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Lung

Interaction of Vagal Lung Afferents with Inhalation of Histamine Aerosol in Anesthetized Dogs

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Abstract. In seven alpha-chloralose anesthetized dogs we examined the contribution of lung afferents to the rapid, shallow breathing induced by inhalation of 10 breaths of histamine aerosol. In four spontaneously breathing dogs, the inhalation of histamine caused an increased respiratory frequency, decreased tidal volume, and decreased dynamic lung compliance. Selective blockade of pulmonary C-fibers abolished a reflex-induced increase in respiratory frequency but did not significantly affect the reductions in tidal volume or lung compliance. Terbutaline treatment in combination with C-fiber blockade abolished the reductions in tidal volume and lung compliance induced by histamine. In three separate alpha-chloralose anesthetized, open-chest, mechanically ventilated dogs, we recorded an increase in the inspiratory activity of rapidly adapting pulmonary stretch receptors (RARs) induced by the inhalation of histamine aerosol. Selective C-fiber blockade abolished histamine-induced increases in RAR activity while only partially attenuating reductions in lung compliance. We conclude that the increase in RAR activity induced by histamine depends on intact C-fibers and not on a direct effect of histamine on RARs or an indirect effect of histamine reducing lung compliance. In addition, our data illustrate the multiple interactions that occur between the various vagal afferents and their roles in the reflexes induced by histamine inhalation.

Key words: Histamine—C-fibers—Rapidly adapting pulmonary stretch receptors—Pulmonary defense reflex—Capsaicin.

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Introduction

Many lung irritants (e.g., inhaled dust, ammonia, SO_2) and lung autacoids (e.g., histamine, bradykinin, serotonin, prostaglandins) initiate a pattern of protective reflexes known collectively as the airway defense reflexes. These include gasps and/or periods of apnea, cough, rapid shallow breathing, bronchoconstriction, increased mucus secretion, and, in man, respiratory irritant sensations. These airway defense reflexes are thought to be initiated by the excitation of one or more types of neural afferents that innervate the airways and lung parenchyma [3]. Rapidly adapting pulmonary stretch receptors (RARs) are excited by many of the agents that initiate the airway defense reflexes and are excited with a time course similar to these reflexes [3, 15, 23], suggesting that RARs are the receptors that are at least in part responsible for initiating airway defense reflexes. However, many of these same agents have also been shown to excite bronchial and pulmonary C-fibers [3, 9, 13, 22]. When excited, lung C-fiber afferents can independently initiate reflexes identical to the airway defense reflexes [3]. It is therefore likely that lung C-fibers also contribute to the initiation of the airway defense reflexes.

The relative role played by either RARs or C-fibers in initiating airway defense reflexes appears to depend on the lung irritant used and the species studied [3]. In addition, recent studies suggest that the pattern of afferent discharge and the resulting reflex responses are the outcome of multiple interactions involving central nervous system integration and chemical and/or mechanical coupling within the lung [2, 5, 12, 14, 24, 26]. For example, cough initiated by lower airway irritation is a complex reflex response involving RARs and lung C-fibers [26]. Centrally, lung C-fiber input appears to inhibit cough [26]. However, C-fiber–induced reflex bronchoconstriction and C-fiber release of substance P increase RAR activity indirectly facilitating cough [12, 26]. In rabbits the release of substance P in the lung appears to contribute to the RAR response to pulmonary venous congestion [2] and capsaicin aerosol challenge [14]. We have shown that the inhalation of ozone in dogs induces a reflex tachypnea and bronchoconstriction [24] that is initiated by the excitation of bronchial C-fibers and RARs. In this model of airway injury and irritation the stimulation of RARs appeared to occur secondary to bronchial C-fiber–mediated bronchoconstriction [5, 24].

Histamine was used in this study because of its important role in allergic airway reactions. The purpose of this study was to further examine the activation of RARs and lung C-fibers after histamine inhalation in dogs. We hypothesized that RARs are not directly stimulated by histamine, but rather that RARs are stimulated secondary to C-fiber stimulation. We recorded the pulmonary reflex response and RAR activity induced by histamine before and after selective conduction block of afferent vagal C-fibers [25] and after C-fiber block plus terbutaline aerosol treatment (a beta-agonist bronchodilator). The use of selective vagal C-fiber block allowed us to examine the relative role of RARs and lung C-fibers in the airway defense reflexes evoked by histamine aerosol. The use of terbutaline allowed us to examine the mechanical coupling of lung C-fiber–evoked bronchoconstriction and RAR excitation that appears to be important in this species.

Methods

General

Seven mongrel dogs weighing 20–35 kg (26.5 ± 1.5) were initially anesthetized with 1.2–2.2 mg/kg xylazine (IM) and 40 mg/kg alpha-chloralose (IV). Supplemental doses of alpha-chloralose (4–6 mg/kg) were given hourly. A tracheotomy was preformed low in the neck, and the airway was intubated with an 8.0-mm ID tracheal tube. The left femoral artery was cannulated and arterial blood pressure (P_a) was recorded by a Spectramed DXT pressure transducer (Oxnard, CA). Arterial O_2 tension (Pa_{O_2}), CO_2 tension (Pa_{CO_2}) and pH were measured at regular intervals with a Corning 178 pH/blood gas analyzer, and any metabolic acidosis was corrected by intravenous infusion of $NaHCO_3$ solution. The left femoral vein was cannulated to administer anesthetic, $NaHCO_3$ solution, and succinylcholine chloride.

