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Cough reflex in allergic dogs

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Abstract

This study investigated the effects of antigen challenge on the cough reflex in dogs that were neonatally sensitized to ragweed. Tidal volume (V_T), respiratory rate (f), pulmonary resistance (R_L), dynamic lung compliance (C_{Dyn}) and the number and amplitude (increase in mean peak expiratory pressure) of coughs induced by mechanical stimulation of the intrathoracic trachea were measured in propofol-anesthetized dogs. Aerosolized ragweed challenge had no effect to induce spontaneous cough but increased f and R_L and reduced V_T and C_{Dyn}. Mechanical stimulation of the intrathoracic trachea at this time produced 19 ± 5 coughs with an average increase in cough amplitude of 11 ± 1 cm H_2O which differed significantly from the number (9 ± 2 coughs) and amplitude (30 ± 5.5 cm H_2O) of mechanically induced coughs after treatment with aerosolized saline. Both the number and amplitude of mechanically induced coughs returned to baseline values by 24–48 h after the ragweed challenge. Similar results were obtained after challenge with aerosolized histamine (0.3–1% histamine) that did not induce spontaneous coughs but increased f, reduced V_T and decreased C_{Dyn} and increased the number but reduced the amplitude of the mechanically induced coughs. In conclusion, both antigen and histamine bronchoprovocation changed the characteristics of the mechanically induced cough in dogs to a response of increased cough number but reduced mean expiratory cough amplitude.

Keywords: Cough; Allergic, dog; Histamine

1. Introduction

Dogs that have been neonatally sensitized to ragweed demonstrate many characteristic features of human asthma. These include the presence of elevated serum levels of immunoglobulin E (Correa et al., 1991), an acute phase bronchospasm to antigen challenge (Mapp et al., 1985; House et al., 2001), the presence of eosinophils and neutrophils in the lungs after antigen (Chung et al., 1985; Redman et al., 2000) and nonspecific airway hyperresponsiveness to several bronchoconstrictor agents (Chung et al., 1985; Mapp et al., 1985; Becker et al., 1989; House et al., 2001). Additionally, an exaggerated increase in breathing frequency to histamine bronchoprovocation occurs in allergic dogs 24 h after antigen challenge (House et al., 2001), suggesting that a condition of sensory nerve hyperresponsiveness exists in dogs after antigen provocation.

Cough has been previously measured in dogs (Sullivan et al., 1979; Jackson, 1988; Tatar et al., 1994; Chapman et al., 2001), but there are no studies that have investigated the cough reflex in this species after antigen challenge. In sensitized guinea pigs, antigen challenge stimulates coughing and heightens the cough response to inhaled capsaicin (Bolser et al., 1995; Xiang et al., 1998; Liu et al., 2001), and in humans, an exaggerated cough reflex is seen in many different lung diseases including asthma and chronic obstructive pulmonary disease (Irwin et al., 1981; Nimi et al., 1998; Doherty et al., 2000a), eosinophilic bronchitis (Gibson et al., 1989; Brightling et al., 2000), eosinophilic tracheobronchitis (Fujimura et al., 2000) and cryptogenic fibrosing alveolitis (Doherty et al., 2000b). Interestingly, there is no change in cough receptor sensitivity to inhaled capsaicin in human asthmatics 24 h after antigen challenge (Minoguchi et al., 2003) which differs from results found in guinea pigs (Xiang et al., 1998; Liu et al., 2001).

Because of this possible species difference, the cough reflex was measured in dogs that were neonatally sensitized to ragweed under baseline conditions before antigen

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challenge and at several time points after antigen bronchoprovocation. Cough was also measured after challenge with aerosolized histamine which is an important mediator of allergic reactions in dogs (Chiesa et al., 1975; Gold et al., 1977; Chrusch et al., 1999) and triggers rapid, shallow breathing that is similar to the breathing pattern typically seen after antigen challenge in dogs (Mapp et al., 1985; Chung et al., 1985; Becker et al., 1989; House et al., 2001). Cough was produced by mechanical stimulation of the carina using methods previously established to assess the cough reflex in dogs (Chapman et al., 2001).

