

Mode of Action of Halothane on Histamine-induced Airway Constriction in Dogs with Reactive Airways

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To determine if clinical concentrations of halothane have direct relaxant effects on airway smooth muscle, the authors compared dose-response curves to histamine in the control state (thiopental) and during halothane anesthesia (1.0 and 1.5 MAC), in six basenji-greyhound (BG) dogs untreated and pretreated with atropine aerosols ($10 \text{ mg} \cdot \text{ml}^{-1}$). Pulmonary resistance (R_L) and dynamic compliance (C_{dyn}) were continuously monitored. Baseline airway tone was not significantly different during thiopental, halothane (1.0 MAC and 1.5 MAC), and after atropine aerosol administration. During thiopental anesthesia, histamine produced dose-related increases in R_L and decreases in C_{dyn} . Both halothane and atropine significantly attenuated the bronchoconstriction induced by histamine $1 \text{ mg} \cdot \text{ml}^{-1}$. There were no significant differences in the extent of antagonism of histamine-related bronchoconstriction between halothane (1.0 MAC and 1.5 MAC) and the atropine aerosol. Moreover, in four dogs halothane anesthesia in the presence of atropine offered no additional protection compared with atropine alone. Because the protection afforded by halothane was not greater than that of atropine pretreatment alone, and the addition of halothane to atropine failed to increase the protection, it is concluded that block of vagal reflexes was the major action of halothane responsible for the attenuation of histamine-induced bronchoconstriction. (Key words: Anesthetics, volatile: halothane. Complications, asthma: airway resistance; bronchoconstriction. Lung: asthma; compliance; respiratory resistance. Parasympathetic nervous system: atropine.)

ALTHOUGH HALOTHANE PREVENTS and reverses airway constriction in subjects with asthma¹⁻³ and blocks a variety of airway reflexes,^{4,5} it is not known whether halothane in clinically used concentrations has direct effects on airway smooth muscle.

Histamine triggers airway constriction by both a direct action on airway smooth muscle *via* histamine-1 receptors and a vagal reflex evoked by the stimulation of subepithelial neural receptors within the airway⁶⁻⁹ (fig. 1). Anticholinergic drugs abolish the reflex component by antagonizing the actions of endogenously released acetylcholine at the neuromuscular junction.^{10,11}

Because atropine aerosols can block the acetylcholine-mediated reflex component of histamine-induced bronchoconstriction, they provide a means of determining whether halothane in clinically used concentrations has direct effects on the airways. We therefore compared, in dogs with nonspecific airway reactivity, dose-response

curves to histamine aerosols in the control state and during halothane anesthesia, untreated and pretreated with atropine.

Methods

Six basenji-greyhound (BG) cross-bred dogs, 2-3 yr of age and weighing 17 to 22 kg, were selected for use in this study. The studies were conducted in random order with a 1-week interval between successive studies in any one dog. Each animal served as its own control. The unpremedicated dogs were anesthetized in the standing position, supported by a sling. After induction of anesthesia with intravenous thiopental ($12 \text{ mg} \cdot \text{kg}^{-1}$), the dogs were paralyzed with succinylcholine ($0.5 \text{ mg} \cdot \text{kg}^{-1}$) and intubated with an 8.5 or 9 mm cuffed endotracheal tube. Each dog was ventilated with 100% oxygen by a piston-type ventilator (Harvard Apparatus, Millis, MA) set to deliver a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$, at a frequency of $15 \cdot \text{min}^{-1}$. The electrocardiogram was monitored continuously throughout anesthesia. An esophageal balloon (Dynasciences, Blue Bell, PA) was placed in the esophagus under direct vision and positioned at the point where the recorded end-expiratory pressure was the lowest. The balloon contained 0.8-1.5 ml of air. A separate catheter, connected to suction, was placed in the esophagus to keep it empty of air and liquid.

