Mechanism of Action of Inhalational Anesthesia on Airways

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To separate reflex from direct actions of anesthetics on airways, we studied the effects of halothane and isoflurane (1.5 MAC) on Ascaris antigen-induced (a mixed reflex and direct stimulus) and methacholine-induced (a direct acting stimulus) airway constriction in Basenji-Greyhound dogs. Prior to aerosol challenge, pulmonary resistance (Rt) and dynamic compliance (Cdyn) were not different during control (thiopental), halothane, and isoflurane anesthesia. Rt was 1.93 ± 0.15 (mean ± SE), 1.81 ± 0.23 and 2.1 ± 0.12 cm H2O\cdot1\textsuperscript{1}\textsuperscript{-1}\cdot s during thiopental, halothane, and isoflurane, respectively. Cdyn was 116 ± 6, 106 ± 16 and 110 ± 9 ml/cmH2O during thiopental, halothane, and isoflurane anesthesia, respectively. In control studies (thiopental), Ascaris antigen increased Rt by 9.4 ± 2.44 fold and decreased Cdyn to 0.29 ± 0.02 times the prechallenge value. Both halothane and isoflurane anesthesia significantly attenuated the increase in Rt provoked by Ascaris antigen challenge and halothane significantly attenuated the decrease in Cdyn. During halothane and isoflurane anesthesia, Ascaris antigen increased Rt by 3.8 ± 0.96 and 3.5 ± 0.57 fold, respectively, and decreased Cdyn to 0.48 ± 0.09 and 0.38 ± 0.07 times the prechallenge value, respectively. In control studies (thiopental anesthesia), methacholine produced dose-related increases in Rt and decreases in Cdyn. Both halothane and isoflurane attenuated the increase in Rt and the decrease in Cdyn provoked by methacholine with halothane being more effective than isoflurane with regards to Cdyn. The mechanism of action of halothane and isoflurane on airways is similar and complex, involving depression of airway reflexes as well as direct effects on airway smooth muscle. (Key words: Airway: resistance. Anesthetics, volatile: halothane; isoflurane. Complications: asthma. Lung: Compliance.)

IN THE ANESTHETIC MANAGEMENT of patients with bronchospastic disease, the aim of the anesthesiologist is to prevent the development of airway constriction. Potent inhalation anesthetics may accomplish this indirectly by blocking airway reflexes or directly by relaxing the smooth muscle of the airway. The action of anesthetics on airway reflexes has been studied for decades and the ability of potent inhalation anesthetics to block a wide variety of airway reflexes has been well established. On the other hand, very little is known about direct effects of anesthetics on airways in vivo. Clinically useful concentrations of halothane are relatively ineffective at relaxing tracheal smooth muscle in vitro—implying that in the intact animal or human, the major bronchodilator action of halothane is mediated by the depression of airway reflexes. Airway constriction can be provoked in animal models by aerosol challenge with many agents that elicit airway constriction by specific mechanisms. Aerosol challenge with antigen provokes airway constriction indirectly by activating airway reflexes, as well as directly, by releasing mediators that constrict airway smooth muscle. Aerosol challenges with cholinergic agonists, such as methacholine, provoke airway constriction directly by stimulating cholinergic receptors located on the airway smooth muscle with no reflex (indirect) effects.

To determine whether potent inhalation anesthetics have other than reflex (indirect) effects in vivo, we compared the ability of anesthetics to prevent the development of airway constriction provoked by Ascaris antigen and methacholine in the Basenji-Greyhound (BG) dog model of asthma. Moreover, we compared two inhalation anesthetics, halothane and isoflurane with thiopental, both prior to, and following aerosol challenge, to determine if these mechanisms are a common property of many potent inhalation anesthetics or are distinctive of halothane.

Methods

Seven Basenji-Greyhound dogs, ranging in age from 1 to 3 years, and weighing 16 to 22 kg, were subjects in these studies. The dogs were not premedicated and were anesthetized in the standing position, supported by a sling. After induction of anesthesia with intravenous thiopental (12 mg/kg), the dogs were paralyzed with succinylcholine, intubated with a cuffed endotracheal tube of 8.5 or 9 mm (internal diameter), and ventilated with 100 per cent oxygen. An esophageal balloon (Dyneasciences, Blue Bell, Pennsylvania) was placed in the esophagus and positioned at the point where recorded end-expiratory pressure was lowest. The balloon contained 0.8 ml air. A separate catheter connected to suction was placed in the esophagus to keep it empty of air and liquid. The dogs were ventilated with a piston-type ventilator (Harvard Apparatus, Millis, Massachusetts) set to deliver a tidal volume of 400 ml at a frequency of 15/min.