2. Materials and methods

2.1. Animals

Studies were performed in both allergic and nonallergic male beagle dogs (weight range 8–15 kg). The allergic dogs were actively sensitized to ragweed at birth as described in detail by Theodorou et al. (1997). The nonallergic dogs were from a colony of dogs used previously for studies with experimentally induced cough (Chapman et al., 2001), but were never exposed to ragweed. The dogs were fasted overnight, but given water ad libitum. The experiments performed herein were approved by the Animal Care and Use Committee of Schering-Plough Research Institute which is a facility accredited by the American Association for the Accreditation of Laboratory Animal Care.

2.2. Animal preparation

The front paw was shaved and a Surflo® catheter (Terumo Medical; Elkton, MD, USA) was inserted into the cephalic vein. A Surflo® injection plug was connected to the i.v. catheter to facilitate the injection of drugs. Anesthesia was induced by i.v. bolus injection of propofol (Diprivan; Zeneca Pharmaceuticals, Wilmington, DE, USA) at a dose of 8 mg/kg given over a 1-min period. Immediately following the propofol injection, a cuffed endotracheal tube (Rusch, Waiblingen, Germany; size 7.0 mm) was inserted into the trachea with the aid of a laryngoscope. A balloon-tipped polyethylene catheter (i.d. = 2 mm) was inserted through the mouth into the esophagus and positioned at a location in the mid-thoracic region. Propofol was infused continuously throughout the experiments (0.3–0.8 mg/kg/min) using an infusion pump (Gemini, PC-2TX; Imed, San Diego, CA, USA). The rate of propofol infusion was optimized for each dog such that cough was produced upon deflation and reinflation of the cuff on the endotracheal tube as previously described (Chapman et al., 2001). The dogs were studied in the supine position.

The endotracheal tube was connected to a heated pneumotachograph and the differential pressure across the pneumotachograph was measured with a transducer (model MP 45-14-871; Validyne, Northridge, CA, USA) for the derivation of pulmonary airflow ($\dot{V}$). Tidal volume (V_T) was measured by electrical integration of the flow signal. Transpulmonary pressure (Ptp) was measured with a differential pressure transducer (model MP-45-24-87; Validyne) as the pressure difference between the esophageal catheter and a port at the front of the endotracheal tube. The $\dot{V}$, V_T and Ptp signals were used for the derivation of pulmonary resistance (R_L) and dynamic lung compliance (C_{Dyn}) according to the method of Roy (1974) using a pulmonary function analyzer (model XA; Buxco Electronics, Sharon, CT, USA). Additionally, the $\dot{V}$, V_T and Ptp signals were displayed on a chart recorder (MFE, Beverly, MA, USA).

Mean arterial blood pressure was measured throughout the experiments with a Dinamap veterinary blood pressure monitor (model 8300; Critikon, Tampa, FL, USA) using an inflatable cuff around the hind paw. Arterial oxygen saturation and heart rate were measured with a pulse oximeter (model 8500V, Nonin Medical, Minneapolis, MN, USA) that was clipped onto the tongue. End-tidal CO_2 was measured directly at the tip of the endotracheal tube using a Cardiocap monitor (Datex-Engstrom, Helsinki, Finland).

2.3. Induction of cough

Cough was induced by mechanical stimulation of the intrathoracic trachea. This was produced by disconnecting the endotracheal tube from the pneumotachograph and cough was stimulated by inserting and withdrawing a predetermined length of fishing line (25-lb test, Berkley, Spring Lake, IA, USA) through the endotracheal tube. The length of the fishing line was set to extend approximately 2 in. beyond the tip of the endotracheal tube to stimulate the intrathoracic trachea in the region of the carina. Cough was defined behaviorally and the number and amplitude of coughs were measured for each cough trial (see Experimental protocols) with amplitude measured as the increase in mean expiratory pressure (P_{EXP}) (cm H_2O) over the baseline values which were obtained during normal tidal breathing immediately before the induction of cough. These measurements were obtained from the chart recorder.