Pulmonary resistance (R_L) and dynamic compliance (C_{dyn}) were calculated from simultaneous pressure and flow curves during fixed volume controlled ventilation.^{12,†} Transpulmonary pressure was measured with a differential pressure transducer (Hewlett-Packard 270, Waltham, MA) connected to the esophageal balloon and to a needle inserted into the tracheal tube. Air flow was measured with a pneumotachograph head (Hewlett-Packard 21071B, Waltham, MA) and a differential flow transducer (Hewlett-Packard 47304A, Waltham, MA). Tidal volume was obtained by continuous electrical integration of the flow signal. Pressure, flow, and volume signals were recorded with a thermal tip recorder (Hewlett-Packard 7754A, Waltham, MA) and simultaneously fed to a pulmonary mechanics computer (Buxco 6, Buxco Electronics, Inc., Sharon, CT). Calculated values of R_L and C_{dyn} were converted to digital signals *via* a DL-12 data logger (Buxco Electronics, Inc., Sharon, CT) and then printed as R_L and

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‡ Rattennborg CC, Kain M: Cardiopulmonary Facts (English translation) 2:1-13, 1961.

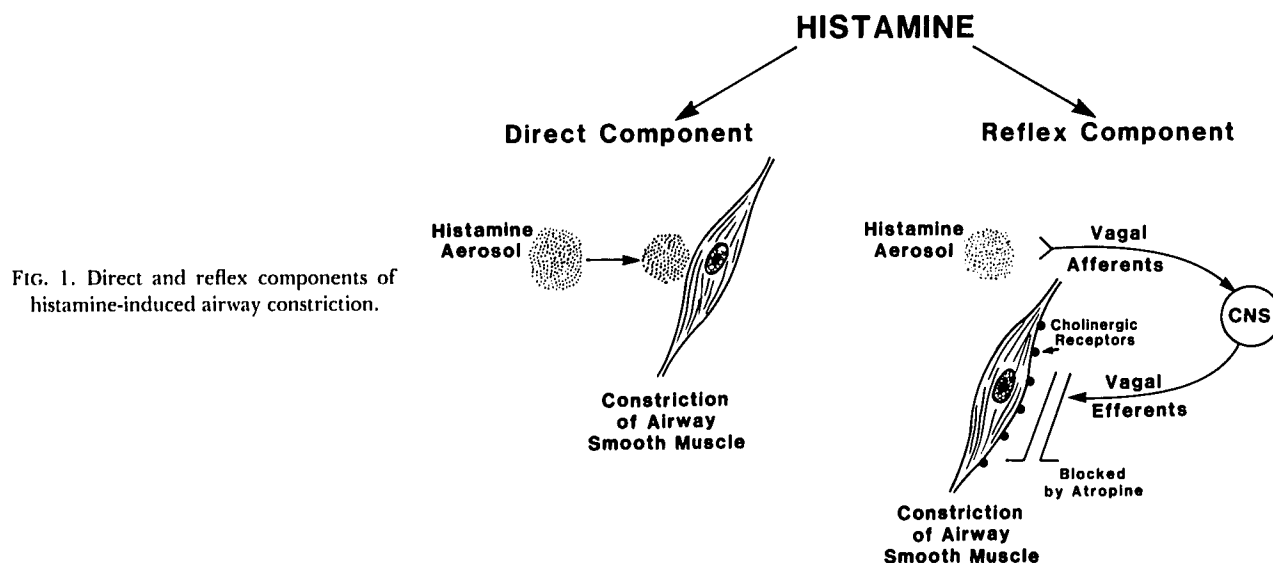


FIG. 1. Direct and reflex components of histamine-induced airway constriction.

C_{dyn} on an input-output terminal (Texas Instruments 703, Temple, TX). Running averages of the integrated values were printed every 12 s.

Histamine aerosols from freshly prepared solutions were administered as a series of challenges, with increasing drug dose (0.1, 0.3, and 1.0 $\text{mg} \cdot \text{ml}^{-1}$), for 5 breaths with a 10-min interval between challenges. Breaths were standardized by occluding the expiratory port of an Ayre's T-piece until an inflation pressure of 15 cmH_2O was attained, for each of the 5 breaths. Reproducibility of the airway response to histamine was confirmed in three dogs.

