Relaxation by sevoflurane, desflurane and halothane in the isolated guinea-pig trachea via inhibition of cholinergic neurotransmission†

C. U. Wiklund1*, S. Lim2, U. Lindsten1 and S. G. E. Lindahl1

1Department of Anaesthesiology, Karolinska Hospital and Institute, S-171 76, Stockholm, Sweden.
2Dayton Children’s Hospital Dayton Ohio, OH, USA

*Corresponding author

We have studied relaxation of airway smooth muscle by sevoflurane, desflurane and halothane in the isolated guinea-pig trachea. Ring preparations were mounted in tissue baths filled with physiological salt solution (PSS), aerated continuously with 5% carbon dioxide in oxygen. Electrical field stimulation (EFS) elicited cholinergic contractions that were abolished by tetrodotoxin, indicating nerve-mediated responses. Anaesthetics were added to the gas aerating the tissue baths. Halothane, sevoflurane and desflurane at 0.5–1.0 MAC markedly attenuated cholinergic contractions to EFS. Initiation of contractile responses to acetylcholine (ACh) were not affected by volatile anaesthetics, suggesting prejunctional inhibition (i.e. inhibition of acetylcholine release). When added to a maintained submaximal contraction to ACh, volatile anaesthetics induced relaxation, indicating postjunctional inhibition. We conclude that sevoflurane, desflurane and halothane inhibited postganglionic cholinergic neuroeffector transmission in the trachea. The effect was probably exerted via pre- and postjunctional mechanisms (i.e. inhibition of acetylcholine release and direct muscle actions). Sevoflurane and desflurane were more potent than halothane both pre- and postjunctionally.

Br J Anaesth 1999; 83: 422–9

Keywords: anaesthetics volatile, desflurane; anaesthetics volatile, halothane; anaesthetics volatile, sevoflurane; nerve, neurotransmission; parasympathetic nervous system; lung, trachea; guinea-pig

Accepted for publication: February 2, 1999

It is well known that volatile anaesthetic agents relax airway smooth muscle.1 2 The mechanisms of action are also well studied, in particular direct muscle action and Ca2+-dependent intracellular functions.3–5 There are fewer investigations of inhalation anaesthetic agents on muscarinic receptor affinity and neurotransmitter release and many of these have been concerned primarily with brain function.6 7 There are also investigations of inhalation anaesthetics on neurotransmitter release or nerve-mediated effects in airway smooth muscle. Dog trachea was examined in vitro via double sucrose gap, microelectrode and tension recording.8 Halothane was suggested to inhibit acetylcholine (ACh) release and to reduce or inactivate intracellular increases in Ca2+ in smooth muscle cells. Halothane was also shown to attenuate histamine-induced bronchoconstriction in Basenji greyhound dogs.9 Pulmonary resistance and dynamic compliance were calculated from simultaneous pressure and flow curves. The authors concluded that block of vagal reflexes was the main mechanism of action behind attenuation of histamine-induced bronchoconstriction by halothane. Direct and neurally mediated effects of halothane were measured in mongrel dogs in vivo.10 Bronchoconstriction induced by vagal nerve stimulation or by nebulized acetylcholine was attenuated by halothane. Lung volume was measured with a body plethysmograph. Halothane was suggested to inhibit bronchoconstriction via both nerve-mediated actions and direct effects on airway smooth muscle cells. In an in vitro study in the mongrel dog trachea, the effects of halothane, enfurane and isoflurane on the peripheral vagal motor pathway were examined.11 Effects were studied at three levels: (1) nicotinic receptors in intramural parasympathetic ganglia, with 1,1-dimethyl-4-phenyl-piperazinium iodide (DMPP), (2) postganglionic cholinergic fibres, with electrical field stimulation (EFS) and (3) muscarinic cholinergic receptors on smooth muscle cells, with ACh. The authors suggested inhibitory effects by the volatile anaesthetics at all three sites of action.

†Presented in part at the Annual Meeting of the European Society of Anaesthesiologists, London, June 1996.
Clinically, halothane has been used successfully in patients with airway obstruction. In spite of its potent relaxation of airway smooth muscle there are negative effects with prolonged and repeated treatment, such as catecholamine-sensitizing effects on myocardial cells and halothane-induced hepatitis, which limit its use for long-term treatment. However, volatile anaesthetics have been used successfully in the prolonged treatment of status asthmaticus in intensive care where other therapies have been inadequate. Isoflurane is the most popular volatile anaesthetic in clinical practice and its bronchorelaxing properties have been studied previously. Hence, we studied the airway smooth muscle relaxing properties of sevoflurane and desflurane and compare them with those of halothane which for many years has been the volatile anaesthetic of choice for asthmatic patients.

