

A magnetic resonance imaging evaluation of histamine-mediated allergic response in the guinea pig nasopharynx

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Background: Magnetic resonance imaging (MRI) is a powerful technique for visualizing tissues with a high water content. In this study we used MRI to evaluate the effect of antigen and mediators of allergic responses on the nasopharyngeal airway of guinea pigs.

Methods and Results: Longitudinal relaxation time-weighted transverse images of the nasopharyngeal airway revealed a clearly defined airway lumen and mucosa. Topical administration of ovalbumin (0.00006% to 0.06%) to the nasopharyngeal airway of sensitized guinea pigs caused a concentration-dependent reduction ($34\% \pm 1\%$, maximum) in airway luminal volume and a corresponding increase ($28\% \pm 3\%$, maximum) in the volume of the airway mucosa. These effects were duplicated by histamine (10^{-5} to 10^{-3} mol/L), but not by methacholine (10^{-3} mol/L). The antigen-induced changes in airway and mucosal volumes were dose-dependently inhibited by the H_1 -antagonist loratadine (0.3 to 3 mg/kg, administered orally). On the other hand, topical administration of a decongestant drug, oxymetazoline (250 μ g per guinea pig), had no effect on the response to antigen.

Conclusions: These results indicate that MRI is a useful technique to measure allergic responses in the airways and identify that histamine is an important mediator of the obstruction that occurs in the nasopharyngeal airway of guinea pigs after antigen challenge. (*J ALLERGY CLIN IMMUNOL* 1993;92:435-41.)

Key words: Magnetic resonance imaging, nasopharynx, mucosa, guinea pig, antigen, histamine, loratadine

Nasal obstruction, swelling of the mucus membranes, and production of watery or mucoid rhinorrhea are typical symptoms of nasal allergies.¹⁻⁴ A major cause of the nasal obstruction is dilation of capacitance vessels in the nasal septum and turbinates, which leads to a reduction in the diameter of the airways.^{5, 6} A secondary cause of the nasal obstruction is edematous swelling of nasal mucus membranes, which causes further airway narrowing.^{7, 8} Third, fluid in the airways increases from direct secretions.^{2, 9, 10}

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Abbreviations used

CSA: Cross-sectional area
MRI: Magnetic resonance imaging
PBS: Phosphate-buffered saline
T₁: Longitudinal relaxation time

Proton magnetic resonance imaging (MRI) is a powerful, noninvasive technique for imaging soft tissues of the body and is particularly sensitive for imaging tissues with high water content.¹¹ Experimentally, MRI has been used to identify changes in cardiovascular function.¹² MRI has also been used diagnostically to identify pathologic abnormalities in the nose and upper airway, particularly in regions of the paranasal sinuses,¹³⁻¹⁶ turbinates,¹⁷ and nasopharynx.¹⁸⁻²⁰ In some of these areas, particularly the nasopharynx,^{18, 19} MRI shows excellent differentiation of the mucosa surrounding the airway lumen. Recently, Reo et al.^{21, 22} have used MRI to study the effects of challenge with histamine and methacholine in the

upper airways of ferrets. Furthermore, MRI has been used to visualize changes in the nasal turbinates of guinea pigs after antigen challenge.²³

In the present study, we used MRI to measure changes in the size of the nasopharyngeal airway and the thickness of the surrounding airway mucosa after antigen challenge in guinea pigs. The response to antigen was compared with the changes in airway size and mucosal thickness after topical infusions of histamine and methacholine. The results show that antigen and histamine, but not methacholine, cause a large decrease in nasopharyngeal airway size and an increase in thickness of the surrounding airway mucosa. The changes caused by antigen are inhibited by the antihistamine loratadine.

MATERIAL AND METHODS

Immunization and operation

Male Hartley guinea pigs were actively sensitized to ovalbumin by the injection of 5 mg ovalbumin intraperitoneally and 5 mg subcutaneously in 1 ml saline on day 1 and of 5 mg ovalbumin intraperitoneally on day 4. The sensitized animals were used 3 to 4 weeks later.

Studies were performed on sensitized and nonsensitized guinea pigs (350 to 550 gm) that were anesthetized with intramuscular injection of ketamine (60 mg/kg) and xylazine (5 mg/kg). An incision was made in the neck and the trachea was sectioned below the larynx. Two catheters were inserted into the trachea, one caudally through which the animal breathed and the other rostrally for the instillation of antigen and challenges to the upper airways. The rostral catheter was positioned at the entrance of the nasopharynx and the tongue was compressed against the soft palate with a rubber band to occlude the oral cavity. A long section of polyethylene tubing was attached to the end of the rostral catheter to facilitate the instillation of challenge solutions to the nasopharynx.