Experimental Protocols

Two different protocols using different animals were used in this study. In the first protocol (reflex protocol; $n = 4$), tidal volume, respiratory frequency, transpulmonary pressure, and dynamic lung compliance were measured in spontaneously breathing dogs for 10 breaths before, during, and after the inhalation of 10 breaths of histamine aerosol (1 mg/mL). This series of measurements was made before vagal perineural capsaicin treatment, after perineural capsaicin treatment, and after 5 min of terbutaline aerosalization (1 mg/mL) given after the capsaicin treatment. In the second protocol (afferent protocol; $n = 3$), the animals were paralyzed with succinylcholine chloride (0.06 mg/kg IV), and the chests of the dogs were opened in the midsternal line as the lungs were ventilated at constant tidal volume (15 mL/kg) and frequency (18–20 cycles/min) by a Harvard pump (model 607D) with a positive end-expiratory pressure of 3–5 cmH_2O. The experimental protocol was similar as previously described for the reflex study (i.e., action potentials were recorded for 10 breaths before, during, and after the inhalation of 10 breaths of histamine aerosol for the three experimental conditions [before capsaicin treatment, after capsaicin treatment, and after capsaicin plus terbutaline treatment]).

Generation and Delivery of Aerosols

Aerosols were generated using a De Vilbiss Ultra Neb 99 ultrasonic nebulizer. In the reflex studies, aerosols were delivered using a “blow-by” system that allowed for the continuous measurement of breathing pattern and lung mechanics (Fig. 1). Histamine aerosol was added to a constant airflow of 20 L/min by turning two three-way valves that diverted the system flow through the nebulizer. The dogs inhaled air or air containing aerosol from this airflow. Expired air and excess bias flow were directed through a manifold consisting of four PAL small particle filters in parallel. Airflow exiting this manifold was then directed through a pneumotachograph. This system produced a constant increase in tracheal pressure of 1 cmH_2O. In the afferent study, the three-way valve/nebulizer assembly was placed in line with the inspiratory side of a constant volume ventilator.

Breathing Pattern and Pulmonary Mechanics

Inspiratory and expiratory airflows were measured with a pneumotachograph (Hans Rudolph 4700) connected to the exhaust of the aerosol delivery system (Fig. 1). From the pneumotachograph, tidal volume (V_T, mL), respiratory frequency (f_R, breaths/min), and minute ventilation (V_E, L/min) were determined before and after each experimental intervention. Transpulmonary pressure was measured with a differential pressure transducer (Validyne MP45). The positive end of the transducer was connected to a T-tube attached to the tracheal tube, and the negative end of the transducer was attached to a balloon-tipped catheter placed in the

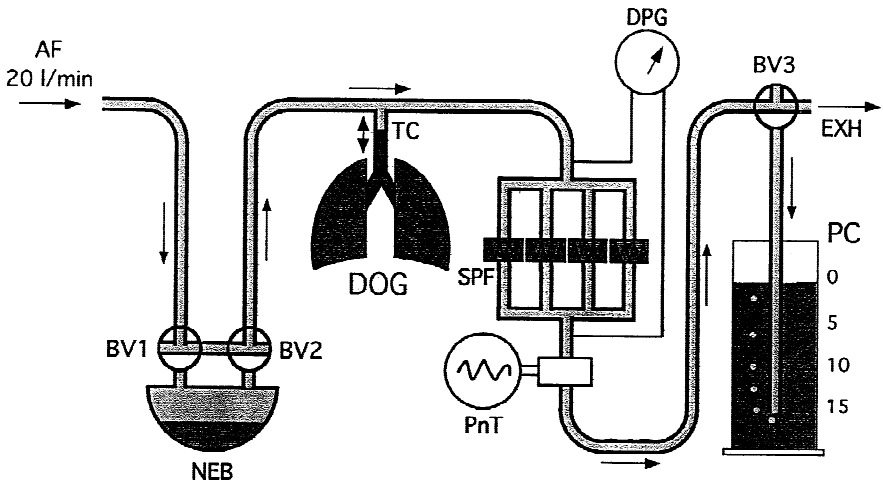

Fig. 1. Schematic of blow-by aerosol delivery system. Twenty L/min airflow (*AF*) was directed past the tracheal cannula (*TC*). During aerosol delivery, airflow was directed through the nebulizer chamber (*NEB*) utilizing two bypass valves (*BV1, BV2*). Exhaust flow was passed through four low-resistance small particle filters (*SPF*) in parallel and through a pneumotachograph (*PnT*). Pressure across the SPF was monitored by a differential pressure gauge (*DPG*). The exhaust flow was then passed through another bypass valve (*BV3*) and either exhausted (*EXH*) to the atmosphere or directed through a PEEP chamber (*PC*) set at 15 cmH_2O.

midthoracic region of the esophagus. Dynamic lung compliance ($C_{L,dyn}$) was calculated breath-by-breath by the method of Amdur and Mead [1]. All analog signals were recorded on a Gould multichannel recorder (model ES2000).