To our knowledge, the effects of desflurane and sevoflurane on neuroeffector transmission have not been studied in great detail. In this study, we have assessed the effects of volatile anaesthetics on postganglionic cholinergic neurotransmission and on initiation and maintenance of contractile responses to muscarinic receptor stimulation. This was done via: (1) contractile responses to electrical field stimulation (EFS) in the presence of diclofenac to abolish the influence of inhibitory non-adrenergic non-cholinergic nerve activity; (2) cumulative contraction response curves to ACh; and (3) reversal of steady-state contractile responses to a submaximal single dose of ACh.

**Materials and methods**

Approval from the Local Ethics Committee for Animal Studies was obtained before the start of the study. Guinea-pigs of both sexes (weighing 300–600 g) were killed by carbon dioxide narcosis and exsanguination. The lungs and trachea were placed immediately in ice-cold physiological salt solution (PSS) (composition in mmol litre⁻¹: Na 149, K 2.9, Ca 1.8, Mg 0.5, Cl 144, HCO₃ 23.8, H₂PO₄ 0.4 and glucose 5.5), aerated continuously with 5% carbon dioxide in oxygen. Rings of the mid-portion of the trachea, three cartilages wide, were dissected free from connective tissue and mounted in 25-ml water-jacketed tissue baths, made of glass (Section of Engineering, Mayo Clinic). The temperature of PSS was increased from 4 to 37°C over 60 min. The ring preparations were given an initial isometric load of 5 mN. After the temperature had reached 37°C, EFS was applied and basal muscle tone increased spontaneously during the following 60 min to 15 mN (i.e. optimal tension).

Motor activity was recorded isometrically by Grass force-displacement transducers (FT03) and tracings were made on a Grass polygraph.

**Experimental conditions**

Isolated ring preparations of guinea-pig trachea were stimulated supramaximally (0.5 ms pulse duration, monophasic pulses, 10 Hz, 15 V, 100 pulses, that is 10-s stimulation duration at 8-min intervals) by EFS. EFS was provided by a direct current amplifier (Section of Engineering Mayo Clinic) triggered by a stimulator (model S44, Grass Medical Instruments) via two parallel platinum electrodes (10×50 mm), 8 mm apart (Section of Engineering Mayo Clinic). They responded with rapid contraction, followed by fast relaxation and a slow return to basal tone (Fig. 1). Contraction was abolished by atropine 10⁻⁶ mol litre⁻¹, indicating ACh dependency. Relaxation was not sensitive to atropine or propranolol, suggesting non-adrenergic non-cholinergic (NANC) nerve activity. High basal muscle tone was attenuated by diclofenac 3×10⁻⁶ mol litre⁻¹, indicating prostaglandin mediation. In the presence of diclofenac, NANC responses were abolished and cholinergic contractions appeared clearly (Fig. 1). NANC nerve activity was not antagonized by diclofenac but interference between NANC relaxations and cholinergic contractions was eliminated. The contractile response to EFS in the presence of diclofenac was not affected by propranolol and was abolished by atropine. As there was no apparent interaction between adrenergic or NANC and postganglionic cholinergic nerve activity under basal conditions, experiments were performed in the absence of propranolol and a ganglion blocker. Although propranolol and a ganglion blocker would have eliminated interference from adrenergic neurones and from neurones with cell bodies (i.e. ganglia in the smooth muscle preparation) they would not have eliminated possible interference from neurones without ganglia in the muscle wall. EFS stimulates all axons in the smooth muscle preparation, including those without ganglia. Therefore, experiments with EFS were performed in the presence of diclofenac. Inhibitory effects by volatile anaesthetics on contractile responses to EFS were interpreted as probably dependent on inhibition of postganglionic cholinergic neuro-effector transmission, although stimulation of inhibitory nerve activity could not be ruled out.

