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Halothane, Enflurane, and Isoflurane Attenuate Both Receptor- and Non–Receptor-mediated EDRF Production in Rat Thoracic Aorta

Mark J. Uggeri, M.D., D.D.S., George J. Proctor, B.A.,† Roger A. Johns, M.D.‡*

EDRF (endothelium-derived relaxing factor) is a cellular and intercellular messenger that activates soluble guanylate cyclase. In blood vessels it is released from the endothelium and causes relaxation of vascular smooth muscle. Halothane previously has been shown to attenuate EDRF-induced vasodilation elicited by the receptor-mediated vasodilators acetylcholine and bradykinin and to alter muscarinic receptor activity. We examined and compared the effects of the inhaled anesthetics halothane, enflurane, and isoflurane on endothelium-dependent vasodilation and tested the hypothesis that these agents inhibit EDRF-mediated vasodilation solely through inhibition of endothelial cell receptor-mediated EDRF release. Isolated rat thoracic aortic rings were mounted for isometric tension recording and preconstricted with phenylephrine. Cumulative dose–response curves were obtained to methacholine, a receptor-mediated endothelium-dependent dilator; to A23187, a nonreceptor-mediated endothelium-dependent dilator; and to sodium nitroprusside, a direct-acting endothelium-independent dilator before, during, and after inhalational anesthetic exposure. Both receptor-mediated and non–receptor-mediated endothelium-dependent relaxation by methacholine and A23187, respectively, were significantly ($P < 0.01$ to $P < 0.05$) and reversibly attenuated by halothane, enflurane, and isoflurane at 2 MAC and by isoflurane at 1 MAC. Endothelium-independent relaxation by sodium nitroprusside, an agent that acts directly on the vascular smooth muscle cell to activate guanylate cyclase, was unaffected by any of the anesthetics at any concentration tested. Indomethacin had no significant effect on the inhibition of endothelium-dependent vasodilation by these inhalational anesthetics. We conclude that halothane, enflurane, and isoflurane inhibit endothelium-dependent vasodilation; that isoflurane is more potent than halothane and enflurane in this regard. Inhaled anesthetic inhibition of stimulated EDRF-dependent vasodilation is reversible, is not primarily due to inhibition of a receptor mediated response of the endothelial cell, and is proximal to the site of guanylate cyclase activation in vascular smooth muscle. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Artery: vascular smooth muscle. Endothelium: endothelium-derived relaxing factor.)

ENDOTHELIUM-DERIVED RELAXING FACTOR (EDRF) is a potent vasodilator released from the endothelium of blood vessels under basal conditions and in response to a wide variety of chemical mediators.[1] Recent evidence has suggested that EDRF may be nitric oxide or a similar nitrogen oxide–containing compound[2] and that it may serve as a messenger for the activation of soluble guanylate cyclase in a wide variety of cell types. In blood vessels, EDRF is produced by endothelium and mediates vasodilation.[1] Macrophage and neutrophil cytotoxic effects appear to be mediated by EDRF.[3,4] EDRF is produced in and activates soluble guanylate cyclase in cerebellar neurons and in posterior pituitary, adrenal medulla, hypothalamus, and nonadrenergic noncholinergic neurons.[5–7] EDRF is a labile compound with a biologic half-life of 6.3–50 s in *in vitro* preparations.[8] It is produced in endothelial cells from the amino acid L-arginine by a constitutive enzyme, EDRF synthase, which is calcium-, calmodulin-, and NADPH-dependent and which exists in both soluble and particulate forms.[9] There is also evidence for a nonconstitutive, inducible form of EDRF synthase that is not agonist-activated and that is induced by endotoxin and a variety of cytokines.[10] This inducible form is not present in the endothelium under basal conditions. Following its release from the endothelium, EDRF activates vascular smooth muscle guanylate cyclase, leading to vasodilation.[11]

Muldoon *et al.* reported that 2% halothane reversibly and significantly attenuated the endothelium-dependent relaxation observed in isolated rat aortic rings to the endothelium-dependent, receptor-mediated vasodilators acetylcholine and bradykinin but did not affect the nitroglycerin-induced, endothelium-independent, cyclic GMP–mediated relaxations in these vessels.[12] The mechanism of this inhibition was not evaluated, although it was suggested that receptor inhibition may play a role. Acetylcholine effects on muscarinic receptors in skeletal muscle and sympathetic nerve endings had previously been shown to be altered by halothane.[13]

This study compares the ability of halothane, enflurane, and isoflurane to inhibit endothelium-dependent dilation and tests the hypothesis that they cause such inhibition by interfering with receptor-mediated responses of the endothelial cell. To do so, we compared the effects of

* Chief Resident in Anesthesiology.

