Effects of Halothane, Propofol, and Thiopental on Peripheral Airway Reactivity

Elon H. Mehr, M.D., Karen S. Lindeman, M.D.*

Background: General anesthetics modify airway responsiveness by several mechanisms, including direct effects on airway smooth muscle and reductions in neural reflex activity. Halothane has been shown to reduce responsiveness through both of these mechanisms. The airway effects of barbiturates are controversial, and the effects of propofol are unknown.

Methods: To compare the direct effects of halothane, thiopental, and propofol in vivo, canine peripheral airways were constricted with two stimuli, histamine and hypocapnia, which are thought to directly contract smooth muscle. The authors then investigated the role of ATP-sensitive potassium (KATP) channels as a mechanism for attenuating these responses. Basenji-Greyhound (BG) dogs were anesthetized with either halothane (1.5 MAC), thiopental (7.5 mg·kg⁻¹·min⁻¹ intravenously) plus fentanyl (25 μg intravenously every 20-30 min), or propofol (0.6 mg·kg⁻¹·min⁻¹ intravenously). A wedged bronchoscope technique was used to measure peripheral airway resistance (Rₚₒ). After a stable baseline was obtained, dose-response curves to histamine (50, 100, or 200 μg intravenously bolus) or hypocapnia (0% CO₂ for 2 min with 100, 200, or 400 ml/min collateral flow) were constructed. On separate occasions, the same sublobar segments were pretreated with glibenclamide (2 mg/ml aerosol), a KATP channel blocker, and dose-response curves to hypocapnia were repeated.

Results: Dose-response curves to histamine were similar during all three anesthetics. Halothane decreased airway responsiveness to hypocapnia, compared with either thiopental or propofol (P<0.05). Pretreatment with glibenclamide abolished the effect of halothane on hypocapnia-induced airway constriction.

Conclusions: These results indicate that propofol afforded no benefit over thiopental or halothane in reducing peripheral airway responsiveness. Furthermore, the beneficial effects of halothane in reducing responsiveness to hypocapnia appear to be mediated by the opening of KATP channels. (Key words:


POTENT inhalational anesthetics are considered the anesthetics of choice in asthmatic subjects, because they prevent or reverse intraoperative bronchospasm. These effects occur through inhibition of airway reflexes and direct relaxation of airway smooth muscle.

Effects of other general anesthetics on airway responsiveness are controversial. Thiobarbiturates can inhibit vagal reflexes and directly contract or relax airway smooth muscle, depending on dose and on the species studied.

The effects of propofol on airway responsiveness are largely unknown. Bronchospasm has been reported to occur, or not occur, after induction of anesthesia with propofol in human subjects. Propofol also stimulates histamine release from tissue mast cells in vitro, but the clinical significance of this effect has not been determined.

To investigate the direct effects of general anesthetics on airway responsiveness in vivo, we compared peripheral airway responses during halothane, propofol, or thiopental anesthesia in Basenji-Greyhound (BG) dogs, a model of asthma. We constricted the peripheral airways with two stimuli, hypocapnia and intravenous histamine, which are thought to contract airway smooth muscle directly. The peripheral airways, which lack vagal input, provide the ideal site for studying direct effects of general anesthetics. Because halothane, when compared with the other general anesthetics, nearly abolished responses to hypocapnia, but not to histamine, we investigated the mechanism of this protective effect. We questioned whether halothane attenuated hypocapnia-induced bronchoconstriction by activating potassium (K⁺) channels in airway smooth muscle.