Pulse duration response curves were produced to determine optimal stimulation variables and to identify nerve-mediated stimulation. EFS was applied at 15 V, 10 Hz with 100 pulses, that is 10-s stimulation duration at 8-min intervals. Pulse duration was increased gradually from 0.01 to 5.0 ms every second stimulation. This was also repeated in the presence of tetrodotoxin 3×10⁻⁷ mol litre⁻¹, a blocker of fast neuronal sodium channels. At 0.5 ms pulse duration, responses were maximal, with negligible responses remaining in the presence of tetrodotoxin. Hence, responses to EFS with 0.5 ms pulse duration and 10 s stimulation duration, were regarded as nerve mediated, and were used throughout the study (Fig. 2).

Direct effects on tracheal smooth muscle cells were studied with contractile responses to exogenously applied acetylcholine. This was performed in the presence of tetrodotoxin 10⁻⁶ mol litre⁻¹ to prevent stimulation of intramural parasym pathetic ganglia from contributing to the induced contraction. Pretreatment with a selective nicotinic
Fig 1 Responses to electrical field stimulation (EFS) (10 Hz, 0.5 ms, 100 pulses, that is 10-s stimulation duration at 8-min intervals) in isolated guinea-pig trachea. Basal tone was high as a result of prostaglandin production. Nerve stimulation elicited a cholinergic contraction followed by non-adrenergic non-cholinergic (NANC) relaxation and a slow return to basal tone. The prostaglandin synthase inhibitor diclofenac $3 \times 10^{-6}$ mol litre$^{-1}$ attenuated basal tone, unmasked cholinergic contractions and abolished NANC relaxations. Sevoflurane at 0.5 MAC reversibly inhibited cholinergic contractions to nerve stimulation.

Fig 2 Pulse duration response curves for guinea-pig trachea. Electrical field stimulation (EFS) at 10 Hz, 100 pulses, that is 10-s stimulation duration at 8-min intervals. Open symbols = control preparations; filled symbols = preparations incubated with tetrodotoxin $3 \times 10^{-7}$ mol litre$^{-1}$, a blocker of neuronal fast sodium channels. □, △ = Cholinergic contractions; ○, ▲ = NANC relaxations. Responses are shown as percentage of control responses with 5.0 ms pulse duration (n=7).

receptor antagonist may have been pharmacologically more correct but we chose to use tetrodotoxin as other investigators have done previously.$^{11}$

Cumulative dose–response curves to ACh
In two ring preparations, cumulative dose–response curves to ACh were obtained in the presence of tetrodotoxin. ACh was added cumulatively to the tissue baths (10$^{-9}$–10$^{-4}$ mol litre$^{-1}$) in log-increments with 5 min allowed for stabilization of the contractile response to each concentration. The stabilized contractile response to ACh 10$^{-4}$ mol litre$^{-1}$ after the first cumulative application was considered the maximal response and was set at 100%. After the first application, the preparations were washed thoroughly and allowed to equilibrate for 30 min after which repeated cumulative dose–response applications were performed in both preparations. After 15 min equilibration, a volatile anaesthetic was added to one of the preparations. The other preparation served as a control for the effect of time. In some preparations, basal tone was slightly lower after the first dose–response application of ACh compared with before the first application. This resulted in some cases in time-adjusted control contractions slightly larger than 100% (see Fig. 4B, C).

Reversal of ACh contractions
In another two preparations, single doses of ACh 10$^{-6}$ mol litre$^{-1}$ were added and allowed to stabilize for 10 min, after which a volatile anaesthetic was added to one preparation while the other served as a control for the effect of time. A concentration of 10$^{-6}$ mol litre$^{-1}$ was close to the ED$_{50}$ for ACh and produced a contractile response in the range 100–200% of the contractile response to EFS in the presence of diclofenac. Volatile anaesthetics reversed ACh contraction with a slow onset and a stabilized effect after 10–12 min. The contractile response to ACh 10$^{-6}$ mol litre$^{-1}$ after 10 min of stabilization was used as the control contractile response and set at 100%.

Anaesthetic gas application
Halothane, sevoflurane or desflurane was added via commercially available vaporizers to the gas aerating the PSS. Concentrations of the anaesthetics in PSS were measured by gas chromatography, with a Varian gas chromatograph 7400. Effects were studied at 0.5 and 1.0 MAC. Halothane was also studied at 3.5 MAC. With our experimental set-up, higher concentrations than 1.0 MAC of desflurane and sevoflurane were not achievable. Maximal concentrations from vaporizers with maximal aerating intensity in the tissue chambers, without eliciting tension artefacts caused by violent bubbling, produced no more than 1.0 MAC of desflurane or sevoflurane in PSS.

