Effects of Intravenous Anesthetics on Normal and Passively Sensitized Human Isolated Airway Smooth Muscle

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Background: General anesthetics may modify airway responsiveness. The authors investigated the effect of thiopental, propofol, and etomidate on airway smooth muscle.

Methods: Contraction experiments were done in human airway rings that were either normal or passively sensitized with asthmaic serum. The effect of propofol and etomidate was also studied on both [Ca\(^{2+}\)] increase measured by microspectrofluorimetry in isolated myocytes and isometric contraction in the rat trachea.

Results: In human bronchi, thiopental (10\(^{-7}\) to 10\(^{-5}\) m) induced a concentration-dependent contraction. Neither propofol nor etomidate altered baseline tone, but both anesthetics reduced histamine-induced contraction. In human immunologically sensitized isolated bronchi, propofol (3 \times 10^{-4} m) reduced histamine reactivity (ΔF\(_{\text{max}}\) in %) to a greater degree than in nonsensitized tissues (6.4 ± 15.7% and 16.4 ± 8.5%, respectively; n = 6, P < 0.05), whereas the effect of etomidate (10\(^{-3}\) m) was similar in both types of tissue (24.1 ± 6% and 22.3 ± 15%, respectively, n = 6). In rat isolated tracheal myocytes, propofol (3 \times 10^{-3} m) and etomidate (10\(^{-4}\) m) altered the [Ca\(^{2+}\)] signal in response to the depolarizing agent potassium chloride and the muscarinic agonist acetylcholine. Accordingly, the two anesthetics also reduced the mechanical response of rat tracheal rings to these agonists.

Conclusions: Whereas thiopental contracts human isolated bronchi, propofol and etomidate reduce histamine-induced contraction in human isolated airway smooth muscle that were either not sensitized or passively sensitized with asthmaic serum. This effect involves inhibition of both electro- and pharmacomechanical coupling. (Key words: Contraction; etomidate; excitation-contraction coupling; human bronchi; intracellular calcium; propofol; rat trachea.)

The effect of intravenous anesthetics on airway responsiveness is important to consider because patients with asthma who require general anesthesia with such compounds are considered to be at increased risk for the development of bronchospasm during anesthesia. Although not as potent as volatile anesthetics, some of the intravenous anesthetics have been shown to decrease airway reactivity by a direct action at the site of airway smooth muscle cell, by an indirect one on airway neural control, or both. Whereas thiobarbiturates contract guinea pig airway smooth muscle, ketamine exhibits a marked relaxant effect in various species, including humans, via mechanisms that have been studied in some detail. The effects of etomidate and propofol on airway reactivity have been less characterized. In vitro, both compounds antagonize bronchoconstriction, including in patients with hyperreactive airway disease, whereas in vitro, the effect appears to depend on both the species and the site along the bronchial tree. Furthermore, the presence of airway hyperresponsiveness may also play a role in the effect of propofol.

The present study was designed to investigate the effect of thiopental, propofol, and etomidate in human isolated airway smooth muscle. Because we observed that propofol and etomidate inhibited histamine-induced contraction, we also studied the effect of both compounds in human airways exhibiting in vitro hyperresponsiveness to histamine; that is, in human tissues immunologically sensitized with asthmatic serum. Finally, we investigated further the cellular mechanism of this inhibitory action. So far, the direct relaxing effect on smooth muscle of various general anesthetics has been ascribed to a reduction in the concentration of intracellular free Ca\(^{2+}\) ([Ca\(^{2+}\)]), to a decrease in
the sensitivity to Ca\(^{2+}\) of the smooth muscle contractile apparatus, or to both.\(^{19,23-25}\) Thus we studied the effect of propofol and etomidate on both [Ca\(^{2+}\)], increase measured by microspectrofluorimetry with the fluorescent dye indo-1 in isolated myocytes and isometric contraction in the rat trachea, an airway preparation that we recently characterized in terms of Ca\(^{2+}\) homeostasis.\(^{26}\)