† Medical Student.

‡ Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Johns: Department of Anesthesiology, Box 238, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908.

these agents on both receptor-mediated and non–receptor-mediated endothelium-dependent vasodilation, and on sodium nitroprusside–mediated endothelium-independent vasodilation.

Materials and Methods

Preparation of Vascular Rings

Male Sprague-Dawley rats (300 g) were killed in accordance with institutional Animal Care Committee standards. The descending thoracic aorta was dissected free, and surrounding connective tissue and fat were removed under magnification while the vessel was bathed in modified Krebs solution (NaCl 111 mM, KCl 5 mM, NaH_2PO_4 1 mM, $MgCl_2$ 0.5 mM, $NaHCO_3$ 25 mM, $CaCl_2$ 2.5 mM, and dextrose 11.1 mM). The aorta was then cut into 2.5-mm rings, which were suspended on Grass FT-03 force transducers at 2 g resting tension in 10 ml temperature-controlled baths (37° C) containing modified Krebs solution continuously gassed with 95% O_2/5% CO_2. Care was taken to preserve the endothelium by careful dissection and gentle handling.

Isometric Tension Recordings

The rings were equilibrated at 2 g resting tension (determined to be optimal in preliminary length–tension experiments) for 60–90 min, during which the bathing solution was changed every 15–20 min. Active tone (1.4 ± 0.1 g active tension) was then induced with an EC_{50} dose of phenylephrine (that concentration which produces 50% maximal tension development; 1×10^{-7} M), and the integrity of the endothelium was confirmed by observation of a greater than 30% relaxation to methacholine (1×10^{-6} M). The rings were then washed in three changes of Krebs buffer until resting tension again stabilized at 2 g. Time control experiments established that phenylephrine-induced contractions and vascular reactivity were stable throughout all experiments.

The experimental protocols were performed as follows. Active tension was produced in all rings with the addition of phenylephrine (1×10^{-7} M). Dose–response curves for methacholine (1×10^{-8} M to 1×10^{-6} M), A23187 (1×10^{-8} M to 3×10^{-7} M), and sodium nitroprusside (1×10^{-10} M to 1×10^{-8} M) were obtained. The rings were then washed in three changes of Krebs buffer, and again, active tone was developed with an EC_{50} dose of phenylephrine. Each ring served as its own control. During halothane and enflurane exposure and during control dose–response curves, the phenylephrine dose was 1×10^{-7} M. During isoflurane exposure, 3×10^{-7} M phenylephrine was used because of the observation of a greater and persistent relaxation of baseline tension in the presence of isoflurane vapor. This provided an active tone during isoflurane exposure that was within 10% of the pre- and postisoflurane control cycles. After a stable plateau was achieved, a clinically relevant concentration of halothane vapor at 0.75% (1 MAC) or 1.5% (2 MAC; volume/volume gas), enflurane vapor at 1.7% (1 MAC) or 3.4% (2 MAC), or isoflurane vapor at 1.15% (1 MAC) or 2.3% (2 MAC) was added to the aerating mixture of 95% O_2/5% CO_2 using a calibrated vaporizer and a flow rate of 4 l/min.[14,15] Dose–response curves to methacholine, the calcium ionophore A23187, and sodium nitroprusside were again obtained in the presence of the inhalational anesthetic. The inhalational anesthetic was then removed from the aerating gas mixture, and the rings were washed in three changes of modified Krebs solution (45 min). Active tension was again developed with phenylephrine (1×10^{-7} M) and the dose–response curves repeated. The presence of intact endothelium was confirmed at the termination of the experiment by observation of greater than 30% relaxation to methacholine (1×10^{-6} M) following wash in three changes of Krebs buffer and active tension development with phenylephrine (1×10^{-7} M).

In a separate series of experiments, the dose–response curves for methacholine, the calcium ionophore A23187, and sodium nitroprusside in the presence of halothane (1.5%), enflurane (3.4%), and isoflurane (2.3%) were repeated in the presence of indomethacin (2.8×10^{-5} M) in the bathing solution. Control rings from the same animal, but without indomethacin, were performed in parallel.