After incubation of PSS 5 ml and room air 15 ml in gas-tight syringes at 37°C for 20 min during continuous shaking, 4 ml of air from the syringes were analysed using a Varian
gas chromatograph 7400. The method depends on complete equilibration between liquid and gas phases in the syringe. It has been shown for blood-gas equilibration that even for sulphur hexafluoride, which has a very low solubility, 30 min of equilibration is sufficient. For the volatile anaesthetics, 10 min equilibration time is adequate. Concentrations of anaesthetic gases in PSS were calculated. Actual guinea-pig MAC levels were deduced.

**Drugs**

ACh, atropine sulphate, diclofenac, propranolol hydrochloride and tetrodotoxin were purchased from Sigma (St Louis, MO, USA). Sevoflurane and desflurane were gifts from Abbott and Pharmacia and Upjohn, respectively. Halothane was purchased from Zeneca AB (Gothenburg, Sweden).

**Statistical analysis**

Contractile responses in tracheal rings exposed to a volatile anaesthetic were compared with responses of tissues not exposed to a volatile anaesthetic. In tracheal rings exposed to anaesthetic, the contractile response to ACh was adjusted for time using the following equation:

\[ C_t = (C_2/C_1) \times C_{va} \]

where \( C_t \) = time-adjusted control contraction of volatile anaesthetic muscle; \( C_1 \) = contractile response of control muscle (initial measurement); \( C_2 \) = contractile response of control muscle (measured in parallel with volatile anaesthetic muscle); in ACh-precontracted preparations, \( C_1 \) and \( C_2 \) were the contractile responses in control preparations 10 min after adding ACh and after 10–12 min exposure to anaesthetic, in the volatile anaesthetic muscle; \( C_{va} \) = contractile response in volatile anaesthetic muscle (initial measurement, i.e. before exposure to the anaesthetic). Responses to EFS were adjusted for the effect of time accordingly. Experimental data are expressed as mean (SD). Statistical analysis was performed using SPSS for windows. Statistical significance was tested with repeated measures analysis of variance or Student’s t test for paired or unpaired variables. \( P<0.05 \) was regarded as statistically significant; \( n \) represents the number of guinea-pigs.

**Results**

Because of the study design, only cholinergic activity was measured at a lowered basal tone, achieved by prostaglandin synthase inhibition which also abolished NANC relaxations (Fig. 1). Concentrations of anaesthetics were normalized to guinea-pig MAC values of approximately 1\% for halothane, 6\% for desflurane and 2\% for sevoflurane. Equi-anaesthetic concentrations were used and only one concentration of volatile anaesthetic was given to each muscle preparation.

**Effects of anaesthetics on nerve-mediated contraction**

Halothane, sevoflurane and desflurane inhibited cholinergic contractions to nerve stimulation in a dose-dependent and reversible manner (at 1.0 MAC, \( P<0.01 \) for halothane, \( P<0.001 \) for desflurane and \( P<0.001 \) for sevoflurane compared with controls. At 1.0 MAC, sevoflurane and desflurane were more potent than halothane (\(* * P<0.01\) (n=6–7).

**Effects on initiation of contractile responses to ACh**

Contractile responses of the tracheal rings to cumulative doses of ACh revealed an \( ED_{50} \) of 1.6 (1.2)×10^{-6} mol litre^{-1}. A second set of cumulative dose–response curves was produced after incubation with 1.0 MAC of halothane, sevoflurane or desflurane. The anaesthetics did not affect \( ED_{50} \) or efficacy (i.e. force development). Thus there were no indications of any interaction of these anaesthetics with initiation of contractile responses to ACh (Fig. 4A, B, C).

**Effects on maintenance of contractile responses to ACh**

In tracheal rings, submaximally precontracted with acetylcholine 10^{-6} mol litre^{-1}, all three anaesthetics dose-dependently and reversibly induced slow relaxations (at 1.0 MAC, \( P<0.05 \) for halothane, \( P<0.001 \) for desflurane and \( P<0.001 \) for sevoflurane compared with controls). At 0.5 MAC, desflurane was more potent than halothane (\( P<0.05 \) and
Fig 4 Contractile responses to exogenously applied acetylcholine (ACh). Responses are expressed as percentage of control response to ACh $10^{-4}$ mol litre$^{-1}$. Halothane, sevoflurane and desflurane did not affect contractions to ACh. Open symbols = time-adjusted control contractions; filled symbols = contractions in the presence of anaesthetic ($n=6$).

at 1.0 MAC both sevoflurane ($P<0.01$) and desflurane ($P<0.05$) were more potent than halothane (Fig. 5).