Selective C-fiber Block by Vagal Perineural Capsaicin Treatment

Nonmyelinated pulmonary C-fibers were blocked by the method of Schelegle et al. [25]. Two- to 3-cm segments of each vagus nerve were isolated in the midcervical region. Each vagal segment was desheathed and placed in silicone elastomer (Silastic) troughs. To remove excess connective tissue each segment was treated with a solution of 1,000 units collagenase and 1,000 units hyaluronidase in Krebs solution with 5 mM calcium for 20 min. A 1% solution of capsaicin in 10% Tween 80 and 90% mineral oil was placed on each vagal segment for 10–15 min. Effectiveness of the block was evaluated by the abolition of the C-fiber–evoked pulmonary chemoreflex in the presence of an unaffected slowly adapting receptor evoked Hering-Breuer inflation reflex.

The pulmonary chemoreflex (bradycardia, hypotension, and apnea followed by rapid shallow breathing) was evoked by injecting 20 μg/kg of capsaicin into the right atrium by way of the jugular catheter. The Hering-Breuer inflation reflex (prolonged expiratory pause after lung inflation) was evoked by temporarily directing the expiratory airflow through a positive end-expiratory pressure chamber set at 15 cmH_2O (Fig. 1).

Recording of Afferent Vagal Impulses

Using conventional techniques, we dissected fine slips of the right or left cervical vagus nerve cranial to the site of capsaicin treatment and recorded impulses arising from afferent endings in the lower trachea, extrapulmonary bronchi, or lungs. Fine slips of the left cervical vagus nerve were dissected and single fibers were

placed on a recording electrode. Action potentials were measured by a Grass P5 Series AC preamplifier and filtered through a Winston Electronics window discriminator and a ratemeter. Impulses were recorded from slips containing a functional single fiber or two active fibers whose spikes could be distinguished by their different amplitudes. Rapidly adapting receptors were identified by their characteristic pattern of discharge and by their response to hyperinflation and collapse of the lung [8]. At the beginning of each experiment, the location of the endings to be investigated was determined by exploring the airways and lungs with a fine probe. Endings that could not be located in the lower respiratory tract were discarded. Impulse frequencies were counted by ratemeters whose window discriminators were set to accept potentials of a particular amplitude.

Data Analysis and Calculations

A one-way ANOVA with repeated mean contrasts was used to examine the differences between the vagal treatments (before capsaicin treatment, after capsaicin treatment, and after capsaicin plus terbutaline treatment) using the absolute changes in V_T, f_R, $C_{L,dyn}$, and RAR impulse activity from before histamine inhalation to after histamine inhalation. A two-way ANOVA examining the effect of histamine aerosol inhalation and the vagal treatments was performed using repeated mean contrasts to determine significant interactions. Statistical significance for both tests was set at $p \leq 0.05$. All values are reported as means ± S.E.

Results

Reflex Protocol

Tracings obtained from a dog during the reflex protocol are presented in Fig. 2; tabulated mean data can be found in Table 1.

Effectiveness of Vagal Perineural Capsaicin Treatment. The mean inhibitory ratio for the Hering-Breuer reflex was 5.50 ± 0.51 before and 5.58 ± 0.95 after vagal perineural capsaicin treatment. The inhibitory ratio for the pulmonary chemoreflex was 6.66 ± 4.13 before and 1.27 ± 0.28 after vagal perineural capsaicin treatment. In addition, the percent change in heart rate during the pulmonary chemoreflex was −64.2 ± 17.9% before and −6.7 ± 10.6% after vagal perineural capsaicin treatment.

Airway Mechanics. Inhalation of histamine produced a marked significant decrease in dynamic lung compliance ($C_{L,dyn}$) both before and after vagal blockade with perineural capsaicin treatment (Table 1), with there being no significant difference between before and after capsaicin treatment. After the combined vagal blockade and terbutaline treatments, breathing histamine aerosol did not significantly change $C_{L,dyn}$ (Table 1).