Drugs

Phenylephrine, methacholine, and A23187 were obtained from the Sigma Chemical Company (St. Louis, MO). Phenylephrine and methacholine were prepared and diluted in distilled and deionized water. Sodium nitroprusside was obtained from Fisher Scientific Company (Fair Lawn, NJ) and similarly prepared. A23187 was initially dissolved in dimethyl sulfoxide and subsequently diluted in distilled and de-ionized water. Indomethacin was obtained from Sigma, dissolved in $NaHCO_3$ 10^{-3} M and *p*H-corrected to 7.4 with HCl. Accurate vaporizer calibration was confirmed using Raman spectroscopy (Rascal, Albion Laboratories, UT). Halothane (Halocarbon Laboratories, Hackensack, NJ), enflurane, and isoflurane (Anaquest, BOC Health Care, Madison, WI) concentrations in the tissue bath buffer were determined by gas chromatography. Vapor concentration after equilibration of a bath aliquot with a measured volume of air was compared to a standard curve of known concentrations obtained by vaporizing measured volumes of liquid anesthetic in a measured volume of air. Concordance with the dial concentration within ±0.2% error was found when using the Krebs/air partition coefficient for calculations.[16]

Statistical Analysis

Data are presented as mean ± SEM. Statistical comparisons were made using one-way analysis of variance (ANOVA) with means testing by Newman-Keul's multiple range test when appropriate. $P < 0.05$ was considered significant. Each mean represents 7–12 rings from separate animals.

Results

Halothane (1.5%), enflurane (3.4%), and isoflurane (2.3%) all caused a significant and reversible inhibition of both endothelium-dependent receptor-mediated relaxation by methacholine (1×10^{-8} to 1×10^{-6} M) and endothelium-dependent receptor-independent relaxation by the calcium ionophore A23187 (1×10^{-8} M to 3×10^{-7} M) with a shift of the dose–response curve to the right and a decrease in maximal relaxation (figs. 1 and 2). Halothane (0.75%) and enflurane (1.7%) did not inhibit endothelium-dependent relaxation by methacholine (1×10^{-8} M to 1×10^{-6} M) or A23187 (1×10^{-8} M to 1×10^{-7} M) (figs. 1 and 2). Isoflurane (1.15%) did cause a significant reversible inhibition of both endothelium-dependent receptor-mediated relaxation by methacholine (1×10^{-8} to 1×10^{-6} M) and endothelium-dependent receptor-independent relaxation by the calcium ionophore A23187 (1×10^{-8} to 1×10^{-7} M) (figs. 1 and 2). In contrast, relaxation by sodium nitroprusside (1×10^{-10} M to 1×10^{-8} M), an endothelium-independent vasodilator, which (like EDRF) activates guanylate cyclase, was not significantly affected by any concentration of any of the inhalational anesthetics tested (fig. 3).

Inhibition of cyclooxygenase by indomethacin had no effect on the inhibition of methacholine- and A23187-induced vasorelaxation by halothane (1.5%), enflurane (3.4%), and isoflurane (2.3%) or on their lack of inhibition of sodium nitroprusside–induced vasorelaxation (table 1).

To determine the relative potency of the anesthetics in their ability to inhibit EDRF, comparisons between the inhalational anesthetics were performed by ANOVA of the percent inhibition by each anesthetic at each concentration of each vasodilator. No pattern of statistically significant differences was detected at 2 MAC concentrations. At 1 MAC concentrations, however, isoflurane caused significant inhibition of the relaxations to methacholine and of A23187, whereas halothane and enflurane did not.