2.4. Experimental protocols

To characterize the pulmonary response to mechanical activation of the intrathoracic trachea and determine the optimum stimulation conditions to evaluate the effects of antigen and other interventions, experiments were performed on the 10 allergic dogs before antigen challenge. Pulmonary measurements of V_T, respiratory rate (f), minute volume ($MV = V_T \times f$), R_L and C_{Dyn} were first recorded to obtain baseline values. The endotracheal tube was then

disconnected from the pneumotachograph and the intrathoracic trachea was stimulated for 1 s by inserting then withdrawing the fishing line once through the endotracheal tube. This induced a brief period of coughing followed by a period of apnea. When normal breathing had resumed, the intrathoracic trachea was then stimulated for 5 s produced by inserting then withdrawing the fishing line five times. When normal breathing had resumed, this procedure was then repeated by inserting then withdrawing the fishing line 10 times over a 10-s period. At the end of this 10-s stimulation, when normal breathing had resumed, the endotracheal tube was connected to the pneumotachograph and pulmonary functions were measured for 3 min. At the end of this 3-min period, the anesthesia was discontinued and the dogs were allowed to recover and returned to their cages.

To compare the baseline cough reflex in ragweed-sensitized dogs before antigen challenge to that seen in nonallergic dogs that were never exposed to ragweed, 10 dogs in each group were prepared for the assessment of cough followed by mechanical stimulation of the intrathoracic trachea for 5 s. This stimulus duration was selected for this experiment and for studies with antigen and histamine challenge as both the number of coughs and the expiratory force of the coughs were submaximal compared to the 10-s stimulation but were consistently more than that seen with the 1-s stimulation (see Results).

To evaluate the effect of antigen challenge on the cough reflex, 10 allergic dogs were exposed to aerosolized ragweed (Bayer, Elkhart, IN, USA) or saline. The aerosols were generated with a jet nebulizer (Raindrop; Puritan Bennett, Lenexa, KS, USA) at a flow of 150 ml/min at 40 pounds per square inch (psi) pressure. Previous studies have found this aerosol delivery system to produce an aerosol with a mass median aerodynamic diameter of 3.2 μm (Abraham et al., 1986). Pulmonary functions were measured immediately before 10 consecutive inhalations of either ragweed or saline aerosol that were delivered to the dogs via a one-way breathing valve (Hans-Rudolph). A cough trial was performed using a 5-s stimulation paradigm approximately 9 min after the ragweed or saline challenge to coincide with the peak ventilatory response to the ragweed (see Results). At the end of the cough trial, i.e. approximately 10 min after the ragweed or saline challenge, the dogs were connected to the pneumotachograph and lung functions were measured. The dogs were then recovered from the anesthesia and returned to their cage. Twenty-four hours after challenge with ragweed or saline, the dogs were anesthetized and the cough reflex was measured. This procedure was repeated at 48 h after the ragweed or saline challenge.

In studies involving histamine aerosol challenge, baseline lung functions were measured and a cough trial with 5-s stimulation was performed. The dogs were then challenged with five consecutive breaths of aerosolized histamine dihydrochloride (0.3–1% histamine, free base) that was optimized for individual dogs in pilot studies to yield a clear pharmacological response characterized by rapid, shallow breathing and a reduction in C_{Dyn}. The delivery of the aerosolized histamine was identical to that described for the ragweed challenge. Approximately 1 min after the histamine challenge, a cough trial was performed followed immediately by the measurement of lung functions. These studies were performed in 10 dogs challenged with either aerosolized histamine or aerosolized saline.

2.5. Statistics

Experiments with ragweed and histamine challenge were performed using a randomized, cross-over experimental design. Statistically significant effects for the ragweed experiments were evaluated using a repeated measures analysis of variance with post-hoc analysis using paired *t*-test. A paired *t*-test was also used for the studies with histamine. A P value ≤ 0.05 was considered a statistically significant effect.