**Discussion**

The main findings of our study were that halothane, sevoflurane and desflurane relaxed airway smooth muscle via inhibition of cholinergic neuroeffector transmission, probably by both ACh release and actions on smooth muscle cells. At equi-anaesthetic concentrations, sevoflurane and desflurane were more potent than halothane both pre- and postjunctionally.

Volatile anaesthetics relax airway smooth muscle, an action which is of great benefit for patients with asthma. It may also be important in intensive care for patients with status asthmaticus. In spite of the airway relaxing properties, some volatile anaesthetics irritate the airways in awake patients. Isoflurane and desflurane evoke airway irritation which limit their usefulness, especially for induction of anaesthesia. Isoflurane has been used for many years after i.v. induction of anaesthesia, and desflurane may also be used in asthmatic patients. Halothane and sevoflurane, both devoid of airway irritating effects, are better suited for induction and maintenance of anaesthesia in asthma sufferers. In contrast, halothane has side effects such as a high rate of metabolic degradation and liver toxicity in addition to proarrhythmic actions on the heart. Sevoflurane also has a relatively high rate of metabolic degradation and is known to produce metabolites which are potentially nephrotoxic. Desflurane however, has a low rate of metabolism, one order of magnitude lower than isoflurane, which may make this agent suitable for long-term use in the ICU.

**Effects of anaesthetics on nerve-mediated contraction**

At pulse durations of 0.5 ms or less, responses to EFS, in the presence of tetrodotoxin block of fast neuronal sodium channels, were negligible (Fig. 2). This implies that only an insignificant part of the response to EFS was caused by direct muscle activation. A pulse duration of 0.5 ms was therefore chosen to study responses caused mainly by nerve stimulation and not direct muscle activation.
Contractile responses to EFS were reduced in the presence of volatile anaesthetic agents. This finding can be explained by inhibition of ACh release, inhibition of muscarinic receptor activation or inhibition of intracellular processes responsible for initiation of contraction. However, we also found that anaesthetic agents did not influence cumulative dose–response curves to exogenously applied ACh (Fig. 4). Hence, it is likely that the reduced smooth muscle contraction to EFS after exposure to volatile anaesthetic agents was caused by inhibition of ACh release. This observation confirms the findings of Korenaga, Takeda and Ito, in dog trachea, who found suppression of excitatory junction potentials by halothane without alteration of muscle sensitivity to ACh. Brichant and colleagues also noted inhibition by volatile anaesthetics of ganglionic nicotinic receptor sensitivity, postganglionic cholinergic nerve function and muscarinic receptor sensitivity in dog trachea. In addition, actual measurements of transmitter release have been performed by other groups. Shichino and colleagues found a dose-dependent reduction in cerebrocortical ACh release during exposure to isoflurane and sevoflurane. In contrast, halothane was found to inhibit [3H]norepinephrine release in rat brain in vitro whereas release of [3H]acetylcholine was not affected. Furthermore, isoflurane, enflurane and halothane have been shown to inhibit Ca2+ currents and glutamate release from isolated guinea-pig cerebral synaptosomes. In ganglia, halothane inhibited ACh release from preganglionic nerve terminals. These studies support our suggestion of reduced transmitter release as a mechanism of action for volatile anaesthetics. The responsible cellular mechanism behind inhibition of ACh release could be block of the interaction between transmitter-containing synaptic vesicles and the presynaptic membrane, stabilized axonal membrane or depressed intracellular Ca2+ mobilization. Based on previous results from Miao, Frazer and Lynch, we suggest that the effects on ACh release in our study were caused by altered Ca2+ mobilization, although this requires further investigation.