Discussion

Muldoon *et al.*[12] demonstrated that 2% halothane attenuated EDRF-dependent vasodilation induced by acetylcholine and bradykinin, two receptor-mediated agonists

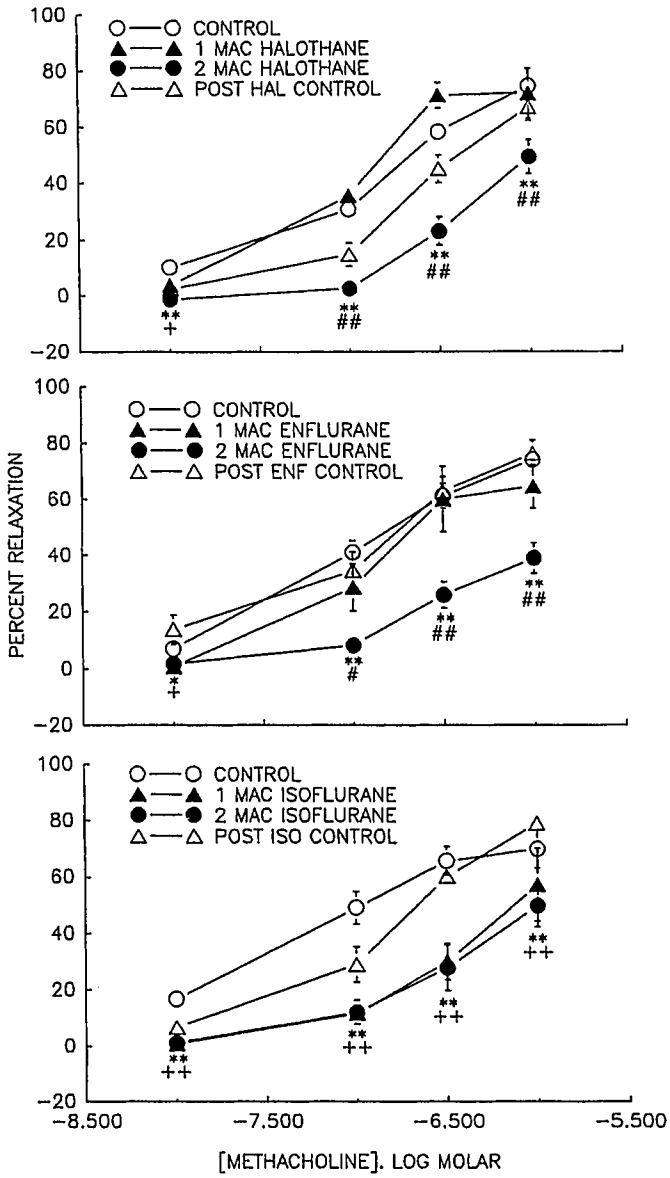

FIG. 1. Effect of volatile anesthetic on methacholine-induced endothelium-dependent vasodilation of rat thoracic aorta precontracted with phenylephrine (1.4 ± 0.1 g active tension). Each data point represents mean ± SEM with n = 7–12 animals. *$P < 0.05$ 2 MAC *versus* control; **$P < 0.01$ 2 MAC *versus* control; +$P < 0.05$ 1 MAC *versus* control; ++$P < 0.01$ 1 MAC *versus* control; #$P < 0.05$ 1 MAC *versus* 2 MAC; ##$P < 0.01$ 1 MAC *versus* 2 MAC.

of EDRF release. They postulated that this effect of halothane may be due to an inhibition of receptor activation by these agonists. Previous work from our laboratory[17] indirectly suggested that enflurane and isoflurane, in addition to halothane, are capable of inhibiting basal EDRF production. In the current report, we have more fully and directly investigated the effect of the inhalational anesthetics on EDRF-mediated vasorelaxation, compared their relative potency of EDRF inhibition, and investi-