**Materials and Methods**

**Tissue Preparation**

Human lung was obtained as previously described at thoracotomy from patients undergoing resection for lung cancer\(^{27,28}\) and rapidly transferred to the laboratory in Krebs-Henseleit solution composed of 118.4 mm NaCl, 4.7 mm KCl, 2.5 mm CaCl\(_2\), 1.2 mm MgSO\(_4\), 1.2 mm KH\(_2\)PO\(_4\), 25 mm NaHCO\(_3\), and 11.1 mm D-glucose, pH 7.4. As in previous studies, specimens were selected from patients whose lung function was within a normal range; that is, whose forced expiratory volume in 1 s (FEV\(_1\)) was more than 80% of the predicted value. Further, analysis of medical records of the patients revealed that none of them had a history of atopy. From a macroscopically tumor-free part of the specimen, segments of bronchi (third, fourth generation; 30–40 mm in length, 3–5 mm in internal diameter) were carefully dissected from surrounding parenchyma and cut into rings that were 3–4 mm long.

Rat tracheae were obtained from male Wistar rats that were 10–15 weeks old and weighed 300–400 g. For each experiment, a rat was anesthetized by intraperitoneal administration of 400 mg ethylcarbamide. Hearts and lungs were removed en bloc and the trachea was rapidly dissected out. For isometric contraction measurements, the trachea was cut into four rings that were all about 5 mm in diameter and 3–4 mm long, as previously described.\(^{29}\)

For fluorescence measurements of [Ca\(^{2+}\)], in freshly isolated cells from rat trachea, the muscular strip located on the dorsal face of the trachea was further dissected under binocular control. The epithelium was removed and the epithelium-free muscular strip was cut in several pieces (1 × 1 mm) and incubated for 10 min in low-Ca\(^{2+}\) (200 μM) physiologic saline solution (PSS; composed of 130 mm NaCl, 5.6 mm KCl, 1 mm MgCl\(_2\), 2 mm CaCl\(_2\), 11 mm glucose, 10 mm Heps, pH 7.4 with NaOH). Tissue was then incubated in low-Ca\(^{2+}\) PSS containing 1 mg/ml collagenase, 0.7 mg/ml pronase, 0.06 mg/ml elastase, and 3 mg/ml bovine serum albumin at 37°C for two successive periods of 25 min. After this time, the solution was removed and the tracheal muscle pieces were incubated again in a fresh enzyme-free solution and triturated with a fire-polished Pasteur pipette to release cells. Cells were stored to attach on glass coverslips at 4°C in PSS containing 0.8 mm Ca\(^{2+}\) and used on the same day.

**Immunologic Passive Sensitization of Human Isolated Bronchial Rings**

Immunologic passive sensitization was carried out as previously described\(^{10,17,30-33}\). The rings were immunologically sensitized by incubation overnight at room temperature in a nondiluted serum pool from patients with atopic asthma whose concentration of both total and specific immunoglobulin E to *Dermatophagoides pteronyssinus* was more than 1,000 International Units (IU)/ml and 17.5 PRU/ml (i.e., +4 radioallergosorbent test titre), respectively. Two remaining rings were incubated overnight in a nondiluted serum pool from persons without atopic asthma whose total immunoglobulin E concentration was less than 10 IU/ml. At the end of each experiment in which immunologically sensitized tissues were used, when baseline tone was reestablished on repeated wash-out of the tissue (see Isometric Contraction Measurement), 0.05 ml (300 units) of *D. pteronyssinus* was administered to all of the bronchial rings to verify that it induced a contractile response only in rings that were immunologically sensitized.