Materials and Methods

These studies were approved by the Animal Research Committee of The Johns Hopkins University. A total of

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nine Basenji-Greyhound (BG) dogs, weighing 17.7-24.5 kg, were anesthetized with three separate anesthetic techniques, performed in random order and separated by at least 1 week. These three techniques (described below) included: 1) thiopental/fentanyl (intravenous); 2) propofol (intravenous); and 3) halothane (inhaled). After induction of anesthesia, the dogs’ tracheas were intubated with an 8.5-mm cuffed endotracheal tube and the lungs were ventilated (Harvard constant-volume ventilator, Millis, MA) with 100% oxygen. Tidal volume was set at 17 ml/kg, and respiratory rate was adjusted to maintain an end-tidal carbon dioxide fraction of 4.5% (BTPS). Rectal temperature was monitored. The electrocardiogram was monitored continuously (Tektronics, Beaverton, OR). Blood pressure was measured either noninvasively (Datascopc, Paramus, NJ) every 2.5 min or via a 20-G percutaneous femoral arterial catheter connected to a pressure transducer. End-tidal carbon dioxide and halothane concentrations (during halothane anesthesia) were sampled continuously using a mass spectrometer (Perkin Elmer 1100, Pomona, CA).

A wedged bronchoscope technique was used to measure peripheral airway resistance (Rₚ), or resistance through pathways of collateral ventilation.⁴ A fiberoptic bronchoscope (5.5-mm OD) was visually guided through the endotracheal tube, and the tip was lodged in a sublobar airway. A double-lumen catheter (5-Fr) was threaded through the suction port of the bronchoscope. Through one lumen, 5% carbon dioxide in air was delivered to the obstructed lung segment. A constant collateral flow of 200 ml/min (Vₗcoli), approximating the resting ventilation to the area subtended by the bronchoscope, was maintained for all measurements. The other lumen of the double-lumen catheter was connected to a transducer to measure the pressure (Pₚ) at the tip of the bronchoscope. Peripheral airway resistance was determined by stopping the ventilator to allow the dog to exhale to functional residual capacity. At this point, Pₚ reached a plateau, and the pressure in the surrounding unobstructed lung (Pₐo) equaled zero. Peripheral airway resistance (cmH₂O·ml⁻¹·s) was calculated as follows: Rₚ = (Pₚ - Pₐo)/Vₗcoli. At the end of the experiment, the anesthetic was discontinued and the dogs were monitored continuously until fully awake.

**Anesthetic Techniques**

On separate days, the dogs were anesthetized with one of three different anesthetic protocols.

**Barbiturate and Opioid.** Anesthesia was induced with intravenous sodium thiopental (15 mg/kg) plus fentanyl (50 μg). Maintenance anesthesia consisted of a continuous infusion of sodium thiopental (7.5 mg·kg⁻¹·min⁻¹) with supplemental doses of fentanyl (25 μg) administered every 10-30 min. Criteria for administration of fentanyl included the following: 1) spontaneous ventilation; 2) systolic blood pressure > 180 mmHg, or increase 10% above baseline within any 5-min period; and 3) heart rate > 120 bpm, or increase 10% above baseline within any 5-min period. Additional sodium thiopental (75 mg) was administered for spontaneous movement.

**Propofol.** Anesthesia was induced with intravenous propofol (6 mg/kg). Maintenance anesthesia consisted of continuous infusion of propofol (0.6 mg·kg⁻¹·min⁻¹). Additional propofol (10 mg) was administered every 10-30 min according to the hemodynamic criteria described for barbiturate anesthesia, or the presence of spontaneous ventilation. Propofol (40 mg) was administered for spontaneous movement.

**Halothane.** Anesthesia was induced with intravenous sodium thiopental (15 mg/kg). Maintenance anesthesia consisted of inhaled halothane started immediately after intubation. An end-tidal halothane concentration of 1.5 MAC was maintained. The MAC value of halothane in the dog was considered to be 0.87%.¹⁵

**Experimental Protocol**

**Histamine Dose-Response.** Six BG dogs were anesthetized on separate days by each of the three protocols described above. On the first experimental day, a map was constructed to locate an individual sublobar segment (five left middle lobes, one right upper lobe). On subsequent experimental days, the original sublobar segment was located by following the map constructed on the first experimental day. Peripheral airway resistance was measured every 5 min until a stable baseline was established for three consecutive readings. Histamine (50 μg) was administered as an intravenous bolus, and Rₚ was subsequently measured 30 s, 2, 5, and 10 min after the bolus. Thereafter, Rₚ was measured every 5 min until it stabilized for three consecutive readings. The experiment was then repeated with increasing doses of histamine (100- and 200-μg intravenous bolus) and Rₚ was measured as described above.