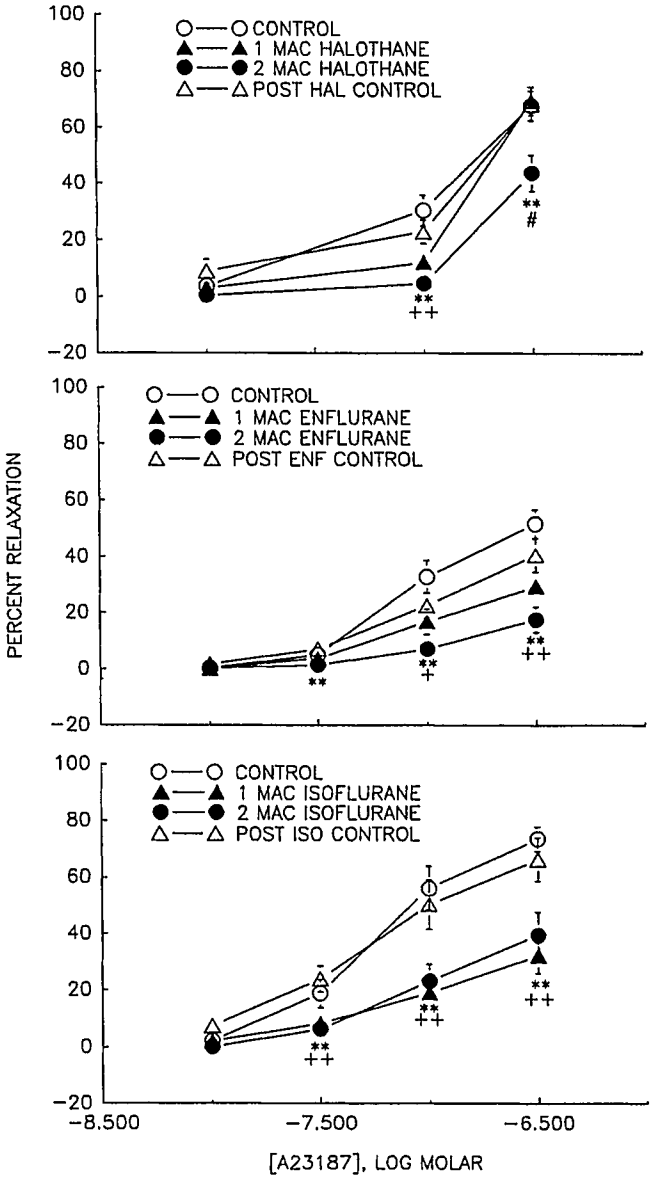

FIG. 2. Effect of volatile anesthetic on A23187-induced endothelium-dependent vasodilation of rat thoracic aorta precontracted with phenylephrine (1.4 ± 0.1 g active tension). Each data point represents mean ± SEM with n = 7–12 animals. *$P < 0.05$ 2 MAC *versus* control; **$P < 0.01$ 2 MAC *versus* control; +$P < 0.05$ 1 MAC *versus* control; ++$P < 0.01$ 1 MAC *versus* control; #$P < 0.05$ 1 MAC *versus* 2 MAC.

gated the site and mechanism of this action with regard to inhibition of receptor-mediated responses.

Our data demonstrate that halothane, enflurane, and isoflurane each inhibit endothelium-dependent vasodilation induced by EDRF-releasing agents. Halothane, isoflurane, and enflurane all inhibit endothelium-dependent vasodilation at 2 MAC concentrations, whereas at 1 MAC concentration only isoflurane causes this inhibition. Active tension was generated with phenylephrine prior to all dose–response curves; during the isoflurane-exposed dose–response curves one-half log higher dose of phenylephrine was used than during halothane, enflurane, or control in order to develop an equivalent degree of active tension. We measured the EDRF-mediated vasorelaxation at equivalent active tension to allow more direct comparison of the degree of attenuation of EDRF-mediated vasorelaxation.

We have demonstrated previously that volatile anesthetics may stimulate the release of a dilating prostaglandin from endothelium.[17] Because several agonists that stimulate EDRF production may also stimulate the production of the vasodilating prostaglandin, prostaglandin