Histamine aerosols were administered to each dog under four separate circumstances at least 1 week apart: thiopental control (fig. 2A), atropine thiopental (fig. 2B), halothane (fig. 2C), and atropine halothane (fig. 2D). The six animals received thiopental 12 $\text{mg} \cdot \text{kg}^{-1}$ initially followed by 3 $\text{mg} \cdot \text{kg}^{-1}$ at 15-min intervals in control studies (fig. 2A) and in studies involving atropine aerosol pretreatment (fig. 2B) (10 $\text{mg} \cdot \text{ml}^{-1}$ administered for 5 min). In studies involving halothane, the six dogs received thiopental 12 $\text{mg} \cdot \text{kg}^{-1}$ followed by halothane (fig. 2C). End-tidal halothane concentration was continuously measured with a mass spectrometer (Perkin Elmer 1100, Pomona, CA) until a steady-state end-tidal halothane concentration at the desired MAC (1 MAC or 1.5 MAC) was established and baseline values of R_L and C_{dyn} recorded prior to histamine challenge. MAC of halothane was taken to be 0.87%.¹³ In four of the six dogs, the airway response to histamine was also measured after atropine aerosol pretreatment during halothane 1.5 MAC anesthesia (fig. 2D).

Values of R_L and C_{dyn} 1 min prior to histamine challenge and 1 min after each histamine challenge (peak effect) were used for statistical analysis. R_L and C_{dyn} were expressed as absolute values and as a ratio of the postchal-

lenge to the prechallenge values. All data were reported as mean \pm SEM and were analyzed by the Friedman non-parametric multiple comparison test.¹⁴ The level of statistical significance used was $P < 0.05$.

Results

Baseline R_L and C_{dyn} were not significantly different in control studies (thiopental anesthesia), during anesthesia with halothane 1.0 MAC and 1.5 MAC, and after atropine pretreatment during thiopental anesthesia (table 1).

In control studies histamine aerosols produced dose-related increases in R_L (fig. 3) and decreases in C_{dyn} (fig. 4). Histamine 1 $\text{mg} \cdot \text{ml}^{-1}$ increased R_L 4.0 ± 0.43 (mean \pm SEM)-fold and decreased C_{dyn} to $54\% \pm 4\%$ of the prechallenge value. Halothane 1 MAC, halothane 1.5 MAC, and atropine pretreatment significantly attenuated ($P < 0.05$) the increase in R_L provoked by histamine 1 $\text{mg} \cdot \text{ml}^{-1}$ (fig. 3). R_L increased 3.2 ± 0.39 -fold in the presence of halothane 1 MAC; 3.0 ± 0.29 -fold in the presence of halothane 1.5 MAC and 2.3 ± 0.22 -fold in atropine-pretreated dogs during thiopental anesthesia. There were no significant differences between the effects of halothane 1 MAC and 1.5 MAC and atropine aerosol pretreatment (fig. 3).

Halothane 1 MAC, halothane 1.5 MAC, or atropine, aerosol pretreatment did not significantly attenuate histamine-induced decreases in C_{dyn} (fig. 4). Halothane (1.5 MAC) anesthesia in atropine-pretreated animals had no additional protective effect on histamine-induced airway constriction (tables 2 and 3).

Histamine-induced airway constriction is reproducible in BG dogs over time. In three BG dogs anesthetized with