Transpulmonary pressure (Ptp) was measured with a differential pressure transducer (Hewlett-Packard 270, Waltham, Massachusetts) connected to the esophageal balloon and to a needle inserted in the endotracheal tube.
Airflow (V) was measured with a pneumotachygraph head (Hewlett-Packard 2100, Waltham, Massachusetts) and a differential flow transducer (Hewlett-Packard 4730A, Waltham, Massachusetts). Pressure and flow signals were recorded with a Hewlett-Packard 47601 recorder (Waltham, Massachusetts).

Dynamic pulmonary compliance (Cdyn) was calculated by dividing the tidal volume by the absolute difference in transpulmonary pressure at zero flow. Pulmonary resistance (Rl) was calculated using the method of Von Neergaard and Wirz.6,8 The elastic component of Pw was subtracted from the total Pw at mid-tidal volume. The remaining Pw was divided by the mid-tidal inspiratory flow rate. Apparatus resistance, determined by ventilating a mechanical lung analog with known parameters, was subtracted from the resulting value to obtain Rl. All volumes were corrected to BTPS. RL and Cdyn were reported as the mean of five consecutive breaths.

For control studies, additional increments of thiopental were administered as needed, which usually occurred at 15-min intervals. After measurement of RL and Cdyn, halothane or isoflurane was administered until a steady state end-tidal anesthesia concentration of 1.5 MAC (MAC is defined as the minimal alveolar concentration required to prevent movement in 50 per cent of animals when painfully stimulated10) was established. MAC values of halothane and isoflurane in the dog were taken to be 0.87 per cent10 and 1.48 per cent,11 respectively. End-tidal gases (halothane, isoflurane, oxygen, and CO2) were sampled continuously using a Perkin-Elmer 1100 mass spectrometer (Pomona, California). The electrocardiogram was monitored throughout using a Tektronix 4108 monitor (Beaverton, Oregon).

Five of a group of seven animals were used in each set of studies. Each animal served as its own control. At least one week elapsed between successive studies in any one animal. Studies were performed in a random order. Dogs were challenged with aerosols 40 min after the start of administration of inhalation anesthesia—the time needed to establish a reasonably steady state end-tidal anesthetic concentration of 1.5 MAC. Aerosol solutions were made up in distilled water and delivered by a Hudson 3000 nebulizer (Temecula, California) driven by compressed oxygen. The nebulizer delivered aerosol particles with a mass median diameter of 5.7 μm.

A purified extract of Ascaris antigen was prepared by Sephadex filtration according to the methods of Mackler et al.12 A dose of 30 μg Ascaris protein in 10 ml water was administered over a 10-min period with the nebulizer inserted between the inspiratory limb of a circle anesthesia system and the endotracheal tube. To avoid residual contamination, the circle was changed after completion of the aerosol challenge. RL and Cdyn were measured immediately at the end of challenge and at 5-min intervals thereafter for 30 min.

Methacholine was administered to the dogs as a series of challenges with increasing drug dose (methacholine bromide 0.075, 0.15, 0.30 mg/ml). Each dose was inhaled for five breaths with a 10-min interval between challenges. An Ayre's T tube was employed and the expiratory port was occluded until an inflation pressure of 15 cm H2O had been obtained for each of the five breaths. RL and Cdyn were measured immediately following challenge. RL and Cdyn were expressed as absolute values and as the ratio of the postchallenge to the prechallenge values. RL and Cdyn were compared during thiopental, halothane, and isoflurane anesthesia at 5-min intervals following antigen challenge, and at each of the three doses following methacholine challenge by a two-way analysis of variance13 and a Student-Newman-Keuls test for multiple comparisons.14 The level of statistical significance used throughout was 0.05.

Results

Prior to Ascaris aerosol challenge, RL and Cdyn were not significantly different during thiopental, halothane, and isoflurane anesthesia. RL averaged 1.93 ± 0.15 (mean ± SE), 1.81 ± 0.25, and 2.10 ± 0.12 cm H2O·l-1·s during thiopental, halothane, and isoflurane anesthesia, respectively. Cdyn averaged 116 ± 8, 107 ± 0.16, and 110 ± 9 ml/cm H2O during thiopental, halothane, and isoflurane anesthesia, respectively. Increasing concentrations of anesthesia with halothane and isoflurane did not significantly increase or decrease RL or Cdyn.