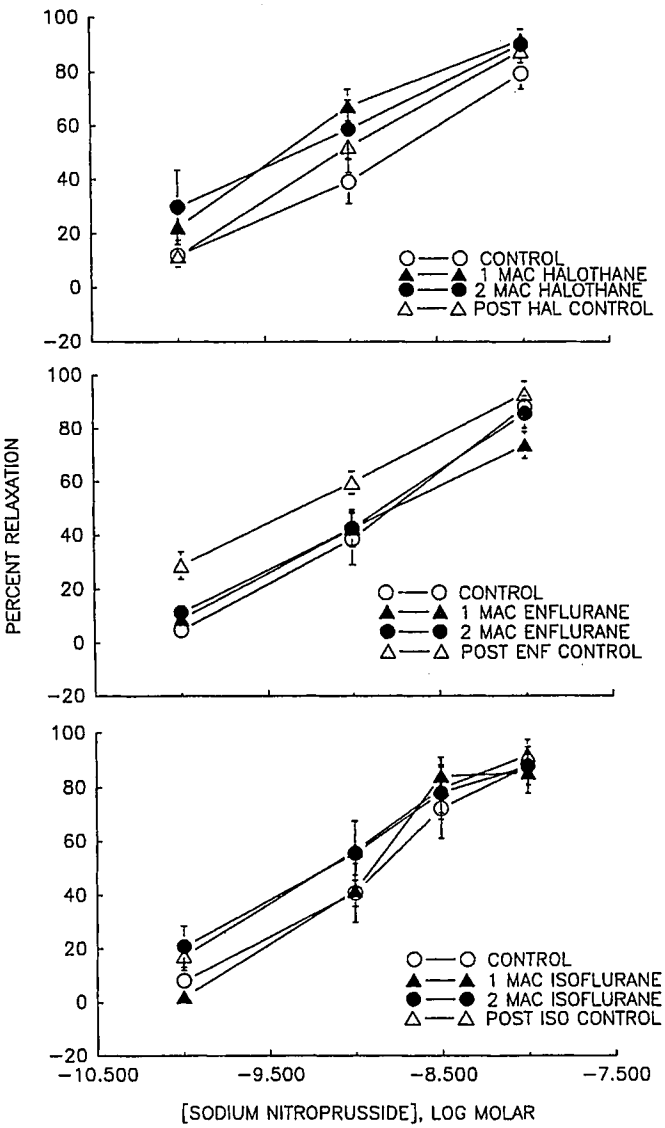

FIG. 3. Effect of volatile anesthetic on sodium nitroprusside–induced endothelium-independent vasodilation of rat thoracic aorta precontracted with phenylephrine (1.4 ± 0.1 g active tension). Each data point represents mean ± SEM with n = 7–12 animals.

TABLE 1. Effect of Indomethacin 2.8×10^{-5} M on Vasodilation of Rat Thoracic Aorta Precontracted with Phenylephrine

	1.5% Halothane		3.4% Enflurane		2.3% Isoflurane	
	Indo(−)	Indo(+)	Indo(−)	Indo(+)	Indo(−)	Indo(+)
Methacholine						
10^{-8} M	−1.2 ± 1.1	0 ± 0	2.1 ± 0.9	0 ± 0	1.2 ± 0.8	1 ± 1
3×10^{-8} M	2.7 ± 1.9	7.3 ± 4.9	8.8 ± 3.0	0.7 ± 0.7	12.2 ± 4.3	7.7 ± 7.7
10^{-7} M	23.1 ± 5.0	23.6 ± 9.0	27.8 ± 4.8	14.9 ± 4.4	27.9 ± 8.0	18.7 ± 13.3
10^{-6} M	49.3 ± 6.0	41.6 ± 5.3	40.6 ± 5.8	33.4 ± 8.1	49.8 ± 7.2	31.1 ± 18.5
A23187						
10^{-8} M	0.4 ± 0.4	0 ± 0	0.2 ± 0.1	1.0 ± 1.0	0.2 ± 0.1*	3.5 ± 2.2
3×10^{-8} M	—	—	1.4 ± 0.6	2.2 ± 2.2	6.1 ± 1.6	6.6 ± 4.6
10^{-7} M	4.7 ± 1.1	9.1 ± 1.8	7.0 ± 2.1	7.5 ± 3.6	20.5 ± 4.8	21.1 ± 7.7
3×10^{-7} M	43.9 ± 6.4	54.8 ± 0.5	17.6 ± 4.6	15.8 ± 3.9	36.1 ± 6.5	38.3 ± 12.2
Sodium nitroprusside						
10^{-10} M	16.6 ± 7.6	0.6 ± 0.6	11.4 ± 2.5*	0 ± 0	20.8 ± 7.6	0.2 ± 0.2
10^{-9} M	43.0 ± 8.4	20.8 ± 3.9	42.6 ± 6.2	38.2 ± 2.2	55.4 ± 12.4	47.2 ± 12.2
10^{-8} M	84.4 ± 3.2	92.7 ± 5.5	85.6 ± 5.4	83.3 ± 12	87.8 ± 7.0	96.6 ± 2.6

Values are percent relaxation ± SEM with n = 7–12 rings. * $P < 0.05$ indo(+) *versus* indo(−).

I_2, we also studied the EDRF-inhibiting effect of the inhalational anesthetics in the presence of indomethacin, an inhibitor of cyclooxygenase. Cyclooxygenase metabolites of arachidonic acid do not appear to play a role in these inhibitory effects, because anesthetic-induced inhibition was the same in the presence and absence of indomethacin.