3. Results

3.1. Characterization of the cough reflex

The results in Fig. 1 show the number and P_{EXP} of coughs in the 10 allergic dogs after stimulation of the intrathoracic trachea for 1, 5 and 10 s, respectively. There was an increase in both the number and the P_{EXP} of the coughs after stimulation for 1, 5 and 10 s, although the P_{EXP} tended to plateau in response to the 10-s stimulation. The duration of cough for the 1-, 5- and 10-s stimulation was

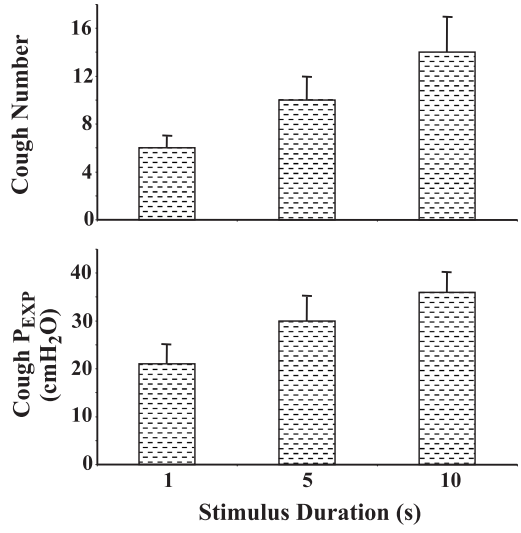

Fig. 1. Effect of mechanical stimulation of the intrathoracic trachea for 1, 5 and 10 s on the number and peak expiratory pressure (P_{EXP}) of coughs in allergic dogs. Values are mean ± S.E.M. ($n = 10$).

Table 1
Lung functions after stimulation of the carina for 10 s[a]

	Post-stimulation			
	Baseline	30 s	1 min	3 min
V_T (ml)	120 ± 11	114 ± 8	124 ± 11	130 ± 8
f (breaths/min)	22 ± 3	23 ± 2	21 ± 2	20 ± 2
MV (ml/min)	2437 ± 164	2570 ± 215	2490 ± 107	2486 ± 140
R_L (cm H_2O/l/s)	4.53 ± 0.20	4.71 ± 0.20	4.82 ± 0.26	4.69 ± 0.17
C_{Dyn} (ml/cm H_2O)	53 ± 6	52 ± 5	48 ± 4	49 ± 4

Definition of abbreviations: V_T = tidal volume; f = respiratory frequency; MV = minute volume; R_L = pulmonary resistance; C_{Dyn} = dynamic lung compliance.
[a] Values are mean ± S.E.M. (n = 10).

8 ± 2, 17 ± 3 and 21 ± 3 s, respectively. There were no significant changes in V_T, f, MV, R_L or C_{Dyn} for up to 3 min after the final 10-s stimulation (Table 1). All subsequent experiments were performed with the 5-s stimulation.

3.2. Effect of antigen on cough

The results show in Fig. 2 show the cough count and the P_{EXP} generated during the cough after mechanical stimulation of the intrathoracic trachea in both sensitized dogs before ragweed challenge and nonsensitized dogs that were never exposed to ragweed. There was no difference between these two groups for both the number and the P_{EXP} of coughs (Fig. 2), nor was there any difference in the duration of cough and the period of apnea following the cough (approximately 15 s) between these two groups (data not shown).