**Isometric Contraction Measurement**

Isometric contraction was measured in airway smooth muscle rings that were mounted between two stainless steel clips in vertical 20-ml organ baths of a computerized isolated organ bath system (IOS\(_1\), EMKA Technologies, Paris, France) previously described.\(^{31,34}\) Baths were filled with Krebs-Henseleit solution maintained at 37°C and bubbled with a 95% oxygen and 5% carbon dioxide gas mixture. The upper stainless clip was connected to an isometric force transducer (EMKA Technologies). Tissues were set at optimal length by equilibration against a passive load of 1.5 g, as previously determined for these types of preparations.\(^{30,35}\) At the beginning of each experiment, a supramaximal stimulation with acetylcholine chloride (10\(^{-3}\) M final concentration in the bath) was administered to each of the rings to elicit a reference response that was used to normalize subsequent contractile responses. After washing the rings with fresh Krebs-Henseleit solution to eliminate the acetylcholine response, general anesthetics were adminis-
tered to the bath in a concentration-dependent manner, to assess the effect on airway resting tone. In another series of experiments, the effect of propofol and etomidate was assessed on the cumulative concentration-response curve (CCRC) for histamine (10^-8 - 10^-3 M). In these experiments, propofol and etomidate were added 20 min before the beginning of the CCRC at the desired concentration. Similar experiments were performed in passively sensitized human bronchial rings. In a final set of experiments designed to examine the effect of propofol and etomidate on [Ca^{2+}], homeostasis, CCRC for KCl (10^-2 - 10^-1 M) and carbachol (10^-8 - 10^-4 M) in the absence and in the presence of these two compounds were also constructed in rat isolated tracheal rings. These experiments were conducted in parallel with fluorescence measurement of [Ca^{2+}], in isolated airway myocytes.

Fluorescence Measurement and Estimation of [Ca^{2+}]

Changes in [Ca^{2+}], were monitored fluorimetrically using the Ca^{2+}-sensitive probe indo-1, as described previously. Freshly isolated rat tracheal smooth muscle cells were loaded with indo-1 by incubation in PSS containing 1 µM indo-1 penta-acetoxyethyl ester (indo-1 AM) for 25 min at room temperature and then washed in PSS for 25 min. Coverslips with attached cells were then mounted in a perfusion chamber and continuously superfused at room temperature. The recording system included a Nikon Diaphot inverted microscope fitted with epifluorescence (Nikon France, Charenton-le-Pont, France). A single cell was illuminated at 360 ± 10 nm. Emitted light from a window slightly larger than the cell was counted simultaneously at 405 nm and 480 nm by two photomultipliers (P100, Nikon). Voltage signals at each wavelength were stored in an IBM-PC computer for subsequent analysis. The fluorescence ratio (405:480) was calculated on-line and displayed with the two voltage signals on a monitor. [Ca^{2+}], was estimated from the 405:480 ratio using a calibration for indo-1 determined within cells. Acetylcholine (10^-5 M) or KCl (110 mM) were applied to the tested cell by a 30-s pressure ejection from a glass pipette located close to the cell. No changes in [Ca^{2+}], were observed during test ejections of PSS (data not shown). Generally, each record of [Ca^{2+}], response to acetylcholine or KCl alone or in the presence of an additional substance was obtained from a different cell. Each type of experiment was repeated for the number of cells indicated in the text.

Chemicals and Drugs

Acetylcholine chloride, carbamylcholine chloride (carbachol), histamine, pronase (type E), elastase (type 3), and bovine serum albumin were purchased from Sigma Chemical Company (Saint Quentin Fallavier, France). Collagenase (type CLS1) was obtained from Worthington Biochemical Corporation (Freehold, NJ). Indo-1 AM was from Calbiochem (France Biochem, Meudon, France). Indo-1 AM was dissolved in dimethyl sulfoxide. The maximal concentration of dimethyl sulfoxide used in our experiments was <0.1% and had no effect on the resting value of the [Ca^{2+}], nor on the variation of the [Ca^{2+}], induced by acetylcholine (data not shown).