Breathing Pattern. Inhalation of histamine aerosol produced rapid, shallow breathing. The results of these experiments indicate that the two components of rapid, shallow breathing, namely f_R and V_T, are uncoupled by the series of treatments we used. The inhalation of histamine resulted in a significant increase in f_R only during control conditions before capsaicin treatment (Table 1). Inhalation of histamine aerosol after blockade of C-fibers with capsaicin resulted in a insignificant increase in f_R. After blockade plus terbutaline treatment, no further significant effects on f_R occurred. In

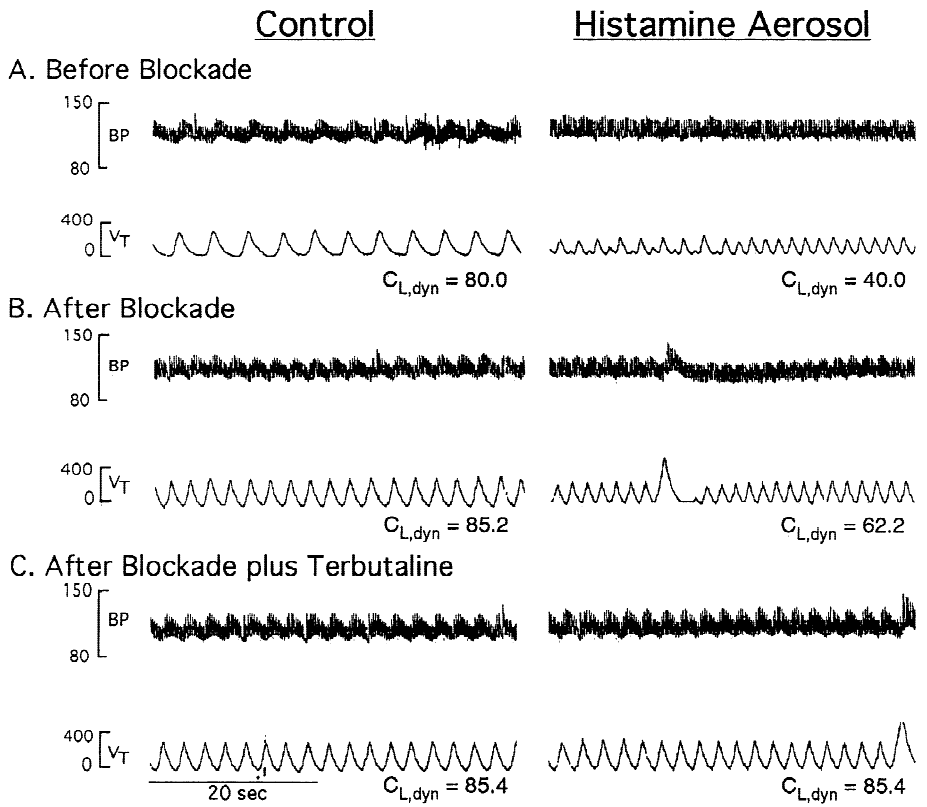

Fig. 2. Recordings from a spontaneous breathing dog showing the effect of histamine inhalation on blood pressure (*BP*, mmHg) and tidal volume (V_T, mL) before and after vagal blockade and after combination of the vagal blockade and terbutaline. Values for dynamic lung compliance ($C_{L,dyn}$, mL/cmH_2O) are given.

contrast, the two treatments used in these experiments resulted in a progressive decrease in V_T induced by histamine. The inhalation of histamine aerosol resulted in a significant decrease in V_T both before and after blockade, whereas after blockade plus terbutaline, histamine did not significantly effect V_T. The decrease in V_T after blockade was midway between that observed before blockade and after blockade plus terbutaline. Before histamine inhalation the mean minute ventilations were 8.0 ± 2.2, 9.1 ± 2.0, and 13.4 ± 2.9 L/min for the before blockade, after blockade, and the terbutaline plus blockade conditions with the increase in the terbutaline plus blockade condition being significant compared with the other two conditions. When examined as a percent change from before histamine baseline, histamine inhalation did not significantly affect minute ventilation in the before blockade and after blockade conditions (1.3 ± 15.8% and −2.8 ± 7.0%, respectively). In contrast, after blockade plus terbutaline, histamine inhalation resulted in a significant increase of 127.6 ± 37.4%.

Afferent Protocol

Tracings obtained from a dog during the afferent protocol are presented in Figs. 3 and 4; tabulated mean data can be found in Table 2.

Table 1. Effect of histamine inhalation on dynamic lung compliance, tidal volume, and breathing frequency before and after vagal blockade and after combination of vagal blockade and terbutaline

	Before vagal blockade		After vagal blockade		After vagal blockade and terbutaline	
	Before H	After H	Before H	After H	Before H	After H
$C_{L,dyn}$ (mL/cmH_2O)	66.8 ± 5.6	38.4 ± 5.8[a]	65.0 ± 9.6	45.3 ± 8.8[a]	60.7 ± 9.7	58.5 ± 9.6[b,c]
V_T (mL)	431 ± 32	228 ± 23[a]	455 ± 41	363 ± 24[a,b]	507 ± 52	488 ± 54[b]
f_R (br/min)	18.2 ± 4.7	33.7 ± 7.4[a]	19.4 ± 3.2	23.6 ± 4.1[b]	25.6 ± 3.7	28.7 ± 2.9[b]

Values presented as means ± S.E.M.
Vagal blockade, vagal perineural capsaicin treatment; H, histamine; V_T, tidal volume; f_R, respiratory frequency; $C_{L,dyn}$, dynamic lung compliance
[a] Significantly ($p \leq 0.05$) different from before H (within treatment)
[b] Significantly different from before vagal blockade (across treatment)
[c] Significantly different from after vagal blockade (across treatment)