**Hypocapnia Dose-Response.** Six BG dogs were anesthetized on separate days by each anesthetic protocol. Three of these dogs were also used for histamine

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Table 1. Baseline Values of Peripheral Airway Resistance (R<sub>p</sub>), Blood Pressure, and Heart Rate Before Histamine and Hypocapnic Challenges

<table>
<thead>
<tr>
<th>Anesthesia</th>
<th>Baseline R&lt;sub&gt;p&lt;/sub&gt; (cmH&lt;sub&gt;2&lt;/sub&gt;O·m&lt;sup&gt;-1&lt;/sup&gt;·s)</th>
<th>Baseline Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prehistamine (n = 6)</td>
<td>Prehypocapnia (n = 6)</td>
</tr>
<tr>
<td>Thiopental</td>
<td>0.27 ± 0.05</td>
<td>0.30 ± 0.05</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.28 ± 0.07</td>
<td>0.27 ± 0.04</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.21 ± 0.05</td>
<td>0.24 ± 0.06</td>
</tr>
</tbody>
</table>

<sup>*</sup> P < 0.05 versus other anesthetic techniques.
<sup>†</sup> P < 0.05 versus propofol.

challenge (described above). A fiberoptic bronchoscope tip was wedged in a sublobar segment (three right middle lobes, two left middle lobes, and one right upper lobe). Maps to these segments were constructed on the first experimental day and were followed to the same sublobar segment on subsequent experimental days. Peripheral airway resistance was measured every 5 min until a stable baseline was established for three consecutive readings. Hypocapnic challenge was administered by changing the collateral flow to air (0% carbon dioxide) for 2 min at a 100-mL/min flow rate. At the end of the challenge, the flow rate was returned to 200 mL/min and R<sub>p</sub> was measured 30 s and 2, 5, and 10 min postchallenge. Thereafter, R<sub>p</sub> was measured every 5 min until it stabilized for three consecutive readings. The experiment was then repeated twice using higher flow rates of hypocapnia (200 and 400 mL/min) and R<sub>p</sub> was measured as described above.

Any dog that did not exhibit an increase in R<sub>p</sub> ≥ 0.3 cmH<sub>2</sub>O·m<sup>-1</sup>·s after histamine or hypocapnic challenges during any of the anesthetics was considered to be unresponsive to these challenges and, therefore, was excluded from the study. Three animals were unresponsive by these criteria, and another animal was selected at random to replace each unresponsive animal.

**Glibencamid Pretreatment.** On separate days, the six dogs previously challenged with hypocapnia were anesthetized with either sodium thiopental plus fentanyl or halothane (inhaled), as previously described. The original maps were followed to locate the same sublobar segments, and a bronchoscope was inserted. After establishment of a stable baseline, the catheter was removed from the suction port of the bronroscope, and the ATP-sensitive potassium (K<sub>ATP</sub>) channel blocker, glibencamid (2 mg/ml in ethanol), was aerosolized by an ultrasonic nebulizer (DevVibbiss model 35A, Somerset, PA) and delivered at a flow rate of 200 ml/min for 3 min. This dose of glibencamid was selected based on a previous study demonstrating its effectiveness in canine peripheral airways. Peripheral airway resistance was measured every 5 min until a stable baseline was obtained for three consecutive readings. Dose-response curves to hypocapnia were then constructed as described.

**Statistical Analysis.** Analysis of variance and Fisher multiple comparison tests were used to analyze mean differences of R<sub>p</sub>, blood pressure, and heart rate, and differences between dose-response curves. Raw data were used for all statistical analyses. A P value < 0.05 was used to indicate statistical significance. Data are expressed as mean ± SEM.

**Results**

**Cardiovascular Effects**

Baseline blood pressure was 144 ± 6 mmHg during thiopental/fentanyl anesthesia (n = 15), 122 ± 5 mmHg during propofol anesthesia (n = 9), and 95 ± 6 mmHg during halothane anesthesia (n = 15) (table 1). These baseline blood pressure readings were significantly different (P < 0.05) from each other.