Ascaris antigen challenge produced changes in RL and Cdyn, which were maximal 5-min after the end of antigen aerosol administration (fig. 1). During thiopental anesthesia (control studies), RL increased by 9.4 ± 2.44 times the prechallenge value while Cdyn decreased to 0.29 ± 0.02 times the prechallenge value (fig. 1). Both 1.5 MAC halothane and 1.5 MAC isoflurane attenuated the increase in RL provoked by antigen challenge (P < 0.05). There was no significant difference in RL between isoflurane and halothane. During halothane anesthesia, RL increased 3.8 ± 0.96 fold and during isoflurane anesthesia, RL increased 3.5 ± 0.57 fold (fig. 1). Halothane significantly attenuated the decrease in Cdyn provoked by antigen challenge. The attenuation of Cdyn during isoflurane anesthesia experiments was not statistically significant. Cdyn decreased to 0.48 ± 0.09 and 0.38 ± 0.07 times the prechallenge Cdyn during halothane and isoflurane anesthesia, respectively (fig. 1).

During thiopental anesthesia (control studies), methacholine produced dose-related increases in RL (fig. 2) and decreases in Cdyn (fig. 2). Both halothane and isoflurane
(1.5 MAC) significantly attenuated the increases in $R_L$ provoked by methacholine. Although a statistically significant difference in $R_L$ was not noted during isoflurane and halothane anesthesia, $R_L$ was lower during halothane compared with isoflurane anesthesia in all five dogs at 0.075 and 0.3 mg/ml methacholine and in four of five dogs at 0.15 mg/ml methacholine. Both halothane and isoflurane attenuated the decrease in $C_{dyn}$ provoked by methacholine (fig. 2). Halothane was significantly more effective ($P < 0.05$) than isoflurane (fig. 2). End-tidal $CO_2$ averaged 4.4 per cent during the studies. No ECG abnormalities were observed during the studies.

Discussion

The mechanism of action of potent inhalation anesthetics on airways is complex and involves depression of airway reflexes (indirect effects) as well as direct effects on airway smooth muscle.

A number of mechanisms interact to produce airway constriction after antigen challenge in animal models of acute asthma. Direct bronchoconstriction results from the effects of mediators released by sensitized cells directly on airway smooth muscle, whereas in reflex bronchoconstriction, these chemical mediators first stimulate subepithelial irritant receptors with subsequent reflex bronchoconstriction. We have previously demonstrated that in our population of Basenji-Greyhound dogs, the prior administration of intravenous atropine or lidocaine reduced antigen-induced increases in $R_L$ by approximately one third. Halothane and isoflurane produced a slightly greater effect (about a 50 per cent reduction in the antigen response) suggesting that these anesthetics have effects on airways in addition to blocking reflex pathways. Our studies involving methacholine challenge confirm this, as cholinergic agonists act directly on specific receptors on airway smooth muscle with little or no reflex effects. Although it is difficult to interpret changes in dose-response curves in studies involving intact animals, our data suggest that sensitivity of the cholinergic receptor is unaltered by both isoflurane and halothane, but that the subsequent muscle contraction is impaired. Thus, the threshold concentration of methacholine required to initiate contraction (0.075 mg/ml) is similar in control (thiopental) and in halothane- and isoflurane-anesthetized dogs; but the amplitude of contraction is depressed throughout the dose-response curve during halothane and isoflurane anesthesia. The methacholine responses were near maximal at 0.30 mg/ml and were not significantly increased at higher concentrations (0.75 mg/ml). It should be noted that although the pul-

![Graph](image1)

**Fig. 1.** Increase in $R_L$ and decrease in $C_{dyn}$ following Ascaris antigen challenge during thiopental, halothane, and isoflurane anesthesia. Abscissa shows elapsed time from end of antigen administration.

![Graph](image2)

**Fig. 2.** Increase in $R_L$ and decrease in $C_{dyn}$ following incremental doses of methacholine during thiopental, halothane, and isoflurane anesthesia.
monary response to methacholine was attenuated by 1.5 MAC anesthesia, it was not abolished. Thus, our studies indicate that potent inhalation anesthetics in clinically useful concentrations have a small direct action on airway smooth muscle.

Anesthetics may act on airways by a number of other mechanisms. Anesthetics may conceivably stabilize mast cell membranes and prevent mediator release, and may alter permeability of the bronchial epithelium allowing greater or lesser access to the subepithelial irritant receptors. Our experiments were not designed to look at these mechanisms. In 1967, Klide and Aviado\textsuperscript{16} concluded from a study in mongrel dogs that halothane causes bronchodilation by stimulation of beta adrenergic receptors in the airway. These investigators demonstrated a decrease in $R_\text{L}$ and an increase in $C_\text{dyn}$ with increasing concentrations of halothane in mongrel dogs with high baseline airway tone. After pretreatment with beta adrenergic blocking agents (M J 1999 and nethalide), they could no longer demonstrate decreases in $R_\text{L}$ or increases in $C_\text{dyn}$ with increasing concentrations of drug. We question their interpretation of the results because $R_\text{L}$ was lower and $C_\text{dyn}$ higher in those particular dogs which were beta adrenergically blocked, than in dogs that were unblocked. Beta adrenergic antagonists may have central nervous system depressant effects similar to those produced by local anesthetics, which could have relaxed airway tone before administration of halothane. Therefore, halothane produced no further relaxation.