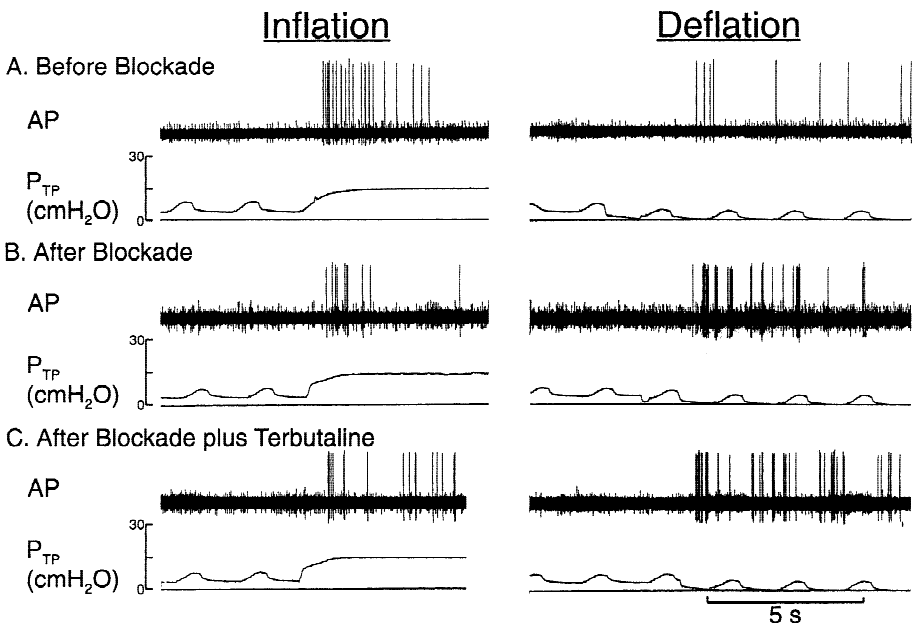

Fig. 3. Recordings of action potentials (*AP*) of a single rapidly adapting pulmonary stretch receptor during lung inflation and deflation before and after vagal blockade and after combination of the vagal blockade and terbutaline. Lung inflation was set at a transpulmonary pressure (P_{TP}) of 15 cmH_2O and lung deflation was set at a P_{TP} of 0 cmH_2O.

Airway Mechanics. When the dogs breathed histamine aerosol during the afferent experiments, changes in $C_{L,dyn}$ were very similar to the changes induced by histamine during the reflex experiments. Dynamic lung compliance decreased significantly in response to histamine aerosol both before and after vagal blockade. After the combined

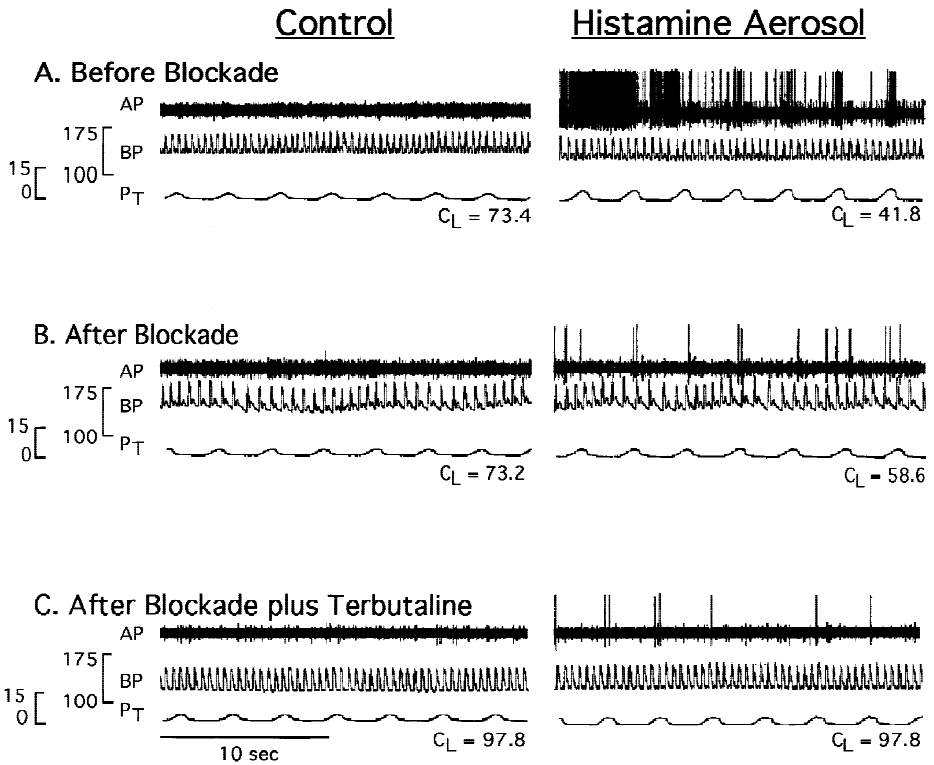

Fig. 4. Recordings from the afferent protocol of one animal showing the effect of histamine on rapidly adapting pulmonary stretch receptor activity (*AP*, impulses/s), blood pressure (*BP*, mmHg), and transpulmonary pressure (P_{TP}, cmH_2O) before and after vagal blockade and after combination of the vagal blockade and terbutaline. Values for dynamic lung compliance ($C_{L,dyn}$, mL/cmH_2O) are given.

vagal blockade and terbutaline treatments, breathing histamine aerosol did not significantly change $C_{L,dyn}$ (Table 2).