Compared to the baseline values, ragweed challenge to sensitized dogs increased f (178% ↑), reduced V_T (22% ↓) and increased MV (90% ↑) (Table 2). Ragweed challenge to these dogs also increased R_L (30% ↑) and reduced

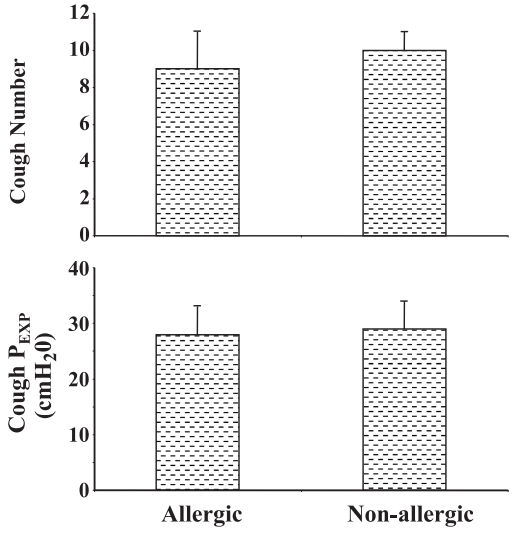

Fig. 2. Effect of mechanical stimulation of the intrathoracic trachea (5-s duration) on the number and peak expiratory pressure (P_{EXP}) of coughs in allergic and nonallergic dogs. Values are mean ± S.E.M. (n = 10 per group).

Table 2
Effect of antigen on ventilation and lung mechanics in dogs

Parameter	Baseline	Antigen[a]
V_T (ml)	135 ± 8	105 ± 12
f (breaths/min)	18 ± 2	50 ± 11[b]
MV (ml/min)	2258 ± 216	4291 ± 760[b]
R_L (cm H_2O/l/s)	4.46 ± 0.26	5.78 ± 0.47[b]
C_{Dyn} (ml/cm H_2O)	58 ± 8	35 ± 5[b]

Values are mean ± S.E.M. (n = 10).
[a] Measurements obtained approximately 10 min after challenge with aerosolized ragweed.
[b] P < 0.05 compared to baseline.

C_{Dyn} (40% ↓), and the effects of ragweed on each of these parameters peaked between 5 and 9 min after challenge, but persisted for at least 15 min after the challenge. Aerosol saline challenge had no effect on ventilation or on lung mechanics (data not shown).

The results in Fig. 3 show the cough count induced by mechanical stimulation of the intrathoracic trachea at 10 min, 24 and 48 h after aerosolized saline or ragweed challenge in the 10 allergic dogs. Also shown is the mechanically induced cough count in these same 10 dogs under baseline conditions of no aerosol challenge. There was a statistically significant increase in the number of mechanically induced coughs 10 min and 24 h after ragweed challenge compared to the saline control. By 48 h after ragweed, the number of mechanically induced coughs was similar to that seen in the saline-challenged controls and to the number of coughs seen under the baseline conditions. When the results are analyzed in terms of cough frequency, mechanical stimulation of the intrathoracic trachea under baseline conditions (0.59 ± 0.07 coughs/s) did not change by 10 min (0.62 ± 0.10 coughs/s), 24 h (0.66 ± 0.06 coughs/s) or 48 h (0.64 ± 0.06 coughs/s) after aerosolized saline. However, after aerosolized ragweed challenge, cough frequency significantly (P < 0.05) increased at 10 min (1.40 ± 0.16 coughs/s), but returned to

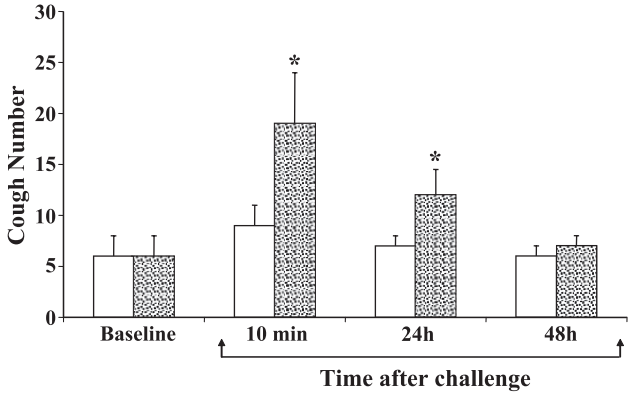

Fig. 3. Number of coughs induced by mechanical stimulation of the intrathoracic trachea (5-s duration) in allergic dogs before (baseline) and after challenge with aerosolized saline -□- or ragweed -⊠-. Values are mean ± S.E.M. (n = 10 per treatment). *P < 0.05 compared to saline.