Baseline heart rate was 102 ± 4 bpm during thiopental/fentanyl anesthesia (n = 15), 122 ± 8 bpm during propofol anesthesia (n = 9), and 111 ± 7 bpm during halothane anesthesia (n = 15) (table 1). The heart rate during thiopental/fentanyl anesthesia was significantly less (P < 0.05) than the heart rate during propofol anesthesia.

**Effect of Histamine**

Anesthetic technique did not significantly affect baseline R<sub>p</sub> (table 1, fig. 1). Peak R<sub>p</sub> occurred between 30 s and 2 min after histamine challenge under all con-
ditions (fig. 1). The largest dose of histamine (200 μg intravenously) increased $R_p$ to $1.33 \pm 0.46$ cmH₂O·ml⁻¹·s⁻¹ (n = 6) during thiopental anesthesia (389% increase over baseline), 1.02 ± 0.42 during propofol (264% increase), and 1.11 ± 0.33 during halothane anesthesia (425% increase). These increases did not differ significantly from each other.

Histamine challenge produced dose-related increases in $R_p$ (fig. 2). Responsiveness to histamine was similar during the three anesthetic techniques (fig. 2). There were no significant differences in the dose-response curves to histamine challenge during any of the three anesthetic regimens.

**Effect of Hypocapnia**

Before hypocapnic challenge, there were no significant differences in baseline $R_p$ during the three conditions (table 1, fig. 3). Halothane attenuated responses to hypocapnic challenge when compared with the two other anesthetic techniques (figs. 3 and 4). During propofol or thiopental/fentanyl anesthesia, peak $R_p$ occurred between 30 s and 2 min after hypocapnic challenge (fig. 3). The largest dose of hypocapnia (400 ml/min) increased $R_p$ to $0.95 \pm 0.27$ cmH₂O·ml⁻¹·s⁻¹ (n = 6) during thiopental/fentanyl (217% increase over baseline) and 1.05 ± 0.26 during propofol (289% increase over baseline), but only 0.45 ± 0.15 during halothane anesthesia (not significantly different from baseline).

Hypocapnic challenge produced dose-related increases in $R_p$ during thiopental/fentanyl or propofol anesthesia ($P < 0.05$), but not during halothane anesthesia (fig. 4). Halothane attenuated the peripheral airway responses to hypocapnic airway challenge, as evidenced by a shift of the dose-response curve to the right compared with thiopental/fentanyl ($P < 0.05$) or propofol ($P < 0.05$). There were no significant differences between the dose-response curves during thiopental/fentanyl or propofol anesthesia. During halothane anesthesia, responses to hypocapnic collateral flow at 200 ml/min were significantly less than responses during propofol ($P < 0.01$) or thiopental/fentanyl anesthesia ($P < 0.05$). At collateral flow of 400 ml/min, hypocapnia-induced airway constriction was significantly attenuated during halothane anesthesia compared with thiopental/fentanyl ($P < 0.01$) or propofol anesthesia ($P < 0.01$).

**Glibenclamide Pretreatment**

During thiopental/fentanyl anesthesia, baseline $R_p$ was similar in control dogs and dogs pretreated with glibenclamide (table 1). Likewise, during halothane anesthesia, baseline $R_p$ was not significantly different in control dogs and dogs pretreated with glibenclamide (table 1). Peripheral airway resistance increased briefly after treatment with aerosolized glibenclamide and returned to baseline within 5–10 min. Peak increases were $26 \pm 7\%$ (n = 6) and $73 \pm 24\%$ (n = 6) above baseline 30 s after the glibenclamide aerosol in the halothane and thiopental groups, respectively.