Imaging of the nasopharynx

Imaging was performed on a 1.5 Tesla magnet (Signa, General Electric Medical Systems, Milwaukee, Wis.). The animal was placed in a lateral recumbent position and centered visually with the aid of laser cross hairs before it was moved into the MRI apparatus.

A multislice longitudinal relaxation time (T_1)-weighted spin-echo imaging sequence was used to acquire proton density images. Images were acquired with a T_R (recovery time) of 800 msec and a T_E (echo time) of 25 msec. T_1 -weighted sagittal views were first obtained to determine the region in which transverse sections would be taken. This region was from the tip of the nares to the junction of the oropharynx. Serial, contiguous T_1 -weighted transverse sections (3 mm thick) were then made of this region. Transverse views allowed for calculation of the cross-sectioned area

(CSA) of the airway lumen and mucosa with the use of Image 1.17 software (National Technical Information Services, Arlington, Va.) and a Macintosh II computer (Apple Computer Inc., Cupertino, Calif.). Airway and mucosal volumes were calculated from six contiguous 3-mm slices (slices 10 to 15, see Results section). The total imaging time was approximately 8 minutes. Each determination was made in triplicate and performed in a randomized fashion by two persons who were blinded to the treatments.

Ovalbumin infusion in sensitized and nonsensitized guinea pigs

Transverse images of the nasopharyngeal airway of sensitized ($n = 21$) and nonsensitized ($n = 6$) guinea pigs were taken immediately before the instillation of ovalbumin. Ovalbumin (0.00006% to 0.06% in sensitized animals and 0.06% in nonsensitized animals) was then instilled through the nasopharyngeal airway catheter until fluid exited at the tip of the nares. Each animal received a single dose of ovalbumin. The ovalbumin was allowed to dwell in the airways for 10 minutes, after which time 10 ml of air was flushed through the catheter. The air wash was repeated nine times to remove all fluids from the airway. Transverse images of the nasopharyngeal airway were then obtained after the ovalbumin instillation.

Histamine and methacholine infusion in nonsensitized guinea pigs

A protocol similar to that described for ovalbumin challenge was also used to assess the local effects of histamine ($n = 10$) and methacholine ($n = 3$). These studies were done in nonsensitized guinea pigs and concentrations of 10^{-5} to 10^{-3} mol/L histamine and 10^{-3} mol/L of methacholine were used.

Ovalbumin infusion after treatment with loratadine in sensitized guinea pigs

These experiments were performed on sensitized guinea pigs ($n = 16$) to evaluate the role of histamine H_1 -receptors in mucosal and airway responses to ovalbumin. Fasted guinea pigs were treated with the histamine H_1 -receptor antagonist loratadine, given orally 2 hours before challenge with ovalbumin (0.002%). The choice of ovalbumin concentration used for this study was based on results obtained from the antigen dose-response experiment and was chosen to produce a prominent response, yet not the maximum response seen at higher (0.006%) concentrations.

Ovalbumin infusion followed by oxymetazoline in sensitized guinea pigs

Experiments were performed on antigen-challenged sensitized guinea pigs ($n = 3$) to determine the effect of the decongestant drug oxymetazoline. Transverse images of the nasopharyngeal airway were obtained immediately before and after ovalbumin instillation