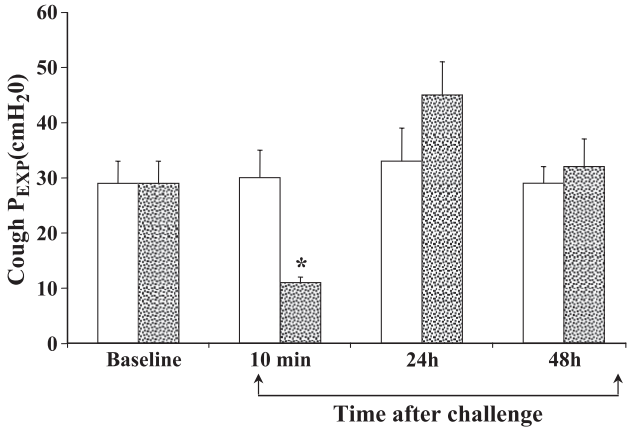

Fig. 4. Cough peak expiratory pressure (P_{EXP}) to mechanical stimulation of the intrathoracic trachea (5-s duration) in allergic dogs before (baseline) and after challenge with aerosolized saline -□- or ragweed -⊠-. Values are mean ± S.E.M. ($n = 10$ per treatment). *$P < 0.05$ compared to saline.

baseline values by 24 h (0.68 ± 0.09 coughs/s) and 48 h (0.49 ± 0.08 coughs/s) after challenge. The ragweed challenge by itself did not induce cough.

The amplitude of the mechanically induced coughs was significantly ($P < 0.05$, analysis of variance) changed by ragweed challenge to the 10 allergic dogs with statistically significant reductions in cough P_{EXP} seen 10 min after ragweed challenge compared to aerosol saline-challenged controls (Fig. 4). In contrast, 24 h after the challenge, the mechanically induced cough P_{EXP} was slightly but not significantly ($P = 0.13$) higher in ragweed-challenged dogs compared to saline-challenged controls. By 48 h after ragweed, cough P_{EXP} was not different to that seen in the saline-challenged controls or to the cough P_{EXP} seen under the baseline conditions.

3.3. Effect of histamine on cough

Histamine aerosol challenge (0.3–1% histamine) did not induce spontaneous coughs but increased *f* and MV, reduced V_T and C_{Dyn} and slightly increased R_L (Table 3). Mechanical stimulation of the intrathoracic trachea immediately after the histamine challenge increased the number of coughs compared to values seen in the same dogs immediately before the histamine challenge (Fig. 5). Furthermore, the cough

Table 3
Effect of histamine on ventilation and lung mechanics in dogs

Parameter	Baseline	Histamine[a]
V_T (ml)	127 ± 14	70 ± 6[b]
f (breaths/min)	25 ± 6	73 ± 7[b]
MV (ml/min)	2391 ± 287	3389 ± 704
R_L (cm H_2O/l/s)	5.49 ± 0.36	5.97 ± 0.49
C_{Dyn} (ml/cm H_2O)	40 ± 3	26 ± 3[b]

Values are mean ± S.E.M. ($n = 10$).
[a] Measurements obtained approximately 2 min after challenge with aerosolized histamine.
[b] $P < 0.05$ compared to baseline.