**Effects on initiation and maintenance of contractile responses to ACh**

The lack of effect of volatile anaesthetics on initiation of contractile responses to ACh and inhibition of maintenance of ACh-induced contractions may seem contradictory. Some investigators, using a similar technique to ours, found inhibitory effects of volatile anaesthetics on initiation of contractile responses to ACh, whereas others did not. Initiation and maintenance of a contractile response to muscarinic receptor activation in airway smooth muscle have been suggested to be linked to different intracellular processes. During initiation of contraction, cytosolic Ca2+ increases, which leads to activation of myosin light-chain kinase (MLCK), which phosphorylates myosin light-chain (MLC). Steady-state tone is maintained in spite of dephosphorylation of MLC and cytosolic Ca2+ concentrations lower than during the initial phase of contraction. One population of rapidly cycling phosphorylated cross bridges is responsible for muscle shortening and establishment of tone, whereas a second population of slowly cycling dephosphorylated cross bridges, or latch bridges, are responsible for maintenance of steady-state tone. This may explain the difference in effect on initiation and maintenance of contractile responses to ACh in our study. This was a consistent finding with all three agents and is in agreement with previous reports that volatile anaesthetic agents have no effects on agonist binding to muscarinic ACh receptors in rat brain.

Although we did not measure muscarinic receptor binding or intracellular actions, our results are compatible with the suggestion that volatile anaesthetics do not affect muscarinic receptor activation or intracellular processes responsible for initiation of ACh-mediated contraction.

**Effects on maintenance of contractile responses to ACh**

All three anaesthetics relaxed tracheal rings precontracted with ACh. The relaxing effect of volatile anaesthetic agents on airway smooth muscle was caused not only by inhibition of ACh release, as discussed above, but also by a direct effect on precontracted airway smooth muscle, as indicated by the observed dose-dependent relaxing effects (Fig. 5). It is likely that volatile anaesthetics interact with dephosphorylated latch bridges or other intracellular mechanisms responsible for maintenance of muscarinic contraction. The relaxing effect of the volatile anaesthetics was more pronounced with combined pre- and postjunctional actions (Fig. 3) than with an isolated postjunctional action (Fig. 5). Hence, pre- and postjunctional actions seem to be additive. These postjunctional effects are likely to be caused by modulation of intracellular Ca2+ functions as several groups have found inhibition of voltage-dependent Ca2+ channels by volatile anaesthetics in airway or vascular smooth muscle cells. Others have shown halothane to inhibit the enhancing effect of cholinergic stimulation on Ca2+ sensitivity of the contractile apparatus of airway smooth muscle cells. Whether these effects are different for various volatile anaesthetic agents, explaining the seemingly more potent effect of sevoflurane and desflurane compared with halothane, need further study.

In agreement with our results in guinea-pig tracheal smooth muscle, Mazzeo and colleagues found desflurane to be more potent than halothane in relaxing ACh-precontracted airways in canine distal bronchi. However, they found equipotency for halothane and desflurane in proximal bronchi, whereas in distal bronchi, desflurane was more potent than halothane. These findings suggest airway tree heterogeneity regarding the relaxant effects of volatile anaesthetics. Park and colleagues reported isoflurane and halothane to be equipotent in relaxing 5-HT-precontracted rat bronchi. Furthermore, Kai and colleagues showed halothane to be more potent than sevoflurane and isoflurane for inhibition of Ca2+ sensitivity.
during muscarinic receptor stimulation in canine trachea.\textsuperscript{4} Yamakage, Hirshman and Croxton found the following potencies on inhibition of voltage-activated Ca\textsuperscript{2+} currents in porcine tracheal smooth muscle: halothane $>$ isoflurane $>$ sevoflurane.\textsuperscript{3} According to the findings in this study, sevoflurane and desflurane relaxed guinea-pig airway smooth muscle to the same extent and were more potent than halothane.

In summary, halothane, sevoflurane and desflurane reduced airway smooth muscle tone probably by inhibition of ACh release and by direct interference with the intracellular contractile processes of airway smooth muscle cells. None of the agents interfered with the mechanisms responsible for initiation of contractile responses to muscarinic receptor activation. Sevoflurane and desflurane were more potent than halothane both pre- and post-junctionally. This may indicate a greater effect on airway obstruction during anaesthesia with these agents. The actions and potency relationships for volatile anaesthetics described in guinea-pig trachea may not be identical to those in other species, including humans. Species differences may exist.

**Acknowledgements**

Supported by the Karolinska Institute, the Swedish Society of Medicine, the Medical Research Council (1995: B96-17X-10401–04B S0183; 1997: K97-17X-10401–05CK U0274), Abbott, Pharmacia and Upjohn.

**References**

Volatile anaesthetics relax trachea


33 Park KW, Dai HB, Lowenstein E, Kocher ON, Sellke FW. Isoflurane- and halothane-mediated dilation of distal bronchi in the rat depends on the epithelium. Anesthesiology 1997; 86: 1078–87