Thiopental (Pentotal; Abbott Laboratories, Rungis, France), propofol (Diprivan; Zeneca Laboratories, Cergy, France), and etomidate (Hynomodane; Janssen Laboratories, Boulogne Billancourt, France) were obtained from their clinically used presentations. We verified that the vehicle of each of the drugs had no specific effect on the [Ca^{2+}], and contractile responses. In particular, the solvent for propofol (Ivelip 10%; Clinteck Nutrition Clinique, Amiely, France) had no effect up to the maximal concentration used in the present experiments (i.e., 0.5%).

Data Analysis

In contraction experiments, the contractile response to each ring was expressed as a percentage of the maximal reference acetylcholine response in that ring. Because duplicate airway rings were studied in each experimental condition, from the individual CCRC constructed in each ring, a mean CCRC was obtained for the two rings either control or test to be representative of that trachea or human lung specimen and repeated on five to nine different specimens. Overall mean CCRC were generated in control and test tissues and paired comparisons between the curves were made. The parameters derived from the CCRC were as follows. F_{max}, the contractile force on the CCRC in response to the maximum agonist concentration, was expressed as the mean ± SEM. The potency of an agonist was characterized as the EC_{50}, the concentration producing a contractile force of F_{max}/2 calculated in each curve using a least-squares linear regression and expressed as the geometric mean with 95% confidence interval limits (95% CIs). The change in airway smooth muscle responsiveness was defined as $\Delta F_{max}$, the difference between F_{max} in test and control rings expressed as a percentage of F_{max} in the control ring. Because experiments were designed
pairwise, statistical comparisons of paired mean CCRC were made using first an analysis of variance (two-way analysis of variance) for two or three variables along the whole curve to determine whether the curves were different from each other, using the BMDP statistical software. Then, when the F test was significant, modified Student's paired t tests (two-tailed) using the Bonferroni correction factor were done to identify the concentrations for which the responses were statistically different. Mean EC_{50} values of CCRC in the presence and in the absence of anesthetic compounds were also compared using Student's paired t tests. Results were considered significant at $P < 0.05$.

Results of [Ca^{2+}], are expressed as the mean ± SEM, with n as the sample size. Significance was tested by analysis of variance (one-way analysis of variance) and, when the F value was significant, a modified unpaired Student's t test was done using the Bonferroni method. Qualitative data (frequency of responding cells) were tested by $\chi^2$ tests or exact tests for small sample sizes.

**Results**

**Effects of Thiopental, Etomidate, and Propofol on Baseline Tone in Human Isolated Bronchi**

In human isolated bronchial rings, thiopental from $10^{-7}$ to $10^{-4}$ M induced a concentration-dependent contraction up to $22.2 \pm 4.2\%$ of the acetylcholine reference contraction. Indomethacin ($10^{-5}$ M) reduced but did not abolish the thiopental-induced contraction, and its effect was significant only at low concentrations of thiopental (n = 9, fig. 1).

Neither etomidate ($10^{-5}$ to $3 \times 10^{-4}$ M) nor propofol ($3 \times 10^{-5}$ to $10^{-3}$ M) altered the baseline tone of isolated human bronchi (data not shown).

**Effect of Etomidate and Propofol on Histamine-induce Contraction in Human Isolated Bronchi**

In nonsensitized human bronchus, histamine ($10^{-8}$ to $10^{-3}$ M) produced a contraction that reached $66.3 \pm 7.8\%$ of the acetylcholine reference contraction (n = 12). At the concentrations of $10^{-5}$ and $3 \times 10^{-5}$ M, etomidate did not alter the histamine CCRC, with $\Delta F_{max}$ between tissues in the presence and in the absence of the anesthetic compound between $1.8 \pm 10\%$ and $-2.6 \pm 6\%$, respectively (fig. 2A). Similarly, at the concentrations of $3 \times 10^{-5}$ and $10^{-4}$ M, propofol did not significantly alter the histamine CCRC, $\Delta F_{max}$ between tissues in the presence and in the absence of propofol being $-10.3 \pm 12\%$ and $-10.4 \pm 12.2\%$, respectively (fig. 2A). However, for concentrations of $10^{-4}$ and $3 \times 10^{-4}$ M, etomidate and propofol, respectively, reduced the histamine responsiveness (fig. 2B and 2C, table 1). Thus these concentrations were the lowest "effective" concentrations. The contraction induced by $10^{-7}$ M to $3 \times 10^{-5}$ M histamine (n = 6) was statistically reduced by $3 \times 10^{-4}$ M propofol. Etomidate ($10^{-4}$ M) significantly reduced the maximal histamine-induced contractions (n = 6). Neither etomidate nor propofol altered histamine EC_{50} (table 1).