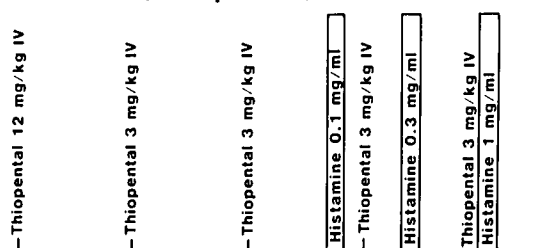
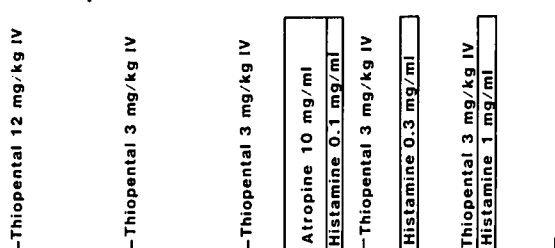
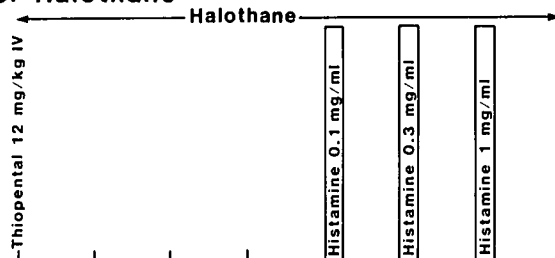
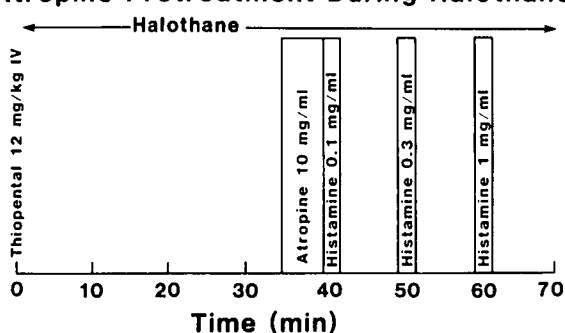
A. Control (Thiopental)**B. Atropine Pretreatment****C. Halothane****D. Atropine Pretreatment During Halothane**

FIG. 2. Study protocol for thiopental control (A), atropine thiopental (B), halothane (C), and atropine halothane (D) studies. The bars represent times of aerosol administration.

thiopental, histamine aerosols induced similar increases in R_L and decreases in C_{dyn} (table 4) in repeated trials in the same animals.

Discussion

This study demonstrates that BG dogs react to histamine in a dose-related manner, that a significant component of this response is vagally mediated, and that hal-

TABLE 1. Baseline Values for Resistance (R_L) and Compliance (C_{dyn})

	R_L $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$	C_{dyn} $(\text{ml} \cdot \text{cm H}_2\text{O}^{-1})$
Control	2.0 ± 0.14	66 ± 7
Halothane 1.0 MAC	1.9 ± 0.18	74 ± 8
Halothane 1.5 MAC	1.9 ± 0.10	77 ± 11
Atropine	2.0 ± 0.13	72 ± 10

All values represent the mean \pm SE of six dogs.

othane in clinically used concentrations mainly blocks the reflex component of this response.

BG dogs, like asthmatic people,¹⁵ demonstrate airway hyperreactivity to a variety of challenge aerosols, including methacholine¹⁶ and histamine.¹⁷ This means that the airways of these dogs and asthmatic persons react to concentrations of these agonists that are far lower than those concentrations effective in other dogs and normal people.