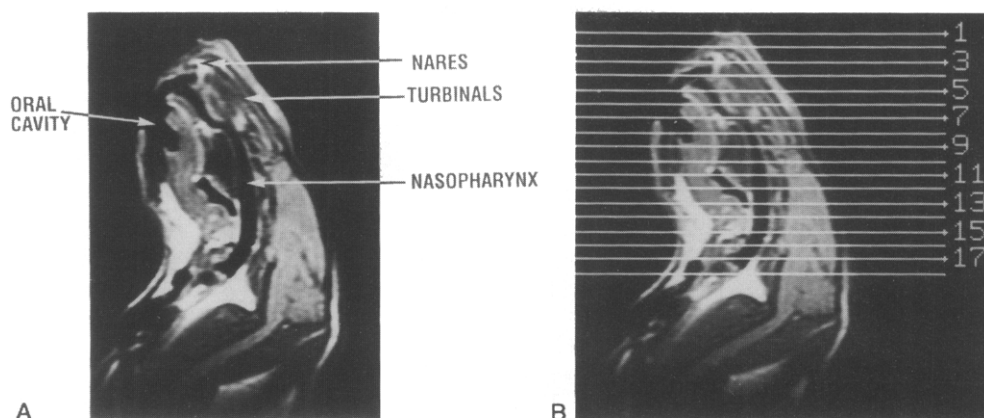


FIG. 1. Representative T₁-weighted sagittal view of head and neck of guinea pig (A). Eighteen 4-mm thick transverse slices were obtained over entire upper airways (B). Slices 10 through 15 were used to calculate changes in nasopharyngeal airway and mucosal CSA.

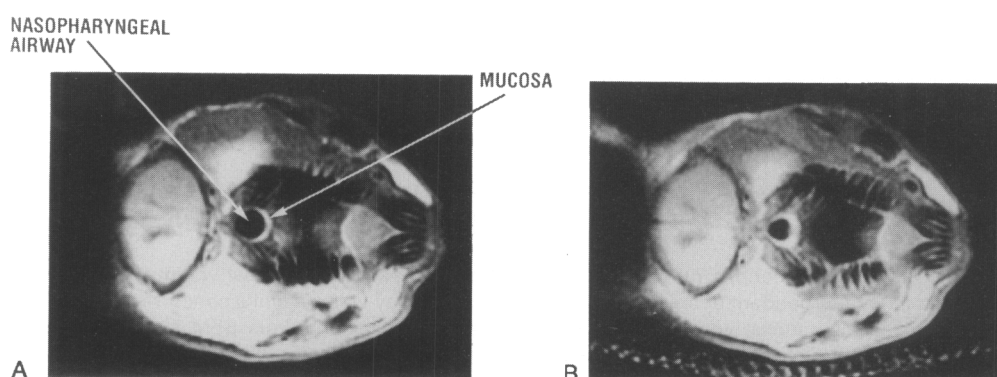


FIG. 2. Representative T₁-weighted transverse slice in sensitized guinea pig before (A) and after (B) ovalbumin challenge. Circumferences of mucosa and nasopharyngeal airway were measured for calculation of areas. Note that enhanced brightness is caused by increased fluid and smaller nasopharyngeal airway area and enlarged mucosal area are seen after challenge with ovalbumin (0.06%).

(0.002%) as described earlier. This was followed by the infusion of oxymetazoline (250 µg per guinea pig) through the nasopharyngeal airway catheter. The oxymetazoline was allowed to dwell in the airways for 10 minutes, after which time air (10 times 10 ml) was flushed through the catheter to remove the drug. Transverse images were then obtained after the oxymetazoline infusion.

Animal care and use

This study was done in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act in a program accredited by the American Association for the Accreditation of Laboratory Animal Care.

Statistics

A Duncan's multiple range statistic was used to test for significant effects of (1) ovalbumin, histamine, and methacholine on the volumes of the airway lumen and

mucosa and (2) the inhibition by loratadine of the changes in airway and mucosal volume caused by ovalbumin.

Compounds

The ovalbumin, histamine dihydrochloride, and methacholine chloride used in this study were purchased from Sigma Chemical Co. (St. Louis, Mo.); loratadine and oxymetazoline dihydrochloride were synthesized at Schering-Plough (Union, N.J.). Ovalbumin, histamine, methacholine, and oxymetazoline were dissolved in phosphate-buffered saline (PBS). All solutions were warmed to 37° C before infusion. Loratadine was prepared in 0.4% methylcellulose in isotonic saline and given orally in a volume of 0.2 ml per 100 gm body weight.

RESULTS

A representative T₁-weighted sagittal view of the guinea pig upper airway is shown in Fig. 1, A.

