine were markedly reduced by elevating the mean lung volume during measurements.

After mivacurium administration, changes in G do not always mirror those in Raw. For instance, significant elevations in G (15.5%) were still observed even during mild airway constrictions (6.6%) in the animals pretreated with antihistamine, a circumstance implying that a real parenchymal response to mivacurium may have also occurred.

Effects of Antihistamine

Although it has been suggested that H1 receptors are primarily responsible for the constrictor response of the lung,[21,22] H2 receptors have been shown to exist in the airways,[23–25] and a combination of H1 and H2 antagonists has been demonstrated to provide adequate hista-

mine antagonism.[26] Therefore, in the current study we administered clemastine and ranitidine, H1 and H2 receptor blockers used commonly in clinical practice, in order to ensure complete saturation of the histamine receptors.

In agreement with previous findings, antihistamine pretreatment exerted a protective effect against the lung constriction induced by exogenous histamine.[22–25,27] In addition, H1 and H2 blockade completely abolished the increases in the airway and parenchymal parameters after an exogenous histamine challenge. To our knowledge, this is the first demonstration of the protective effect of an antihistamine against the bronchospasm induced by a histamine-releasing drug. Despite this significant protection, statistically significant responses in Raw and G remained after mivacurium administration. This may suggest that the degranulation of mast cells or other inflammatory cells by mivacurium liberated mediators other than histamine, such as leukotrienes,[28] cytokines,[28] and serotonin.[29] . These mediators may also have contributed to the lung response to mivacurium, and their effects were not inhibited by antihistamine pretreatment. Accordingly, it appears that the increases in Raw caused by mivacurium are largely mediated by histamine, whereas the increases in G imply that these other mediators selectively affect the parenchymal properties.

Although there was no difference between the study groups in any respect and the experiments were performed in random sequence, the mechanical parameters were generally lower in the rabbits that received antihistamine pretreatment, even under control conditions. This systematic but statistically not significant difference can most probably be attributed to a lowering of the baseline bronchial smooth muscle tone *via* blockade of the effects of endogenous histamine, demonstrated to be present in the circulation even under control conditions.[30]

Summary and Conclusions

The results of the current study demonstrate that endogenous histamine released by a myorelaxant, mivacurium, is at least partly systemic in origin. Partitioning of the lung response into airway and parenchymal components revealed that elevation of the endogenous histamine level induced mainly airway constriction with substantial ventilation heterogeneities. The histamine-induced airway constriction was prevented completely by pretreatment with H1 and H2 receptor–blocking agents. However, the difference in the protective effects of H1 and H2 receptor blockade against exogenous histamine and mivacurium administration indicates that other mediators that have the potential to alter airway and parenchymal mechanics may also contribute to the lung response after an anaphylactoid reaction.

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