Afferent Activity. Three RARs from three different dogs were identified by their characteristic pattern of discharge when the lung was hyperinflated (by increasing end-expiratory pressure by 15 cmH_2O) and then allowed to deflate to residual volume (Fig. 3). This procedure was done before each histamine administration. Both hyperinflation and deflation of the lung produced marked increases in RAR activity. Vagal blockade or vagal blockade in combination with terbutaline treatment did not affect the ability of RARs to conduct at a high-impulse frequency with either inflation or deflation.

Inspiratory and expiratory RAR activity were examined separately. When the dogs inhaled histamine, there was a large significant increase in inspiratory activity before vagal blockade (Table 2). There were smaller insignificant increases in inspiratory activity after blockade and after the combined vagal blockade and terbutaline treatments. There was no statistically significant change in expiratory activity after histamine in any of the three conditions.

Table 2. Effect of histamine inhalation on dynamic lung compliance and rapidly adapting pulmonary stretch receptor activity before and after vagal blockade and after combination of vagal blockade and terbutaline

	Before vagal blockade		After vagal blockade		After vagal blockade and terbutaline	
	Before H	After H	Before H	After H	Before H	After H
$C_{L,dyn}$ (mL/cmH_2O)	69.2 ± 2.6	41.7 ± 4.8[a]	72.9 ± 6.4	55.0 ± 9.6[a,b]	75.9 ± 8.2	72.8 ± 8.7[b,c]
Inspiratory RAR activity (imp/sec)	0.03 ± 0.03	10.13 ± 1.57[a]	1.77 ± 1.72	2.59 ± 0.36[b]	0.73 ± 0.73	1.57 ± 0.80[b]
Expiratory RAR activity (imp/s)	0.21 ± 0.21	3.11 ± 2.22	0.00 ± 0.00	1.41 ± 1.14	0.00 ± 0.00	0.19 ± 0.19

Values presented as means ± S.E.M.

Vagal blockade, vagal perineural capsaicin treatment; H, histamine; $C_{L,dyn}$, dynamic lung compliance; RAR, rapidly adapting pulmonary stretch receptors

[a] Significantly ($p \leq 0.05$) different from before H (within treatment)

[b] Significantly different from before vagal blockade (across treatment)

[c] Significantly different from after vagal blockade (across treatment)

Discussion

In this investigation we used vagal perineural capsaicin treatment to selectively block the impulse conduction of capsaicin-sensitive vagal C-fibers. We have previously shown in dogs that this technique significantly reduces the C wave of the compound action potential, while not significantly affecting the A wave [25]. In addition, we demonstrated that perineural capsaicin treatment blocked the lung C-fiber–mediated pulmonary chemoreflex, while not blocking the slowly adapting pulmonary stretch receptor (SAR)–mediated Hering-Breuer inflation reflex [25]. The data from this study confirm these observations. In this study, conduction of RARs survived vagal blockade as demonstrated by the observation that we were still able to record the increase in RAR impulse activity initiated by lung hyperinflation and deflation cranial to the site of blockade (Fig. 3). This observation further extends the demonstration of the selectivity of vagal blockade in the dog.

We examined the pulmonary defense reflex response to aerosolized histamine in dogs before and after vagal C-fiber blockade and after vagal C-fiber blockade in combination with aerosolized terbutaline. Inhalation of histamine before vagal C-fiber blockade caused a significant reduction in dynamic lung compliance and tidal volume and a large increase in respiratory frequency and inspiratory RAR afferent activity. After vagal blockade, inhalation of histamine still caused a significant reduction in dynamic lung compliance and tidal volume. In contrast, changes in breathing frequency and RAR activity were significantly attenuated despite the fact that RARs remained sensitive to lung inflation and deflation. Inhalation of terbutaline after vagal blockade completely abolished the histamine-induced reductions in dynamic lung compliance and tidal volume. These data are consistent with the tachypnea and to a lesser extent the reduced tidal volume component of histamine-induced rapid, shallow breathing

being dependent on the conduction of intact vagal C-fibers. Our afferent recordings show that the histamine-induced increases in RAR activity were greatly attenuated by vagal blockade, whereas decreases in lung compliance were only partially attenuated. Thus, we believe our limited afferent recordings ($n = 3$) of RAR activity indicate that histamine-induced increases in RAR activity depend on intact vagal C-fibers and to a lesser extent on reductions in lung compliance.