**Effect of Etomidate and Propofol on Histamine-induced Contraction in Human Passively Sensitized Isolated Bronchi**

In passively sensitized tissues, the maximal contraction induced by histamine, which was $79.5 \pm 9.7\%$ of the acetylcholine reference contraction (n = 7), was greater than that obtained in nonimmunologically sensitized bronchi. Propofol and etomidate, at the same concentrations as those used in the previous experiments, still reduced histamine responsiveness for all of the tested histamine concentrations (fig. 3A and 3B). Both compounds had a
limited effect on EC₅₀ values (table 2). The amplitude of propofol and etomidate effect was assessed as ΔFₘₐₓ. Comparison of ΔFₘₐₓ in immunologically sensitized and nonsensitized bronchi showed that propofol reduced histamine reactivity to a greater degree than in nonsensitized tissues (64.4 ± 15.7%, n = 6 and 16.4 ± 8.5%, n = 7, respectively; P < 0.05), whereas the effect of etomidate was similar in both types of tissue (24.1 ± 6% and 22.3 ± 15%, respectively; P > 0.05; fig. 3C).

**Effect of Etomidate and Propofol on Excitation-Contraction Coupling in Rat Airway Muscle**

To get insight into the effect of etomidate and propofol on excitation-contraction coupling, a series of experiments was performed in the rat trachea, an airway preparation that we recently characterized in terms of Ca²⁺ homeostasis. As in human bronchi, etomidate and propofol altered rat tracheal responsiveness for the same range of concentrations. That is, 10⁻⁴ M and 3 ± 10⁻⁷ M etomidate and propofol, respectively, were the lowest ‘effective’ concentrations.

In response to the depolarizing agent KCl (110 mM K⁺), an agent that activates the electromechanical coupling, propofol (3 ± 10⁻⁴ M) significantly reduced both the number of responding cells from 100% (n = 24) to 60% (n = 10) (fig. 4B), and the amplitude of the [Ca²⁺]i, increase from 153 ± 23 nm (n = 24) to 25 ± 6 nm (n = 10; P < 0.05; figs. 4A, 4B). Accordingly, propofol also reduced the mechanical response of rat tracheal rings to KCl. Contraction at 110 mM K⁺ was decreased from 54.4 ± 2.2% to 12 ± 2.8% of the acetylcholine reference contraction (n = 5, P < 0.05) by 3 × 10⁻⁴ M propofol (fig. 4C). In isolated myocytes, etomidate significantly reduced only the number of the responding cells to 110 mM K⁺ to 71% (n = 7) but not the amplitude of the [Ca²⁺]i increase (97 ± 46 nm; n = 7; P > 0.05). Etomidate reduced the mechanical response of tracheal rings to KCl. Contraction with 110 mM K⁺ was decreased from 53.6 ± 6.3% to 26.4 ± 2.3% of the acetylcholine reference contraction (n = 5; P < 0.05) by 10⁻⁴ M etomidate (fig. 4C).

In response to the muscarinic agonist acetylcholine (10⁻⁵ M), which activates the pharmacomechanical coupling, propofol (3 × 10⁻⁴ M) again significantly reduced both the number of responding cells from 100% (n = 32) to 60% (n = 27) and the amplitude of the [Ca²⁺]i.