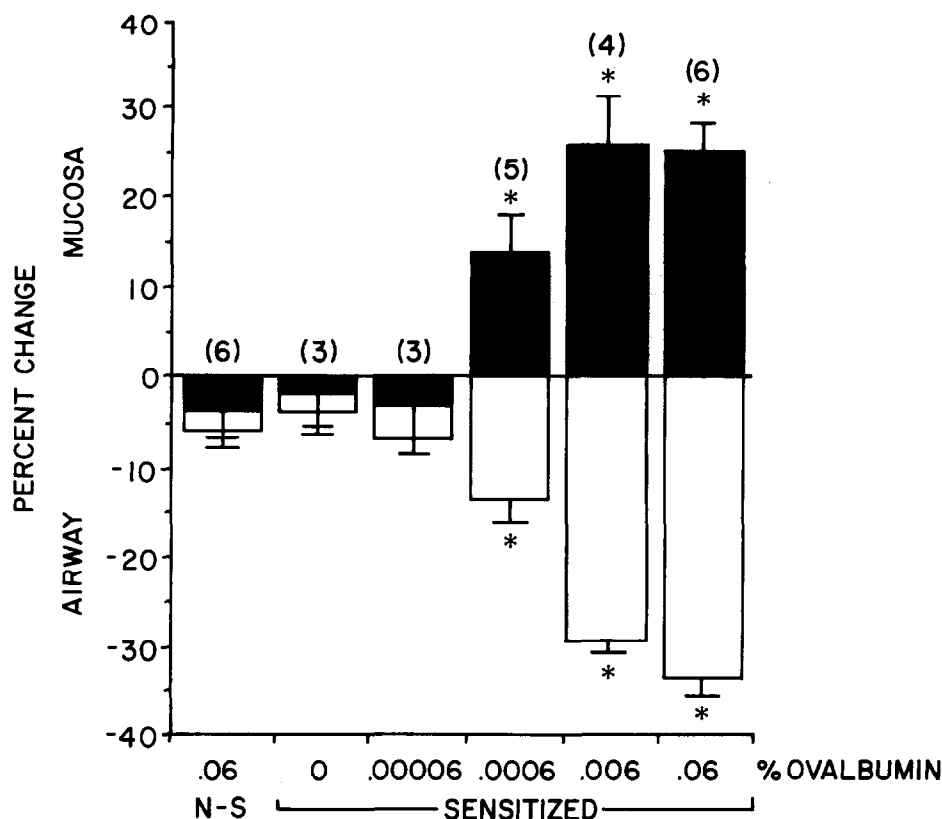


FIG. 3. Effect of ovalbumin on nasopharyngeal airway lumen and mucosal volume. Ovalbumin caused a dose-dependent decrease in nasopharyngeal airway volume while concurrently causing an increase in mucosal volume. Values represent mean plus or minus SEM percent change caused by ovalbumin in nonsensitized (N-S) and sensitized guinea pigs. Numbers in parentheses represent number of animals per group. Asterisks indicate $p < 0.05$ compared with antigen challenge of nonsensitized animals.

Structures visible include the tongue, oral cavity, nares, and nasopharynx. From this sagittal view, contiguous transverse sections (slices 10 through 15) of a portion of the nasopharynx (Fig. 1, B) were used to evaluate the changes after administration of ovalbumin, histamine, and methacholine.

Ovalbumin infusion in sensitized and nonsensitized guinea pigs

A representative transverse view of a particular slice (slice 12) of the nasopharyngeal airway from a sensitized guinea pig before ovalbumin instillation is shown in Fig. 2, A. The mucosa surrounding the airway shows up as an area with high signal intensity. Also, the thickness of the mucosa is shown to be increased after topical administration of ovalbumin (0.06%) and there is a corresponding decrease in the CSA of the airway lumen (Fig. 2, B). In this particular slice, the CSA of the airway lumen decreased by 33% from 11.4

to 7.6 mm² and the mucosa increased by 39% from 9.8 to 13.6 mm².

Infusion of ovalbumin caused a concentration-dependent (0.00006% to 0.06%) decrease in airway luminal volume (slices 10 through 15) in sensitized guinea pigs (Fig. 3). There was a corresponding increase in mucosal volume. Statistically significant ($p < 0.05$) changes were seen with infusion of 0.006% ovalbumin. The largest decrease ($34\% \pm 1\%$) in nasopharyngeal airway luminal volume, from 173 ± 13 mm³ to 118 ± 10 mm³, occurred after infusion of 0.06% ovalbumin. These concentrations of ovalbumin produced no evidence of labored breathing or dyspnea in the animals and there were no deaths as a result of the treatments. Infusion of PBS into the nasopharyngeal airways of sensitized guinea pigs or ovalbumin (0.06%) infusion into the nasopharyngeal airways of nonsensitized animals had no effect on the volume of the airway lumen or mucosa (Fig. 3).