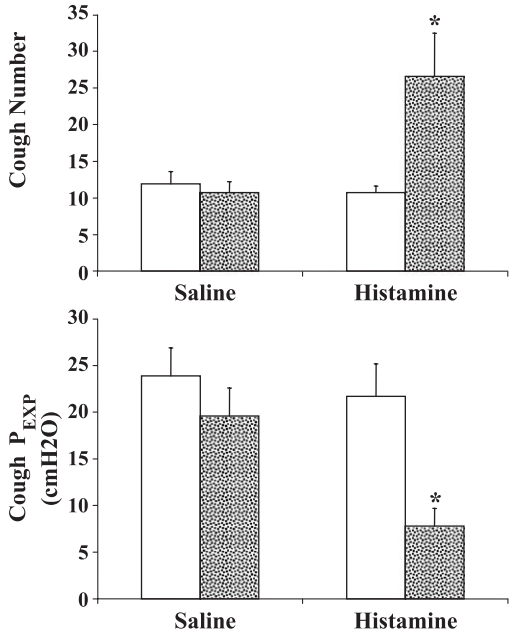

Fig. 5. Effect of histamine on the number and peak expiratory pressure (P_{EXP}) of mechanically induced coughs in allergic dogs. Values are mean ± S.E.M. ($n = 10$ per treatment) before -□- and after -⊠- challenge with aerosolized saline or histamine (0.3–1% histamine). *$P < 0.05$ compared to values before challenge.

frequency induced by mechanical stimulation of the intrathoracic trachea was significantly increased after the histamine challenge (2.17 ± 0.18 coughs/s) compared to values seen before the histamine challenge (0.94 ± 0.08 coughs/s). The magnitude of the cough P_{EXP} after the histamine challenge was significantly reduced compared to values seen before the challenge (Fig. 5). On the other hand, the number, frequency and amplitude of mechanically induced coughs were unchanged immediately after challenge with aerosolized saline (Fig. 5).

4. Discussion

The major findings in this study demonstrate that anesthetized allergic dogs challenged with antigen exhibit an altered cough response to mechanical stimulation of the intrathoracic trachea. Ten minutes after the antigen challenge, mechanical stimulation of the carina produced a cough response of increased cough number but reduced cough amplitude. By 24 h after antigen, the number of mechanically induced coughs was slightly increased relative to that seen in saline-challenged controls, but cough amplitude had returned to normal. By 48 h after antigen, both the number and amplitude of the mechanically induced coughs were identical to that seen in saline-challenged controls. Similar findings were obtained after challenge with aerosolized histamine that produced an increase in the number of mechanically induced coughs with reduced cough amplitudes.

The technique that we used to measure cough is identical to that previously described in dogs to study the cough reflex after intratracheal instillation of water into the airway (Chapman et al., 2001). This method involves the measurement of esophageal pressure to monitor changes in mean expiratory pressure following activation of the cough reflex. In this study, cough was produced by mechanical stimulation of the intrathoracic trachea which is a method widely used to evaluate the cough reflex (Sullivan et al., 1979; Bolser, 1991). Mechanical stimulation of the intrathoracic trachea produced coughs of increasing number and intensity when stimulations were performed over a 1-, 5- and 10-s period. The number of mechanically induced coughs produced after a 5-s stimulation averaged 8 coughs in this study which is similar to the number of coughs generated by a 10–15 s stimulation in cats (Bolser, 1991). The sensory afferent nerves triggering mechanically induced cough are probably the myelinated, rapidly adapting receptors because the region of the carina is densely innervated by these nerves, and bronchial 'C' fibers and slowly adapting stretch receptors, which are the other important sensory nerves in this region of the airway, are relatively insensitive to mechanical stimulation (Coleridge and Coleridge, 1986).

An important finding in this study were the changes in mechanically induced cough after antigen challenge. Immediately after the antigen challenge, mechanical stimulation of the intrathoracic trachea produced coughing of increased frequency but reduced amplitude. In contrast, mechanical stimulation of the carina in these same dogs 24 h later produced a slight increase in the number and amplitude of the coughs. By 48 h after antigen, the number and amplitude of the coughs were back to normal. To our knowledge, these are the first results to show the temporal changes in both the number and amplitude of mechanically induced coughs after antigen challenge, although previous studies in guinea pigs demonstrate a heightened sensitivity in both the number and the frequency of capsaicin-induced coughs after antigen challenge (Xiang et al., 1998; Liu et al., 2001; Katayama et al., 2001).