In the presence of glibenclamide (fig. 5), halothane no longer protected against hypocapnia-induced airway constriction. During halothane anesthesia, dose-response curves were significantly different ($P < 0.01$) in the presence and absence of glibenclamide. In addition, glibenclamide pretreatment completely pre-
Propofol, when compared with thiopental/fentanyl, neither enhanced nor attenuated peripheral airway responsiveness in our study (figs. 2 and 4). In human subjects, information regarding effects of propofol on airway responsiveness is limited. Thompson and Davies reported a case of coughing, followed by bronchospasm, after induction of anesthesia with propofol in a nonasthmatic patient. Laxenaire et al. reported a probable anaphylactoid reaction to propofol in a nonasthmatic patient. Because confounding factors were present, and because asthmatic patients were not involved, the effects of propofol in the presence of airway hyperresponsiveness are largely unknown. In a larger

![Graph showing the relationship between peak \( R_p \) (cm H2O/cm s/m2) and histamine (µg)](image)

**Fig. 2.** Dose-response curves of peak \( R_p \) after histamine (intravenously) in BG dogs anesthetized with thiopental/fentanyl, propofol, or halothane (n = 6).

vented the effect of halothane, because the dose-response curves during halothane anesthesia after glibenclamide pretreatment were not significantly different from those observed during thiopental/fentanyl anesthesia. In contrast, glibenclamide pretreatment did not alter responsiveness to hypocapnia during thiopental/fentanyl anesthesia. There were no differences in the dose-response curves to hypocapnia during thiopental/fentanyl anesthesia with or without glibenclamide pretreatment (fig. 5).

**Discussion**

Results from this study demonstrate that halothane, when compared with thiopental/fentanyl or propofol, attenuated hypocapnic bronchoconstriction, and that this effect is prevented by pretreatment with a \( K_{\text{ATP}} \) channel blocker, glibenclamide. The effect of halothane on histamine-induced peripheral airway constriction did not differ from the other two anesthetic regimens.

![Graph showing the relationship between \( R_p \) (cm H2O/cm s/m2) and time (minutes)](image)

**Fig. 3.** Peripheral airway resistance before and after 400 ml/min hypocapnic challenge (vertical bar) in BG dogs anesthetized with thiopental/fentanyl, propofol, or halothane (n = 6).

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series of patients (1,269), induction of anesthesia with propofol resulted in a 3.2% incidence of cough, without a single episode of bronchospasm.\textsuperscript{11} Although one \textit{in vitro} study\textsuperscript{12} demonstrated propofol-induced histamine release from tissue mast cells exposed to high concentrations of propofol, the results of the current study indicate that this effect may not be clinically significant at anesthetic concentrations. In support of this idea, no evidence of complement activation or increases in plasma histamine concentration occurred in 12 healthy volunteers after induction of anesthesia with propofol, although a cutaneous rash was noted in 5 of the 12 subjects.\textsuperscript{18} In the current study, we detected no direct peripheral airway effects of propofol in animals with airway hyperresponsiveness. The precise relationship between the doses of propofol and thiopental administered to these animals and anesthetic concentrations in human subjects is unknown. If these doses are similar, then the effects of propofol in clinical situations are either mediated through actions external to airway smooth muscle or due to effects on more central airways.

Halothane did not attenuate peripheral airway responsiveness to intravenous histamine (Figs. 1 and 2). In contrast to the current study, previous studies\textsuperscript{5,19,20} demonstrated that halothane attenuated histamine-induced increases in lung resistance ($R_L$). In BG dogs,\textsuperscript{2,20} halothane (1.5 MAC), when compared with thiopental/fentanyl, attenuated responses to histamine aerosols, which increased $R_L$ both through direct activation of histamine-1 receptors and through indirect stimulation of vagal reflexes. Because atropine provided no further protection, the authors concluded that halothane attenuated responses to histamine aerosols primarily by blocking vagal reflexes.\textsuperscript{2} One difference that may explain the absence of a histamine effect in the current study is that responses were measured in the peripheral airways, where the activity of vagal reflexes is very limited.\textsuperscript{13} Moreover, in this study, the airways were constricted with intravenous histamine, which may have relatively less effect on airway reflexes than inhaled histamine used in the previous study. Although one other study\textsuperscript{19} demonstrated that halothane attenuated responses to intravenous histamine, cyclopropane anesthesia served as the control, and differences in baseline $R_L$ were present, making interpretation of the data difficult. Thus, the similarity in peripheral airway responsiveness to histamine during the three anesthetic
regimens in the current study supports the idea that, in BG dogs, the direct effects of volatile anesthetics on histamine-induced airway constriction in vivo are limited.