TABLE 1. Change in the volume of the airway and mucosa after histamine and methacholine administration to nasopharyngeal airways of nonsensitized guinea pigs

Challenge	Concentration (mol/L)	No. of animals	Percent change caused by challenge*	
			Airway	Mucosa
PBS	—	5	-6 ± 3	$+7 \pm 4$
Histamine	10^{-5}	3	-15 ± 5	$+2 \pm 5$
	10^{-4}	4	$-24 \pm 3^\dagger$	$+30 \pm 9^\dagger$
	10^{-3}	3	$-33 \pm 1^\dagger$	$+31 \pm 2^\dagger$
Methacholine	10^{-3}	3	-9 ± 2	$+7 \pm 1$

*Values represent the mean plus or minus SEM.

 $^\dagger p < 0.05$ compared with PBS.

Histamine and methacholine infusion in nonsensitized guinea pigs

Instillation of histamine (10^{-5} to 10^{-3} mol/L) caused a reduction in the volume of the nasopharyngeal airway and an increase in mucosal volume (Table 1). The maximum changes produced by histamine were similar in magnitude to those produced by 0.006% to 0.06% ovalbumin. In contrast, instillation of 10^{-3} mol/L methacholine had no effect on airway and mucosal volumes.

Ovalbumin infusion after treatment with loratadine in sensitized guinea pigs

Ovalbumin (0.002%) produced a decrease ($33\% \pm 2\%$) in volume of the nasopharyngeal airway and an increase ($41\% \pm 4\%$) in volume of the nasopharyngeal mucosa. The magnitude of these changes after ovalbumin instillation was large compared with previous results obtained in the dose-response study (Fig. 3) and probably reflected a greater sensitivity to antigen in this particular group of animals. Both the decrease in volume of the nasopharyngeal airway and the increase in volume of the nasopharyngeal mucosa after ovalbumin instillation were dose-dependently inhibited by the H_1 -receptor antagonist loratadine (0.3 to 3 mg/kg, administered orally; Fig. 4).

Ovalbumin infusion followed by oxymetazoline in sensitized guinea pigs

The decrease in volume of the nasopharyngeal airway was not changed by treatment with the decongestant drug oxymetazoline. In this study the airway volume before ovalbumin infusion was 190 ± 9 mm³ and decreased to 122 ± 10 mm³ after ovalbumin infusion (0.002%). After topical administration of oxymetazoline (250 μ g per

guinea pig) the airway volume averaged 121 ± 4 mm³. Similar results were obtained for the increase in mucosal volume after ovalbumin infusion; the increase in mucosal volume also did not change after oxymetazoline.

DISCUSSION

MRI is a powerful technique for imaging soft tissues of the body and produces high-resolution images of tissues with a high water content. In the nose where the fluid is contained mainly in blood, nasal secretions, and airway mucosa, MRI has been used to image the paranasal sinuses,¹³⁻¹⁶ turbinates,^{17, 22} and nasopharynx.¹⁸⁻²⁰ In this study we used MRI to image the nasopharyngeal airways of guinea pigs after topical administration of antigen, histamine, and methacholine and found that antigen and histamine, but not methacholine, caused a reduction in airway luminal size caused by swelling of the surrounding airway mucosa. The possible mechanisms that would cause an increase in thickness of the nasopharyngeal mucosa are (1) vascular engorgement and vasodilation, (2) increased permeability of blood vessels with edematous leakage of plasma into the mucosal interstitium and airway, and (3) increased glandular secretions.²⁻⁴

Topical administration of antigen to the nasopharyngeal mucosa caused an increase in mucosal thickness and reduction in airway luminal size. This study is the first to visualize the changes in nasopharyngeal airway caliber after antigen provocation in guinea pigs, although Robinson et al.²³ used MRI to visualize the changes in nasal turbinates after antigen provocation to guinea pigs. Therefore the nasopharyngeal airway and nasal turbinates are potential sites of airway obstruction that typically occur after antigen provocation to the upper airways of guinea pigs.²⁴