Several factors may contribute to the change in cough pattern after antigen challenge. Histamine is an important allergic mediator in dogs (Chiesa et al., 1975; Gold et al., 1977; Chrusch et al., 1999) and is involved in acute phase allergic reactions in this species such as bronchoconstriction and rapid shallow breathing. In canine airways, histamine does not stimulate the rapidly adapting receptors directly, but sensitizes these receptors to mechanical deformation (Coleridge et al., 1978; Dixon et al., 1979). Additionally, histamine constricts airway smooth muscle and reduces lung compliance in dogs which may also sensitize the rapidly adapting receptors (Coleridge and Coleridge, 1986). Therefore, endogenously released histamine may contribute to the increased cough numbers seen after mechanical stimulation of the intrathoracic airway in allergen-challenged dogs. The fact that exogenous histamine challenge also produced increased numbers of mechanically induced coughs is consistent with this hypothesis. It is possible that other mediators of allergy and inflammation may be involved in the alterations of mechanically induced cough. For example, in guinea pigs, tachykinins sensitize the cough reflex to inhaled capsaicin (Xiang et al., 1998; Liu et al., 2001), and in dogs, tachykinins have a number of pharmacological effects on airway nerves (Sherwood et al., 1997, 1998). Prostaglandins and leukotrienes are also important allergy mediators in dogs (Kleeberger et al., 1986; Correa et al., 1991; Chrusch et al., 1999), and these agents may sensitize airway sensory nerves (Coleridge and Coleridge, 1986). Additional studies will be required to fully elucidate the interactions of these mediators on the cough reflex in allergic dogs.

There may also be a contribution from the change in respiratory drive to the altered cough pattern seen in the allergic dogs immediately after antigen or after histamine bronchoprovocation. Ventilation changed to a rapid shallow breathing pattern after both antigen and histamine challenge. Under these conditions, there may be insufficient time for inspiration to expand lung volume to a level necessary for the genesis of large amplitude coughs. Furthermore, the increased cough frequency seen after antigen or histamine may be due to the altered respiratory cycle pattern. In other words, the rapid, shallow breathing pattern may contribute to the increased cough frequency and low cough amplitudes seen immediately after the antigen and histamine challenge. Consistent with this hypothesis, Tatar et al. (1988) found that the strength of the cough reflex induced by mechanical stimulation of the tracheobronchial mucosa in cats was reduced during the rapid shallow breathing phase after i.v. injection of the C-fiber stimulant, phenylbiguanide.

The results of this study have several important implications to the pathogenesis of cough clinically. For example, a heightened cough frequency was found during the acute phase allergic response in our dogs. Similar findings have been reported during acute severe exacerbations of asthma in children who exhibit cough as a major symptom of their diseases (Chang et al., 1997). Following the acute phase response to antigen challenge, the changes in pattern of mechanically induced cough diminished over time and, by 48 h after antigen had returned to normal. Furthermore, there was no difference between allergic and nonallergic dogs in the number and amplitude of mechanically induced coughs under baseline conditions. Therefore, a long-lasting state of altered cough responsiveness does not exist in these allergic dogs. Similar results to these are found in human asthmatics that find no change in cough receptor sensitivity a few days after antigen challenge or following an acute asthma exacerbation (Chang et al., 1997; Minoguchi et al., 2003). Finally, clinical studies in human asthmatics find no correlation between the degree of bronchoconstrictor hyperresponsiveness and hypersensitivity of the cough reflex (Doherty et al., 2000a; Ternesten-Hasséus et al., 2002). These findings are similar to the results found in our study that demonstrate a return of the

altered cough profile back to normal by 48 h after antigen challenge even though a prolonged period of bronchoconstrictor hyperresponsiveness exists in dogs for several months after antigen challenge (Becker et al., 1989).

In summary, the results in this study demonstrate an altered cough reflex in allergic dogs after antigen challenge. Similar findings were obtained after challenge with aerosolized histamine suggesting that endogenously released histamine may contribute to this altered cough response. These results build upon a growing body of evidence that show allergic dogs possess many of the characteristic features of human inflammatory airway diseases including changes in the cough reflex immediately after antigen challenge.

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