Histamine has both direct and reflex effects on airway

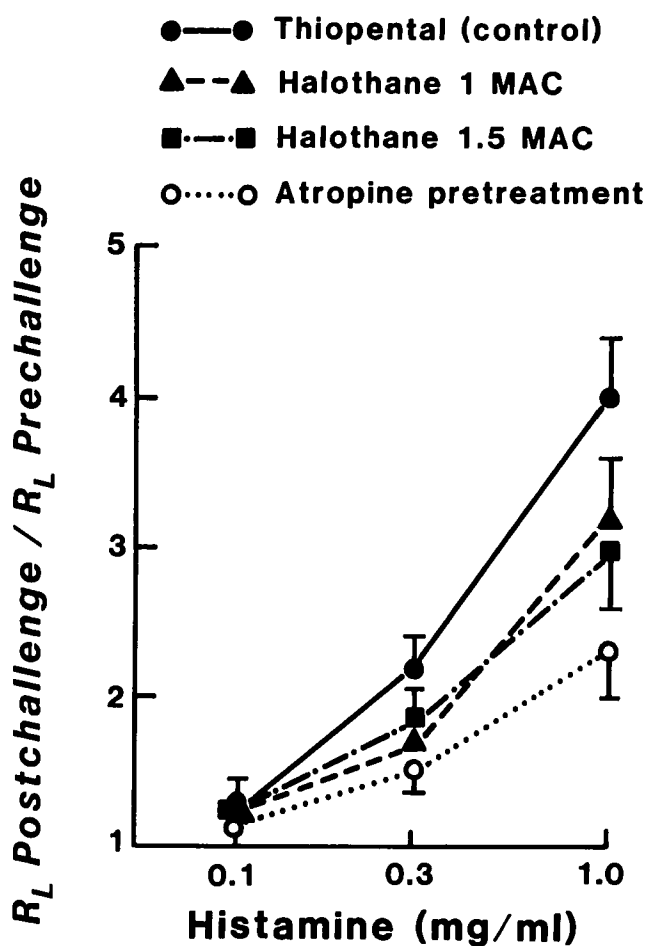


FIG. 3. Change in pulmonary resistance after increasing concentrations of histamine in the same six dogs during thiopental anesthesia, halothane 1 MAC, halothane 1.5 MAC, and after atropine pretreatment during thiopental anesthesia.

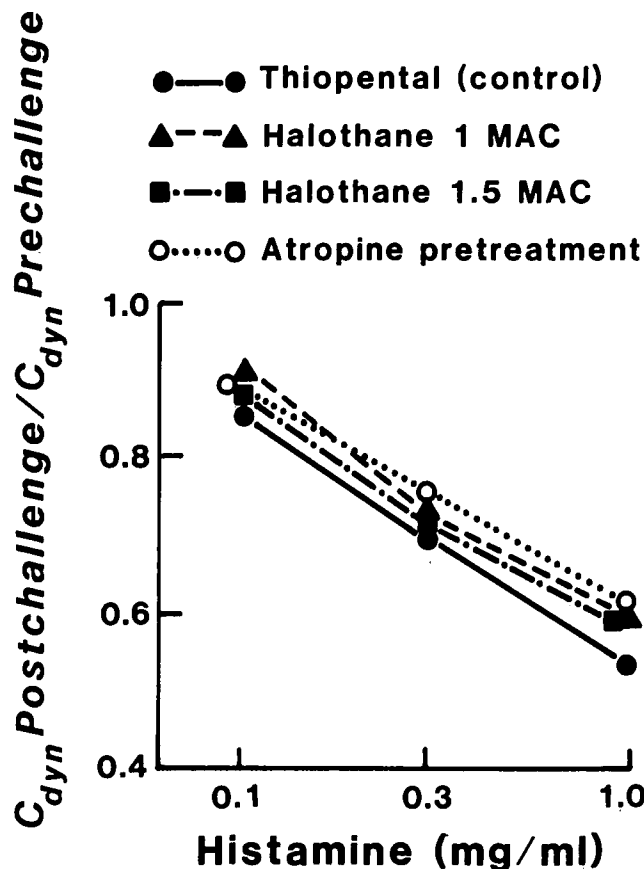


FIG. 4. Change in dynamic compliance after increasing concentrations of histamine in the same six dogs during thiopental, halothane 1 MAC, and 1.5 MAC anesthesia and after atropine pretreatment during thiopental anesthesia.

smooth muscle. However, the precise contribution of each of these components to the bronchoconstriction evoked by histamine has varied in numerous studies. Some studies have shown that most of the bronchoconstriction that occurs with histamine is reflexly mediated^{8,9} whereas other studies have shown primarily a direct effect.^{6,7}

This study demonstrates that in BG dogs, a large component of the response is reflexly mediated. Because the airways of BG dogs are hyperreactive to histamine, extremely low concentrations are required to elicit a response. This agrees with Shore *et al.*¹⁸ who demonstrated a major reflex component in the airway constrictor response to low but not to high concentrations of inhaled histamine.

Halothane may exert its beneficial effects on airways by: 1) blocking airway reflexes; 2) directly relaxing airway smooth muscle; 3) inhibiting mediator release; and 4) augmenting beta adrenergic tone.¹⁰ A number of studies have clearly demonstrated that halothane, in clinically used concentrations, blocks airway reflexes.^{3-5,19} The relative importance of the other mechanisms is less clear.