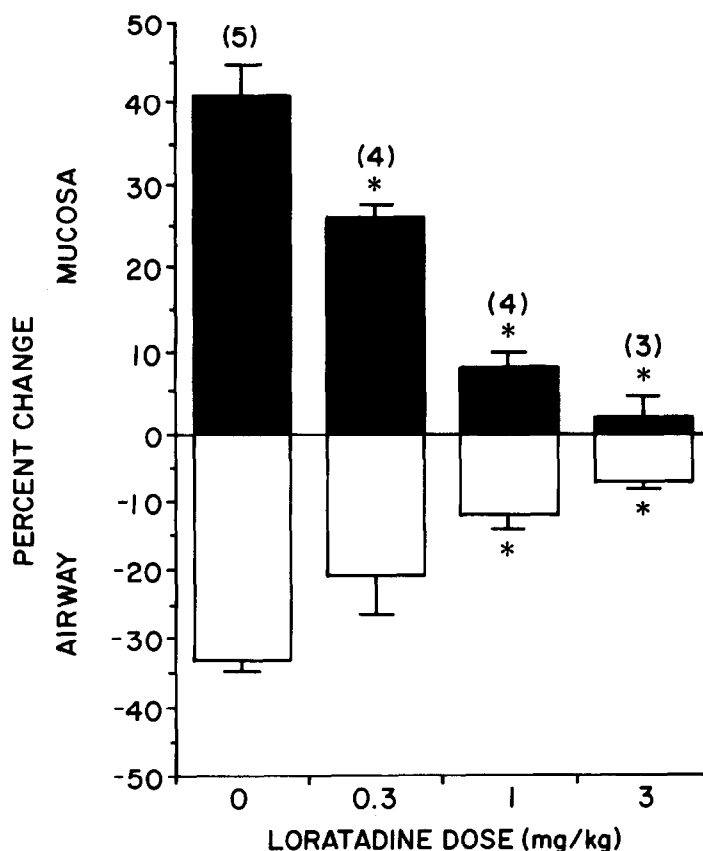


FIG. 4. Inhibition of antigen-induced changes in nasopharyngeal airway and mucosal volumes by the H_1 -receptor antagonist loratadine. Treatment with loratadine dose-dependently inhibited changes in nasopharyngeal airway and mucosal volume caused by ovalbumin (0.002%). Values represent mean plus or minus SEM percent change caused by ovalbumin. Numbers in parentheses represent number of animals per group. Asterisks indicate $p < 0.05$ compared with 0 mg/kg loratadine.

The effects of antigen on these changes in nasopharyngeal airway caliber undoubtedly involve the release of histamine because pretreatment with loratadine, an H_1 -histamine receptor antagonist,²⁵ blocked the effects of ovalbumin. Furthermore, instillation of histamine increased mucosal volume and reduced nasopharyngeal airway size to a degree similar to that found after antigen challenge. These results are consistent with those in reports that show histamine is an important mediator of allergic airway responses in guinea pigs.^{26, 27} It is of interest that histamine is also an important mediator of allergic responses in man as demonstrated by the relative efficacy of H_1 -antihistamines such as loratadine against human allergic nasal responses.²⁸

Unexpectedly, topical administration of the vascular decongestant oxymetazoline had no effect on the size of the mucosa after antigen challenge. These results are clearly different from responses seen in human allergic rhinitis in which a decon-

gestant effect of oxymetazoline has been demonstrated.³ The posterior portion of the guinea pig nasal cavity is sparsely vascularized,^{29, 30} and our results indicate that the increase in mucosal thickness after antigen was not a result of vascular engorgement and vasodilation. The mucosal swelling after antigen could not be a result of glandular hypersecretion because instillation of methacholine, which is a potent secretagogue of nasal glands,¹⁰ had no effect. On the other hand, mucosal thickening after antigen challenge may be a result of increased permeability of nasopharyngeal blood vessels. Previous studies have demonstrated that histamine increased microvascular leakage in guinea pig airways,^{27, 31} and we found that histamine was an important mediator of the nasopharyngeal mucosal thickening after antigen challenge. In this regard, it is not surprising that oxymetazoline had no effect on the size of the mucosa after antigen challenge because oxymetazoline does not inhibit the exudation of plasma

into human nasal airways after provocation with allergic mediators.³²

In conclusion, with the use of MRI we found that antigen provocation caused a reduction in the size of the nasopharyngeal airway in allergic guinea pigs. This was the result of an increased thickness of the airway mucosa. Pretreatment with loratadine, an H₁-histamine receptor antagonist, blocked the effects of antigen provocation, which indicated that histamine is an important mediator in this allergic airway response. These results show that MRI is a useful technique to study the pathophysiology and pharmacology of upper airway allergic responses.

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