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<th>Table 1. Fₘₐₓ and EC₅₀ in Nonimmunologically Sensitized Human Bronchial Rings Unexposed and Exposed to Propofol and Etomidate</th>
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Mean maximal force in response to carbachol (Fₘₐₓ; % reference response to AC₅₀) and geometric mean half-maximal effective concentration (EC₅₀; nM) in nonimmunologically sensitized human bronchial rings unexposed (control) and exposed to propofol (3 × 10⁻⁴ M) and etomidate (10⁻⁴ M). Values for Fₘₐₓ are mean ± SEM. Values in parentheses are lower and upper limits of the 95% confidence interval; n = 6.

*P < 0.05.
on the amplitude of acetylcholine-induced $[\text{Ca}^{2+}]_i$ increase ($453 \pm 51$ nm; $n = 10$; $P < 0.05$). It did reduce the mechanical response of tracheal rings to carbachol, with the maximal response decreased to $89.9 \pm 6.5\%$ of the acetylcholine reference contraction ($n = 5$, $P < 0.05$) by $10^{-3} \text{M}$ etomidate. In this regard, both anesthetic compounds shifted to the right the CCRC to carbachol. The mean EC$_{50}$ (95% CI) was $1.2 \mu\text{M}$ (0.9 - 1.5 $\mu\text{M}$) in control conditions and $3.7 \mu\text{M}$ (2.8 - 4.8 $\mu\text{M}$) and $1.9 \mu\text{M}$ (1.1 - 3.6 $\mu\text{M}$) for propofol and etomidate, respectively.

**Discussion**

The results of the current study indicate that, whereas thiopental contracts human isolated bronchi, propofol and etomidate reduce histamine-induced contraction in human isolated airway smooth muscle either nonsensitized or immunologically passively sensitized with asthmatic serum. The mechanism of this relaxing effect involves inhibition of electro- and pharmacomechanical coupling in airway smooth muscle.

As in animal airway tissue, we observed that thiopental contracts human isolated bronchi to approximately 20% of the reference response to a cholinergic agonist. This contraction occurred at concentrations within the clinical range, i.e., $3 \times 10^{-5}$ M, taking into account the affinity of thiopental to plasma proteins. It has been shown clearly that thiopental inhibits voltage-dependent $\text{Ca}^{2+}$ channels in porcine tracheal smooth muscle cells, and it is likely that such an effect also occurs in human airway smooth muscle because these channels are very similar in both species. However, this

![Image](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931270/)
Fig. 4. Effect of propofol and etomidate on KCl-induced responses in the rat trachea. (A) Effect of KCl (110 mM) on [Ca^{2+}] in freshly isolated smooth muscle cells loaded with indo-1. Each trace is representative of 7–24 different cells. (B) Percentage of responding cells (as a percentage; left ordinate scale) and amplitude of the first [Ca^{2+}] peak (the maximal increase above resting baseline concentration) (expressed as nanomoles; right ordinate scale) in control cells (open columns), in the presence of propofol (5 × 10^{-5} M; solid columns) and in the presence of etomidate (10^{-5} M; cross-hatched columns). Vertical bars are SEM. *P < 0.05. (C) Mean concentration–response curve for KCl in the absence of anesthetic compounds (closed circles) and in the presence of propofol (5 × 10^{-3} M; open triangles down) and of etomidate (10^{-3} M; open triangles up) in rat isolated tracheal rings. Each symbol represents a mean value calculated from five different specimens. Contractile force is expressed as a percentage of a reference response to acetylcholine (1 mM). Vertical bars indicate SEM. *P < 0.05.

Direct inhibitory effect of thiopental on calcium homeostasis in airway smooth muscle cannot account for the contractile effect observed in the present study. The fact that indomethacin, at an appropriate concentration to block cyclooxygenase in this tissue, did not reduce thiopental-induced contraction confirms that, in humans as in animals, thiobarbiturates act indirectly by releasing eicosanoids that constrict airway smooth muscle.