One additional difference in this study is in the measurement of resistance. Several previous studies investigating effects of anesthetics on airway responsiveness measured changes in $R_t$. However, $R_t$ may not solely reflect airway resistance, because measurements of $R_t$ include both airway and tissue components. Viscoelastic properties of the lung parenchyma generate flow resistance, known as tissue viscosity or hysteresis of lung recoil. In the absence of a constrictor stimulus, tissue viscoelastic can comprise greater than 75% of $R_t$ in dogs ventilated with tidal volumes and respiratory rates similar to those used in this study. Increases in tissue viscoelastic provide a significant contribution to the increase in $R_t$ after stimulation with histamine. Furthermore, a large component of protection against reflex-induced increases in $R_t$ is provided by attenuation of the tissue response. Thus, the protection against histamine-induced increases in $R_t$ seen in previous studies reflects reduced tissue viscoelastic, as well as reduced airway resistance.

In contrast, the wedged bronchoscope technique provides a true measure of airway resistance. This technique was originally developed to measure resistance to flow through collateral pathways. Although the precise site of the resistance measurement is unknown, recent evidence indicates that $R_t$ reflects resistance at the level of the terminal respiratory bronchioles and alveolar ducts. Our findings with respect to histamine, therefore, support the idea that potent inhalational anesthetics have relatively little effect on changes in distal airway resistance produced by direct-acting contractile agonists.

In contrast to its effects on histamine-induced airway constriction, halothane abolished responses to hypcapnia, when compared with thiopental/fentanyl or propofol (figs. 3 and 4). In previous studies, both in vivo and in vitro, halothane attenuated responses to hypcapnia in dogs that lacked airway hyperresponsiveness. Alexander et al. found that halothane and isoflurane, when delivered through the bronchoscope, produced dose-related reductions in peripheral airway responses to hypcapnia. Because, in our study, the anesthetic was delivered only through the endotracheal tube to the unobstructed lung, we presume that the peripheral airway effects of halothane resulted from its absorption into the blood and transport to the tissues.

The differences between the anesthetics with respect to hypcapnia-induced constriction did not appear to reflect differences in anesthetic depth. Although baseline mean arterial blood pressure (MAP) was significantly lower during halothane anesthesia than during thiopental/fentanyl or propofol anesthesia, the potent negative chronotropic and inotropic actions of halothane, as well as its vasodilator properties, could explain these findings in the absence of a difference in anesthetic depth. Furthermore, sufficient intravenous anesthetics were administered to eliminate spontaneous movement or respiration, ensuring a minimum anesthetic depth. This dose of propofol was selected based on a previous study demonstrating that autonomic responses were similar during halothane anesthesia (2 MAC) and propofol (0.8 mg·kg⁻¹·min⁻¹). Most importantly, if small differences in anesthetic depth were present, the peripheral airway effects of these differences were not sufficient to alter responsiveness to intravenous histamine (figs. 1 and 2).

The mechanism of hypcapnia-induced bronchoconstriction is not fully understood. In peripheral airways, responses to hypcapnia are not attenuated by atropine, indomethacin, or chlorpheniramine. These findings indicate that neither cholinergic reflexes nor the release of cyclooxygenase products or histamine is involved. It is more likely that hypcapnia directly stimulates airway smooth muscle by opening voltage-sensitive calcium channels (VSCC), because both nifedipine and verapamil nearly abolished the response. A dose-response curve for hypcapnia can be constructed using increasing collateral flow, presumably by reducing CO₂ in the airways more rapidly, thereby increasing the stimulus at the active site.