Our results do not show a correlation between RAR activity and alterations in dynamic lung compliance (r^2 = insignificant 0.59). Before vagal treatment, we saw a 40.1% decrease in lung compliance and an increase in RAR activity of 6.5 impulses/s over the ventilator cycle with histamine inhalation. After vagal treatment, we saw a 25.7% decrease in lung compliance that was associated with an increase in RAR activity of 1.1 impulses/s. If the relationship between changes in lung compliance and RAR activity is linear as shown by Jonzon et al. [10], we would have expected an increase in RAR activity of about 4.2 impulses/s after vagal treatment. Further illustrating the poor relationship between changes in dynamic lung compliance and RAR activity, after vagal treatment and terbutaline, there was a greater increase in RAR activity for a given decrease in lung compliance than in the vagal treatment condition alone (−4.4% change in lung compliance with a 0.50 impulse/s increase in RAR activity). This would suggest that RAR activation with histamine inhalation depends on a C-fiber–mediated reflex, other than bronchoconstriction, that is abolished by vagal blockade. Further, our data after vagal blockade and vagal blockade in combination with terbutaline are also consistent with previously reported effects of bronchoconstriction on SAR activity that would be expected to decrease tidal volume [3].

Direct C-fiber stimulation by capsaicin in dogs causes reflex bradycardia, systemic hypotension, apnea followed by rapid shallow breathing, bronchoconstriction, and a reduction in dynamic lung compliance [3]. In dogs these responses are independent of RAR activity [3]. In addition, injection of capsaicin into the pulmonary circulation of dogs and sheep cause large increases in bronchial blood flow [4, 17]. In dogs, this reflex is evoked primarily by centrally mediated reflex pathways but also in part by locally mediated release of neuropeptides by way of C-fiber axon reflexes [17, 19]. Our data show that the direct or indirect histamine-induced decrease in dynamic lung compliance was not completely responsible for the increase in RAR activity. We suggest that a C-fiber–mediated reflex increase in bronchial blood flow [17] may have played a role in this C-fiber–dependent stimulation of RARs because perineural capsaicin treatment affects the conduction of action potentials at the site of application immediately and only slowly causes the depletion of neuropeptides from C-fiber terminal endings [7]. Like us, Ravi [21] showed that histamine-induced RAR activity was independent of airway smooth muscle contraction as measured by a change in airway mechanics. Ravi et al. [21] have hypothesized that the histamine-induced increase in bronchial vascular permeability [16] leading to fluid increases in the extrapulmonary space may be responsible for histamine's effect on RAR activity. Lending support to this view is the fact that pulmonary venous congestion [11] and obstruction of lymphatic fluid [20] leads to RAR activation. Such a vascular-dependent mechanism for the stimulation of RARs would appear to be mutually exclusive from those studies whose data support that RARs monitor lung compliance in dogs [10, 18]. However, these studies used negative airway pressure to produce a transient decrease in lung

compliance. How lung collapse influences airway fluid balance, however, is unclear. Such a stimulus might be expected to alter Starling forces within the airway to favor filtration and therefore increase airway interstitial pressure and provide an additional stimulus for RARs.

After vagal blockade, inhalation of histamine aerosol continued to induce shallow breathing that was abolished by the bronchodilator terbutaline. Further, on the basis of our RAR recordings, our data suggest that shallow breathing that survived vagal blockade is not mediated by RARs. By exclusion this suggests that this blockade-resistant shallow breathing is mediated by histamine-induced alterations in SAR discharge pattern. This is consistent with previous observations of the effects of decreases in lung compliance [18, 27] and bronchoconstriction [6] on SAR discharge pattern. Yu et al. [27] found that a 30% reduction in compliance resulted in a significant increase in SAR discharge at peak inflation. Davenport et al. [6] found that acetylcholine-induced bronchoconstriction markedly increased the activity of all SARs studied during inflation. If similar alterations in SAR discharge pattern during inflation occurred in our study after histamine aerosol inhalation, we would expect SARs to contribute to the observed reduction in tidal volume [3] and possibly play an important role blunting baseline minute ventilation and increases in minute ventilation after histamine inhalation. Consistent with this possibility is that when the airways are dilated with terbutaline, the braking effect of SARs on minute ventilation appears to be lost and histamine inhalation produces a large significant increase in minute ventilation.

Although limited our data suggest a complicated interaction between the activation of lung C-fibers, RARs, and SARs and the contribution of this interdependent afferent activation to changes in lung mechanics, breathing pattern, and minute ventilation before and after the inhalation of histamine aerosols. In addition, the limited number of RARs studied appeared to be primarily activated by some C-fiber–mediated reflex other that bronchoconstriction, with either C-fiber reflex–dependent or independent changes in lung mechanics playing a minor role.