In our studies, the effects of halothane and isoflurane were compared with thiopental, both prior to aerosol challenge (unstimulated airway) and after challenge (stimulated airway). Thiopental, in doses used in our studies, has little effect on airway reflexes,\textsuperscript{5} or on other mechanisms since changes in $R_\text{L}$ and $C_\text{dyn}$ were similar after challenge in awake and thiopental-anesthetized dogs.\textsuperscript{17} Thiopental has been shown to constrict smooth muscle in some species.\textsuperscript{18} However, the concentrations needed to produce this effect are higher than achieved in blood during clinical anesthesia.

Neither halothane nor isoflurane altered $R_\text{L}$ and $C_\text{dyn}$ in the unstimulated airway; nor did $R_\text{L}$ or $C_\text{dyn}$ change as anesthetic depth increased. These findings agree with previous studies by Hickey and co-workers and Colgan\textsuperscript{19} in intact halothane-anesthetized dogs. Klide and Aviado,\textsuperscript{16} on the other hand, found a reduction in $R_\text{L}$ in spontaneously breathing dogs, as the inspired halothane concentration increased from 0.5 to 3 per cent; but the initial $R_\text{L}$ measured in their studies was two to three times higher than in our studies and studies by others in dogs,\textsuperscript{1,10} suggesting that their animals had airway constriction initially. In contrast, our dogs and most other dogs have dilated airways in the unstimulated state, and increasing concentrations of anesthesia have no further effect. Humans appear to be similar to the dog in this regard.\textsuperscript{20,21} Increasing concentrations of halothane\textsuperscript{20} produced no significant change in airway tone. Rehder and co-workers\textsuperscript{22} found isoflurane to be similar to halothane in this regard, although they found a small but significant increase in $R_\text{L}$ in the same subjects during isoflurane anesthesia compared to the awake state. However, their anesthetized subjects were intubated, and these investigators did not separate the reflex effects of the endotracheal tube and isoflurane on $R_\text{L}$. The constriction of airways distal to the endotracheal tube in intubated subjects recently described by Gal\textsuperscript{22} could well be responsible for the increase in $R_\text{L}$ in their subjects.

Both halothane and enflurane have been shown to be effective at reversing antigen-induced bronchoconstriction in experimental asthma in Basenji-Greyhound dogs.\textsuperscript{23} The ability of isoflurane to either prevent or reverse airway constriction in vivo has not, to our knowledge, been previously studied. Because isoflurane is less depressant to the cardiovascular system than halothane or enfurane,\textsuperscript{24} one may speculate that it may be of particular advantage in asthmatic patients with limited cardiac reserve whose airways require a higher concentration of halothane or enfurane than their heart will tolerate. Moreover, isoflurane, like enfurane, has a higher arrhythmogenic threshold to catecholamines than halothane,\textsuperscript{25} thereby decreasing the incidence of life-threatening arrhythmias.

There was no significant difference in the ability of halothane and isoflurane to prevent increases in $R_\text{L}$. There were, however, differences in $C_\text{dyn}$. Halothane (1.5 MAC) was more effective than isoflurane in preventing the decrease in $C_\text{dyn}$ provoked by both antigen and methacholine-aerosol challenge. Because $C_\text{dyn}$ is a function of a number of physiologic factors, including parenchymal distensibility, airway patency, and the uniformity of distribution of inspired air,\textsuperscript{6} the differences between halothane and isoflurane are difficult to interpret. Moreover, one can never be certain that 1.5 MAC of one anesthetic produces the same depressant effects as 1.5 MAC of another anesthetic or that the published MAC of anesthetics in mongrel dogs is similar in Basenji-Greyhound dogs.\textsuperscript{10}

The Basenji-Greyhound dog model of asthma used in these studies appears to mimic symptomatic asthma in humans more closely than previously described animal models with respect to the changes in lung volumes following challenge,\textsuperscript{26} the magnitude of airway constriction,\textsuperscript{27} and the presence of nonspecific airway hyperreactivity.\textsuperscript{28} These studies in the dog may not necessarily be applicable to humans but suggest that both halothane
and isoflurane may be effective in preventing airway constriction in humans and that their mechanism of action involves depression of reflex pathways, as well as direct effects on airway smooth muscle.

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