Because the mechanisms of constriction are entirely different, it is not surprising that halothane attenuated responses to hypcapnia without affecting responses to histamine. One possible explanation of these findings is an effect of halothane on K⁺ channels. A novel class of bronchodilators, initially developed as vasodilators, are thought to act by opening K⁺ channels in airway smooth muscle. Different subtypes of K⁺ channels open in response to a variety of stimuli. K⁺ channels found in airway smooth muscle include voltage-sensitive, calcium-activated, and ATP-sensitive (KATP) channels. Opening of these channels allows influx of intracellular K⁺, hyperpolarizes the plasmalemma, and produces electrical stability of the muscle membrane. New bronchodilators that selectively open K⁺ channels include cromakalim and lemakalim. Many
of the effects of cromakalim and lemakalim can be prevented or reversed by pretreatment with agents that block K\textsubscript{ATP} channels.\textsuperscript{36} These channels are opened and closed physiologically by decreases and increases in intracellular ATP. To our knowledge, the role of K\textsubscript{ATP} channels in contributing to bronchodilation by anesthetics has not been described.

In a recent study,\textsuperscript{10} lemakalim, like halothane in this study, inhibited canine peripheral airway responses to hypcapnia, but not to an agonist (acetylcholine). The most likely mechanism was opening of K\textsuperscript{+} channels in airway smooth muscle, allowing efflux of K\textsuperscript{+} and hyperpolarizing the plasma membrane. Because responses to hypcapnia\textsuperscript{28,29} but not to various receptor agonists,\textsuperscript{37-39} are highly dependent on influx of calcium through VSCCs, hyperpolarizing the membrane would inhibit responses to hypcapnia, but not to histamine or acetylcholine. The similar peripheral airway effect of lemakalim and halothane is consistent with similar mechanisms of action.

The ability of glibenclamide to prevent halothane from attenuating responses to hypcapnia supports the idea that halothane acts by opening K\textsubscript{ATP} channels in airway smooth muscle. Glibenclamide is one of a number of antihyperglycemic sulfonylurea agents that reduce blood sugar by blocking K\textsubscript{ATP} channels in pancreatic acinar cells, causing depolarization of the plasma membrane and release of insulin.\textsuperscript{40} In the airways, glibenclamide may prevent the effects of halothane by preventing membrane hyperpolarization. Glibenclamide did not enhance airway responsiveness nonspecifically, because responses to hypcapnia were similar during thiopental/fentanyl anesthesia in the presence or absence of glibenclamide (fig. 5). Moreover, because glibenclamide is a potent blocker of K\textsubscript{ATP} channels,\textsuperscript{41} rather than of voltage-sensitive or calcium-activated K\textsuperscript{+} channels, these findings implicate K\textsubscript{ATP} channels in the mechanism of halothane's effect on hypcapnic bronchoconstriction.

The interaction between volatile general anesthetics and K\textsuperscript{+} channels has been examined only to a limited extent, primarily in neuronal cells. Volatile anesthetics enhanced\textsuperscript{42,43} K\textsuperscript{+} currents, depending on the tissue and the subtype of K\textsuperscript{+} channel under investigation. In isolated canine cerebral and coronary arteries, pretreatment with the K\textsuperscript{+} channel blocker tetraethylammonium (TEA) enhanced volatile anesthetic-induced vasorelaxation.\textsuperscript{44} These data indicate that halothane depressed K\textsuperscript{+} currents in vascular smooth muscle. However, TEA does not block K\textsubscript{ATP} channels specifically, providing further evidence that the actions of anesthetics on K\textsuperscript{+} channels may depend on the type of tissue, as well as the type of K\textsuperscript{+} channel. Although we did not measure K\textsuperscript{+} currents in this study, our findings indicate that one mechanism for the beneficial effects of halothane is the enhancement of K\textsuperscript{+} efflux through K\textsubscript{ATP} channels in airway smooth muscle.

In summary, changes in R\textsubscript{p} in BG dogs were similar during thiopental/fentanyl and propofol anesthesia. If these findings apply to human asthmatic subjects, maintenance anesthesia with propofol has little direct effect on peripheral airway responsiveness. Halothane, in contrast to the other anesthetics, inhibited responsiveness to hypcapnia, and this inhibition was prevented by blocking K\textsubscript{ATP} channels. Thus, the direct effects of potent inhalational anesthetics on hypcapnia-induced airway constriction appear to be mediated through activation of K\textsubscript{ATP} channels.

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