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References

1. Amdur MO, Mead J (1958) Mechanics of respiration in unanesthetized guinea pigs. Am J Physiol 192:364–368
2. Bonham AC, Kott KS, Ravi K, Kappagoda CT, Joad JP (1996) Substance P contributes to rapidly adapting receptor responses to pulmonary venous congestion in rabbits. J Physiol 493:229–238
3. Coleridge HM, Coleridge JCG (1986) The control of breathing, Part I: Reflexes evoked from tracheobronchial tree and lungs. In: Fishman AP, Cherniack NS, Widdicombe JG, Geiger SR (eds) Handbook of Physiology, Section 3: The Respiratory System. American Physiological Society, Bethesda, MD, pp 395–429
4. Coleridge HM, Coleridge JCG, Green JF, Parsons GH (1992) Pulmonary C-fibers stimulation by capsaicin evokes reflex cholinergic bronchial vasodilation in sheep. J Appl Physiol 72:770–778
5. Coleridge HM, Coleridge JCG, Schelegle ES, Green JF (1993) Acute inhalation of ozone stimulates bronchial C-fibers and rapidly adapting receptors in dogs. J Appl Physiol 74:2345–2352
6. Davenport PW, Lee LY, Lee K, Yu LK, Miller R, Frazier DT (1981) Effect of bronchoconstriction on the firing behavior of pulmonary stretch receptors. Respir Physiol 46:295–307

7. Games R, Holzer P, Lembeck F (1980) Decrease in substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br J Pharmacol 58:207–213
8. Green JF, Kauffman MP (1990) Pulmonary afferent control of breathing as end-expiratory lung volume decreases. J Appl Physiol 68:2186–2194
9. Hargreaves M, Ravi K, Kappagoda CT (1993) Effect of bradykinin on respiratory rate in anaesthetized rabbits: role of rapidly adapting receptors. J Physiol 486:501–513
10. Jonzon A, Pissari TE, Coleridge JCG, Coleridge HM (1987) Rapidly adapting receptor activity in dogs is inversely related to lung compliance. J Appl Physiol 61:1980–1987
11. Kappagoda CT, Man GCW, Teo KK (1987) Behaviour of canine pulmonary vagal afferent receptors during sustained acute pulmonary venous pressure elevation. J Physiol 394:249–265
12. Karlsson JA (1996) The role of capsaicin-sensitive C-fibre afferent nerves in the cough reflex. Pulm Pharmacol 9:315–321
13. Kauffman MP, Coleridge HM, Coleridge JCG, Baker DG (1980) Bradykinin stimulates afferent vagal C-fibers in intrapulmonary airways of dogs. J Appl Physiol 48:511–517
14. Matsumoto S, Yamasaki M, Kanno T, Nagayama T, Tanno M, Shimizu T (1994) Substance P antagonist does not block the stimulation of rapidly adapting pulmonary stretch receptors by ammonia. Lung 172:31–45
15. Mills JE, Sellick H, Widdicome JG (1970) Epithelial irritant receptors in the lungs. In: Porter R (ed) Breathing: Hering-Breuer Centenary Symposium. Churchill, London, pp 77–92
16. Pietra GG, Fishman AP (1978) Lung water and solute exchange. In: Staub NC (ed) Lung Biology in Health and Disease, vol. 7. Marcel Dekker, Inc., New York, pp 407–422
17. Pissari TE, Coleridge JCG, Coleridge HM (1993) Capsaicin-induced bronchial vasodilation in dogs: central and peripheral neural mechanisms. J Appl Physiol 74:259–266
18. Pissari TE, Jonzon A, Coleridge JCG, Coleridge HM (1990) Rapidly adapting receptors monitor lung compliance in spontaneously breathing dogs. J Appl Physiol 68:1997–2005
19. Pissari TE, Zimmerman TE, Adrian TE, Coleridge JCG, Coleridge HM (1999) Bronchial vasodilator pathways in the vagus nerve of dogs. J Appl Physiol 86:105–113
20. Ravi K, Teo KK, Kappagoda CT (1988) Stimulation of rapidly adapting pulmonary stretch receptors by pulmonary lymphatic obstruction in dogs. Can J Physiol Pharmacol 66:630–636
21. Ravi K, Teo KK, Kappagoda CT (1989) Action of histamine on the rapidly adapting airway receptors in the dog. Can J Physiol Pharmacol 67:1499–1505
22. Roberts AM, Kaufman MP, Baker DG, Brown JK, Coleridge HM, Coleridge JCG (1981) Reflex tracheal contraction induced by stimulation of bronchial C-fibers in dogs. J Appl Physiol 51:485–493
23. Samson SR, Vidruk EH (1975) Properties of 'irritant' receptors in canine lung. Respir Physiol 25:9–22
24. Schelegle ES, Carl MI, Coleridge HM, Coleridge JCG, Green JF (1993) Contribution of vagal afferents to respiratory reflexes evoked by acute inhalation of ozone in dogs. J Appl Physiol 74:2338–2344
25. Schelegle ES, Mansoor JK, Green JF (1995) Influence of background vagal C-fiber activity on eueupneic breathing pattern in anesthetized dogs. J Appl Physiol 79:600–606
26. Widdicome JG (1996) Sensory neurophysiology of the cough reflex. J Allergy Clin Immunol 98:S84–S90
27. Yu J, Pissari TE, Coleridge JCG, Coleridge HM (1991) Response of slowly adapting pulmonary stretch receptors to reduced lung compliance. J Appl Physiol 71:425–431

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