In contrast to thiopental, neither etomidate nor propofol altered human airway baseline tone. Although we did not observe a direct relaxant effect of both drugs, they reduced histamine-induced contraction, an effect that could be of clinical interest. To further assess this effect, we also studied both anesthetic compounds in human airways exhibiting in vitro hyperresponsiveness to histamine; that is, in human tis-
sues passively sensitized with asthmatic serum. As is the case for airway tissues from spontaneously or actively sensitized animals, immunologically passive sensitization produces hyperresponsiveness of human isolated airways and provides the opportunity to study the interaction between allergic factors and smooth muscle behavior. As previously shown, we observed that the response to histamine in passively sensitized tissues was greater than that in nonimmunologically sensitized ones. In human immunologically sensitized airways, etomidate and propofol still exhibited a relaxant effect, and this
effect was even more pronounced for propofol. The enhancement of the effect of propofol in passively sensitized airways is likely to be related to the action of this compound on excitation-contraction coupling in airway smooth muscle and, in particular, to its marked effect on the electromechanical coupling.

We must be cautious in extrapolating in vitro data to those from in vivo conditions, even though the present study was done in human bronchi immunologically sensitized with asthmatic serum. In particular, in terms of concentrations, the present results generally correspond with those observed in various animal muscular tissues, regardless of whether they were obtained from the respiratory tract.3-5,7,18,20,43,44 However, the concentrations required to obtain a marked in vitro effect appear higher than those encountered clinically for both anesthetics.45,46 For example, the high therapeutic range for propofol is approximately 10 µg/ml, which translates to 10⁻⁷ M. However, because of the high protein binding of this compound, free propofol concentrations are approximately 1-3 µM; that is, two orders of magnitude lower than the “effective” concentration in the present study, although the actual in vivo concentration of drugs at the site of the airway smooth muscle cell membrane is not known.

The fact that propofol and etomidate inhibited histamine-induced contraction at a relatively high concentration also suggests that the effect of these anesthetic compounds could be due to a nonspecific action on Ca²⁺ homeostasis, on the sensitivity of the contractile apparatus to Ca²⁺, or on both, as has been suggested before.5,18,20,22,25,40 rather than to an action via specific receptors. To investigate this hypothesis, we studied the action of both anesthetic compounds on calcium responses to agonist acting via different excitation-contraction coupling mechanisms; that is, KCl and acetylcholine in freshly isolated rat tracheal smooth muscle cells, an airway preparation that we recently characterized in term of [Ca²⁺], homeostasis.39 Previously we showed that, in these cells, KCl induces a transient [Ca²⁺] increase due to calcium-influx via voltage-operated channels (i.e., electromechanical coupling) because it is blocked by the voltage-operated calcium channel blocker, verapamil,26 whereas acetylcholine-induced [Ca²⁺] response depends only on calcium release from intracellular stores (i.e., pharmacomechanical coupling), at least for short stimulation, as in the present study.26 The fact that propofol and etomidate inhibited both types of [Ca²⁺], response indicates that these anesthetic compounds act on both the release of Ca²⁺ from intracellular stores and Ca²⁺ influx via voltage-dependent channels. These results may explain the reduction of histamine-induced contraction in human bronchial rings, because research has shown that histamine acts via both pharmaco- and electromechanical coupling in this preparation.16,41 Furthermore, these findings correspond with the direct demonstration of the inhibitory effect of propofol (3 × 10⁻⁴ M) on voltage-dependent Ca²⁺ channels observed in porcine tracheal smooth muscle cells.20 In the same connection, it has been shown in canine myocardial cells that both propofol and etomidate, at concentrations in the same range as those used in the present study, decreased calcium channel currents.43 In conclusion, we have observed that high concentrations of propofol and etomidate reduce histamine-induced contraction in human isolated airway smooth muscle, including in immunologically sensitized tissues.

The authors thank Dr. X. Villanove and Mrs. H. Crevel for assistance and the “Service de Chirurgie Toracique, C.H.U. de Bordeaux” for supplying human tissues.

References