The inhibition of EDRF by inhalational anesthetics is not simply due to an interaction with receptor-mediated responses. These anesthetics inhibited EDRF released by both the receptor-mediated agonist methacholine and by the non–receptor-mediated agent, the calcium ionophore A23187. Calcium activation of EDRF synthase is necessary for EDRF production in the endothelial cell. Methacholine acts on the muscarinic receptor on the endothelial cell surface, resulting in a receptor-mediated increase in cytosolic calcium from both extracellular and intracellular sources and a subsequent production of EDRF. A23187 is a calcium ionophore that increases cytosolic calcium directly by transporting calcium across the cell membrane. Although an effect of inhalational anesthetics on receptor activation cannot be ruled out by these studies, it is clear that non–receptor-mediated EDRF release is inhibited to a similar extent as methacholine-induced release, implying a significant action distal to receptor activation.

The data also demonstrate that this inhibition is due to an effect on the production, transport, or release of EDRF and is independent of any effect on guanylate cyclase activation in the vascular smooth muscle. Sodium nitroprusside–induced relaxation, which is mediated by a direct activation of vascular smooth muscle soluble guanylate cyclase following its breakdown to nitric oxide, was not affected by any of the anesthetics.[18]

There are multiple sites at which inhalational anesthetics may potentially inhibit EDRF production or release based on the known mechanisms of EDRF synthesis and action and on the observed effects of these anesthetics in other cell types. As discussed above, inhalational anesthetics have been shown to impair receptor activation.[13] It has been demonstrated that EDRF synthesis from endothelium is calcium- and calmodulin-dependent and that an increase in intracellular calcium accompanies its release.[19,20] Inhalation anesthetics have also been demonstrated to have significant effects on cytosolic calcium concentration in other cell types through an effect on calcium movement into the cell, either by changing calcium influx through receptor- or voltage-activated membrane calcium channels or by an alteration in calcium release from or uptake into the sarcoplasmic reticulum.[21,22] Halothane may interact with calmodulin, as is suggested in other *in vitro* systems, where it was shown to mimic known calmodulin inhibitors, perhaps by interacting with hydrophobic sites on the protein.[23] In the endothelial cell, EDRF synthase is 80–90% membrane-associated.[9] Inhalational anesthetics could directly impair EDRF synthase activity by interacting with a hydrophobic site on the enzyme or by altering the fluidity or structure of enzyme-associated membrane. EDRF activity may be attenuated by an interaction with the phospholipase C–inositol phosphate pathway in the endothelial cell. It is also possible that inhalational anesthetics may inactivate EDRF following its production, either *via* a direct interaction or indirectly, by enhancing free radical activity within the endothelial cell, leading to the inactivation of EDRF by superoxide.[10,24]

This work, as well as previous work from our laboratory and others',[12,17] suggests that inhalational anesthetics possess vascular actions other than those of direct vasodilation. Although diminished vasorelaxation of *in vitro* vascular rings when exposed to inhalational anesthetics may seem counterintuitive to the clinician who views these drugs as vasodilators, this effect is consistent with whole-

animal and human studies. For example, while halothane has been shown to have minimal effect on systemic vascular resistance in human volunteer studies, it has also been demonstrated to have vasodilating effects in several regional beds.[25,26] Because the measured total vascular resistance represents the net resistance of all regional vascular beds, for a minimal net result on total vascular resistance to occur, increased resistance must occur in other beds. Vasoconstriction caused by volatile anesthetics has also been observed directly in *in vivo* microvascular preparations.[27] In addition, anesthetics' inhibition of EDRF in a particular vascular bed does not imply that they constrict that vascular bed. EDRF is only one of many inputs to vascular tone. The net hemodynamic effects of inhalational anesthetics are a composite of vascular, myocardial, central, and peripheral nervous and endocrine effects, and so the current results contribute to an understanding of a defined portion of the global effects of these agents.

In conclusion, we have shown that the inhalational anesthetics halothane, enflurane, and isoflurane each attenuate EDRF-dependent vasodilation at a site distal to endothelial cell receptor-mediated responses but proximal to guanylate cyclase activation of vascular smooth muscle. Isoflurane appears to be a more potent inhibitor of stimulated EDRF release than is halothane or enflurane. The specific site(s) and mechanism(s) of this inhibition in the endothelial cell remain to be determined.

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