TABLE 2. Increase in R_L^* to Histamine Aerosols after Atropine Alone and Atropine with Halothane 1.5 MAC

	Histamine (mg · ml ⁻¹)		
	0.1	0.3	1.0
Atropine	1.1 ± 0.06	1.5 ± 0.18	2.3 ± 0.35
Halothane and atropine	1.1 ± 0.04	1.3 ± 0.10	2.0 ± 0.30
Control	1.2 ± 0.07	2.2 ± 0.23	3.8 ± 0.68

All values represent mean ± SEM of four dogs.

* R_L values are R_L postchallenge ÷ R_L prechallenge.

Using the BG dog model, Hermens *et al.*²⁰ demonstrated that halothane attenuated antigen-induced airway constriction, but plasma histamine concentrations were not significantly different from the control group. The contention that halothane augments beta-adrenergic tone²¹ has never been substantiated. Controversy exists regarding the direct effects of halothane on airway smooth muscle. Fletcher *et al.*²² suggested that halothane has a direct relaxant effect. Their study agrees with the elegant study of Korenga *et al.*¹⁹ demonstrating that the direct effects of halothane on airways occur in concentrations of halothane far greater than can safely be used in humans.

Using BG dogs, we have demonstrated that 1.5 MAC halothane slightly attenuated methacholine-induced airway constriction and concluded that halothane had some direct effects on the airway.² This conclusion, however, is based on the assumption that the only effect of methacholine was on airway smooth muscle. Because methacholine may also have effects on nerves, this assumption may not be entirely correct. Furthermore, it should be emphasized that the effect of halothane on methacholine-induced airway constriction was exceedingly small. The major conclusion that can be drawn from both that study and the present study is that the major action of halothane on airways is indirect and represents a block of airway reflexes.

Although both halothane and atropine attenuated the increase in R_L provoked by histamine, C_{dyn} was not significantly altered, which is consistent with our present understanding of innervation of the airway.²³ When si-

TABLE 3. Decrease in C_{dyn}^* after Atropine Alone and Atropine with Halothane 1.5 MAC

	Histamine (mg · ml ⁻¹)		
	0.1	0.3	1.0
Atropine	0.90 ± 0.03	0.75 ± 0.04	0.60 ± 0.05
Halothane and atropine	0.91 ± 0.02	0.80 ± 0.03	0.67 ± 0.06
Control	0.89 ± 0.03	0.70 ± 0.03	0.48 ± 0.02

All values represent mean ± SEM of four dogs.

* C_{dyn} values are C_{dyn} postchallenge ÷ C_{dyn} prechallenge.

TABLE 4. Reproducibility of Airway Response to Histamine Aerosol in Three Dogs

Dog No.	R_L (cm H ₂ O · l ⁻¹ · s ⁻¹) Histamine (mg · ml ⁻¹)				C_{dyn} (ml · cm H ₂ O ⁻¹) Histamine (mg · ml ⁻¹)			
	0	0.1	0.3	1.0	0	0.1	0.3	1.0
1	1.7	2.3	4.1	5.4	37	30	23	20
	1.8	2.3	4.3	9.2	49	42	36	26
	1.9	2.1	3.2	7.2	70	60	45	32
2	1.6	2.0	4.1	6.3	98	82	64	46
	1.6	2.2	4.4	6.5	85	72	56	45
3	1.8	2.2	5.0	7.2	63	55	40	32
	1.8	2.5	4.9	7.8	60	47	38	34

multaneous measurements of R_L and C_{dyn} are made, changes in R_L primarily reflect changes in more central airways, whereas changes in C_{dyn} reflect changes in the more peripheral airways. Because parasympathetic innervation to the airways is mainly central,²³ the major neurally mediated effects of halothane and atropine should be seen as changes in R_L , not C_{dyn} .

In summary, this study demonstrates that histamine produces dose-related bronchoconstriction in BG dogs. Atropine pretreatment attenuates this effect, indicating that a major component of this response is mediated by vagal reflex pathways. Halothane also attenuated, but by no means abolished, histamine-induced airway constriction, with maximal effects at 1 MAC. The protection afforded by halothane was not greater than that of atropine pretreatment alone. The addition of halothane to atropine failed to increase the protection. We therefore conclude that the major action of halothane in attenuating histamine-induced bronchoconstriction is primarily due to block of vagal reflexes.

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